Фармакоэкономика
theory and practice

IX НАЦИОНАЛЬНЫЙ КОНГРЕСС С МЕЖДУНАРОДНЫМ УЧАСТИЕМ «РАЗВИТИЕ ФАРМАКОЭКОНОМИКИ И ФАРМАКОЭПИДЕМИОЛОГИИ В РОССИЙСКОЙ ФЕДЕРАЦИИ»
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ОРИГИНАЛЬНЫЕ РОССИЙСКИЕ ФАРМАКОЭКОНОМИЧЕСКИЕ ИССЛЕДОВАНИЯ
Abstract: The aim of this study was to determine optimal medical technique based on assessing cost and efficacy of treatment of von Willebrand disease using blood clotting factor concentrates (blood clotting factor VIII + von Willebrand factor): Wilate, Haemate P, Immunate. It was determined that in studies on assessing the efficiency of the concentrates more than 95% of patients rated hemostasis excellent/good. However, the studies were based on different scales of efficiency assessment, different vWF:RCo doses and different data for vWD patients (severity of the disease), therefore the efficiency of blood clotting factor concentrates might be not equal. Results of present study with the assumption about equality of groups, that were analyzed in studies on assessing the efficiency of the concentrates (although, studies on Wilate included more severe patients), evidence that prescribing blood clotting factor concentrate Wilate lead to cost savings compared to the older generation products.

Key words: von Willebrand disease, prophylaxis, dental surgery, minor surgery, major surgery, cost analysis, effectiveness analysis, «budget impact» analysis.

Willebrand disease is a coagulopathy associated with qualitative and/or quantitative von Willebrand factor disorders [5]. The first cases were described in 1926 by Erik Adolf von Willebrand in Finland. According to experts’ estimates, the disease is found in approximately 1% of population. At that 9 cases out of 10 remain undiagnosed [15]. In 2012 World Federation for Hemophilia registered 66123 patients; this number is 2.5-fold higher than it was in 1999 [34]. As of 02.04.2014, 1491 patients with Willebrand disease have been registered in the Russian Federation [4]. According to regional chief hematologists, average value of Willebrand disease prevalence in the Russian Federation is 2.92 ± 2.15 per one hundred thousand population.

Probability of inheritance is identical for both genders. However, since females have regular menses and may have long-term postpartum bleedings, Willebrand disease is more commonly diagnosed in females [15]. In 2012 the register included 22637 (35%) males and 33297 (50%) females; gender was not established in the remaining 15% [34].

The main therapy purpose is to normalize blood clotting. Depending on severity of symptoms, preventive or on-demand therapy may be prescribed. The following medicines may be used in treatment schemes of von Willebrand disease: desmopressin, vWF-FVIII concentrates, hormones, antifibrinolytic drugs [5].

The first vWF and FVIII concentrates were developed in 1982 and currently a range of drug products are marketed. However, they vary greatly, especially in terms of vWF/FVIII ratio [21]. Depending on production method, blood clotting factor concentrates are classified into:

• recombinant concentrates (under clinical investigation);
• donor blood concentrates [11].

The drug products from donor blood vary depending on their multimer structure and vWF ratio (vWF:RCo to vWF:Ag; FVIII to vWF).

Contemporary blood clotting factor concentrates should meet the following criteria:

• Efficacy: preserving natural characteristics of clotting factors:
  – structure (Functional properties of von Willebrand factor are determined by the amount of high molecular weight multimers and an intact triplet structure comparable to standard human plasma is important for the proper function of vWF);
  – ratio (excessive content of FVIII vs. vWF may result in clotting);
  – functional properties of clotting factors [5].


The aim of this study was to determine optimal medical technique from the pharmacoeconomic analysis perspective based on cost-efficacy ratio in the treatment of von Willebrand disease using blood clotting factor concentrates (blood clotting factor VIII + von Willebrand factor): Wilate, Haemate P, Immunate.

Population characteristics
The analyzed population was represented by the patients with von Willebrand disease registered in the Russian Federation. According to the data of the Department for Pharmacological Support and Regulation Medical Devices Circulation of the Ministry of Health of Russia (02.04.2014), 1491 patients were included in the respective register [38].

Average weight of patients in this study complied with the weight of...
statistically average human being in the territory of the Russian Federation (71.42 kg) and was obtained from the results of the study performed by London School of Hygiene and Tropical Medicine [39]. Preventive treatment regimen was prescribed to 447 patients (from the condition that 30% patients, which are severely ill [5], need regular prophylaxis). It was accepted that these patients developed on average 4.5 bleedings per month which complied with the data of clinical studies [14]. Pharmacoeconomic modeling horizon was 1 year.

