

EFFECT OF CRYOPRECIPITATE ON NEOANGIOGENESIS IN PATIENTS WITH PURULENT PYELONEPHRITIS

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⊗ **The aim of the study** is to investigate the effectiveness of conservative therapy with the inclusion of cryoprecipitate in its composition and its effect on the angiogenesis of renal blood vessels in patients with purulent pyelonephritis. **Materials and methods.** The study included 30 patients aged from 20 to 45 years (6 men, 24 women) with acute purulent pyelonephritis. All patients were assessed for markers of angiogenesis in blood plasma: vascular endothelial growth factor (VEGF-A), angiopoietin 1 (Ang1) and angiopoietin 2 (Ang2). The patients were divided into two groups. Patients of group 1 ($n = 15$) received conservative therapy with the inclusion of cryoprecipitate, patients of group 2 ($n = 15$) received surgical treatment. The control group consisted of 10 healthy donors aged 20–35 years, whose blood angiogenesis markers were determined to obtain reference values. **Results.** In the course of preliminary studies, the blood content of angiogenesis markers was determined in 10 healthy donors. The level of VEGF-A in patients of both groups and the level of Ang1 in patients of group 1 at admission to the hospital significantly exceeded the corresponding values in the control group. In group 2 patients, the level of VEGF-A and Ang1 remained elevated during treatment, which indirectly indicated an ongoing inflammatory process. The level of Ang2 in patients of both groups did not change significantly. Conservative treatment of group 1 patients showed high efficiency, which was confirmed by positive dynamics of clinical and laboratory indicators, as well as data from instrumental examination. **Conclusions.** The results obtained indicate the effectiveness of conservative therapy with the administration of cryoprecipitate in patients with purulent pyelonephritis, and the effectiveness of such treatment is comparable to the effectiveness of surgical treatment. The use of cryoprecipitate has an endothelioprotective and anti-inflammatory effect on blood vessels, stabilizes the processes of angiogenesis, which contributes to limiting the inflammatory process and its regression.

⊗ **Keywords:** purulent pyelonephritis; VEGF-A; Ang1; Ang2; cryoprecipitate.

ВЛИЯНИЕ КРИОПРЕЦИПИТАТА НА НЕОАНГИОГЕНЕЗ У БОЛЬНЫХ ГНОЙНЫМ ПИЕЛОНЕФРИТОМ

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⊗ **Цель исследования.** Изучение эффективности консервативной терапии с включением в ее состав криопреципитата и ее влияние на ангиогенез почечных кровеносных сосудов у больных гнойным пиелонефритом. **Материалы и методы.** Под наблюдением находились 30 пациентов с острым гнойным пиелонефритом в возрасте от 20 до 45 лет (6 мужчин, 24 женщины). Всем определяли содержание маркеров ангиогенеза в плазме крови: фактора роста эндотелия сосудов (VEGF-A), ангиопоэтина 1 (Ang1) и ангиопоэтина 2 (Ang2). Пациенты были разделены на две группы: в 1-й группе ($n = 15$) получали консервативную терапию с включением в ее состав криопреципитата; во 2-й ($n = 15$) — проводили хирургическое лечение. Контрольную группу

составили 10 здоровых доноров в возрасте 20–35 лет, у которых определяли содержание маркеров ангиогенеза в крови для получения референсных значений. **Результаты.** В ходе предварительных исследований у 10 здоровых доноров определено содержание в крови маркеров ангиогенеза. Уровень VEGF-A у пациентов обеих групп и уровень Ang1 в 1-й группе при поступлении в стационар достоверно превышали соответствующие значения в контрольной группе. У пациентов 2-й группы в процессе лечения уровень VEGF-A и Ang1 оставался повышенным, что косвенно указывало на продолжающийся воспалительный процесс. Уровень Ang2 у пациентов обеих групп статистически значимо не изменился. Консервативное лечение больных 1-й группы показало высокую эффективность, что подтверждалось положительной динамикой клинических и лабораторных показателей, а также данными инструментального обследования. **Выводы.** Полученные результаты свидетельствуют об эффективности консервативной терапии с назначением криопреципитата у пациентов с гнойным пиелонефритом, причем эффективность такого лечения сопоставима с эффективностью оперативного лечения. Применение криопреципитата оказывает эндотелиопротективное и противовоспалительное действие на кровеносные сосуды, стабилизирует процессы ангиогенеза, что способствует ограничению воспалительного процесса и его регрессии.

⊗ **Ключевые слова:** гнойный пиелонефрит; VEGF-A; Ang1; Ang2; криопреципитат.

