

RESEARCH ARTICLE

Cost-effectiveness analysis of prophylaxis vs. “on demand” approach in the management in children with hemophilia A in Mexico

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ABSTRACT

Background. Hemophilia A is due to a deficiency of factor VIII. Treatment consists primarily of increasing the concentration of FVIII in the blood using replacement products. The aim of this study was to estimate the clinical and economic benefits of prophylactic management with factor VIII in children with hemophilia A in Mexico. We undertook this study to estimate the clinical and economic benefits of prophylactic management (PROF) with factor VIII (FVIII) in children with severe hemophilia in Mexico.

Methods. We carried out an economic evaluation of PROF vs. treatment on demand (OD). The strategies compared were management with PROF consisting of recombinant FVIII (rFVIII) 25 IU kg every other day vs. OD management consisting of plasma-derived FVIII (pdFVIII) 40 IU kg. A Markov model was performed with a time horizon of 16 years in patients with severe hemophilia for 2 years, reporting the number of bleeding events averted. We used a discount rate of 5%. The results are expressed in Mexican pesos (2012).

Results. The incremental cost of PROF regarding SD was \$ 7,727,554 pesos. PROF management provides a reduction of 112 BA vs. OD management (162.9 vs. 50.7). Cost per averted bleed was \$68,876 pesos.

Conclusions. Management with PROF reduces the number of bleeding events facing children with hemophilia A compared to OD management. PROF is a cost-effective alternative to reduce bleeding (\$68,876 pesos per bleed averted) according to the willingness to pay established by health authorities in Mexico.

Key words: hemophilia A, prophylaxis, FVIII, cost-effectiveness.

INTRODUCTION

Hemophilia is a rare bleeding disorder that is attributed to a deficiency of coagulation factors VIII, IX and XI. This deficiency leads to a tendency of moderate to severe bleeding. This disorder occurs mainly in males, who represent 97.32% of cases.¹

Hemophilia A is caused by a factor VIII (FVIII) deficiency.² Globally it is estimated that the prevalence of hemophilia A in 2012 was 363,668 cases.³ In Mexico there were 3582 cases reported in 2010.¹ In general, it is believed that ~60% of cases of hemophilia are severe,⁴ i.e., when the concentration of clotting factor is <0.01 IU/mL.^{5,6}

Hemophilia patients are at risk of bleeding in different parts of the body. The joints are the most affected and ~80% of the bleeding occurs in knees, elbows and ankles.⁷ As a result of the repeated joint hemorrhages, there are alterations in the tissues that make up the joint which, in turn, degenerate into chronic synovitis and destruction of the surfaces that make up the joint (hemophilic arthropathy).⁵

Currently, liver transplantation is the only option to cure hemophilia. On the other hand, the goal of treatment is to increase blood concentration of FVIII using replacement products in order to prevent and stop spontaneous bleeding (during the daily life of the patients) or excessive bleeding (during surgery).⁵

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Currently there are two types of FVIII for replacement therapy without a significant difference in terms of effectiveness: the plasma derivative (pdFVIII) and the recombinant (rFVIII). However, when the criterion is the safety of the patient, the situation is different. Although the current technology of plasma purification allows for virus inactivation with a lipidic envelope (human immunodeficiency, hepatitis B and C), the risk of transmission of diseases caused by prions such as the Creutzfeldt-Jakob disease variant is present.⁸

National and international hemophilia guidelines recommend the use of recombinant coagulation factors as a first option, especially for patients who have never been exposed to concentrated coagulation factors with viral inactivation derived from plasma.^{2,9-12} When there are no recombinant coagulation factors available, it is recommended that concentrated coagulation factors of plasma origin with least two processes of viral inactivation be given.^{2,11,12} According to the World Federation of Hemophilia (WFH), consumption of rFVIII represents 52.2% of the total worldwide consumption of FVIII, whereas the remainder (47.8%) corresponds to pdFVIII.¹ In Mexico, consumption of rFVIII represents only 3.6% of the total consumption of FVIII.¹

There are two ways of administering replacement therapy: on demand (OD) and prophylaxis. For the former, the coagulation factor is administered once hemorrhage is present (20 to 30 bleeding episodes per year).^{5,13} For the latter, the coagulation factor is administered on a regular basis so as to decrease the frequency with which the bleeding episodes occur and secondly for a lesser incidence of joint complications.^{14,15} In this manner, the scheme of administration of the replacement therapy to which the patients are subjected has a definitive impact on their quality of life.¹⁶⁻¹⁸

Prophylactic management for patients with hemophilia is the standard of care in developed countries especially in young patients with severe hemophilia and is in agreement with the recommendations of the WFH clinical guidelines.^{19,20} In this approach, the principal component of the total cost of the treatment (72-96%) corresponds to the cost of the FVIII.²¹⁻²⁵

In this sense, the objective of the present study was to evaluate the potential costs and health results of the implementation of the prophylactic approach with rFVIII and the OD management with pdFVIII in pediatric patients with hemophilia A.

