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Clinical case

COMPARATIVE STUDY OF EFFECTIVENESS OF ANTIHEMOPHYLIC FACTORS AND PLASMA IN PATIENTS WITH HEMOPHILIA

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Abstract

Over 15 years ago, hemophilic bleeding complications were treated only by plasma/cryoprecipitate in Armenia. Nowadays plasma is used as an alternative measure only in those countries where antihemophylic factors are absent or insufficient.

The aim of present study is the analysis of the frequency of joint and infection complications, depending on the treatment and disease severity.

Ambulatory-dispensary cards, hospital registers, as well as register data of Hematology Center after R.H. Yolyan, MH RA, were the materials of the study. The data have been supplemented by the registration information on the causes of death. Conducted retrospective analysis of 173 outpatient cards identified patients with hepatitis C virus, hepatitis B surface antigen, hepatitis B core infections. Prospective serological survey was carried out on analyzer by test system. The presence of antibodies was carried out with the help of coagulometer. Obtained data were processed with the help of SPSS statistical program, intercomparison of therapy methods, $\chi 2$ and Student *t-test.*

As a result of the study, infection complications were registered only in 71 (64%) out of 111 studied patients of I group. Among observed infectious complications hepatitis C was dominating in 62 (55.9%) cases; hepatitis B was recorded in 8 (7.2%) patients; hepatitis B and C in 6 (5.4%) cases and 1 patient (1.16%) with human immunodeficiency virus. Comparative analysis showed, that detectability of antibodies was higher in patients of I group in comparison with II group (19.8% vs. 3.22%). An identical pattern was observed during the arthropathy (91.9% vs. 64.5%).

Therefore, it can be concluded, that the application of antihemophylic factors excludes infection complications. Immunological complications, formation of antibodies, as well as joint complications in mild forms of the disease comprise a low percentage.

Keywords: *hemophilia, plasma complications, antihemophylic factors, arthropathy, joint complications.*

Introduction

According to contemporary perceptions, hemophilia is ranked among the seven most expensive diseases, the only treatment of which is the addition of insufficient or missing antihemophylic factor with the application of appropriate antihemophylic factor from human plasma or recombinant factors. Over 10-15 years ago, the hemorrhagic complications of hemophilia were treated only by fresh frozen plasma and cryoprecipitate. Nowadays fresh frozen plasma is used as an alternative measure only in those countries where antihemophylic factors are absent or insufficient [*Knobe K, Berntorp E, 2012; Cuesta-Barriuso R et al., 2013; Franchini M, Mannucci P, 2013*].

Indeed, economic crisis and high cost of antihemophylic factors in Armenia should be taken into account in the organization of comprehensive health care and in the prevention of disability. Many attempts are made in order to fill the insufficiency of antihemophylic factors with alternative treatment to some extent using components of blood, cryoprecipitate and fresh frozen plasma, however, that method has its own side effects (immunization, transfusion shock in case of high-vol-

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ume infusions, infectious security, etc.). One bag of fresh frozen plasma contains 70-100 *mM* antihemophylic factors; therefore, in massive bleeding case 10 bags of plasma are necessary to replace of 1000 points of factor, which is particularly impossible, mostly in every 12 hours.

As it was already mentioned, the sufficient quantity of antihemophylic factors is necessary in order to implement the effective treatment (based on the patient's blood factor levels the dosage of VIII, IX factor is calculated for infusion).

The aim of the study is to conduct the analysis of the probability of articular and non-articular complications' development in case of the treatment with fresh frozen plasma in contrast with only antihemophylic factor treatment.

Material and methods

A perspective and retrospective study of patients with various types of hemophilia, registered in hemophilic registration of Hematology Center after R. Yolyan, was conducted from 2005 to 2014 in Armenia. The materials of retrospective studies were the ambulatory-dispensary cards, hospitalization registers and clinical history. Demographic data were obtained in National Statistical Service of RA. For the calculation of standardized indicators, the data from the Demographic Journal Armenia (2015) were taken as a basis. The retrospective analysis of 173 outpatient cards identified patients with hepatitis C virus, hepatitis B surface antigen, hepatitis B core infections. Prospective study was carried out on STAT FAX analyzer (Awareness Technology, USA) in serological department of Hematology center by test system of "Vector Best" company (Russia). The presence of antibodies was conducted in coagulologic laboratory on Stago coagulometer (France) by Bethesda method. The obtained data were processed statistically by SPSS statistical program, intercomparison of therapy methods, $\chi 2$ and Student t-test.

The comparison of these data with those of the national and regional statistics was conducted based on Student's t-test.

