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Original Scientific Paper

ARTERIOVENOUS FISTULA FOR HEMODIALYSIS IN RELATION TO THE TIMING OF CREATION: ANALYSIS OF KEY FACTORS

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SUMMARY – Timely creation of an arteriovenous fistula is not always feasible. The aim was to determine the key factors for functionality and maturation of arteriovenous fistulas in relation to timing of its creation. The research was conducted at the Department of Nephrology and Dialysis, Kragujevac University Clinical Center, Kragujevac, Serbia, in patients who had had a fistula surgically created over a period of fifteen years. A total of 1089 patients were registered. All clinical and biochemical parameters that were of interest for this study were analyzed. The group of patients with fistulas created before the start of hemodialysis was statistically different from the group of patients whose fistulas were created after the start of hemodialysis according to vein lumen (p=0.005), systolic blood pressure (p<0.001), total cholesterol (p<0.001), HDL cholesterol (p=0.008) and LDL cholesterol (p<0.001). Predictive parameters of the initial dysfunction were vein diameter (p=0.004), cholesterol (p=0.008) and LDL cholesterol (p=0.033), while the maturation parameter was systolic blood pressure (p=0.042). In conclusion, predictive parameters of initial fistula dysfunction are vein diameter, cholesterol and LDL cholesterol, while systolic blood pressure is most important for maturation.

Key words: *Predictive parameters; Initial function; Maturation; Arteriovenous fistula; Timing of creation*

Introduction

Due to numerous risk factors for the development of chronic renal failure, an increase in the number of patients in need of dialysis depuration is also evident[1], which in 2010 ranged between 4.9 and 9.7 million[2]. It is predicted that the number of patients who need hemodialysis will double by 2030[3]. Based on the increase in the number of patients with end-stage kidney disease, it is expected that more patients will need a vascular access for hemodialysis. Mature and functional arteriovenous fistula is considered the best modality of vascular access for hemodialysis. The process of maturation of arteriovenous fistulas is pathophysiologically extremely complex and insufficiently clear. Almost half of the newly created arteriovenous fistulas are initially afunctional, and

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approximately one-third of arteriovenous fistulas will fail to become useful to conduct successful hemodialysis[4,5]. The percentage of insufficiently mature arteriovenous fistulas ranges from 28% to 53%, and the maturation process itself often takes up to 6 months or more[6].

The aim of this investigation was to determine the key factors in the functioning and maturation of arteriovenous fistula for hemodialysis according to the time of creation (before or after hemodialysis initiation).

Materials and Methods

This research included collection of retrospective data, which involved identification of predictive parameters of functioning and maturation of arteriovenous fistula for hemodialysis in patients with fistula created before and after hemodialysis initiation. The survey was conducted at the Department of Nephrology and Dialysis, Kragujevac University Clinical Center, Kragujevac, Serbia, as a retrospective, descriptive-analytical study.

The basic requirement for patient selection was information on the time of fistula formation (before or after the start of hemodialysis treatment) in the period of fifteen years. Based on the basic criteria for patient selection (timing of arteriovenous fistula formation), 1089 patients were registered out of a total of 1200 fistulas created at our Center, which were, for the most part created by the first author as a nephrologist.

In the group of subjects whose arteriovenous fistula was created before hemodialysis initiation, there were 392 (36%) patients, while the group whose fistula was created after hemodialysis initiation included 697 (64%) patients.

The research strategy included information on the maturation and initial fistula function.

We analyzed demographic and gender structure, etiologic cause of renal failure, and data on the initial fistula function and maturation. Doppler ultrasound determined the place of creation and quality of blood vessels used for anastomosis. Systolic and diastolic components of blood pressure were recorded in all respondents as the mean of preoperative, intraoperative, and postoperative values.

Of laboratory variables, we analyzed red blood cell (RBC), leukocyte, and platelet counts, hemoglobin concentration, total protein, albumin, glycemia, urea and creatinine concentration, cholesterol, triglycerides, HDL cholesterol and LDL cholesterol.

