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Systemic embolism risk factors in kidney transplant recipients during long-term post-operative period

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Summary

Objective

To assess systemic embolism risk factors in kidney transplant recipients, who manifested atrial fibrillation in long-term post-operative period.

Materials and methods

A prospective cohort study of 175 kidney transplant recipients was carried out in the Republican Scientific and Practical Center of Organ and Tissue Transplantation of the healthcare institution «9th municipal clinical hospital». The risk stratification of ischemic stroke and systemic embolism development was performed using the $CHA_2DS_2VAS_c$ score.

Results

It was found out that the occurrence of risk factors of thromboembolic complications was high in kidney transplant recipients who had atrial fibrillation in long-term post-operative period; it required indirect anticoagulants prescription in addition to a combined immunosuppressive therapy in 62% of cases.

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Conclusion

Warfarin prescription in this category of patients was not accompanied with increased frequency of severe hemorrhagic complications in comparison with general population during 3 years of observation.

Key words

Organ transplant recipients, systemic embolism, atrial fibrillation, anticoagulant therapy.

Introduction

The frequency of thromboembolic complications (TEC) in general population is 1-2 cases for 1000 individuals per year. Risk of thromboembolism development mostly depends on genetic and exogenous factors; the degree of risk varies depending on performed surgical interventions [1]. TEC development risk for abdominal surgery is 0.6-3.1%. Appendectomy, cholecystectomy and hernia repair belong to the group of surgical interventions with low risk (0.6%). Gastrointestinal tract operations are characterized with moderate risk (1.8%) and splenectomy corresponds to high risk (3.1%). 50% of patients who underwent orthopedic operations without preoperative preventive interventions develop venous thromboembolism, and anticoagulants' administration reduces thromboembolism risk up to 18 cases for 1000 individuals per year. According with published data, organ transplantation increases the risks of venous thromboembolism for surgical intervention and immunosupressive therapy [1, 2].

From the moment of the start of calcineurine use the number of TEC after kidney transplantation has decreased, varying from 2 to 14%. The results of retrospective study that involved 480 donor kidney recipients were published in 1987, and it demonstrated that 8.3% of patients had pulmonary artery embolism with the peak of morbidity during first 4 months after transplantation. The study that had been performed during the period from 1985 to 1995 and involved 1833 patients revealed lower frequency of TEC complications (4.2%) with the peak of morbidity between third and fifth months after transplantation. The risk of development of late TEC occurring 1.5-3 years after the transplantation estimated using Medical Care database, which included 28924 kidney transplant recipients, was 1.5%. Published data demonstrate high frequency of TEC development after kidney transplantation [3-6].

Risk factors of venous and systemic TEC in general population include surgical interventions, history of deep veins' thrombosis, elderly age, cancer, obesity, renal failure, long immobilization, presence of central venous catheters, pregnancy and postpartum period, oral contraceptives administration, presence of inherited and acquired thrombophilia, abnormal cardiac rhythm and conductivity, chronic heart failure, diabetes mellitus, arterial hypertension (AH). Organ transplants' recipients belong to the group of risk not only due to the presence of traditional risk factors of venous and systemic thromboembolism, but also due to the causes directly related to transplantation [7, 11]. Procoagulative effect of immunosuppressive drugs has been reproduced in in vitro conditions, but it is impossible to assert that these changes in organism occur just because of administered therapy, not taking into account other risk factors acquired in the post-operative period.

Abnormal blood coagulation increases the risk of transplant loss due to transplant vessels' thrombosis and thrombotic complications after organ transplantation. Transplant thrombosis' prevention in the early post-operative period after donor organ transplantation is provided by early post-transplantation anticoagulant therapy. Therefore, it is recommended to concentrate on TEC risk factors' and blood clotting abnormalities' detection in advance, in particular, in patients with recurring thrombosis of vascular bypass or present history of TEC. It is strictly required to perform well-timed and detailed examination before transplantation in this category of patients. In particular, it is necessary to evaluate such characteristic like antithrombin III and protein C activity, activated protein C (Factor V Leiden) and protein S resistance and antiphospholipid antibodies' concentration. Kidney transplantation may be performed in patients receiving antithrombotic therapy: warfarin, aspirin, clopidogrel. It is necessary to take into account characteristics of blood clotting process and perform coagulation tests in these patients in case of surgical intervention.

