CLINICAL AND PROGNOSTIC VALUE OF TAMX INDEX OF INTERLOBAR ARTERIES OF THE MIDDLE SEGMENT IN PATIENTS AFTER ALLOGRAPH KIDNEY TRANSPLANTATION IN THE LATE POSTOPERATIVE PERIOD

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Abstract

Introduction. Kidney transplantation has become the best treatment for patients with end-stage of chronic renal failure. The issues of studying the causes and mechanisms of the development of renal transplant dysfunction in the late postoperative period, the search for high-precision minimally invasive methods for early diagnosis of renal transplant dysfunction remain relevant, since this largely determines the further normal functioning of the organ and prognosis for the patient.

The aim of the study was to investigate the clinical and prognostic value of the time-averaged peak velocity (TAMX) index of the interlobar arteries of the middle segment in patients after allograft transplantation in the long-term postoperative period.

Material and research methods. For the period 2014-2015 ultrasound scan of renal grafts were performed in 26 patients with creatinine levels within the normative values. The average age of recipients in this group was 31.4 ± 1.67 years. Among the recipients there were 15 men (57.7%), 11 women (42.3%). Living related kidney transplantation (LRKT) were

performed in 61.54% of patients, in 38.46% – cadaveric kidney transplantation (CKT). In all patients, the plasma creatinine level met the standard value or exceeded them by no more than 25%, fluctuating on average from 94 to 130 μmol / L, averaging 114.5 ± 3.85 μmol / L.

The second study is based on the results of ultrasound scan of renal transplants in 26 patients with creatinine levels exceeding the standard values for the period 2015-2016. The average age of recipients in this group was 38.99 ± 2.32 (34.35-43.62) years. There were 14 men (53.84%) among the recipients, and 12 women (46.16%). LRKT were performed in 6 patients, in 20 – CKT. In all patients the plasma creatinine level was above normal values, fluctuating on average from 155 to 629 μmol / L, averaging 259.46 ± 35.33 μmol / L. The groups were comparable in terms of the main clinical and demographic parameters.

Results. The method for predicting complications by the level of TAMX of the interlobar arteries of the middle segment of the kidneys during Doppler ultrasonography of the renal blood flow (<15 cm / s) has a fairly high sensitivity (83.87%), specificity (79.31%), positive and negative predictive significance (81.25% and 82.14%, respectively) in the diagnosis of a high risk of developing late nephrodysfunction in recipients after organ transplantation. Recipients with allograft with a TAMX level of interlobar arteries (middle segment) of more than 15 cm / s, as a result of our examination, had a serum creatinine level 2.35 times less, and the glomerular filtration rate is almost 2 times higher than similar indicators in patients with a TAMX level less 15 cm / s (p <0.01), which confirms the presence of more expressive manifestations of chronic allograft dysfunction.

The interdependence between the TAMX of the interlobar arteries of the middle segment and serum creatinine, which is gradually regressing in a parabola, shows that more than half of the entire variance of the creatininemia sign can be associated with a change in the TAMX indicator (as a sign of deterioration in the renal blood flow of the graft), and the largest "failure" of the function were observed in the range from 12 to 15 cm / s TAMX, where in the overwhelming majority of cases (about 80%) there were impaired renal hemodynamics and the available laboratory markers of impaired renal function (creatinine above 200 μmol / l).

Conclusions. A reliable prognostic value of TAMX of interlobar arteries (middle segment) was shown in spectral Doppler ultrasonography of renal blood flow in a priori assessment of the risk of developing post-transplant nephropathy, which allows us to consider it as a cumulative predictor of an unfavorable prognosis and a potential factor not only for the formation of graft dysfunction, but also for rejection in the late postoperative period.

Key words: logistic regression; late graft dysfunction; pulsation index; Wald test; Doppler ultrasound.

Introduction. Kidney transplantation has become the best treatment for patients with kidney failure, also called end-stage renal disease (ESRD), which is the last stage of chronic kidney disease. Normal organ function one year after kidney transplantation reaches 80%, after ten years this figure decreases to 42-48% [1]. The survival of recipients 10 years after surgery is 70% [2]. For today non-sensitized recipients of the first graft (cadaveric and living donors) can expect at least 95% patient survival and 90% graft survival during the first year [3].

Despite advances in the treatment of chronic renal failure with donor organ transplantation, problematic issues in this field of medicine have been discovered. It should be noted the constant shortage of kidneys needed for transplantation. The solution for this problem was the use in world practice of kidneys from living relatives, which were recognized as compatible by the results of analyzes. In recent decades, the number of operations performed using kidneys from living donors has increased many times [4]. Kidney transplantation can be not only from a living but also a cadaveric donor. During the time from the removal of the kidney from the donor to the restoration of blood flow to the recipient, the kidney transplant is affected by many factors, including traumatic and ischemic, which leads to imbalance of all structures and systems of the organ, and affects the viability of the graft in the future [5].