In most of our patients, the technique of creating an anastomosis involved the use of the termino-lateral and termino-terminal type anastomosis on the non-dominant upper extremity whenever possible. Most procedures were performed under local anesthesia.

During the intervention to create an arteriovenous fistula, we used systemic application of anticoagulant therapy, including administration of 5000 IU of intravenous heparin.

The primary criterion for selecting the site of arteriovenous fistula formation and type of anastomosis is based on Doppler findings of blood vessels of upper extremities. When, for whatever reason, it was not possible to explore blood vessels with Doppler, we used the methods of inspection, palpation, percussion and Allen test, on the extremity where arteriovenous fistula formation was planned.

If there were no conditions for successful fistula formation, such patients were referred for peritoneal dialysis or Hickman catheter placement.

All patients whose fistula was constructed after hemodialysis initiation used a hemodialysis catheter, most often in the right jugular vein, some of them in the femoral vein, and only rarely in the subclavian vein. On the other hand, only a small number of patients whose fistula was constructed before hemodialysis initiation had a catheter for hemodialysis.

Definitions of end points

A nonmature vascular access was defined as a vascular access that could not be used successfully for hemodialysis[7]. Vascular access was deemed successfully used for dialysis if it could be used with two-needle cannulation for three consecutive hemodialysis sessions[8], and if it provided sufficient blood flow for adequate hemodialysis for at least 30 consecutive days[9,10].

The study was approved by the Ethics Committee of the Kragujevac University Clinical Center, Kragujevac, Serbia, in accordance with the Helsinki Declaration for Medical Research.

Statistical analysis

Data were summarized as frequencies or percentages for categorical variables, and as means ± standard deviation (SD) or medians and range for numerical

variables. To test differences between cases and controls, Pearson's χ^2-test was used for categorical variables and, depending on data distribution, the independent samples t test and Mann-Whitney U test were used for numerical variables. All variables that were significant at the probability level of p≤0.05 were entered into a multiple logistic regression model with the initial function and maturation as the dependent variable. Statistical analysis was performed using SPSS version 21.0 (SPSS, Chicago, IL, USA) software program.

Results

Patients whose fistula was created before hemodialysis initiation had the mean value of venous diameter of 2.24±0.37 mm. Patients whose arteriovenous fistula was created after the start of hemodialysis had the mean values of vein lumen of 2.33±0.48 mm. The difference between the examined groups according to diameter of the vein used for anastomosis was statistically significant (p=0.005). The mean systolic blood pressure was 151.9±24.4 mm Hg in the group of patients whose fistula was created before hemodialysis initiation and 145.4±25.9 mm Hg in the group of patients whose arteriovenous fistula was created after the start of hemodialysis. The difference between the examined groups according to the systolic blood pressure was statistically significant (p<0.001) (Table 1).

By correlating biochemical parameters between the groups of patients whose arteriovenous fistulas were created before and after hemodialysis initiation, a statistically significant difference was recorded according to the level of cholesterol (4.8±1.3 *vs.* 4.2±1.3; p<0.001); HDL cholesterol [1 (0.4-2.1) *vs.* 0.9 (0.3-3.9); p=0.008] and LDL cholesterol [(3 (0.6-7.9) *vs.* 2.3 (0.6-7.7); p<0.001] (Table 2).

Multivariate logistic analysis of patients with initial arteriovenous fistula function included those risk factors that were statistically significant. The model contained five risk factors listed in Table 3, and statistically significant parameters were vein diameter (B=-1.640; p=0.004), odds ratio (OR) 0.19; cholesterol (B=1.309; p=0.008; OR=3.7), and LDL cholesterol (B=-1.098; p=0.033; OR=0.33) (Table 3).

