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# The retrospective study of cost-effectiveness for prophylactic and on-demand treatment of the pediatric patients with hemophilia A in Iran

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Hemophilia is the second most common inherited bleeding disorder after von Willebrand disease. Delayed clotting is usually observed in all main types of hemophilia caused by deficiencies in blood coagulation factors. Primary prophylaxis is considered the gold standard to prevent acute hemarthrosis and chronic arthropathy in patients with severe hemophilia A. However, some low-income countries, like Iran, have to prioritize access to preventive care to balance the financial resources and per capita access to coagulation factors. In order to compare the cost-effectiveness of on-demand and preventive treatment, we conducted a retrospective study on 55 patients with hemophilia A. We collected data from two groups of patients: those who had received routine prophylactic treatment and those who had received on-demand (episodic) treatment. The results of our study revealed a significant difference in the annualized bleeding rates (ABRs) between the two groups: ABR in the prophylactic treatment group was lower than in the on-demand treatment group (2.19 vs 7.25). In addition, we found substantial differences between the prophylactic and on-demand treatment groups in the number of hospital visits per year (9.8 vs 14.41), the annual number of infusions (107.35 vs 229.58), and in the mean cost of treatment (30.96€ vs 63€). In conclusion, prophylactic therapy seems to be more effective than on-demand treatment. This study was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of the Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (IR.AJUMS.REC.1398.456). Written informed consent was obtained from the patients' parents.

**Key words:** *hemophilia, prophylaxis, on-demand, bleeding, retrospective study*

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Congenital hemorrhagic diseases are characterized by homeostasis dysfunction resulting in ineffective and abnormal formation of blood clots that may lead to prolonged or spontaneous bleeding [1]. Hemophilia is the second most common inherited bleeding disorder after von Willebrand disease. About 8200 people in Iran are diagnosed with hemophilia [2]. Deficiencies of blood coagulation factors cause delayed clot formation and are usually observed in all main types of hemophilia [3]. Type A hemophilia is caused by the deficiency of coagulation factor VIII (FVIII), while the lack of factor IX (FIX) leads to type B hemophilia. These disorders are characterized by recurrent episodes of bleeding, mainly in the joints and muscles [4]. In the long-term, repeated bleeding in the joints can damage cartilage and bones leading to chronic arthropathy and, eventually, disability [5].

Following the advent of replacement therapy with the missing clotting factors, the treatment and management of hemophilia have changed significantly. Life expectancy has increased from early adolescence to over 75 years due to improvements in healthcare services [6]. Treatment has also changed from the use of crude plasma preparations such as cryoprecipitate (in the 1960s) and high-purity and recombinant concentrates (in the 1980s) to new extended half-life drugs. These agents have significantly reduced the burden of treatment on patients [7].

Hemophilia is usually treated with coagulation factor replacement therapy. Treatment options include prophylaxis (prevention of bleeding) and on-demand treatment (episodic treatment after the onset of bleeding) [8]. Prophylaxis is the preferred treatment option for patients with severe hemophilia (commonly defined as < 1% baseline coagulation factor activity level). It significantly decreases the total number of bleeding events and joint hemorrhages. Consequently, prophylactic treatment reduces the occurrence of hemophilia-induced arthropathy compared to on-demand treatment [9]. Magnetic resonance imaging of axial joints has shown that prophylactic treatment can prevent chronic microbleeds in the joints and hemarthrosis. Moreover, prophylactic therapy may be associated with fewer days of absence from work or school, improved physical health, pain relief, and higher health-related quality of life (QoL) scores (measured by general or hemophilia-specific questionnaires) [10]. Recent studies have also suggested that initiating prophylaxis as soon as possible (before the occurrence of joint bleeding) can be more effective

[5]. Early or primary prophylaxis is initiated before or shortly after the first hemorrhagic episode and within the second year of life, when joints might still be pristine. Secondary prophylaxis is referred to as preventive measures started later, because irreversible joint changes may occur even after a few bleeding episodes in the same joints [11]. According to the statements made by the World Health Organization and the World Federation of Hemophilia, initiation of prophylactic treatment at an early age is the best option for pediatric patients with severe hemophilia A [12]. However, there are still some limiting factors for patients undergoing prophylactic treatment. For example, conventional FVIII and FIX concentrates have a short half-life and are administered intravenously. Repeated injections and frequent visits are burdensome for patients [13–15], which can lead to reduced treatment compliance [16]. High rates of non-adherence to treatment, high expenses, and no access to medical products are among the major clinical challenges of managing hemophilia patients [13–15]. In addition, the development of inhibitors against FVIII or FIX (alloantibodies) counterbalances the activity of coagulation factors, inhibits alternative therapies, prevents patients from receiving long-term prophylaxis, increases the risks of mortality and morbidity, and consequently, decreases the QoL [13, 17, 18]. Prophylaxis with coagulation factor concentrates is currently the gold standard in the management of hemophilia patients. However, there have been concerns regarding expenses and poor access to prophylactic therapy (< 1 unit of factor concentrate per capita) that prevents some countries, such as Iran, from proper implementation of prophylactic treatment plans. Hence, the present study aimed to establish the best treatment options for patients with hemophilia A in terms of cost-effectiveness.