In the absence of data about acute rejection, the 5-year survival of the graft reaches 88% [6]. Approximately 10% of patients within the first year after transplantation may have graft dysfunction as a result of chronic transplant nephropathy [7]. Important in the development of this complication is the toxicity of immunosuppressive therapy in proportion to the dose and type of drug. Early diagnosis and careful treatment of complications prevents premature kidney transplant loss and reduces patient mortality. The increase in serum creatinine is the main clinical criterion for referral of patients after kidney transplantation for biopsy under ultrasound control [8].

Graft function is affected by the presence of episodes of graft rejection, which is especially evident in the long term in the form of chronic rejection. Early diagnosis of rejection and its prevention in surgical treatment reduces the degree of tissue damage, which can cause chronic deterioration of graft function in later periods [9]. An increase in the immune response or a delay in the diagnosis of an episode of rejection can lead to irreversible

processes. Serum creatinine is probably not an absolute diagnostic indicator for rejection, because a transplanted kidney can be significantly damaged before increasing serum creatinine levels [10].

Therefore, the study of the causes and mechanisms of renal graft dysfunction in the late postoperative period, the search for highly accurate minimally invasive methods for early diagnosis of renal graft dysfunction, as it largely determines the further normal functioning of the body and determine the prognosis for the patient.

The aim of the study was to investigate the clinical and prognostic value of the time-averaged peak velocity (TAMX) index of the interlobar arteries of the middle segment in patients after allograft transplantation in the long-term postoperative period.

Material and research methods. For the period 2014-2015 ultrasound scan of renal grafts were performed in 26 patients with creatinine levels within the normative values. The average age of recipients in this group was 31.4 ± 1.67 years. Among the recipients there were 15 men (57.7%), 11 women (42.3%). Related kidney transplantation (LRKT) were performed in 61.54% of patients, in 38.46% – cadaveric kidney transplantation (CKT). In all patients, the plasma creatinine level met the standard value or exceeded them by no more than 25%, fluctuating on average from 94 to 130 µmol / L, averaging 114.5 ± 3.85 µmol / L.

The second study is based on the results of ultrasound scan of renal transplants in 26 patients with creatinine levels exceeding the standard values for the period 2015-2016. The average age of recipients in this group was 38.99 ± 2.32 (34.35-43.62) years. There were 14 men (53.84%) among the recipients, and 12 women (46.16%). LRKT were performed in 6 patients, in 20 – CKT. In all patients the plasma creatinine level was above normal values, fluctuating on average from 155 to 629 µmol / L, averaging 259.46 ± 35.33 µmol / L. The groups were comparable in terms of the main clinical and demographic parameters.

The ultrasound examination was performed with a Toshiba (Xario) device using a convex multi-frequency transducer at 3-5 MHz and included the state assessment and topometry of kidney transplant, the state of perirenal space assessment, color Doppler and spectral Doppler. To assess the kidney transplant state, we determined the kidney contour, homogeneity and echogenicity of the parenchyma, the clarity of cortical-medullary differentiation, the renal pelvis system and ureter state. Length and front-rear sizes of kidney transplant were dimensioned by topometry. The parenchyma and cortical layer thickness was calculated as the average value of the three measurements in the middle segment of kidney transplant.

The renal arteries blood flow was measured at the renal artery trunk and the interlobar branches of the renal artery (IBRA) levels by the spectral Doppler ultrasound evaluating the linear velocity indices. In addition, "almost angle-independent" indicators of peripheral vascular resistance (resistivity) were used. The renal vessels vascular resistivity was calculated by processing the Doppler waveforms using standard formulas.

The Doppler spectral waveform shape was evaluated and the following parameters were determined: peak systolic velocity (PSV), end-diastolic velocity (EDV), resistance index (RI) and pulsatility index (PI) of the blood flow, systolic-diastolic ratio (SDR), acceleration time (AT), time-averaged maximum velocity (TAMX) both in the renal and interlobar arteries. The angle of insonation was in the range from 30° to 60°. The average indicators of blood flow were analyzed throughout 3 - 6 cardiac cycles by Dopple spectrum. In addition, the linear blood flow velocity (LFV) in the renal vein was also evaluated.

Serum creatinine concentration was measured using the Jaffe color reaction (Popper method). All biochemical studies were performed at the Central Clinical and Express Biochemical Laboratories of the Zaporizhzhia Regional Clinical Hospital.

The data were fist examined for nomality using the Kolmogorov-Smirnov test. Parametric and non-parametric methods of data analysis were used. The results were presented as mean and standard error of representativeness of the sample standard value. The study results were processed using the statistical package of the licensed program "STATISTICA® for Windows 6.0" (StatSoft Inc., N AXXR712D833214FAN5), "SPSS 17.0" and "Microsoft Excel 2010". Separate statistical procedures and algorithms were implemented as specially written macros in the corresponding programs. Statistical significance was defined as $p < 0.05$ for all types of differences.