Multivariate logistic analysis of patients regarding fistula maturation included those risk factors that were statistically significant. In the multivariate logistic regression model, a statistically significant parameter was systolic blood pressure (B=-0.022; p=0.042), OR 0.98 (Table 4).

Discussion

Arteriovenous fistula is considered the optimal first choice of vascular access despite the high rate of primary failure, or failure to mature. Some studies indicate that early thrombosis occurs in 5% to 30% of all created fistulas within 24 hours[11]. The rate of initial dysfunction of arteriovenous fistulas in our total patient population was 27.3%. Among patients who had a fistula formed before hemodialysis initiation, there were 28.1% with the initial fistula dysfunction, while the rate of initial fistula dysfunction was 26.8% in patients with a fistula created after hemodialysis initiation. Based on the initial dysfunction of arteriovenous fistula, there was no statistically significant difference when correlating the group of patients whose fistula was created before hemodialysis and the group of patients whose fistula was created after the beginning of the hemodialysis process.

Dember *et al*. report an unmatured fistula rate of 65% in their study[12]. The National Kidney Foundation recommends that arteriovenous fistulas be created at least 6 months before hemodialysis initiation treatment to allow sufficient time for access creation and evaluation, and vein maturation[13-15]. In our study, the rate of successful fistula maturation was 70.9% in patients whose fistula was created before hemodialysis initiation and 66.2% in the group of patients whose fistula was created after hemodialysis initiation.

The existing guidelines for the arteriovenous fistula referral are inconsistent and based on individual opinion and personal experience[16]. The Kidney Disease Outcomes Quality Initiative (KDOQI) recommendations have varied from referral for arteriovenous fistula creation when hemodialysis is anticipated within 12 months (2000)[17], within 6 months (2006)[18], or when the estimated glomerular filtration rate (eGFR) decreases to 30 mL/min/1.73 m^2 (2002)[19], that is 15-20 mL/min/1.73 m^2 [20]. Timely creation of arteriovenous fistula is not always feasible because of the unpredictability of renal failure progression and other reasons. On the other hand, late arteriovenous fistula creation cannot prevent the need for the use of a central venous catheter[21]. The experience and attitude of our Department regarding timing of the arteriovenous fistula creation refer not only to the estimated renal function but also to the

Table 1. Correlation of clinical characteristics of study patients

Examined parameter	Total number of arteriovenous fistulas (N=1089)		p
	Arteriovenous fistula created before hemodialysis initiation (n=392)	Arteriovenous fistula created after hemodialysis initiation (n=697)	
Gender, n (%) Men Women	 250 (63.8) 142 (36.8)	 446 (64) 251 (36)	0.13
Age (years); median (range)	62 (20-87)	61 (21-85)	0.32
Diagnosis, n (%) Diabetes mellitus Hypertension Polycystic kidney disease Obstructive nephropathy Other	 99 (25.3) 75 (19.1) 39 (9.9) 39 (9.9) 140 (35.7)	 163 (23.4) 172 (24.7) 74 (10.6) 52 (7.5) 236 (33.9)	0.20
Initial functioning of arteriovenous fistula, n (%) Yes No	 282 (71.9) 110 (28.1)	 510 (73.2) 187 (26.8)	0.66
Maturation, n (%) Yes No	278 (70.9) 114 (29.1)	461 (66.2) 235 (33.8)	0.11
Vein diameter, χ±SD	2.24±0.37	2.33±0.48	0.005*
Artery diameter, χ±SD	2.31±0.47	2.37±0.50	0.10
Use of Doppler ultrasound, n (%) Yes No	 193 (49.2) 199 (50.8)	 305 (43.8) 392 (56.2)	0.08
Systolic blood pressure, (mm Hg), χ±SD	151.9±24.4	145.4±25.9	<0.001*
Diastolic blood pressure, (mm Hg), χ±SD	82.9±14	82.6±16.1	0.78

*statistically significant parameter; SD = standard deviation; N = total number of patients; n = number of samples/patients in individual groups

