Original Research

The efficacy of Tivortin® in the treatment of patients with stable effort angina

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Key words: stable effort angina, Tivortin®

Cardiovascular disease is the leading cause of morbidity and mortality in Ukraine. According to official data, the fraction of cardiovascular mortality within the structure of overall mortality is 63%. More than 1000 persons per 100,000 of general population succumb to cardiovascular disease annually. In most cases, the immediate cause of death in patients with cardiovascular disease is ischaemic heart disease (IHD). In absolute numbers, there are approximately 8 million patients with chronic IHD in Ukraine [4]. Reduced or lacking endogenous NO production in the setting of endothelial dysfunction is considered one of the key reasons behind atherosclerotic and ischaemic changes (primarily in the coronary arteries), leading to different variants of IHD. [5, 7].

Bearing this in mind, one of the most promising novel therapeutic approaches is using the natural precursor of NO, L-arginine. This is an essential amino acid and an active cellular regulator of multiple vital functions in the body. L-arginine is a substrate of NO-synthase, an enzyme catalysing NO production in endothelial cells. It penetrates from endothelial cells into the smooth muscle cells of the vascular wall and activates guanylate cyclase, which increases the levels of cGMP, which, in turn, results in relaxation of blood vessels [2, 3, 6].

The aim of our study was to evaluate the efficacy and safety of using L-arginine (Tivortin®, manufactured by Yuria-Pharm Ltd., Ukraine) as a part of multimodality therapy in patients with stable effort angina, Grade II-III.

Materials and Methods

We have performed case-by-case follow-up and treatment in 15 patients (5 males, 10 females) aged 50-65 years (mean 61.53±5.73 years) with stable effort angina, Grade II-III according to the Canadian Cardiovascular Society grading. Of these patients, 8 (53.3%) had Grade II effort angina and 7 (46.7%) had Grade III effort angina. History of myocardial infarction was present in 3 (20%) patients; 4 (26.7%) patients had concomitant hypertension, 2 patients (13.3%) had concomitant Type 2 diabetes and 1 patient (6.6%) had atherosclerosis in blood vessels of the lower limbs.

Study subjects received conventional background therapy, which included statins, beta-blockers, aspirin, and ACE inhibitors in their respective optimal doses for at least a month prior to study enrolment; the baseline therapy was not changed throughout the entire course of follow-up. Short-acting nitrates were used in attacks of angina.

For 10 days, the patients had daily infusions of 4.2% Tivortin® solution, 100 mL per dose.

The screening stage included history, physical examination and routine biochemical tests. To verify IHD and to determine exercise tolerance, bicycle ergometry test was performed using the R 8000 hardware/software complex. The authors have compared exercise challenge time to ST depression on EKG and/or to angina attack and the threshold challenge before and after treatment.

The study also included clinical assessment of daily counts of angina attacks before the treatment cycle and after the treatment cycle.

All patients had their quality of life (QL) assessed before and after treatment using the WHO-approved SF-36 instrument (a standardised assessment of eight sections of health) [1].

Statistical processing of data was performed using the Statistica 6.0 statistical software package. The results are presented as M±m; the differences were considered significant at $p<0.05$.

Results and discussion

Daily counts of angina attacks and the intake of nitroglycerin tablets were used as important criteria to assess treatment efficacy (see Table 1).

Table 1

Changes in angina attack counts and the number of nitroglycerin tablets (before and after treatment)

The parameter	Pre-treatment (at baseline)	After treatment
Daily count of angina attacks	4.26± 0.57	2.01±0.25*
Daily number of nitroglycerin tablets	6.21±0.67	3.75±0.28*

Note: *p<0.001

As a result of treatment, all patients had fewer angina attacks per day (a reduction from 4.26±0.57 to 2.01± 0.25; p<0.001) and took fewer tablets of nitroglycerin (a reduction from 6.21±0.67 to 3.75±0.28; p<0.001). Three patients with stable effort angina, Grade III, no longer experienced attacks of angina at rest.

One of the reliable efficacy assessments of anti-anginal therapy is bicycle ergometry (see Table 2).

Table 2

The findings of bicycle ergometry test in study subjects

The parameter	Pre-treatment (at baseline)	After treatment
Exercise challenge time to ST depression on EKG and/or angina attack, min	6.18±0.61	8.62±0.72*
Threshold challenge, W	82.5±3.1	97.5±3.3**

Note: *p<0.01; ** p<0.001

Longer time to ST depression and/or to angina attack (when Tivortin® was added to the therapeutic schedule) is an important landmark of the anti-ischaemic effect. This parameter has increased from 6.18±0.61 to 8.62±0.72 (p<0.01), that is, by 14%. A similar pattern of changes has been noted with the threshold challenge. This parameter has increased by 18% (from 82.5±3.1 to 97.5±3.3; <0.001). Therefore, exercise tolerance has notably increased, which can be viewed as improved quality of life in the patients.

Since QL, being an important health marker in patients with IHD/effort angina, allows for assessing not only baseline severity of the condition, but can also be used as one of treatment efficacy parameters, we have assessed how the QL parameters changed with time (see Table 3).

Physical functioning provides an integral assessment of patient responses concerning the feasibility of various physical functions, from minimal challenge (self-care) to maximal challenge (engaging in sports). There was a significant increase in physical activity post-treatment (from 16.75±1.16 to 21.79±1.50 points; p<0.05). The improved physical activity dimension of QL in the setting of Tivortin® therapy reflects reduced restrictions of patient's activity of daily living (ADL) and favourably influences the success of recommended treatment.

There were very low levels of Physical Role Functioning (the SF-36 parameter characterising the impact of physical problems on the feasibility of ADL and restrictions upon professional activities and household chores). In the setting of treatment, there was a pronounced and significant increase (p<0.001) in Physical Role Functioning (from 3.12±1.66 to 17.97±3.07 points).