## MATERIALS AND METHODS

This retrospective study is based on the archived records of 55 patients with hemophilia who were referred to the Baghai Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, between 2015 and 2018. To meet the study objectives, the data were collected for two groups of patients. One group received routine prophylaxis ($n$ = 31) and the other received on-demand therapy ($n$ = 24). None of the studied patients abandoned treatment. The collected data included age at diagnosis, age at the initiation of treatment, annualized bleeding rate (ABR), a history of surgical treatment due to hemophilia, the amount of coagulation factors used per IU/kg/year, the duration of prophylaxis, and the cost treatment. The groups were matched by age, gender, and body mass index. All the included patients met the following criteria: age less than 17 years old, the diagnosis of severe hemophilia A (FVIII < 1%), and the availability of at least one-year follow-up records. Patients with a history of inhibitory antibodies against FVIII and those who had missing information in their medical records were excluded. This study was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of the Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (IR.AJUMS.REC.1398.456). Written informed consent was obtained from the patients' parents.

### Statistical analysis

Descriptive analysis was used to describe the characteristics of the study participants. Percentage differences were further evaluated with the Chi-square or Fisher's exact test, as appropriate. In addition, the Mann-Whitney U test was utilized to compare differences between the two groups. We also applied the two-tailed significant test, and a $p$-value less than 0.05 was considered significant. All statistical analyses were carried out using the SPSS software (ver.16).

## RESULTS

The mean age of the patients in the prophylaxis group was 10 years compared with 8 years for the on-demand group. However, we did not find any significant differences between the groups when matched by age. There was a significant difference in ABR between the two groups. In addition, those children who received prophylaxis had lower bleeding rates. Moreover, the annual number of infusions was significantly lower in the children undergoing prophylactic treatment ($p$ < 0.001). Fewer infusions in the prophylaxis group lead to fewer hospital referrals and decreased expenses compared to the on-demand therapy group. These results are detailed in *table*.

About 75% of the patients in the on-demand group had a history of surgery compared to 25% in the prophylaxis group (*figure*). The chi-square test showed a significant association between the type of treatment and a history of surgery ($p$ < 0.05).

## DISCUSSION

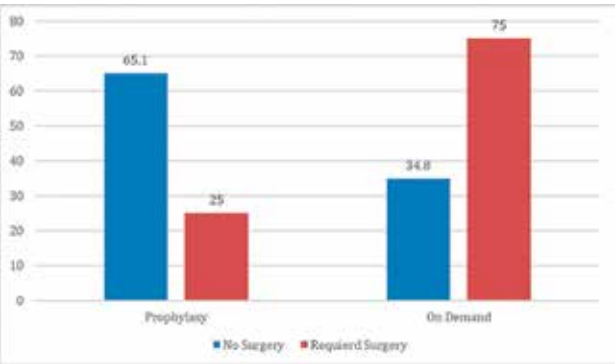
Until 2014, the treatment of choice for all age groups with hemophilia in Iran was on-demand therapy. At present, prophylactic treatment is divided into three priority groups:

1) start of prophylactic treatment after the first bleeding episode confirmed by radiological examination and before the second episode of bleeding in large joints for patients under 3 years old;

**Table**
The demographic and clinical characteristics of the patients, coagulation factor use, clinical outcomes, and expenses in the on-demand and prophylactic treatment groups

| Variables | On-demand therapy | Prophylactic therapy | *p*-value |
|---|---|---|---|
| Age (mean ± SD), years | 10.58 ± 3.36 | 8.35 ± 3.33 | 0.1 |
| Age at diagnosis (mean ± SD), months | 23.25 ± 22.64 | 11.32 ± 9.87 | – |
| Age at treatment initiation (mean ± SD), months | 28.04 ± 22.94 | 32.19 ± 34.34 | – |
| Sex (male:female) | 20:4 | 28:3 | 0.078 |
| Body mass index, kg/cm$^2$ | 21.54 ± 3.05 | 19.61 ± 3.36 | 0.3 |
| ABR (mean ± SD) | 7.25 ± 2.52 | 2.19 ± 0.98 | < 0.001 |
| Number of hospital visits per year (mean ± SD) | 14.41 ± 3.82 | 9.80 ± 2.480 | 0.001 |
| Number of prophylaxis use per year (mean ± SD) | – | 5.58 ± 2.69 | – |
| Number of injections per year (mean ± SD) | 229.58 ± 41.12 | 107.35 ± 53.59 | < 0.001 |
| Number of injections per week (mean ± SD) | – | 2.06 ± 1.03 | – |
| Expenses (mean ± SD), € | 63.000 ± 10.30 | 30.96 ± 13.84 | 0.001 |

**Figure**
A comparison of surgical treatment between the study groups




2) start of prophylactic treatment after the second episode of bleeding in large joints confirmed by radiological examination;

3) start of prophylactic treatment after clinical evidence of joint damage to stop progression.