Besides, a treatment regimen at which patients receive blood clotting factor concentrates to prevent bleeding during surgeries was analyzed. The number of such patients was 1044 which was equal to the number of patients that need no prophylaxis.

Efficacy analysis

Despite numerous studies of replacement therapy with blood clotting factor concentrates FVIII/vWF, unique system of efficacy assessment has not been yet developed. Most published studies are based on 4-step assessment, however, 3-step ratings are also found (table 41) [23].

The search for literature data was performed using the requests “Immunate”, “Wilate”, “HemateP” (“HaemateP”) at Google.ru, Haematologica.org, PubMed.

Literature review revealed a number of studies analyzing the clotting factor concentrates in question:
- Immunate – 2 studies;
- Haemate P – 11 studies;
- Wilate – 7 studies.

However, no studies devoted to direct comparison of efficacy of the concentrates have been found. All twenty studies found during the information search analyzed separate administration of the products. Due to significant heterogeneity among the cohorts, different efficacy evaluation methods and differences in the completeness of the necessary data, only ten publications were taken to perform present study.

It should be noted that, according to the results of the publications, “excellent/good” efficacy was noted in almost 100% for the concentrates.

However, taking into account the discrepancies in study cohorts (different ratio of persons with various types of Willebrand disease and, therefore, disease severity) and variations in doses prescribed (the number and amount of doses), identical efficacy of the concentrates cannot be stated.

Efficacy analysis in this study was based on comparison of the drug product dosage and number of bleedings during its use.

In whole, efficacy analysis consisted of two parts:
1. Efficacy analysis of blood clotting factor concentrate use in the regimen “Prophylaxis” (regular administration of concentrates);
2. Efficacy analysis of blood clotting factor concentrate use in the regimen “Prevention of surgical hemorrhages”.

The objects of efficacy analysis of blood clotting factor concentrate use in the regimen “Prophylaxis” (regular administration of concentrates) were Haemate P, Wilate, and Immunate.

Due to the fact that there was found no publications devoted to the study of bleeding prophylaxis (regular intake) with clotting factor concentrate Immunate, efficacy analysis was conducted on the basis of data obtained through the survey of experts from two hematological centers (HC) with long experience with this product:
- Morozov Children’s Clinical Hospital, Department of Health of the city of Moscow, hematology department;
- Altai branch of Hematology Research Center, Barnaul.

Data on the efficacy of concentrates Wilate and Haemate P were obtained from published studies (Table 1).

E. Berntorp and J. Windyga performed the study “Treatment and prophylaxis of acute bleedings in von Willebrand disease – efficacy and safety of Wilate, a new generation von Willebrand factor/factor VIII concentrate” noted that average Wilate dose in preventive regimen was 24.3 IU vWF-RCo/kg (dosing frequency – 1.9 doses per week), while average Haemate P dose was 48 IU vWF-RCo/kg (dosing frequency – 2 doses per week). The study also indicates that prior to the study three persons used Haemate P regimen. After switching to Wilate (at similar FVIII doses and 2-fold lower vWF doses), the hemorrhage incidence in such patients remained unchanged or reduced [13, 14].

Analysis of graphical data presented in the results of this study and the calculation of mean change in hemorrhage incidence after switching between concentrates were performed by Cool Ruler Version 1.5 software (developer: Fabsort Inc., 1999). Average number of hemorrhages against Haemate P administration (1.93 hemorrhages/month) was calculated based on the obtained data and data for bleeding frequency during prophylaxis with Wilate (1.40 hemorrhages/month) [14].

Analysis of the therapy regimen “Prevention of surgical hemorrhages” was based on the evaluation of blood clotting factor concentrate use for the prophylaxis of hemorrhages during three types of surgeries (surgery classification was determined by the character of data presented in clinical studies). At that it was taken that average annual number of surgeries performed to one patient was:
- Dental surgery – 1;
- Minor surgery – 1;
- Major surgery – 1.

The objects of efficacy analysis in regimen “Prevention of surgical hemorrhages” were blood clotting factor concentrate Haemate P and Wilate. Blood clotting factor concentrate Immunate was not included in this analysis because the retrieved study results (studies under the supervision of Auerswald G. and Ver Elst K. [10, 32] were analyzed) showed the significant difference in cohort composition (patients’ distribution by the type of von Willebrand disease) from those in the studies of Haemate P and Wilate. Moreover, the interview of experts from above mentioned centers showed that Immunate is not used in this therapy regimen (however, in the patient information leaflet for Immunate Willebrand disease with factor VIII deficiency is specified as an indication) (tab. 2).