The most frequent causes of TEC in the early post-operative period are blood stasis in vessels downstream the iliac vein due to its cross-clamping during anastomosis formation, intima lesions, aggressive dissection in the area of vessels, post-operative immobilization and insufficient hydratation. Lower extremity deep vein thrombosis can extend on renal

vein or become a cause of life-threatening pulmonary embolism.

According with the clinical guideline for kidney transplantation, established by order of the Ministry of Health of the Republic of Belarus №6 from 05.01.2010 and clinical guidelines of the European Association of Urology, patients with lower extremity deep veins thrombosis should receive anticoagulant therapy for not less than 3 months. Heparin therapy should be substituted with warfarin as much early as possible. Since heparin is inactivated by kidney, patients with inadequately functioning transplant have high risk of postoperative bleeding caused by direct anticoagulants overdose.

Patients with high risk of thrombosis should receive 5000 MU of unfractionated heparin subcutaneously before operation, but it is necessary to bear in mind the risk of hemorrhagic complications in renal failure, therefore it is not recommended to administer more than 10000 MU of unfractionated heparin per day taking into account the possibility of additional intraoperative drug introduction for several indications. Kidney transplant recipients should wear compression stockings for several days after operation in order to prevent lower extremity deep vein thrombosis. Anticoagulant therapy with low molecular weight heparin is inadmissible for outpatient conditions, because the extent of anticoagulation may be unpredictable and coagulation control may be complicated. Aspirin administration for thrombosis prevention is more favorable for outpatients in the early post-operative period [8].

In the long-term post-operative period the occurrence of atrial fibrillation (AF), influencing the development of systemic TEC and leading to patients' incapacity, high mortality and higher treatment's costs, increases due to several reasons like improved survivability of kidney transplant recipients, cumulation of such risk factors like AH, heart failure, valvular heart disease, diabetes mellitus, coronary heart disease, thyroid gland disorders in the cohort of patients. Indirect anticoagulants have gained a stable position in TEC prevention, but the risk of bleeding complications during their administration in patients with various comorbid conditions and AF forms makes it relevant to search for additional criteria of optimal antithrombotic therapy selection in organ transplant recipients.

The objective of this study was to assess systemic embolism risk factors in kidney transplant recipients, who manifested AF in long-term post-operative period.

Materials and methods

This prospective cohort study that included 175 kidney transplant recipients was performed on the base of the Republican Scientific and Practical Center of Organ and Tissue Transplantation and the Healthcare Institution «9th municipal clinical hospital of Minsk. 90 (51.4%) of patients were males, 85 (48.5%) of patients were females, average age was 44.7±6.18 years. 78 (44.6%) patients who underwent kidney transplantation were diagnosed with AH, in the long-term postoperative period (>12 months after transplantation), 64 patients (36.5%) had family history of early onset of cardiovascular diseases, 45 patients (25.7%) had burdened family history of diabetes mellitus 2 type, the occurrence of smoking was 13.1% (n=23).

Paroxysmal and/or persistent form of AF was diagnosed in 27 recipients. AH II-III stage that was presented in 48.1% of patients (13 kidney transplant recipients) prevailed in the etiological structure of AF, combination of AH and coronary heart diseases was diagnosed in 9 individuals (33.4% of patients involved in the study), 5 patients (18.5%) were diagnosed with idiopathic form of AF due to lack of known AF causes. Ischemic stroke and systemic embolism development risk stratification was performed using CHA_2DS_2VAS**c** score (Congestive Heart failure, Hypertension, Age (2 points), Diabetes mellitus, Stroke (2 points), Vascular disease, Age, Sex category).

