doi: 10.18484/2305-0047.2017.5.481

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THE EARLY DIAGNOSIS OF RENAL GRAFT DYSFUNCTION

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Цель. Разработать технологию диагностики ишемически-реперфузионного повреждения в посттрансплантационном периоде на основе нарушений баланса про-антиоксидантного состояния организма реципиента.

Материал и методы. Изучены результаты обследования 60 пациентов с хронической болезнью почек (ХБП) 5 стадии. Всем выполнена пересадка почки. Оценивали баланс про-/антиоксидантного состояния организма методом люминолзависимой хемилюминесценции (ЛЗХЛ) плазмы крови до операции и через 24 часа после операции. Для изучения влияния анестезиологического пособия и оперативного вмешательства на состояние про-/антиоксидантного баланса организма исследовали группу пациентов (n=20), которым выполнялось плановое оперативное лечение под общей анестезией.

Результаты. Выявлено, что пересадка почки вызывает у пациентов с ХБП 5 стадии уже в течение первых суток значимое смещение баланса про-/антиоксидантов в сторону прооксидантов и значимое снижение мощности антирадикальной системы организма. При анализе уровня баланса про-/антиоксидантов и мощности антиоксидантной системы организма в группе пациентов с немедленной функцией трансплантата (НФТ) показатель баланса про-/антиоксидантов в первые сутки после операции равнялся 24,0% [11,9; 44,6]%, а мощность антиоксидантной системы составляла 35,8% [12,7; 40,8]%. В группе пациентов с замедленной функцией трансплантата (ЗФТ) в первые сутки послеоперационного периода выявлено более значимое смещение баланса в сторону прооксидантов до 10,7% [6,1; 19,2]% (p=0,011), с истощением антиоксидантной системы организма до 12,7% [6,1; 29,3]% (p=0,024). В группе пациентов, перенесших плановое оперативное лечение, в послеоперационном периоде значимого изменения в показателях про-/антиоксидантного баланса плазмы крови не наблюдалось.

Заключение. Определение тяжести ишемически-реперфузионной травмы у пациентов после пересадки почки может производиться на основании выявления нарушений баланса про-/антиоксидантного состояния и показателя мощности антиоксидантной системы организма реципиента, что расширяет диагностические возможности раннего определения риска развития отсроченной функции трансплантата.

Ключевые слова: трансплантация почки, посттрансплантационный период, ишемически-реперфузионная травма, отсроченная функция трансплантата, баланс проантиоксидантного состояния, люминолзависимая хемилюминесценция, хроническая почечная недостаточность

Objectives. To develop diagnostic technology of the reperfusion injury due to imbalance of pro-/antioxidant state of recipient in the post-transplant period.

Methods. The examination results of 60 patients with the stage 5 chronic kidney disease (CKD) have been analyzed. Kidney transplantation has been performed in all patients. The balance of pro-/antioxidant state of the organism was assessed by the method of luminol-dependent chemiluminescence (LDCL) of the blood plasma before the surgery and 24 hours after it. To study the influence of anesthetic support and surgery treatment on the state of pro-/antioxidant balance, the group of patients (n=20) was examined who underwent the scheduled surgery treatment under general anesthesia.

Results. The kidney transplantation has been found out to cause a significant shift in the balance of pro-/antioxidants to pro-oxidants and a significant reduction of the potency of antiradical body system within the patients with the stage 5 CKD during the first 24 hours already. When analyzing the pro-/antioxidant balance level and the capacity of antioxidant organism system in the group of patients with the immediate graft function (IGF), the index of pro-/antioxidant balance in the first day after the surgery was 24.0 [11.9; 44.6]%, and the capacity of antioxidant system was 35.8 [12.7; 40.8]%. In the group of patients with the delayed graft function (DGF) in the first 24 hours in the postoperative period a more significant balance shift to pro-oxidant up to 10.7 [6.1; 19.2]% (p=0.011) was detected, the antioxidant organism system was exhausted up to 12.7 [6.1; 29.3]% (p=0.024). There were no significant changes identified in the indices of pro-/antioxidant balance level of the blood plasma within the group of patients who underwent the scheduled surgical treatment in the postoperative period.

Conclusions. The determination of the severity of reperfusion injury within the patients after kidney transplantation can be performed on the basis of detection of pro-/antioxidant state imbalance and the potency index of the organism antioxidant system that expands the diagnostic possibilities of early risk detection of the delayed graft function.

