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The Cause of the Bleeding and Thrombosis in Patients with Implanted Left Ventricular Assist Devices

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INTRODUCTION

Chronic heart failure (CHF) is one the main health care problems of the cardiovascular system in the Republic of Kazakhstan. Heart transplantation (HT) is the best treatment for the heart failure (HF) patients which will help to survive and live a better life. However, heart donor is not available to every patient due to the limited number of the heart donors among the world. Nowadays, there is an alternative way of HT is implantation of the mechanical circulatory support devices - left ventricular assist device (LVAD) (Fig. 1) [1-2].
LVAD helps for patients to live a better life. However, this device is followed with side effects after implantation. The most common side effects are thrombosis and bleeding. Normally patients with implanted devices are prescribed with antithrombotic therapy for the prevention of the side effects. Warfarin is the most widely prescribed antithrombotic therapy. The incorrect dosage of the therapy is followed with the side effects such as bleeding and thrombosis. On the other hand some research proves that high shear stress damages platelet receptors which causes bleeding and thrombosis. LVAD patients should be studied about their side effects and their possible genetic associations [3-5].

The purpose of the study is to identify the influence of the coagulation factor F5, F7, FGB gene polymorphisms in HF patients with implanted LVAD devices.

Fig. 1. Schematic representation of the implanted Left Ventricular Assist Device (LVAD)

Table. 1. Type of the implanted LVAD devices in Kazakhstan

	Type of the implanted assist device	Amount of implanted LVAD	In percent
1	HVAD (HeartWare Inc, USA)	18	18,4
2	HeartMate II (non-pulsatile)	34	34,7
3	HeartMate III (pulsatile)	46	46,9
4	Total	98	100

RESULTS

Demographic and clinical profiles of HF patients are shown in Table 2. Statistical analysis was done on IBM SPSS Statistics 23. Continuous variables were summarized by descriptive statistics. Association of SNPs between Case and Control group was found out by Fisher exact test. Case and Control groups were genotyped for SNPs responsible for coagulation factor system. LVAD patients were prescribed with warfarin dosage according to the clinical protocol. On the other hand, warfarin dosage was calculated according to the genetic test results for VKORC1 and CYP2C9 polymorphisms. If patients would be prescribed with the warfarin (before LVAD) according to the genetic test results their dosage would be: min = 2,1 mg/day, max = 7,3 mg/day and mean dosage = 4,6 mg/day. If patients' clinical dosage would be corrected after 1 month of the treatment according to the genetic test results, the dosage would be min = 0,5 mg/day, max = 5,1 mg/day and mean = 1,7 mg/day according to genotyping test results.

Table. 2. Patient characteristics

#	Variables of HF patients	Value (n=98)
1	Gender: Males Females	93.9% 6.1%
2	Average age, years ± SD	52.67 ± 10.95
3	Nationality: Kazakhs Russian Others	78.6% 15.3% 6.1%
4	Body weight, kg (range)	79.81 ± 13.9 (47 till 114)
5	Height (cm)	169.7 ± 6.4 (148 till 183)
6	BMI, kg/m2	27.67 ± 4.5
7	Patient's death: Yes No	37.8% 62.2%
8	Thrombosis cases: Yes No	13.3% 86.7%
9	Bleeding cases: No GI bleeding Nose bleeding and other cases	85.7% 4.1% 10.2%
10	Stroke cases: No Hemorrhagic stroke Ischemic stroke	79.6% 8.2% 12.2%
11	Infection cases: No Yes	60.2% 39.8%
12	Basic INR, mean ± SD	1.21 ± 0.36
13	Target INR, mean ± SD	2.39 ± 0.26
14	Dilated cardiomyopathy	40.8%
15	Ischemic cardiomyopathy	44.9%
16	Hypertrophic cardiomyopathy	10.2%
17	Valvular cardiomyopathy	3.1%
18	Arterial cardiomyopathy	1%

CONCLUSION

Genotyping results on Factor Leiden V (F5) showed that Case and Control groups (99%) have wild type of genotype (C/C) which has no risk to thrombosis. However, statistical result wasn't significant (p =1,000). On other hand, genotyping results of F7 (p=0.202) and fibrinogen beta (FGB) (p=0.555) polymorphisms were not statistically significant too. Results of polymorphism F7 showed wild type of genotype G/G in 76% patients, whereas only 3% patients has mutant genotype A/A which has no risk to thrombosis. Mutant genotype A/A of FGB polymorphism was expressed only in 3% of patients, which reflects high risk to thrombosis. The study suggests that side effects might happen because of the individual genome differences in LVAD patients, but statistical analysis didn't confirm this. Research need to include more patients which might help to reflect significant results.

MATERIALS AND METHODS

Venous blood samples were recruited from the patients (n=100) with implanted LVAD devices such as HVAD, HeartMate2 and HeartMate3 at the "National research cardiac surgery center " (Table.1). 2 patients under 18 years old were excluded from the research. Study included 2 groups: Case study (n=98) and Control group (n=95).
Patients were prescribed with warfarin according to the clinical protocol of the Ministry of Healthcare of the Republic of Kazakhstan. The clinical dosage was min=0,9mg/day and max=7,2mg/day (after LVAD implantation).
Genomic DNA was extracted with PureLink Genomic DNA Mini Kit (cat.no. K1820-00) (Invitrogen). DNA samples were genotyped by real-time polymerase chain reaction (PCR) with TaqMan probes. Genotyping was done for two groups for gene polymorphisms: F5 (rs6025), F7 (rs6046), FGB (rs1800790).

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