Results

As a comparison of two approaches of treatment, the patients were divided into the following groups: I group – patients with hemophilia, who received fresh frozen plasma and/or cryoprecipitate as therapy during their lifetime (n=111), II group – patients with hemophilia, who were treated only with antihemophylic factors (n=62).

Age distribution of patients in the studied groups is presented on figure 1 (a, b).

According to the presented data (Fig. 1a, b), 26-40 year-old patients are dominating in I group, the number of which is 55 (55.5 % cases), and 11-25 year-old patients in II group, respectively 31 (50% cases). Since 2005 up to now, the Hematology Center has received antihemophylic factors through centralized

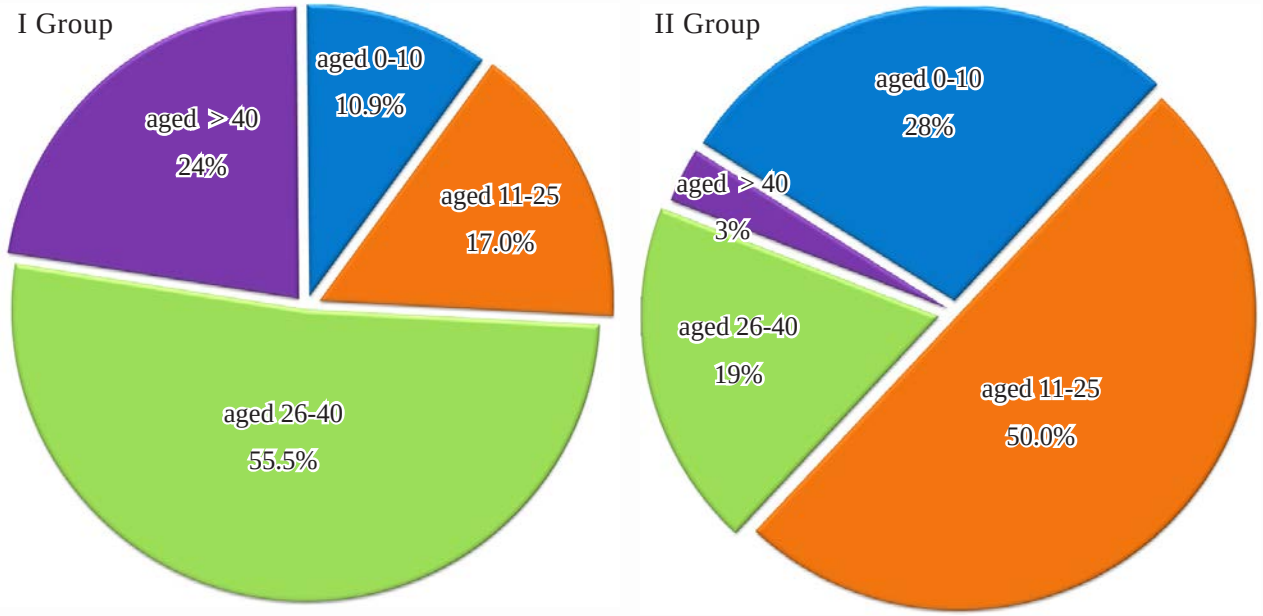

*Figure 1. Age distribution of study groups depending on treatment type: I group **(a)** - patients, who received fresh frozen plasma treatment; II group **(b)** - patients, who received antihemophilic factor treatment.*

purchasing by the Ministry of Health, and all patients younger than 25 years (II group) have already received therapy by antihemophylic factors.

The studied groups have been monitored based on the frequency of developing infections, immunologic and articular complications.

It should be mentioned, that before the use of modern factors of antihemophylic preparations, the prevention of bleeding was carried out with the use of cryoprecipitate or fresh frozen plasma, which had not ever undergone viral inactivation. Therefore, most patients have acquired hepatitis C virus, hepatitis B virus, human immunodeficiency and other diseases. These epidemic cases of carrying the virus boosted the development of the latest ultra-sensitive diagnostic test systems during recent 15 years and their introduction in clinical practice. Over the previous 10 years, not a single case has been recorded on carrying virus from plasma factors, which testifies the secure use of the last ones. According to the findings, infectious complications were registered only in 71 (64%) patients out of 111 studied patients of I group, which confirms the above mentioned (Fig. 2).