It should be noted that Haemate P and Wilate studies also differed in the cohort composition and presented data on the regimen and therapy results for the selected surgery types. At that, the studies on Wilate included persons with more severe types of disease [18, 20, 25, 33].

Table 1. Values used in efficacy analysis of clotting factor concentrates in the regimen “Prophylaxis” (regular administration) in persons with von Willebrand disease.

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>Immunate</th>
<th>Wilate</th>
<th>Haemate P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average dose of vWF administered</td>
<td>49.75 IU/kg</td>
<td>24.30 IU/kg</td>
<td>48.00 IU/kg</td>
</tr>
<tr>
<td>Number of average doses per week</td>
<td>3.25</td>
<td>1.90</td>
<td>2.00</td>
</tr>
<tr>
<td>Number of hemorrhages during prophylaxis treatment per month</td>
<td>1.88</td>
<td>1.40</td>
<td>1.93</td>
</tr>
<tr>
<td>Probability of inhibitor production</td>
<td>0.00%</td>
<td>0.00%</td>
<td>2.33%</td>
</tr>
</tbody>
</table>

* HC - hematological centers

**References**

Immunate: data of 2 HC*  
Wilate [13, 14]  
Haemate: [13, 14]

Immunate: data of 2 HC  
Wilate [13, 14]  
Haemate: [13, 14]

Immunate: data of 2 HC  
Wilate [13, 14]  
Haemate: [13, 14]

* HC - hematological centers

[10,11, 25]
Table 2. Values used in efficacy analysis of clotting factor concentrate in surgery in persons with von Willebrand disease.

<table>
<thead>
<tr>
<th></th>
<th>Wilate</th>
<th>Haemate P</th>
<th>Immunate</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average dose of vWF</td>
<td>Number of doses</td>
<td>Average dose of vWF</td>
<td>Number of doses</td>
</tr>
<tr>
<td>Dental surgery</td>
<td>25.00 IU/kg</td>
<td>1</td>
<td>53.83 IU/kg</td>
<td>1.5</td>
</tr>
<tr>
<td>Minor surgery</td>
<td>31.50 IU/kg</td>
<td>1</td>
<td>61.76 IU/kg</td>
<td>3.5</td>
</tr>
<tr>
<td>Major surgery</td>
<td>22.50 IU/kg</td>
<td>12</td>
<td>75.65 IU/kg</td>
<td>7.5</td>
</tr>
<tr>
<td>Registered cases of thrombosis</td>
<td>No</td>
<td>Yes</td>
<td>Not used in the regimen*</td>
<td>[11, 25]</td>
</tr>
</tbody>
</table>

* - data based the survey of experts from two hematological centers.

Cost analysis
Cost analysis was based on calculation of economic effects of clotting factor concentrates administration at two study regimens: prophylaxis and surgery. General structure of analyzed costs is presented at figures 1 and 2.

Figure 1. Structure of costs in prophylactic treatment of persons with Willebrand disease.

Figure 2. Structure of costs in the treatment of persons with Willebrand disease during surgery.
Calculation of direct costs was based on the data specified in medical assistance standards and patient management protocols. The following standards and patient management protocols were used in the study:

- Standard of primary healthcare for children with Willebrand disease, hemorrhage or bleeding of any localization dated 24.12.12 (Pharmacotherapy is calculated on the basis of Patient management protocol: Willebrand disease. Patient model 4.3 (course dose was increased to 7 days) [35];
- Standard of specialized medical assistance in acute thrombosis of superior and inferior vena cava dated 01.02.2013 [36];
- Patient management protocol: Willebrand disease. Patient model 4.5 [37]

Each abovementioned standard and protocol was calculated including the costs for pharmacotherapy, medical and rehabilitation services, and costs for hospitalization, nutrition during the treatment.

Results

Efficacy analysis established that within the timeframe the least number of hemorrhages was noted in persons at regular prophylactic regimen of Wilate (fig. 3).

At that the lowest average single dose of the concentrate (doses based on von Willebrand factor) corresponded to regular prophylactic administration with Wilate – 1736 IU.

The lowest summary costs for the whole cohort was noted for regular prophylaxis with Wilate. The lowest annual costs for hemorrhage prophylaxis with Wilate per 1 person averaged 8026417 rubles.

In case of switching from regimens: “No prophylaxis”, “Prophylaxis: Immunate concentrate”, “Prophylaxis: Haemate P concentrate”, to the regular preventive administration with Wilate total costs per all population within the analyzed period can be reduced by 21906000 rubles, 22143000 rubles and 5752000 rubles, respectively (fig. 6).

