The level of endothelin-1 as a risk factor for complications of acute epididymitis

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Abstract

Background: Acute epididymitis is an inflammation of the epididymis. It mostly occurs unilaterally and may spread to the testis (‘epididymoorchitis’) if untreated. In this research there was made an attempt to clarify the diagnostic and prognostic significance of changes of the endothelin-1 (Et-1) content in blood plasma of the patients, suffering from acute epididymitis in connection with violation of blood circulation in testis with appendage.

Materials and Method: To determine the concentration of Et-1, the method of immune-enzyme analysis was used. A significant increase of the Et-1 concentration was revealed in all the examined patients before treatment.

Results and Discussion: In the preoperative period, in 43% of patients with irreversible complications (lack of blood flow to a testicle or appendage, the Doppler-signal) the high concentration of Et-1 remained to the 7th day (25,8 ± 3,2 ng/ml, exceeding the norm by 2,5 times), which indicated the irreversible microcirculatory disorders in testicle (appendage), probably because of the increasing of vasoconstriction of blood vessels. In 57% of patients there was no development of complications, ischemic processes were reversible, and under this the concentration of Et-1 gradually decreased, and until the 14th day it was up to 5,8 ± 0,6 ng/ml, returning to the normal range.

Conclusion: The dynamics of change of Et-1 concentration in blood plasma indicates the reversibility of metabolic disorders, related to ischemia of the testicle appendage tissue, as well as the diagnostic and prognostic significance of this factor determination concerning the risk of complications development. TCM-GMJ April 2018; 3 (1):P4-P7

Keywords: acute epididymitis, endothelial dysfunction, endothelin-1, Doppler, predicting complications.

Introduction

Acute epididymitis is an infectious and inflammatory disease of the testicle appendage that lasts less than 6 weeks. In some cases, the inflammatory process spreads on a testicle along with the appendage, and then an epididymo-orchitis is meant. Acute epididymitis represents a common medical condition in the urological outpatient clinic. Mostly, epididymitis is caused by bacterial ascent through the urogenital tract, with pathogens originating either from sexually transmitted diseases or urinary tract infections. Although conservative antimicrobial therapy is possible in the majority of patients and is usually sufficient to eradicate the pathogen, studies have shown persistent oligozoospermia and azoospermia in up to 40% of these patients.1, 2

Heavy epididymo-orchitis can lead to ischemia of the testicle tissue both due to the involvement of the organ tissue in the inflammatory process, and through the compression of the blood vessels of the testicle by swollen tissue of the appendage.3 Vascular factor plays a significant role in the development as well as in the termination of the inflammatory process of the testicle appendage.

Endothelial dysfunction (ED) can be a self-causing disturbance of blood circulation in the organ, as it often provokes angiospasm or vascular thrombosis.4, 5 The endothelium function is regulated by nitrogen monoxide (NO)6, 7, 8.

One of the most important derivatives of the endothelium is endothelin (Et). It is the most powerful vasconstrictor of the bloodstream, the synthesis of which is enhanced with various pathological processes. Nitric oxide and other substances produced by the endothelium dilate blood vessels, which leads to stimulation of Et formation. In addition, beside the vasocostructor effect, Et is involved in the regulation of cell growth. Nowadays it is known 3 types of Et: Et-1, Et-2, Et-3, which are the products of 3 different genes and have expressed differences in the structure and vasocostructor activity.9, 10, 11

After damage of the tissue, the endothelin system reacts first, a sharp increase in the level of Et-1 in the plasma is a marker of the activity of the destruction process. They are diagnostic markers of the involution processes, reorganization and destruction of collagen and elastin of the connective tissue of the scar.12

The dynamics of changing concentration of Et-1 in the blood plasma indicates the reversibility of metabolic disorders, as well as the diagnostic and predictive significance of the determination of this factor in relation to the risk of complications development.6
The study of biochemical markers of acute epididymo-orchitis has a great theoretical and practical interest in terms of dynamic observation of treatment and recovery of patients. One of the possible markers may be endothelin-1 (Et-1), which is a factor of endothelial dysfunction.