INTRODUCTION

Angiogenesis represents a process of formation of blood vessels due to the migration and proliferation of endothelial cells and reconstruction of the capillary network [1]. This is a complex, multi-staged process that is under the control of inducers and inhibitors of angiogenesis [2]. Normally, the level of the latter is such that it prevents the initiation of angiogenesis in healthy tissues. When the action of angiogenesis inducers exceeds that of the inhibitors, the endothelial cells pass from their usual dormant state to an active one, and angiogenesis is initiated [3].

The mechanisms of angiogenesis have been studied in various diseases, including inflammatory ones [4]. The important role of vascular growth in ensuring the healing and scarring of wounds, elimination of foci of inflammation, resorption of blood clots, encapsulation of foreign bodies, as well as the growth and metastasis of tumors has been demonstrated [5]. The process of angiogenesis itself has the following stages. First, endothelial cells are activated, followed by proteolytic degradation of the extracellular matrix and dissolution of the basement membrane using specific proteases, namely plasminogen activators and collagenases that increase the vascular permeability. Endothelial cells migrate from the vascular walls through the perivascular tissue towards the angiogenic stimulus. Thereafter the vascular framework is formed through intracellular vacuoles or extracellular channels. The endothelium reaches functional maturity, new smooth muscle cells and pericytes are formed, and the vasculature is organized [1]. The formation of new vessels is balanced by stimulants and inhibitors of angiogenesis [6].

Additionally, a lack of oxygen (hypoxia or ischemia) acts as a natural stimulus for angiogenesis under physiological and pathological conditions [7]. Hypoxia stimulates the release of hypoxia-inducing factors; namely HIF (HIF 1 α and HIF 1 β) [8], and also stimulates the release of a number of other angiogenesis factors; in particular, vascular endothelial growth factor (VEGF) that is the main regulator of physiological and pathological angiogenesis. These factors are able to penetrate into the cell nucleus and bind to the corresponding sites, changing the transcription of many genes, including the VEGF genes [9]. As a result, the expression of angiogenesis inducers is increased.

VEGF is a biologically active homodimeric glycoprotein with a molecular weight of about 45 kDa and is one of the most important growth factors of the vascular endothelium; ensuring its vital activity. VEGF levels are increased in tissues undergoing active angiogenesis. Its receptors are expressed on the endothelial cells in adjacent blood vessels [10], as well as on cells of the renal tubules and podocytes of the renal glomeruli, thereby regulating vascular permeability [11]. VEGF promotes endothelial proliferation and stimulation of trophic functions [12]. Within the renal tissue it mediates many functions; it stimulates proteinuria, remodels vascular and renal tissue, neoangiogenesis and mesangial collagen synthesis, and has a chemotactic effect on the monocytes [13]. Obstruction of the urinary tract provokes an increase in VEGF expression [14]. The degree of VEGF increase correlates with the severity of the pathological process. Disorders of urodynamics and local inflammation are accompanied by increased

production of pro-inflammatory cytokines. A decrease in the inflammation and ischemia in the tissue due to the resolution of the obstruction is accompanied by a gradual decrease and normalization of pro-inflammatory cytokines and chemokines. A stable level of VEGF indicates the maintenance of regenerative capacity [15]. Injury of the vascular wall alters the vascular tone and enhances renal parenchymal ischemia by stimulating VEGF secretion.

VEGF binds to tyrosine kinase receptors (VEGFR) on the membrane of endothelial cells. Only three VEGF receptors are known (VEGFR1, VEGFR2, VEGFR3) [16]. There are no such receptors on intact endothelial cells in a healthy person. Activation of these receptors triggers many intracellular post-receptor signaling cascades that stimulate angiogenesis and induce pro-inflammatory responses. The VEGF level can be used to assess the degree of renal parenchymal ischemia [17].

The dynamics of changes in the biomarkers of neoangiogenesis and inflammation are of great clinical importance. However, their diagnostic and prognostic significance in patients with purulent pyelonephritis for determining the timing of the renal tissue restoration, relief of inflammation, and the feasibility of further surgical treatment, have not been sufficiently studied.

The study aimed to investigate the effectiveness of conservative therapy using cryoprecipitate in patients with purulent pyelonephritis and its effect on renal vascular angiogenesis.

MATERIALS AND METHODS

A prospective controlled randomized cohort study was conducted at the Department of Urology and Andrology, Altai State Medical University. The study included 30 patients with acute purulent pyelonephritis aged 20–45 years (6 men, 24 women). The study was approved by the local ethics committee of the Altai State Medical University (protocol No. 14 dated 11/18/2016), and all participants signed an informed consent to participate in the study.

Inclusion criteria for the study were patients of both sexes, aged 20–45 years, absence of extra-renal pyoinflammatory processes, absence of diseases of blood or cardiovascular system, signs of a purulent process in the kidneys (renal carbuncle or apostematous pyelonephritis).

Exclusion criteria for the study were pregnancy, HIV infection, hepatitis B or C infection, or other

immunodeficiency and viral diseases, secondary pyelonephritis, renal abscess etc.