Table 2. Correlation of laboratory variables

Examined variable	Total number of arteriovenous fistulas (N = 1089)		p
	Arteriovenous fistula created before hemodialysis initiation (n=392)	Arteriovenous fistula created after hemodialysis initiation (n=697)	
Red blood cells (10^{12}/L), χ±SD	3.1±0.5	3.1±0.5	0.27
Leukocytes (10^9/L), median (range)	7.6 (2.4-23.7)	7.5 (2.7-23.7)	0.68
Hemoglobin (g/L), χ±SD	93±15.6	94.4±15.2	0.19
Platelets (10^9), median (range)	208 (20-625)	212 (33-617)	0.20
Total proteins (g/L), χ±SD	63.9±7.9	64.9±8.9	0.10
Albumin (g/L), χ±SD	34.5±6	34.9±6.5	0.46
Glycemia (mmol/L), median (range)	5.3 (2.6-24)	5.3 (2.3-22.8)	0.80
Urea (mmol/L), median (range)	23.4 (3.3-65)	24.5 (5.2-65.1)	0.20
Creatinine (μmol/L), median (range)	588.5 (106-1993)	610.5 (106-1717)	0.35
Cholesterol (mmol/L), χ±SD	4.8±1.3	4.2±1.3	<0.001*
Triglycerides (mmol/L), median (range)	1.7 (0.6-6.6)	1.6 (0.3-5.7)	0.11
High-density lipoprotein cholesterol (mmol/L), median (range)	1 (0.4-2.1)	0.9 (0.3-3.9)	0.008*
Low-density lipoprotein cholesterol (mmol/L), median (range)	3 (0.6-7.9)	2.3 (0.6-7.7)	<0.001*

*statistically significant parameter; SD = standard deviation; N = total number of patients; n = number of samples/patients in individual groups

Table 3. Odds ratios for initial (a)function of arteriovenous fistulas as dependent variable: multiple logistic regression analysis model

Independent variable	B	p-value	OR	(95% CI)	
				Lower	Upper
Vein diameter	-1.640	0.004*	0.19	0.06	0.60
Systolic blood pressure	-0.018	0.081	0.98	0.96	1
Cholesterol	1.309	0.008*	3.7	1.4	9.6
HDL cholesterol	-1.770	0.08	0.17	0.02	1.28
LDL cholesterol	-1.098	0.033*	0.33	0.12	0.91

*statistically significant parameter; B = estimated regression coefficient; OR = odds ratio; CI = confidence interval

Table 4. Odds ratios for maturation of arteriovenous fistulas as dependent variable: multiple logistic regression analysis model

Independent variable	B	p-value	OR	(95% CI)	
				Lower	Upper
Vein diameter	-0.646	0.12	0.52	0.19	1.39
Systolic blood pressure	-0.022	0.04*	0.98	0.96	1
Cholesterol	0.349	0.42	1.42	0.6	3.3
HDL cholesterol	-0.543	0.58	0.58	0.09	3.94
LDL cholesterol	-0.140	0.76	0.87	0.35	2.15

*statistically significant parameter; B = estimated regression coefficient; OR = odds ratio; CI = confidence interval

etiology of renal failure, demographic characteristics of each patient, preservation of diuresis, presence of comorbidities, etc. Our results indicate that the initial function of arteriovenous fistula was found in 71.9%, in patients whose fistula was created before hemodialysis initiation and in 73.2% of patients in whom fistula was created after hemodialysis initiation. The maturation of arteriovenous fistula was better in the group where fistula was created before hemodialysis (70.9%). In the group of patients where fistula was created after the start of hemodialysis, successful maturation was found in 66.2%.

Accepting the fact that timely creation of arteriovenous fistulas is important for the quality of treatment of patients with terminal renal failure, at our Department, the total rate of fistulas that were created before hemodialysis initiation was 36%. It is extremely important to create objective parameters for determining the time required to refer patients with chronic renal failure to timely creation of arteriovenous fistula, as well as the factors of fistula maturation and initial dysfunction.