Materials and method

The purpose of the study is to study the diagnostic and prognostic significance of the endothelin-1 level in the plasma of patients’ blood regarding to the risk of complications development in the treatment of acute epididymitis.

The main criteria that allowed to participate in the study were: the age from 26 to 72 years; the body weight was in average 78,3 ± 5,2 kg; body mass index – 25,6 ± 2,3 kg/m2, of the patients which receive baseline therapy. The patients with testicular twisting and obvious signs of purulent epididymitis (epididymo-orchitis) were not included in the study.

The examination and complex treatment of 35 patients with acute epididymo-orchitis have been performed. The control group consisted of 15 practically healthy men. Ultrasound signs and major Doppler parameters - peak systolic velocity/speed (PSS), peak diastolic velocity/speed (PDS) and index of resistance (IR) - were determined during the study.

Endothelin-1 in blood plasma was determined using a set of firm "Biomedica" for quantitative determination of endothelin-1 by immunoassay. The normal values of endothelin-1 in human plasma of an anticoagulant EDTA are 0-10 ng/ml. To determine the state of the endothelium of the vessels, the ratio of PSS of the patient to the healthy side and the IR of the testicular artery from the patient side was used.

Patients were divided into 2 groups. The first group - 20 patients with acute epididymo-orchitis, in the process of treatment of which the antibiotic ofloxacin, l-arginine and suppositories with streptokinase 15 000 MU and streptodornase 1250 MU were included, the 2nd group - 15 patients with acute complicated epididymitis (epididymo-orchitis), which were surgically treated. The control group is practically healthy men (15 men).

In order to improve the efficiency of treatment and long-term therapeutic effect, l-arginine was included in combination therapy of the patients of the 1st Group, which is a substrate for NO-synthase – an enzyme that catalyzes the synthesis of nitric oxide in the endothelial cells. The drug activates guanylatecyclase and increases the level of cyclic guanidine-monophosphate (cGMP) in vascular endothelium, reduces the activation and adhesion of leukocytes and platelets to the endothelium of blood vessels, suppresses the synthesis of endothelin-1, which is a powerful vasoconstrictor and stimulator of proliferation and migration of smooth myocytes in the vascular wall.

Distreptaza was also used in the first group in the complex treatment. The mechanism of the drug action lies in the ability to lysis of necrotic masses, manure and fibrin deposits, which leads to resorption of connective tissue. Also the drug facilitates the access of antibacterial drugs to the inflammation zone at the expense of microcirculation improving in the pelvic organs.

For the patients of all 2 groups the therapy was combined with the physiotherapeutic procedure “Bioptron” on the affected side of the wicket.

The effectiveness of the carried therapy was analyzed in 7 and 14 days after the received therapy and evaluated the safety of the use of drugs. The evaluation of the effectiveness of therapy was assessed as excellent when the index of IR (index of resistance) approached the norm (= 0,5), good – the absence of clinical symptoms, the IR – less than 0,5, satisfactory – the presence of clinical symptoms, bad – the lack of treatment effect.

The obtained results were analyzed using the computer software packages of the STATISTICA licensed software StatSoft Inc. and Excel XP for Windows using parametric and non-parametric computing methods.

Results and discussion

The results of studying the dynamics of the level of Et-1 in the blood plasma of patients in different periods of the survey are reflected in the chart.

The patients in each group had got the developing complications during the treatment or treatment was ineffective, which determined the need for surgical treatment: epididymotomy, epididymectomy, resection of the appendage, orchithomy. Operative treatment was usually done on the 5-7th day of hospitalization.

In the preoperative period in the patients with acute complicated epididymo-orchitis, the concentration of Et-1 exceeded the control (median of physiological values of the concentration of Et-1 in blood plasma) in average in 2.5 times (p <0,05), which may be due to a destructive process.

In the preoperative period, there were statistically significant differences in the concentration of this marker in the studied groups, which was characterized by different condition of the disease. In the 1st group of the patients on the 5-7th day of hospitalization, the Et-1 content decreased slightly to 11,4 ± 2,1 ng/ml, and on the 14th day it was 5,8 ± 0,6 ng / ml (p<0,05), which was put into the range of norm (0-10 ng/ml). In the 2nd group of the patients with an adverse preoperative condition in the early treatment period on the 5-7 days, further increase in the concentration of Et-1 (up to 25,8 ± 3,2 ng/ml) was noted, which, after the operative treatment, tended to decrease and on the 14th day was 19,9 ± 2,2 ng / ml (p < 0,05), in comparison with the 1st group in both periods of determination of Et-1 (Figure 1).