In the course of the study, all patients with purulent pyelonephritis received standard conservative treatment that included complex antibacterial, detoxification, and anti-inflammatory therapy. We used broad spectrum antibacterial drugs; namely III and IV generation cephalosporins, fluoroquinolones, and aminoglycosides, both as monotherapy and combinations depending on the severity of the condition. Antibacterial therapy was performed for an average of 3–4 days after the body temperature returned to normal.

The patients were randomized by means of a random number generator using the Random Microsoft Excel program. The patients were distributed into two groups of 15 patients each, and they were matched for age, gender, and ethnicity.

Treatment of group 1 patients ($n = 15$) included transfusion therapy with cryoprecipitate produced at the Altai Regional Blood Center (Barnaul). Cryoprecipitate was administered intravenously, in 3–5 doses per day, for 3–5 days. In group 2, surgical treatment (decapsulation of the affected kidney, incision and excision of the purulent focus) was performed ($n = 15$) 3–4 days after admission to the hospital.

Upon admission to the hospital and on the 6th–7th day of treatment, the severity of the condition was assessed according to the following indicators:

- 1) time of onset and severity of clinical manifestations, disease duration (taking into account the time interval from an increase in body temperature and pain in the lumbar region to the day of hospitalization), and the presence of episodes of impaired consciousness;
- 2) pain intensity at rest and on palpation of the kidneys (changes in time of patients' complaints of pain in the lumbar region were assessed according to a 10-point verbal pain assessment scale – VPAS) [16], severity of fever, blood pressure, heart rate and respiratory rate, comorbidity, and the presence of antecedent diseases;
- 3) data of functional examination methods (ultrasound examination with Doppler sonography, plain and intravenous urography, multispiral computed tomography, and magnetic resonance imaging of the kidneys);
- 4) presence of a systemic inflammatory response syndrome (SIRS) according to the standard criteria [17];

- 5) presence of organ failure in patients with a septic process, as assessed on the qSOFA scale (by the simplified SOFA system) [18].
6. determination of angiogenesis markers in blood plasma, namely vascular endothelial growth factor (VEGF-A), angiopoietin 1 (Ang1), and angiopoietin 2 (Ang2).

To obtain the control values for the levels of angiogenesis markers; VEGF-A, Ang1, and Ang2 were evaluated in 10 apparently healthy donors aged 20–35 years.

Venous blood was sampled from the cubital vein into dry VACUETTE tubes. The blood was centrifuged at 1400 g for 15 min at room temperature. Prior to the enzyme immunoassay, the plasma was stored at -40°C at a freezer storage plant, MDF-192, for 1 day to 1 month.

Statistical analyses of the data for calculating the significance of the difference in the values of indicators before and after the treatment was performed using the Wilcoxon and Fisher tests; the intergroup comparison was performed using the nonparametric Mann–Whitney *U*-test. The critical level of significance of the differences was considered at $p < 0.05$.

RESULTS

When assessing the patient's condition severity, the SIRS syndrome was detected in all patients, and 6–7 days after the treatment, no signs of this syndrome were revealed.

Based on the qSOFA organ dysfunction assessment scale, 1 point was determined in two group 1 patients; while, 2 points were detected in two patients, without signs of impaired consciousness, in group 2. Overall, one patient had 2 points on this scale and two patients had 1 point each. Between the 6th and 7th day after the treatment, the condition of all patients corresponded to 0 points.

Initially in this study, the levels of angiogenesis markers were determined in 10 practically healthy donors. The median levels of VEGF-A, Ang1, and Ang2 were 462.74, 3110.35, and 1729.72.

Table 1 presents the varying blood levels of angiogenesis markers of group 1 and 2 patients during the treatment. It can be seen that VEGF-A levels in patients of both groups and the levels of Ang1 in patients of group 1, upon admission, exceeded those of the practically healthy donors. These data indicate an increase (destabilization) in

the angiogenesis process due to the vascular lesion caused by an intense inflammatory response. During therapy, stabilization of the angiogenesis process in group 1 patients was observed. In group 2, a continuing increase in the levels of VEGF-A and Ang1 was observed that indirectly indicated a progressing inflammatory response. The Ang2 levels in patients of both groups did not show a significant change.

These data indicate that the use of cryoprecipitate stabilizes the angiogenesis process during active renal inflammation and does not induce the development of pathological vascular growth; therefore, it has an endothelioprotective and anti-inflammatory effect.