Keywords: kidney transplantation, postoperative period, reperfusion injury, delayed graft function, balance of pro-/antioxidant state, luminol-dependent chemiluminescence, chronic renal insufficiency

Novosti Khirurgii. 2017 Sep-Oct; Vol 25 (5): 481-487
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Introduction

Transplantation of organs and tissues is an actively developing trend in Belarusian medicine. In 2014, in the Republic of Belarus the transplantation activity made up 43.6 operations per 1 million people. For example: in Poland this figure composes 40, in Lithuania – 22, in Russia – 9.8, in Ukraine – 2.2 [1].

Any transplantation of an organ is accompanied by a reversible cessation of its blood flow, which leads to ischemia of the organ followed by reoxygenation after inclusion into the bloodstream. Thus, primary for transplantation is ischemic and subsequent reperfusion trauma (IRT) of a donor organ of varying severity. The reperfusion injury is a multicomponent pathology that affects an early and long-term function of the allograft. A decrease in the severity of reperfusion injury is known to lead to suppression of excessive expression of transplantation antigens, adhesion molecules, pro-inflammatory cytokines and, as a result, to the reduction in the immunogenicity of the graft [2]. According to the literature data, severe cases of IRT occur up to 30% of all cases, which is accompanied by epithelium necrosis of the nephron tubules with the development of the graft dysfunction [3]. Delayed graft function (DGF) is an important clinical problem, occurring in 6-78.4% of cases [4, 5]. However, the pathogenetic mechanisms of developing the graft dysfunction are not fully understood, despite the high scientific interest and practical significance. It is known that in the pathogenesis of the primary non-functioning graft along with immunological factors, a number of non-immune links take part, the leading role among which belongs to the reperfusion injury [6, 7].

Most of clinical and instrumental signs and laboratory data being determined are not strictly specific for verifying the causes of the kidney transplant dysfunction. Currently, the most reliable in the differential diagnosis of not only pathological, but also functional processes occurring in the kidney transplant, are the morphological methods of investigation. However, a number of morphological changes are not always strictly specific for a particular type of complications. On the other hand, the technique itself is invasive and has the risk for developing complications. Due to the fact that the morphological study requires much time, the results of biopsy will warn clinicians about the already developed morphological changes. In fact, the diagnosis of the evolving processes is belated. Currently, there are not many non-invasive, accurate and fast-performing methods for diagnosing the renal transplant dysfunction [8].

Description of the techniques maximally reflecting the pathogenetic mechanisms of the organ transplant dysfunction development and allowing early diagnosis of these disorders in the existing literature is not available. In turn, the timely diagnosis and adequate correction of the revealed homeostatic disorders during organ transplantation in many respects determine the success of the surgical intervention.

Experimental and clinical studies indicate a correlation between the activity of the processes of peroxidation and antioxidant protection of the body with the functional state of the kidney graft, and also emphasize the need for further research in the field of reperfusion injury due to the limited data available [9]. The pathogenesis of organ disorders occurring and developing during ischemia and reperfusion includes oxygen deficiency, activation of free radical processes – stimulation of lipid peroxidation (LPO) leading to the change in the structure and function of cell membranes, as well as the change in the antioxidant properties of the organism [2]. The activation of free radical oxidation (FRO) is known to be a universal nonspecific reaction of the body, which is necessary to ensure normal metabolic and adaptive processes in the body [10]. At the same time, violation of the balance between the intensity of pro-oxidant and antioxidant processes leads to the development of oxidative stress, when the response activation of antioxidant systems is not able to prevent the harmful effects of pro-oxidants, In the given situation, cellular and subcellular structures are damaged by FRO products with aggravation of the pathological process course. Therefore, in clinical practice, evaluation of pro-/antioxidant balance can be used to monitor the course of the pathological process and to optimize treatment tactics. Due to the multicomponent nature of the redox system, the determination of its individual indicators does not give an idea of whether the identified changes are compensatory in nature or reflect the development of oxidative stress, that is, to assess whether it is a balance or an imbalance [11, 12].

In this regard, particular importance belongs to improving the methods of assessing the balance of the body's pro-/antioxidant system, which reacts to the inclusion of an ischemic donor organ into the bloodstream of the recipient. Intensively developing methods for monitoring the state of the organism's reactivity include the chemiluminescence method for determining pro-/antioxidant blood balance. This method of luminol-dependent chemiluminescence (LDCL) makes it possible to determine the nature

of the disorders and the degree of compensation in the pro- system of antioxidants. The level of luminol-dependent chemiluminescence (LDCL) on the one hand is known to be determined by the formation of free radicals (FR), and on the other – it depends on the level and activity of antioxidants (AO) in the system [13].