Inappropriate blood vessels that are used to create arteriovenous fistulas are another cause of cessation of the arteriovenous fistula function[6]. The results of our study showed that the vein lumen which is used for arteriovenous anastomosis is a statistically significant variable in correlation to the group of patients whose fistula was created before and after hemodialysis initiation. By using multivariate logistic analysis, we determined the vein diameter to be a predictor of initial dysfunction, which was long before confirmed by Reilly *et al*.[22] and Khavanin Zadeh *et al*.[23] , who had found a connection between the vein diameter and success rate of fistula development.

Hypertension contributes not only to atherosclerotic cardiovascular and cerebrovascular sequels but also to thrombosis of the arteriovenous fistula, as a consequence of hemodynamic changes and vascular calcifications[24-27]. In addition to chronic kidney disease, several common comorbidities, in particular diabetes, further enhance the progression of calcification[28]. In our study, multivariate logistic analysis showed that systolic blood pressure was inversely correlated with arteriovenous fistula maturation, that is, the higher the values of systolic blood pressure, the lower was the maturation rate.

Multivariate logistic analysis with five models of risk factors for initial fistula dysfunction indicated that total and LDL cholesterol were the predictive parameters of initial arteriovenous fistula dysfunction. Higher values of LDL cholesterol and total cholesterol had a statistically significant adverse effect on the initial fistula dysfunction. In fact, our study found that patients with elevated cholesterol had a 3.7-fold higher risk for the initial fistula dysfunction. This finding could be interpreted as a consequence of endothelial dysfunction due to lipid imbalance, which is a common metabolic disorder in patients with end-stage kidney disease[29-31].

Conclusion

Our study found that patients with elevated cholesterol had a 3.7-fold higher risk for the initial fistula dysfunction. An important predictive parameter for the initial function of arteriovenous fistulas was lumen of the vein, that is, the smaller the lumen of the vein, the greater was fistula dysfunction. Systolic blood pressure yielded negative correlation with arteriovenous fistula maturation, i.e., it was a statistically significant risk factor for maturation of arteriovenous fistula.

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Sažetak

ARTERIOVENSKA FISTULA ZA HEMODIJALIZU U ODNOSU NA VRIJEME STVARANJA: ANALIZA KLJUČNIH ČIMBENIKA

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Pravodobno stvaranje arteriovenske fistule nije uvijek izvedivo. Cilj je bio odrediti ključne čimbenike za funkcionalnost i sazrijevanje arteriovenskih fistula u odnosu na vrijeme nastanka. Istraživanje je provedeno na Klinici za nefrologiju i dijalizu, Kragujevac, Srbija, kod bolesnika kod kojih je kirurški stvorena fistula. U razdoblju od petnaest godina registrirano je 1089 bolesnika. Analizirani su svi klinički i biokemijski parametri koji su bili od interesa za ovo istraživanje. Skupina bolesnika s fistulama stvorenima prije početka hemodijalize statistički se razlikovala od skupine bolesnika čija je fistula nastala nakon početka hemodijalize u odnosu na lumen vene (p=0,005), sistolički krvni tlak (p<0,001), ukupni kolesterol (p<0,001), HDL kolesterol (p=0,008) i LDL kolesterol (p<0,001). Prediktivni parametri početne disfunkcije bili su promjer vene (p=0,004), kolesterol (p=0,008) i LDL kolesterol (p=0,033), dok je parametar sazrijevanja bio sistolički krvni tlak (p=0,042). Prediktivni parametri početne disfunkcije fistule su promjer vene, kolesterol i LDL kolesterol, dok je sistolički krvni tlak najvažniji za sazrijevanje.

Ključne riječi: *Prediktivni parametri; Početna funkcija; Sazrijevanje; Arteriovenska fistula; Vrijeme stvaranja*