This study aimed to compare prophylactic and on-demand treatment protocols in patients with hemophilia A. In addition, in these two groups we evaluated the following factors: the frequency of bleeding episodes per year, the rate of joint damage, the need for surgery, the number of infusions (coagulation factor), as well as the costs and benefits of prophylactic and on-demand treatment. The results of the study may help all who are involved in patient care, including patients, physicians, and funding agencies, to make better decisions.

In our study, the frequency of bleeding episodes in the prophylaxis group was significantly lower than in the on-demand treatment group. The annual bleeding rates were 7.25 and 2.19 in the on-demand and prophylactic groups, respectively. In 2018, Nugent et al. assessed the value of prophylactic versus on-demand treatments. They measured ABR in 45 patients aged 1 to 7 years with severe hemophilia A and reported that mean annualized bleeding events per patient were 12 and 4 in the on-demand and prophylactic groups, respectively [7]. In another study, Tagliaferri et al. (2015) evaluated 53 patients aged between 12 to 55 years in the on-demand and prophylactic groups with severe hemophilia A. They reported that ABR in the prophylaxis group (~ 2.5) was lower than in the on-demand group (~ 16.7). Prophylaxis resulted in a reduction in bleeding episodes, and a consequent reduction in the frequency of hemarthrosis and arthropathy was predictable. In this study, 65% of the patients undergoing prophylactic therapy did not require surgery, while 75% of those receiving episodic (on-demand) treatment required surgery [19]. In 2019, Rodriguez-Merchan performed a comprehensive study on the role of orthopedic surgery in preventing arthropathy progression and structural joint defects in patients with hemophilia. He believed that prophylactic replacement of coagulation factors could play an important role in preventing and treating hemophilia-induced arthropathy. He also reported that prophylactic treatment with coagulation factors could significantly prevent deficient factors from decreasing to less than 1–3%. As a result, the need for various surgeries such as synovectomy would reduce [20].

For low-income countries, cost-effectiveness is an important factor in choosing an appropriate treatment option for patients with severe hemophilia A. Prophylactic treatment results in a significant decrease in ABR, lower number of infusions per year, and lower factor consumption compared to on-demand treatment. The latter requires frequent hospital visits. Fewer hospital referrals and better joint health in hemophilia patients receiving prophylactic treatment are expected to decrease expenses. Singh et al. compared prophylaxis and on-demand treatment approaches in patients with hemophilia. Following a decrease in ABR and improvement in joint function, clotting factor consumption reduced by 12.33% in the prophylactic group compared to the on-demand group [21]. These findings are in line with the results of our study. Another study in Iran performed a cost-benefit analysis of prophylaxis against on-demand treatment in pediatric male patients with severe hemophilia A. The authors reported that patients receiving prophylactic treatment had fewer bleeding episodes per month but required more concentrate. Furthermore, the average expenses per patient per month in the prophylaxis group were approximately 1.9 times higher than those in the on-demand group. Prophylaxis cost about €213.45 per bleeding event prevented. It was concluded that although prophylactic treatment could significantly

reduce the number of bleeding episodes, it was substantially more expensive [22]. Although hemophilia is partially covered by the national healthcare insurance system in Iran, we see that low-income families are less likely to be on prophylactic treatment. The impact of sociodemographic factors on treatment plans requires further studies. Our study demonstrates that there is a need to facilitate the prerequisites for prophylactic treatment by public health policy-makers of countries with similar conditions.

## CONCLUSION

Prophylactic treatment is the gold standard in the management of patients with severe hemophilia A to prevent joint bleeding episodes and chronic arthropathy. Our study also showed that the frequency of bleeding episodes, the number of hospital visits per year, the annual number of infusions, and treatment costs were higher in the on-demand group than in the prophylaxis group. In conclusion, prophylactic treatment seems to be more effective in patients with hemophilia type A.