Hepatitis C was dominating in 62 (55.9%) cases

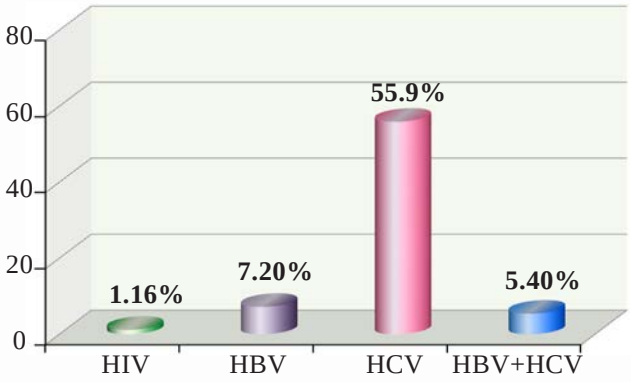

FIGURE 2. *Infectious complications in patients of I group.*

among the observed infectious complications; hepatitis B was recorded in 8 (7.2%) patients; hepatitis B and C in 6 (5.4%) cases and 1 patient (1.16%) with human immunodeficiency virus. The patients with acquired yatrogen infections are more susceptible to bleeding taking into account the fact that most of coagulation factors are produced in the liver, and the liver of these patients is infected.

Comparative results of infectious complications' development depending on the disease severity are presented in table 1.

As table 1 shows infections predominate in patients with mild form of the disease.

TABLE 1.

Infectious complications depending on the disease severity (Group I (n=111))

Disease severity	All patients		Hepatitis-carriers	
	n	%	n	%
Severe form (factor content 0-1%)	10	0.9%	0	
Middle form (factor content 1-5%)	26	23.4%	25	96.2%
Mild form (factor content 5-40%)	84	75.7%	46	54.8%

Taking into account, that antihemophylic preparations are of protein nature, their application leads to the formation of alloantibodies and development of inhibitory hemophilia [*Daghbashyan S et al., 2005; Hay C et al., 2006; Santagostino E et al., 2006; Haya S et al., 2007*]. By saying immunological complications we understand the production of antibodies (inhibitory hemophilia) to antihemophylic factors during the therapy. According to the study, antibodies were detected only in two patients from II group (3.22%) compared to 22 (19.8%) patients of I group (Fig. 3a, b).

For instance, the patient weighing 50 *kg* with internal hemorrhage requires 2,500 *mM* single dosage of factor every 12 hours for 5 days. In the same case, 25 bags will be required every 12 hours for the treatment of the patient with fresh frozen plasma. Of course, it is impossible to perform such transfusions, and therefore the transfusion is combined with certain amount of antihemophylic factors: 1,000 *mM* and 4-6 bags of plasma. This combination makes the treatment more enduring, and hematomas are not being absorbed for months, the appealability of such patients are increasing, the need and amount of spent preparations are increasing, as well.

The analysis on the detection of antibodies depending on the severity of hemophilia showed that immune complications were developed in 34.6% of patients in I group in middle and 13.1% cases in mild form of the disease (Table 2). According to literature data, the detection of antibodies hinders the treatment of hemorrhagic complications, as well as joint arthrocentesis and surgical interventions [*Shapiro A, 2007; Serban M et al., 2009; Lin*

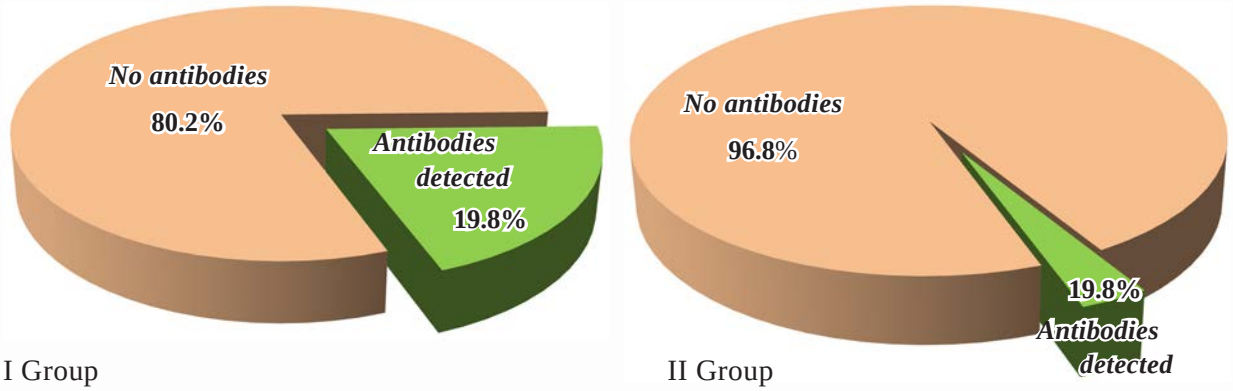

***Figure 3**. Immunological complications: I group – patients, who received fresh frozen plasma treatment, II group – patients, who received antihemophilic factor treatment.*

Y et al., 2011]. The detection of antibodies in patients of II group is recorded in 1 patient (3.3% cases) with mild hemophilia, which testifies the absence of antihemophylic factors and preventive treatment. Overall, antibodies were detected in patients of I group in 18% cases (20 patients) in comparison with 1.6% cases (1patient) of II group.