The established difference in expenses provided at figure 7 can be used for preventative help to additional number of patients with Willebrand disease.

Sensitivity analysis demonstrated that the results are resistant to price changes per 1 IU of FVIII-vWF concentrate within +/- 15% and resistant to the modified number of hemorrhages arising against relevant concentrate within +/- 15% (fig. 8, fig. 9).

![Figure 3](image-url) Number of cases of hemorrhages in the study cohort against relevant treatment regimen within one year.

![Figure 4](image-url) Average single dose of the concentrates (vWF dose) per one person.
Figure 5. Total costs for hemorrhage prophylaxis in one average person with Willebrand disease with treatment regimens within one year.

Figure 6. Results of budget impact analysis: switching from analyzed treatment schemes to Wileate.
Figure 7. Missed opportunity analysis: number of persons that could have been additionally treated within the existing costs when switching to Wilate.

Figure 8. Sensitivity analysis of costs at hemorrhage prophylaxis per one person with Willebrand disease within one year vs. changes in prices for vWF + FVIII concentrates.

Figure 9. Sensitivity analysis of costs at hemorrhage prophylaxis per one person with Willebrand disease within one year vs. changes in the number of hemorrhages per month when using relevant concentrates.
In the prophylaxis of bleedings during surgeries the use of Wilate clotting factor concentrate was associated with lower concentrate doses and lower expenses for the therapy (table 3).

Table 3. Cost of bleeding prophylaxis in the surgery in patients with Willebrand disease.

<table>
<thead>
<tr>
<th>Cost</th>
<th>Haemate P</th>
<th>Wilate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dental surgeries</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost: medical services</td>
<td>40 241 P</td>
<td>40 241 P</td>
</tr>
<tr>
<td>Cost: concentrates vWF + FVIII</td>
<td>157 665 P</td>
<td>157 665 P</td>
</tr>
<tr>
<td>Cost: thrombembolia</td>
<td>3 459 P</td>
<td>3 459 P</td>
</tr>
<tr>
<td>Total cost</td>
<td>201 364 P</td>
<td>123 820 P</td>
</tr>
<tr>
<td><strong>Small surgeries</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost: medical services</td>
<td>40 241 P</td>
<td>40 241 P</td>
</tr>
<tr>
<td>Cost: concentrates vWF + FVIII</td>
<td>422 079 P</td>
<td>105 310 P</td>
</tr>
<tr>
<td>Cost: thrombembolia</td>
<td>3 459 P</td>
<td>- P</td>
</tr>
<tr>
<td>Total cost</td>
<td>465 779 P</td>
<td>145 551 P</td>
</tr>
<tr>
<td><strong>Large surgeries</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost: medical services</td>
<td>40 241 P</td>
<td>40 241 P</td>
</tr>
<tr>
<td>Cost: concentrates vWF + FVIII</td>
<td>1 107 869 P</td>
<td>902 656 P</td>
</tr>
<tr>
<td>Cost: thrombembolia</td>
<td>3 459 P</td>
<td>- P</td>
</tr>
<tr>
<td>Total cost</td>
<td>1 151 569 P</td>
<td>942 897 P</td>
</tr>
</tbody>
</table>

Conclusions
The literature review on the use of blood clotting factor concentrates (FVIII+vWF) in patients with Willebrand disease demonstrated that there is no direct, comparative, clinical, randomized studies to date. The found studies are devoted to the analysis of only one of the clotting factor concentrates available on the pharmaceutical market. Besides, when comparing the studies, a significant heterogeneity of patients (gender, age, disease severity, etc.) and significant differences in the evaluation of concentrates efficacy have been found which makes indirect comparison of the products difficult.

The cost analysis in this study demonstrated that the administration of Wilate is associated with lower costs due to the lower number and amount of average doses as well as the decrease in the number of bleedings occurring when the concentrate is used.

The cost analysis of concentrates administration in bleeding prophylaxis during surgeries has demonstrated that the lowest expenses are associated with the use of Wilate due to the lower dose of the concentrate.

Thus, according to the obtained results, the use of clotting factor concentrate (FVIII+vWF) Wilate in regimen “regular preventative administration” among patients with von Willebrand disease is associated with cost cutting at the amount of 22.1 mln annually in comparison with Immunate and Haemate P, respectively.

References


34. World Federation of Hemophilia Global Survey 2012. URL: http://www.wfh.org


36. Standard of specialized medical assistance in acute thrombosis of superior and inferior vena cava dated 01.02.2013 (Registered in Justice Ministry of Russia 01.02.2013 N 26779).