Research results and their discussion. By performing a ROC analysis, we calculated normative reference values for the TAMX index of the group of patients without renal graft dysfunction. The data obtained show that the relative risk of late graft dysfunction in patients with TAMX of the interlobar arteries less than 15 cm / m is almost 6 times higher (the risk of developing depurative dysfunction of renal graft in this group is 88.89% vs 16.0%, RR = 5.56 at 95% CI, which was 2.24-13.77), and the odds ratio is also more than 40 times for this group (Odds of this group was 8.0 vs 0.191, and OR = 42 at 8.41-209.59 95% CI), compared with a cohort of patients with TAMX of interlobar arteries more than 15 cm / s according to the results of Doppler ultrasound measurements. The evaluation of the Breslow-Day, Taron and logarithm tests allows to maintain the assumption of homogeneity of the odds ratio for weight groups (p> 0.2). The study of the general Mantel-Haenszel analysis odds ratio is

asymptomatically normally distributed under the assumption of equality of 1.00 of the general odds ratio.

Further, to assess not only the degree / focus, but also the nature of the relationship that describes the functional relationship between numerical variables in recipients in the long term after surgery for kidney transplantation, we conducted a regression analysis in which the regression model as an independent variable (predictor) included the level of TAMX of the interlobar arteries (middle segment), and as a dependent variable, prone to influence by an independent argument, used a parameter that reliably characterizes the functional condition of renal graft, a marker of nephropathy – serum creatinine.

According to the data obtained during the evaluation and analysis of the scattering diagram, the relationship between the value of TAMX and serum creatinine was statistically significantly approximated by a regression model of polynomial (square) type:

Creatinine = 763.78-54.35 × TAMX + 1.057 × TAMX2

When constructing a functional relationship between TAMX and serum creatinine, it should be noted that the approximation error and the value of the residual variance show high accuracy of the linear model, thus, the regression analysis can be considered as solved (R = 0.79, R2 = 0.624, normalized R2 = 0, 61 at F = 23.56, standard error 6.31, p <0.01).

Fixed, gradually regressing on a parabola, interdependence shows that more than half of all dispersion of a sign of serum creatinine can be associated with change of the TAMX indicator (as a sign of deterioration of renal blood flow), and the greatest failure of function was observed in the range from 12 to 15 cm / s, in the vast majority of cases (almost 80%) there were a violation of renal hemodynamics and available laboratory markers of impaired renal function (creatinine above 200 μkmol / l).

The obtained data indicate a statistically significant associative relationship between the dynamics of the generally accepted laboratory marker of nephropathy and the severity of hemodynamic disorders and pathological changes in vascular resistance of the interlobar arteries in recipients with renal graft.

Next, using the method of logistic regression, we constructed the equation of probability of occurrence of the event (endpoint – the development of postoperative graft nephropathy in the late postoperative period), we investigated the dependence of the dichotomous variable (presence / absence of graft dysfunction) on the independent, based on which from the above data, the level of TAMX.

The obtained data of the assessment of the universal criteria of the model coefficients and the values of the combined tests ($\chi2 = 145.4$, at the significance level p <0.001) testify to the adequacy of the constructed logistic regression model.

The approximation quality of the regression model is sufficient for a reliable prediction, and the resulting model describes more than 80% of the total variance of the feature.

The measure of the similarity function is the negative value of the double logarithm of this function -2 log (2LL). Entering or deleting a predictor leads to a change in this function, the difference of these functions is denoted as X-square and in our case is significant. The indicators of Cox and Snell's, Nagelkerke's are measures of certainty. These are pseudo-coefficients of determination, obtained on the basis of the relationship of the plausibility function of models only with a constant and with all coefficients. They indicate the part of the variance that can be determined by logistic regression. The degree of certainty according to Cox and Snell's has the disadvantage that a value of 1 is theoretically unattainable. This shortcoming has been eliminated by modifying this measure according to the method of Nagelkerke's. After step 5, the most adequate model was obtained: the criterion $\chi2$ is 48.251 (p <0.001), the coefficient of determination of Nagelkerke's is almost 81%, this percentage of variability of the variable can be explained by using the predictor.

Thus, the sensitivity of the proposed method was more than 80%, which is a fairly high figure. Next, we constructed the equation and considered the regression coefficients.

The probability of recurrence of the disease during the next year is calculated by the formula:

$$p = \frac{1}{1 + e^{-z}} \quad , \text{where}$$

$z = 16.14 - 1.05 \times R_{TAMX}$

R_{TAMX} – the value of TAMX of intralobular arteries (middle segment).