The assessment of the severity of pain in the lumbar region on a ten-point scale provided the following data. The intensity of pain in group 1 patients decreased significantly from 8 points upon admission to 2 points between the 6th and 7th day of therapy ($p = 0.007$). Group 2 patients also showed a decrease in pain intensity from 8 points upon admission to 4 points between the 6th and 7th day ($p = 0.012$). Dysuric phenomena were noted in 93.3% of group 1 patients upon admission and only in 13.3% of patients between the 6th and 7th day ($p < 0.001$). In group 2 patients, urination disorders were detected between the 6th and 7th day in 60% of patients when compared with 100% patients upon admission ($p = 0.017$). Table 2 presents the varying levels of blood and urine parameters in both groups of patients.

The positive effect seen in group 1 patients, who received the cryoprecipitate, compared with those in group 2, manifested as a greater decrease in the severity of pain, degree of dysuria, leukocytosis, leukocyte count in urine, and ESR that indicated, among other signs, the severity of the inflammatory response.

Additionally, in group 1 patients, between the 6th and 7th day of treatment, the ultrasonography revealed a positive trend in that only diffusely heterogeneous changes in the renal parenchyma were identified. This confirmed the regression of the purulent process in the kidneys. In group 2, ultrasound examination was not performed between the 6th and 7th day due to the presence of a surgical wound. The periods of hospital stay also differed between the groups; they averaged 10.8 ± 1.6 and 12.3 ± 1.2 days in group 1 and group 2, respectively.

Table 1 / Таблица 1

Dynamics of angiogenesis markers in blood during treatment in patients of groups 1 and 2 ($n = 30$)
Динамика содержания маркеров ангиогенеза в крови в процессе лечения у пациентов 1-й и 2-й групп ($n = 30$)

Examination terms	Group 1 ($n = 15$)	Group 2 ($n = 15$)	p
VEGF-A			
Upon admission (a)	456.65*	420.91*	$p_{1-2} = 0.32$
After 6–7 days (b)	559.99*	1045.19*	$p_{1-2} = 0.75$
Significance of differences	$p_{a-b} = 0.07$	$p_{a-b} = 0.043$	–
Ang1			
Upon admission (a)	18606.1	20128.3	$p_{1-2} = 0.71$
After 6–7 days (b)	30481.7	38990.1	$p_{1-2} = 0.12$
Significance of differences	$p_{a-b} = 0.16$	$p_{a-b} = 0.043$	–
Ang2			
Upon admission (a)	3858.59*	3862.81	$p_{1-2} = 0.27$
After 6–7 days (b)	2169.84	2379.25	$p_{1-2} = 0.83$
Significance of differences	$p_{a-b} = 0.16$	$p_{a-b} = 0.22$	–

Note. * Significance of differences in the indicator ($p < 0.05$) compared with the data obtained in practically healthy patients from the control group; p_{1-2} – comparison of indicators between groups; p_{a-b} – comparison of indicators at admission and on the day 6–7 therapy within the group.

Table 2 / Таблица 2

Dynamics of laboratory parameters of blood and urine during treatment in patients of groups 1 and 2 ($n = 30$)
Динамика лабораторных показателей крови и мочи в процессе лечения у пациентов 1-й и 2-й групп ($n = 30$)

Examination terms	Group 1 ($n = 15$)	Group 2 ($n = 15$)	p
Blood leukocyte count, $\times 10^9/\text{л}$			
Upon admission (a)	15.8	14.3	$p_{1-2} = 0.122$
After 6–7 days (b)	9.7	12.5	$p_{1-2} = 0.002$
Significance of differences	$p_{a-b} = 0.007$	$p_{a-b} = 0.038$	–
ESR, mm/hour			
Upon admission (a)	29.0	24.2	$p_{1-2} = 0.171$
After 6–7 days (b)	15.9	19.6	$p_{1-2} = 0.030$
Significance of differences	$p_{a-b} = 0.007$	$p_{a-b} = 0.007$	–
Leukocytes in urine, count in the field of view			
Upon admission (a)	134.9	138.9	$p_{1-2} = 0.723$
After 6–7 days (b)	80.4	135.0	$p_{1-2} < 0.001$
Significance of differences	$p_{a-b} = 0.007$	$p_{a-b} = 0.192$	–

DISCUSSION

The damaging effect of the inflammatory process on the renal blood vessels and on the vascular endothelium induces the development of sepsis and organ dysfunction. In the present study, in the treatment of purulent pyelonephritis, the dynamic levels of the main markers of angiogenesis were traced in patients who underwent surgery for this disease (group 2) and in those who did not receive surgical treatment and were instead treated conservatively with the systemic use of cryoprecipitate (group 1). Our data are preliminary, since they were obtained from relatively small cohorts of patients, and require further research that may eventually change the standards of management of patients with purulent pyelonephritis.

CONCLUSIONS

The use of cryoprecipitate as part of the conservative therapy for purulent pyelonephritis has an endothelioprotective and anti-inflammatory effect on blood vessels, and it stabilizes the mechanisms of angiogenesis that help to limit the inflammatory process and aid in its regression.

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