Thus, despite the urgency of the problem, at present there is no unified approach to diagnosing the balance of the pro-/antioxidant state of the organism in reperfusion injury, as well as methods for determining the severity of reperfusion injury in the post-transplant period. Graft dysfunction is an important factor determining the short-term and long-term survival of the transplant; therefore, the development of methods for the earliest "non-invasive" diagnosis of this condition has a high scientific and practical significance.

Objectives. To develop diagnostic technology of the reperfusion injury due to imbalance of pro-/antioxidant state of recipient in the post-transplant period.

Methods

The examination results of 60 patients with chronic kidney disease (CKD) of the stage 5 (group "T"), who were being treated in the surgical department (transplantation, reconstructive and endocrine surgery) of SE "Republican Scientific and Practical Center of Radiation Medicine and Human Ecology" were analyzed. All patients underwent the kidney transplantation. The age of the patients composed 45.5 [37; 54] years, there were 32 males (53%) and 28 females (47%). The clinical study was conducted in accordance with the Helsinki Declaration (1975) with the informed consent of patients and approved by the ethics committees of SE "Republican Scientific and Practical Center of Radiation Medicine and Human Ecology" and EE "Gomel State Medical University". To determine the effect of anesthetic management and surgical intervention on the state of pro-/antioxidant balance of the body, a group of patients undergoing a routine surgical treatment under anesthesia (group "D") was examined. This group consisted of 20 patients operated on for the postoperative ventral hernia (14 patients), as well as patients with obesity who were performed abdominoplasty (6 subjects).

Laboratory studies were performed on the basis of the laboratory of cellular technologies of SE "Republican Scientific and Practical Center of Radiation Medicine and Human Ecology". The state of the pro-/antioxidant balance was assessed by the method of luminol-dependent chemiluminescence (LDCL) of the blood plasma before the operation and 24 hours after the operation. The registration of LDCL of the blood plasma was carried out for 5 minutes on a Cary Eclipse FL1002M003 (Variant, USA) fluorometer / spectrophotometer with automatic determination of the maximum luminescence intensity (Imax) and the light-emission sum of chemiluminescence (S). The result was expressed as a percentage of the degree of oppression of the control glow flare. The entire process of registration of the LDCL plasma and the processing of the results are carried out automatically, which increases the accuracy and objectivity of the information obtained. The received data were processed in accordance with the software package applied to the instrument and the results were fixed in figures and graphically.

The main index of LDCL, the degree of suppression of the luminescence intensity (Imax) of the blood plasma, was calculated by the formula: $((Imax_k-Imax_o)/Imax_k)\times100\%$, where $Imax_k$ is the LDCL luminescence intensity of the control mixture, where $Imax_o$ is the LDCL luminescence intensity of the material (plasma) . This indicator reflects the interaction of pro- and antioxidants in the patient's body, i.e. the balance between the components of the pro-/antioxidant system.

The value of the light-weight sum of chemiluminescence (S) was also calculated according to the the formula: $((S_k-S_o)/S_k)\times100\%$, where Sk is the LDCL glow luminescence sum of the control mixture, So is the LDCL glow luminescence sum of the test material (plasma). The degree of oppression of the LDCL light sum of LDCL in the presence of biological material (blood plasma) reflects the power of antioxidant protection of the organism.

This approach to assessing the pro-/antioxidant balance of the blood plasma allows to level the fluctuations in the LDCL values associated with the use of reagents of different firms, and to compare the results obtained in different laboratories and using different biological material [6].

All patients were divided into two groups with delayed (DTF) and immediate (ITF) kidney transplant function. Kidney DTF criteria are creatinine concentration in the blood of more than 300 μmol / l on the 7th day after the operation and / or the need for one or more dialysis sessions in the postoperative period. Kidney ITF is characterized by the release of urine from the first day after the operation, with the level of the creatinine of the blood on the 7th day less than 300 μmol / ml [8].