Thus, a reliable prognostic value of TAMX of interlobar arteries (middle segment) in spectral Dopplerography of renal blood flow in a priori risk assessment of postoperative graft nephropathy is shown, which allows to consider it as a cumulative predictor of unfavorable prognosis and a potential factor not only in transplant dysfunction and transplant rejection in the late postoperative period.

The method of predicting complications by the level of TAMX of the interlobar arteries of the middle segment of the kidneys during Doppler ultrasound measurements of renal blood flow (<15 cm / s), has a fairly high sensitivity (83.87%), specificity (79.31%), positive and negative predictive value (81.25% and 82.14%, respectively) in the diagnosis of a high risk of developing late nephrodysfunction in recipients after organ transplantation.

The risk of developing late graft dysfunction in recipients in the long term after transplant surgery, according to the calculated odds ratio, is statistically significantly higher in patients with low TAMX of the interlobar arteries of the middle segment, which can be statistically justified to consider it as a cumulative predictor of an unfavorable prognosis.

Recipients with renal graft with the level of TAMX of interlobar arteries (middle segment) more than 15 cm / s as a result of our examination had a serum creatinine level 2.35 times less, and glomerular filtration rate almost 2 times higher than similar values in patients with TAMX level less than 15 cm / s (p <0,01), which confirms the presence of more pronounced manifestations of chronic allograft dysfunction.

The relative risk of late graft dysfunction in patients with TAMX of the interlobar arteries (middle segment) less than 15 cm / m is almost 6 times higher (the risk of developing allograft dysfunction in this group is 88.89% vs 16.0%, RR = 5.56 at 95% CI, which was 2.24-13.77), and the odds ratio is also more than 40 times for this group (Odds of this group was 8.0 vs 0.191, and OR = 42 at 95 % CI (8.41-209.59)), compared with the cohort of patients with TAMX of interlobar arteries of the transplanted kidney, more than 15 cm / s according to the results of spectral Dopplerography of graft blood flow. The evaluation of the Breslow-Day, Taron and logarithm tests allows to maintain the assumption of homogeneity of the odds ratio for weight groups (p> 0.2). The study of the general Mantel-Henzel odds ratio is asymptomatically normally distributed under the assumption of equality of 1.00 of the general odds ratio.

The relationship between the value of TAMX of interlobar arteries (middle segment) and plasma creatinine according to the scatter plot and binary regression analysis was statistically significantly approximated by a regression model of polynomial (square) type: Creatinine = 763.78-54.35 × TAMX + 1.06 the approximation error and the value of the residual variance show the high accuracy of the linear model (R = 0.79, R2 = 0.624, normalized R2 = 0.61 at F = 23.56, standard error 6.31, p <0.01).

Recorded gradually regressing the parabola interdependence of TAMX of the interlobar arteries of the middle segment and serum creatinine shows that more than half of the total variance of the sign of creatinine may be associated with changes in TAMX (as a

sign of deterioration of renal blood flow in transplantation) moreover, the largest "failure" of the function was observed in the range from 12 to 15 cm / s TAMX, where in the vast majority of cases (almost 80%) there were a violation of renal hemodynamics and available laboratory markers of renal dysfunction (creatinine above 200 μkmol / l).

The method of logistic regression was used to construct the equation of the probability of occurrence of the event (end point – the development of renal graft dysfunction), and investigated the dependence of the dichotomous variable (presence / absence of graft dysfunction) on the independent one, which considered the level of TAMX of middle lobe arteries. The probability of late graft dysfunction during the next year is calculated by the formula: $p = 1/1 + e - z$, where $z = 16.14 - 1.05 \times RTAMX$. Combined tests for model coefficients (negative value of the double logarithm of this function -2 log (2LL), $\chi2$ and Cox, Snell's, Nagelkerke's parameters indicate a high probability of a reliable prognosis of the risk of chronic allograft dysfunction).

Conclusions. The obtained data indicate a statistically significant associative relationship between the dynamics of the generally accepted laboratory marker of nephropathy and the severity of hemodynamic disorders and pathological changes in vascular resistance of the interlobar arteries in recipients with allograph kidney transplantation in the late postoperative period.

A reliable prognostic value of TAMX of interlobar arteries (middle segment) was shown in spectral Doppler ultrasonography of renal blood flow in a priori assessment of the risk of developing post-transplant nephropathy, which allows us to consider it as a cumulative predictor of an unfavorable prognosis and a potential factor not only for the formation of graft dysfunction, but also for rejection in the late postoperative period.

Prospects for further research. This study would provide a perspective basis for proposed Doppler sonography parameters using as possible criteria for impaired graft perfusion. These data will allow for a comparative analysis of Doppler indices in recipients with graft dysfunction, to define ultrasound criteria for kidney transplant dysfunction, and thereby to improve diagnosis and prolong graft survival.

Conflicts of Interest: author has no conflict of interest to declare.

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