By analyzing the dynamics of an IR (according to the Figure 2), a sharp decrease of the IR should have been noted on the 5-7 day of the examination and treatment in the 2nd group of patients, which indicated a deterioration in the blood supply and haemodynamics of the affected appendage in the patients and required surgical treatment. As for the first group, the IR gradually increased, indicating improvement in blood supply and recovery of the patients. On the 14th day, an increase in the rate of IR in patients of
the 2nd group after the surgical treatment was noted: 0.48 vs. 0,36, which was associated with the gradual recovery of the patients and the alignment of the hemodynamic index to normal.

Thus, the statistical analysis data indicate that there are substantially significant differences both in absolute indexes and in dynamics of changes in the concentration of Et-1 in the blood plasma of the patients of different groups during the treatment, which is also confirmed by the dynamics of IR.

It is known that the main stimulus of the formation and secretion of Et is ischemia or acute stress. Et, being a powerful constrictor of the blood stream and an inflammatory peptide, causes an increase in the number of T-lymphocytes in the tissues and organs, which in its turn attracts other immunocompetent cells, in particular macrophages, which produce factors that stimulate inflammation and destruction of the hearth, which leads to unfavorable prognosis for normal repair.11, 13 Some authors have proven that macrophages can be differentiated into 2 subpopulations: the first ones are capable to destroy tumor cells, and the latter – to increase their growth.14 The first ones are characterized as cells with pronounced effector properties that can participate in the protection against both microorganisms and against malignant cells. They actively produce various biologically active substances, including NO. Its excessive amount in combination with superoxide leads to the formation of peroxynitrite, which violates the function of hemoglobin and causes hypoxia, which makes the processes of tissue regeneration worse.15

Since Et has a predominantly local effect, it can be assumed that the increase in its formation and its admission into the blood stream may be the cause of the appearance and deepening of the severity of the disease. It is known that at high Et-1 concentrations, it takes place its interaction with a specific receptor Et-1A, that is expressed on the cells of the smooth muscle of vessels, which results in a vasospasm; in the case of low Et-1 concentration, the ligand-receptor complex Et-1 + Et-1B is formed and endothelium dependent vasodilatation develops. Therefore, it can be assumed that critical ischemia of the testicular tissue is associated with vasoconstriction, which occurs when the concentration of Et-1 increases, and it is such as to break the processes that provide reparative regeneration. The increase in the concentration of Et-1 (up to 25,8 ± 3,2 ng / ml), detected by us, in 2.5 times in the early therapeutic period in the patients with acute purulent epididormorchitis suggests that an increase in the level of Et-1 may have a prognostic and diagnostic value for definition of tactics (conservative or operative) in the course of treatment.

Conclusion

In all the examined patients with acute epididormorchitis accompanied by ischemia before surgery, a significant increase of the concentration of Et-1 in blood plasma was detected.

In the preoperative period, in 43,0 % of the patients the irreversible complications developed that manifested by necrosis of tissue of the testicle with appendage. At the same time, the concentration of Et-1 continued to increase until the 7th day (25,8 ± 3,2 ng / ml) and exceeded the norm in 2,5 times, indicating irreversibility of microcirculation disorders in the body and requiring surgical treatment.

In 57,0% of the patients treated with conservative treatment, complications were not noted, with the Et-1 concentration up to the 14th day being 5,8 ± 0,6 ng / ml, returning to the limit of the physiological norm. The dynamics of the change in the concentration of Et-1 in the blood plasma of the patients of this group indicates the reversibility of metabolic disorders associated with ischemia of the tissues of the testicle.

Figure 1. Indexes of the content of Et-1 in the blood plasma of the patients with acute epididymoorchitis.
Figure 2. Dynamics of the resistance index (IR) by groups.

References