The obtained data were processed with the help of the program "Statistica 6.1" (StatSoft, GS-35F-5899H). The normality of the data obtained was determined using the Shapiro-Wilk's test. Quantitative parameters are presented as median (Me) and interquartile range (25th (LQ) – lower

quartile and 75th (UQ) – upper quartile). A nonparametric method of statistical analysis was used: the Fisher exact criterion (for analyzing the differences between two independent groups by qualitative characteristics), the Wilcoxon criterion (for analyzing the differences of two dependent groups by the quantitative characteristic), the Mann-Whitney U-test criterion (for analyzing the differences between two independent groups on a quantitative basis). The critical level of significance of the null statistical hypothesis was assumed to be equal to and less than 0.05.

Results

Patients of the study groups had no significant differences in sex (Fisher-test, p = 0.583), age (Mann-Whitney U-test, p = 0.719, z = -0.360). Also studied groups were comparable in duration of the operation (Mann-Whitney U-test, p = 0.378, z = -0.881), which is presented in Table 1.

The study found that the stability of the balance of pro-/antioxidants in the blood plasma in patients with terminal CKD before the surgery was 34.5 [18.6; 52.5]% and the power of the antioxidant system was 31.1 [20.5; 53.9]%. Within 24 hours kidney transplantation in this group of patients (group "T") caused a significant shift in the balance of pro-/antioxidants to 19.5 [10.5; 36.3]% (Wilcoxon test, p = 0.028, z = 2.203) and a significant reduction in the power of the antiradical system to 25.4 [11.4; 38.9]% (Wilcoxon test, p = 0.044, z = 2.012) (Table 2).

The results of the study of the patients of group «D» indicated the absence of a significant change on the pro-/antioxidant balance of the blood plasma in the postoperative period (Table 3).

The preoperative balance of pro-/antioxidants in patients in group "D" was at the level of 57.9 [39.4; 67.6] %, the power of the antioxidant system was 58.1 [51.5; 77.7]%. On the following day after surgery, the pro-/antioxidant balance level in these patients was 44.3 [43.8; 54.6]% (Wilcoxon test, p = 0.63, z = 1.86) and the power of the antiradical system remained at the level of 57.6 [52.4; 64.1]% (Wilcoxon test, p = 0.94, z = 0.078).

In the group of patients who underwent a kidney transplant with DTF, there were 20 patients, and ITF there were 40 patients. The level of creatinine in the group with DTF on the 7th day was significantly higher than in the group with ITF (480 [398, 642] μmol/ml and 147 [116, 194] μmol/ml, respectively, Mann-Whitney U-test, P <0.001, z = 4.222). When analyzing pro-/antioxidant balance indicators in the first day of the postoperative period, the following results were obtained in these patients (Table 4).

So the level of balance of pro-/antioxidants in patients with ITF in the first 24 hours after the operation was 24.0 [11.9; 44.6]%, and the power of the antioxidant system was 35.8 [12.7; 40.8]%. While

Table 1

Characteristics of groups (Me [Q_{25}; Q_{75}])

Indicator	Group «D»	Group "T"
Sex: males/females (%)	11 (55) / 9 (45)	32 (53) / 28 (47)
Age, years	46 [31; 61]	45.5 [37; 54]
Duration of the operation, min	160 [127.5; 200]	175 [145; 215]

Table 2

Indicators of pro- /antioxidant balance of the blood plasma of patients in "T" group (Me [Q25; Q75])

Indicator	Before operation	After operation
Imax, %	34.5 [18.6; 52,5]	19.45 [10.5; 36.3]*
S, %	31.1 [20.45; 53.9]	25.4 [11.4; 38.85]*

Note: * – significant compared to the value before the operation at p<0.05.

Table 3

Indicators of pro- /antioxidant balance of the blood plasma of patients in "D" group (Me [Q_{25}; Q_{75}])

Indicator	Before operation	After operation
Imax, %	57.9 [39.4; 67.6]	44.3 [43.8; 54.6]
S, %	58.1 [51.5; 77.7]	57.6 [52.4; 64.1]

Table 4

Indicators of pro- /antioxidant balance of the blood plasma of patients in "T" group 24 hours after the operation (Me [Q_{25}; Q_{75}])

Indicator	ITF, n=40	DTF, n=20
Imax, %	24.0 [11.9; 44.6]	10.7 [6.1; 19.2]*
S, %	35.8 [12.7; 40.8]	12.7 [6.1; 29.3]*

Note: * – significant compared to the value in the ITF group, p<0.05.

in patients with DTF, the level of pro-/antioxidant balance was significantly lower than that of patients with ITF and was 10.7 [6.1; 19.2]% (Mann-Whitney U-test, p = 0.011, z = -2.559). The power of the antioxidant system was also significantly lower in patients with DTF compared with the value in patients with ITF and was 12.7 [6.1; 29.3]% (Mann-Whitney U-test, p = 0.024, z = -2.257).