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**CONFLICT OF INTEREST**

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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## References

1. Sarangi S.N., Acharya S.S. Bleeding disorders in congenital syndromes. Pediatrics 2017; 139 (2): e20154360.
2. Rostami S., Namaki Khameneh S., Keikhaei Dehdezi B., Haghighizadeh M.H. The Effect of Family-centered Empowerment on Quality of Life in Children with Hemophilia. Avicenna J Nurs Midwifery Care 2020; 28 (1): 1–10.
3. Ay C., Perschy L., Rejtö J., Kaider A., Pabinger I. Treatment patterns and bleeding outcomes in persons with severe hemophilia A and B in a real-world setting. Ann Hematol 2020; 99 (12): 2763–71.
4. Castaman G., Matino D. Hemophilia A and B: molecular and clinical similarities and differences. Haematologica 2019; 104 (9): 1702–9.
5. Thornburg C.D., Duncan N.A. Treatment adherence in hemophilia. Patient Prefer Adherence 2017; 11: 1677.
6. Mannucci P.M. Hemophilia therapy: the future has begun. Haematologica 2020; 105 (3): 545–53.
7. Nugent D., O'Mahony B., Dolan G.; International Haemophilia Access Strategy Council. Value of prophylaxis vs on-demand treatment: Application of a value framework in hemophilia. Haemophilia 2018; 24 (5): 755–65.
8. Lobet S., Hermans C., Lambert C. Optimal management of hemophilic arthropathy and hematomas. J Blood Med 2014; 5: 207–18.
9. Mancuso M.E.E., Reding M., Negrier C., Kerlin B., Rajgarajan S., Simpson M.L. Decreased Bleeding Rates in Patients with Hemophilia A Switching from Standard-half-life FVIII to BAY 94-9207 Prophylaxis. Thromb Haemost 2021; 121 (8): 1079–86.
10. Krishnan S., Vietri J., Furlan R., Duncan N. Adherence to prophylaxis is associated with better outcomes in moderate and severe haemophilia: results of a patient survey. Haemophilia 2015; 21 (1): 64–70.
11. Manco-Johnson M.J., Soucie J.M., Gill J.C. Joint Outcomes Committee of the Universal Data Collection USHTCN. Prophylaxis usage, bleeding rates, and joint outcomes of hemophilia, 1999 to 2010: a surveillance project. Blood 2017; 129 (17): 2368–74.
12. Ljung R. Aspects of prophylactic treatment of hemophilia. Thromb J 2016; 14 (1): 30.
13. Castaman G., Linari S. Prophylactic versus on-demand treatments for hemophilia: advantages and drawbacks. Expert Rev Hematol 2018; 11 (7): 567–76.
14. Tang L., Wu R., Sun J., Zhang X., Feng X., Zhang X., et al. Short-term low-dose secondary prophylaxis for severe/moderate haemophilia A children is beneficial to reduce bleed and improve daily activity, but there are obstacle in its execution: a multi-centre pilot study in China. Haemophilia 2013; 19 (1): 27–34.
15. Zhao Y., Xiao J., Yang R., Wu R., Hu Y., Beckmann H., et al. Efficacy of standard prophylaxis versus on-demand treatment with bayer's sucrose-formulated recombinant FVIII (rFVIII-FS) in Chinese children with severe hemophilia A. Pediatr Hematol Oncol 2017; 34 (3): 146–56.
16. Gringeri A., Lundin B., Von Mackensen S., Mantovani L., Mannucci P., Group E.S. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study). J Thromb Haemost 2011; 9 (4): 700–10.
17. Morfini M., Haya S., Tagariello G., Pollmann H., Quintana M., Siegmund B., et al. European study on orthopaedic status of haemophilia patients with inhibitors. Haemophilia 2007; 13 (5): 606–12.
18. Rocino A., Franchini M., Coppola A. Treatment and prevention of bleeds in haemophilia patients with inhibitors to factor VIII/IX. J Clin Med 2017; 6 (4): 46.
19. Tagliaferri A., Feola G., Molinari A.C., Santoro C., Rivolta G.F., Cultrera D.B., et al. Benefits of prophylaxis versus on-demand treatment in adolescents and adults with severe haemophilia A: the POTTER study. Thromb Haemost 2015; 114 (1): 35–45.
20. Rodríguez-Merchán E.C. The role of orthopaedic surgery in haemophilia: current rationale, indications and results. EFORT Open Rev 2019; 4 (5): 165–73.
21. Singh A., Mehta S., Goyal L.K., Mehta S., Sharma B.S. Low Dose Prophylaxis vis-a-vis on-Demand Treatment Strategies for Hemophilia: A Cost Effective and Disability Attenuating Approach. J Assoc Physicians India 2019; 67: 52.
22. Daliri A.A.K., Haghparast H., Mamikhani J. Cost-effectiveness of prophylaxis against on-demand treatment in boys with severe hemophilia A in Iran. Int J Technol Assess Health Care 2009; 25 (4): 584.