An important aspect in assessing the efficacy of treatment for IHD/effort angina is patient-reported pain intensity. In the setting of treatment, there was a significant increase (p<0.001) in ADL, which was previously limited by pain (from 14.69±1.08 to 20.01±1.14 points). It is our opinion that adding Tivortin® to the therapeutic regimen is an important way to improve the physical pain dimension of QL, which otherwise prevents the patient with IHD/effort angina from adequately performing his/her household chores and professional activity at the workplace.

Table 3

Assessment of quality of life before and after treatment (pre-treatment/ post-treatment quality of life)

Sections (points)	Pre-treatment	After treatment
Physical Functioning	16.75 ±1.16	21.79 ±1.50**
Physical Role Functioning	3.12±1.66	17.97±3.07*
Bodily pain	14.69±1.08	20.01±1.14*
General Health Perceptions	11.25±1.99	22.78±1.77*
Vitality	15.23±1.26	20.31±1.14*
Social Role Functioning	17.97±1.67	25.00±1.50*
Emotional Role Functioning	5.21±2.27	22.39±3.41*
Mental Health	6.11±2.29	32.22±3.83*

Note: * p<0.001; ** p<0.05.

There also was a significant increase (from 11.25±1.99 to 22.78±1.77 points; p<0.001) in responses reflecting general well-being (both patient-reported assessment of current health and patient-reported future treatment perspectives).

There was a low level of vitality pre-treatment, which indicates the reduced sensation of internal energy and desire for more vigorous activity in patients with IHD/effort angina. There is a significant (p<0.001) post-treatment increase in patients' vitality (from 15.23±1.26 to 20.31±1.14 points).

Social Role Functioning parameters were found to be low at baseline, reflecting the physical and emotional problems in patients with IHD/effort angina, which hinder normal social activity within their family, friends/neighbours and the people of their fold. In the setting of investigational therapy, there was an increase in social contacts and the intensity of communication due to improvements of physical and emotional well-being (p<0.001), from 17.97±1.67 to 25.00±1.50 points.

The pre-treatment condition was also characterised by the comparatively low findings in the Emotional Role Functioning section. The impaired emotional status of the patients caused them to spend more time on their ADLs, to perform less work and with lower quality. In the setting of investigational therapy, there was a significant increase in Emotional Role Functioning (p<0.001) compared to baseline (from 5.21±2.27 to 22.39±3.41 points). Such trends indicate a reduction in depression and anxiety, which frequently cause the patients to experience problems related to their work and other regular activities.

The last category of questions deals with the mental health of the patients. This is a qualitative description of heightened nervousness, a propensity to depressive condition as well as the reduced amount of time over the last month when the respondents felt happiness, tranquillity and peace of mind.

There was a significant (p<0.001) improvement of mental health assessments after treatment (from 6.11±2.29 to 32.22±3.83 points).

Thus, all patients with IHD/effort angina have reduced QL parameters in all sections used. Adding Tivortin® to standard drug therapy produces a significant improvement of all the QL parameters assessed with the SF-36 instrument.

Tivortin® was well tolerated by all patients; no substantial adverse effects were documented when using the product. One patient (6.6%) experienced cramps in the lower extremities during infusion of the product and two patients (13.3%) felt a faster heartbeat. The intensity of these complaints reduced after the rate of infusion was decreased.

Conclusions

Adding Tivortin® to the background therapy of Grade II-III effort angina allows increasing exercise tolerance and reducing daily counts of angina attacks, which facilitates improvement of quality of life. Tivortin® is characterised by excellent tolerability in this patient population.

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ABSTRACT

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Results and discussion. As a result of treatment, all patients had fewer angina attacks per day (a reduction from 4.26±0.57 to 2.01± 0.25; p<0.001) and took fewer tablets of nitroglycerin (a reduction from 6.21±0.67 to 3.75±0.28; p<0.001). Three patients with stable effort angina, Grade III, no longer experienced attacks of angina decubitus. Bicycle ergometry findings have demonstrated longer time to ST depression and/or angina attack when adding Tivortin® to the therapeutic schedule. This value has increased from 6.18±0.61 to 8.62±0.72 (p <0.01), that is, by 14%. A similar pattern of changes has been noted when assessing the threshold challenge. This value has increased by 18% (from 82.5±3.1 to 97.5±3.3; p <0.001). At baseline, quality of life was decreased by all sections of the assessment instrument. Adding Tivortin® to standard drug therapy produces a significant improvement of all the parameters assessed with the SF-36 instrument. Physical Functioning score has improved from 16.75±1.16 to 21.79±1.50 points (p <0.05); Physical Role Functioning score has improved from 3.12±1.66 to 17.97±3.07 points (p <0.001); Bodily Pain score has improved from 14.69±1.08 to 20.01±1.14 points (p <0.001); General Health Perceptions score has improved from 11.25±1.99 to 22.78±1.77 points (p 0.001); Vitality score has improved from 15.23±1.26 to 20.31±1.14 points (p <0.001); Social Role Functioning score has improved from 17.97±1.67 to 25.00±1.50 points (p <0.001); Emotional Role Functioning score has improved from 5.21±2.27 to 22.39±3.41 points (p <0.001). Mental Health score has improved from 6.11±2.29 to 32.22±3.83 points (p <0.001). Tivortin® was well tolerated by all patients; no substantial adverse effects were documented when using the product.

Conclusions. Adding Tivortin® to the background therapy of Grade II-III effort angina allows increasing exercise tolerance and reducing daily counts of angina attacks, which facilitates improvement of quality of life. Tivortin® is characterised by excellent tolerability in this patient population.

Key words: stable effort angina, Tivortin®