Discussion

Despite the urgency of the problem, up to the present time in the Republic of Belarus there have been no studies devoted to studying the balance of the pro-/antioxidant state of the organism in IRT in the post-transplant period after kidney transplantation. Also, there have been no results of studies aimed at developing early prognostic criteria for graft dysfunction based on the severity of the reperfusion injury. There are studies devoted to assessing the state of the oxidation-reduction system in the postoperative period after kidney transplantation based on the technique for measuring the potential of the platinum electrode with an open circuit in the plasma or serum. The method shows the difference of potentials on different days of the postoperative period and is used to monitor the pathological process (graft dysfunction, infectious complications) [12]. There are not so many works devoted to this subject in the international literature, and the vast majority is experimental in nature [14]. At the same time, the researchers study the transplant IRT only on individual biomarkers of lipid peroxidation activation, malondialdehyde, 8-isoprostane, and the level of antioxidant defense of the body according to the concentration of glutathione, S-transferase, catalase and so on. In some publications, these biomarkers were generally considered to be isolated from each other, which according to modern ideas about the functioning of the antioxidant system of the organism (or processes of free radical oxidation) is not entirely correct [6, 14, 15].

Until now, the LDCL method has been used to study various components of the organism's redox system: both for assessing the overall antioxidant activity, total anti-radical activity of the biomaterial, and for evaluating the activity of free radical processes [11]. We have developed the method for recording LDCL, which permits us to evaluate both components of free radical reactions (activation of lipid peroxidation processes (pro-oxidants) and parameters of antioxidant protection, i.e. antioxidants). As a result of the interaction of pro- and antioxidants (pro-/antioxidant balance), we used the intensity of luminescence of LDCL (Imax) of the blood plasma. Having estimated the parameters of LDCL of the blood plasma in patients with CKD of the terminal stage before and 24 hours after kidney transplantation, having compared the obtained data with the clinical picture (restoration of diuresis) and the classical parameters of the function / dysfunction of the transplant (creatinine level), the evaluation of the parameters of LDCL blood plasma, in particular , the level of suppression of LDCL luminescence (Imax) can be used as early markers of the graft dysfunction.

The decrease in the LDCL intensity (Imax) in the early postoperative period after kidney transplantation according to the results of our studies indicates the intensification of the processes of free radical oxidation with reactive activation of the antioxidant defense system and subsequent depletion of its components. These processes characterize the onset of oxidative stress development due to the increase in the blood of unoxidized metabolites formed in an ischemic donor organ. As a result of transplant reoxygenation, a cascade of free radical processes is activated, requiring a certain level and the activity of the antioxidant defense system in the recipient organism. The results of our study indicate a significant decrease in total antioxidant activity (S), which reflects the degree of activity and concentration of antioxidants in the blood plasma of recipients, which characterizes the depletion of antioxidant reserves and a decrease in the ability to react to the activation of free radical oxidation.

In patients operated on for the postoperative ventral hernia and obesity in the postoperative period, there was no significant change in the pro-/antioxidant balance of the blood plasma, indicating a minimal impact of anesthesia and an operational trauma on balance stability. This can be explained by compensatory mechanisms in the group of patients of this profile.

Additionally, the presented method is easy to be performed, sensitive and easily applicable in any healthcare institution where there is a biochemical laboratory equipped with a device for recording superweak luminescence and does not require a large amount of biological material. All reagents used can be prepared in any clinical-diagnostic laboratory.

Conclusions

1. The proposed technique can be used to assess severe reperfusion injury in patients in the early post-transplant period.

2. Reperfusion injury of the donor organ during kidney transplantation already during the first day causes the exhaustion of components of antioxidant protection of the recipient organism.

3. The proposed method extends the diagnostic capabilities of risk early detection of kidney

transplant dysfunction, which will allow for timely preventive therapy and, thereby, will improve the short-term and long-term survival of the transplant.

The work was carried out in accordance with the research plan of EE "Gomel State Medical University".

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Информация о статье

Поступила 24 января 2017 г.
Принята в печать 6 марта 2017 г.
Доступна на сайте 25 сентября 2017 г.

Article history

Arrived 24 January 2017
Accepted for publication 6 March 2017
Available online 25 September 2017