As it was already mentioned, in past, the deficiency or absence of antihemophylic factors was carried out only with fresh frozen plasma transfusion, which had low efficiency and led to serious articular complications including joint ones with further disability of the patient. In recent years, joint interventions were carried out in the presence of antihemophylic factors, certainly with incomplete doses, which even reduced the development of hemophilia arthropathies.

Hemarthrosis is characterized by the damage of periarticular apparatus, cartilage structure and destructive osteoarthrosis. They lead to osteoporosis, joint defiguration, as well as to steady contractures [*Tsailas P, Wiedel J, 2010*]. The development of articular complications in patients of the studied groups is shown in table 3. Based on the results of the survey, arthropathies were revealed in 91.9% of I group patients, while the application of factors (II group) leaded to their development only in 64.5% cases. Such a comparison also indicates the

TABLE 2.

Detection of antibodies depending on the disease severity

Disease severity	All patients	Patients with antibodies
Fresh frozen plasma treatment (n=111)		
Severe form (factor content 0-1%)	1(0.9%)	0
Middle form (factor content 1-5%)	26 (23.4%)	9 (34.6%)
Mild form (factor content 5-40%)	84 (75.7%)	11 (13.1%)
antihemophilic factor treatment (n=62)		
Severe form (factor content 0-1%)	4 (6.5%)	0
Middle form (factor content 1-5%)	28 (45.2%)	0
Mild form (factor content 5-40%)	30 (48.4%)	1(3.3%)

TABLE 3.

Development of articular complications depending on the disease severity

Disease severity	All patients	Patients with joints complications
Fresh frozen plasma treatment (n=111)		
Severe form (factor content 0-1%)	1 (0.9%)	0
Middle form (factor content 1-5%)	26 (23.4%)	25 (96.2%)
Mild form (factor content 5-40%)	84 (75.7%)	77 (91.7%)
antihemophilic factor treatment (n=62)		
Severe form (factor content 0-1%)	4 (6.5%)	1 (25%)
Middle form (factor content 1-5%)	28 (45.2%)	26 (92.9%)
Mild form (factor content 5-40%)	30 (48.4%)	13 (43.3%)

frequency of joint complications while using fresh frozen plasma as hemophilic therapy.

As table 1 shows, joint diseases are most frequently detected in case of moderate flow of hemophilia in 96.2% cases in patients of I group and in 92.9% of II group, respectively. The frequency

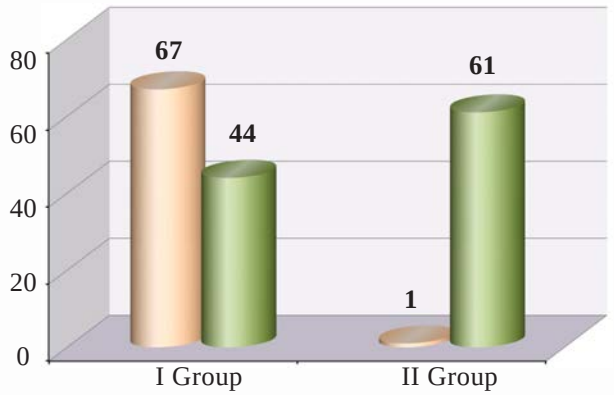

Figure 4. *Frequency of contractures in patients of studied groups.* Presence of Contractures (yellow column), No Contracture (green column)

of articular complications is almost twice high in the mild form of the disease in the I-group of patients than in patients of II group (91.7% vs. 43.3% cases, respectively). This is due to the fact that the application of antihemophylic factors not only prevents or stops articular hemorrhages, but it also facilitates their early reabsorption and mobilization of joint. In case of articular hemorrhage, a child with hemophilia can attend school after a single dose injection of factor without pain syndrome and joint functional disorder, meanwhile after a single dose of plasma injection, the same child has to stay in bed for 3-5 days.

The probability of contracture formations has also been carried out in the study on the background of applied therapy (Fig. 4). The contractures comprised 60.4% (67 patients) cases in patients of I group in comparison with 1.6% (1 patient) cases of II group, which is compatible with the data of other studies [*Tsailas P, Wiedel J, 2010*].

Therefore, summarizing the abovementioned, it can be stated, that the application of antihemophylic factors as therapy excludes infectious complications, decreases the risk of immunological complications' development, and low level of articular complications is registered in case of mild form of the disease.

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