Selected category of patients underwent screening testing of platelets, hemostasis and in-deep examination of several hemostatic complications development markers (D-dimer, von Willebrand factor, antithrombin III, protein C).

Results and discussion

Kidney transplant recipients had lowered protein C concentration (58.24±6.18%), increased D-dimer levels (507.24±19.32 ng/mL) and von Willebrand factor (176.14±21.14%) levels comparing with the reference values during the long-term postoperative period (12 months±1 week). Obtained results allow supposing the presence of reverse cause-and-effect relation in hemostatic abnormalities development in kidney transplant recipients: prothrombotic condition and endothelial lesions may be caused by immunosuppressive therapy, presence of AH or coronary heart disease. It was slightly unexpected to detect lack of correlation between observed hemostasis system changes, underlying disease that had led to renal failure and transplantation type. The percentage of residual factor dispersion (δ^2) was 64%, that does not

allow considering obtained analytic data statistically significant and requires further analysis dedicated to identification of significant cause-and-effect relation between hemostasis' abnormalities and factors leading to their development in the long-term postoperative period. Revealed protein C reduction and endothelial damage markers (increased von Willebrand factor's levels) contributes to a single system of the risk factors of the hemostasis abnormalities development. Protein C concentration in the group of donor kidney recipients can influence the impaired synthesis of natural anticoagulants, because it is difficult to explain the changes with increased intake of anticoagulant proteins due to the lack of the signs of blood clotting activation leading to excessive amount of thrombin [9-10]. At the same time, AF presence aggravated observed hemostasis' abnormalities increasing the risk of TEC development in the long-term postoperative period in spite of successfully performed kidney transplantation.

Ischemic stroke and systemic embolism development risk stratification was performed using CHA_2DS_2VAS**c** score (Figure 1).

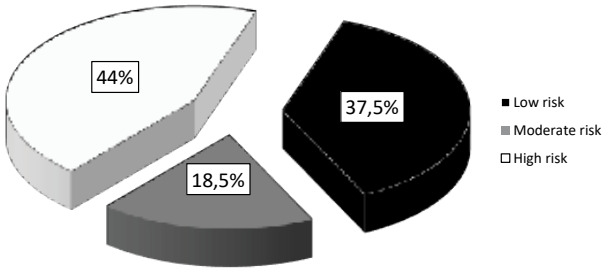

Figure 1. Stratification of ischemic stroke and systemic embolism development risk according with the CHA_2DS_2VAS**c** score.

37.5% of kidney transplant recipients with AF had low risk of systemic embolism development (0 points according with CHA_2DS_2VAS**c**), 18.5% had moderate risk of systemic embolism (1 point of CHA_2DS_2VAS**c** score), 44% of participants had high risk of systemic embolism (>1 points of CHA_2DS_2VAS**c** score). Main risk factors of systemic embolism in kidney transplant recipients with AF were: AH (81.5% of patients), female gender (10 patients (37%)), diabetes mellitus (7 patients (25.9%), vascular diseases (19 (70.4%) individuals). Kidney transplant recipients with A– 19 (70.4%) who had high risk of systemic embolism development received warfarin therapy under international normalized ration (INR) control for the prevention of embolism starting from the moment of arrhythmia detection. During 3 years of observation three patients having >1 points according with the CHA_2DS_2VASc score and receiving therapy with warfarin had been registered with bleeding complications that required admission to hospital and warfarin withdrawal: macrohematuria (1 case), recurrent epistaxis (2 cases).

Conclusion

Kidney transplant recipients with AF have high frequency of TEC requiring indirect anticoagulant prescription in 62.5% of cases in addition to combined immunosuppressive therapy in long-term postoperative period. Three-year therapy with warfarin was not associated with increased number of major bleeding complications in kidney transplant recipients having high risk of systemic embolism development comparing with the general population.

Taking into account the presence of additional hemostasis risk factors (reduced protein C concentration, increased D-dimer's and von Willebrand factor's concentrations), antithrombotic therapy prescription in long-term post-operative period should be considered in all stages of these patients' dynamic observation.

Conflict of interests: None declared

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