PATIENTS AND METHODS

Description of the study

A full economic evaluation was developed to estimate the economic consequences on health and quality of life, of prophylaxis and OD treatment in the management of patients with hemophilia A. The analysis was carried out from the perspective of the health system in Mexico. The study examined the cost of acquiring FVIII and the medical emergency care that the Instituto Mexicano del Seguro Social (IMSS) would provide while caring for this group of patients from 2 to 18 years of age.

Comparative alternatives

Hypothetical patients subjected to prophylaxis were administered rFVIII 25 IU/kg three times a week (according to the clinical practice guidelines in Mexico),^{9,10} whereas hypothetical patients undergoing OD management were administered 40 IU/kg for each event of joint bleeding, the doses that could be repeated until the bleeding stopped (in accordance with the number of rescue infusions required in patients with severe hemophilia reported in the international literature).²⁶

Structure of the model

Using a Markov model, it was sought to properly reflect the possible courses of action that patients follow when they are subjected to the different approaches for management of hemophilia A, passing between mutually exclusive states of health over time. The states of health included in the model are as follows: without bleeding (includes patients who do not present joint bleeding), bleeding in which patients have spontaneous joint bleeding for which emergency medical care is received as well as rescue doses of rFVIII and pdFVIII in patients subjected to prophylaxis and OD treatment, respectively, and death, which is an absorbing state (Figure 1).

The model allows for hypothetical patients of 2 years of age who can be managed either with prophylaxis or treatment OD and are incorporated during the state without bleeding in which they remain during a 2-week cycle (Markov cycle with 14 days duration). At the end of the management, they face the possibility of entering into a state of bleed, death or remaining in the same state (without bleed). The probability of entering other health states or remaining in the same state is directly related with the

efficacy of each approach of hemophilia A management and with the probability of death by age corresponding to the male Mexican population between 2 and 18 years of age. Once the second Markov cycle has finished, each patient again faces the probability of their health status changing, a process that is repeated until the patients reach the age of 18 years or their death. The costs and the consequences on health of each approach to management of the condition are recorded along the horizon of analysis and added at the end of the condition.

An assumption of the model is when patients presenting spontaneous bleeds are subjected to prophylaxis. This bleeding occurs on a day that is not during the regular application of prophylaxis and only requires one application of FVIII in an ambulatory setting in the emergency department (given that they receive on a regular basis one dose each day).

Measures of effectiveness

Number of joint bleeds associated with each of the management schemes of hemophilia A is evaluated. Because of the perspective, acquisition costs of FVIII (rFVIII and pdFVIII) and of the medical emergency care were accounted for in cases that presented with spontaneous bleeds. The cost of generic emergency consultations in a second level of care center were used given that there are no records available that report a specific cost for emergency due to bleed. The study estimates the cost by bleed avoiding additional prophylaxis on the OD scheme, which is equivalent to the incremental cost-effectiveness ratio (ICER).

Parameters used in the model

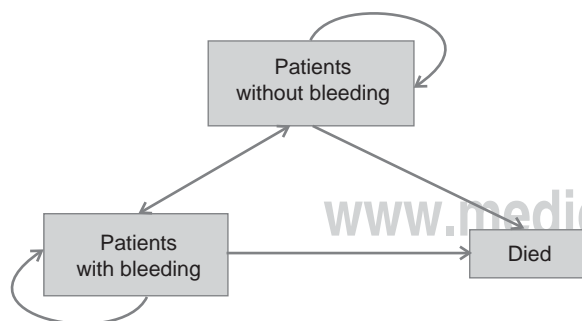


Figure 1. Markov model for patients with hemophilia A. Shown are mutually exclusive health states and possible transitions between them.

The average number of joint bleeds for a year in patients subjected to prophylaxis and OD management were extracted from the study performed Fisher et al.²⁷ who used the average number of joint bleeds from the observational studies by Molho et al. (OD)²⁸ and Fisher et al. (prophylaxis)²⁹ (Table 1).³⁰⁻³⁵

The unit cost of pdFVIII factor corresponds to what is reported in the purchase register of the IMSS for the period from January-June 2012.³⁰ The unit cost of rFVIII was provided by the manufacturer. The cost of emergency care corresponds to what is reported by the IMSS for the second level of medical care in 2012.³¹

For estimation of weights every 14 days of the children, annual weights were taken into consideration for the ages 2 to 13 years reported by the Mexican Association of Pediatrics³³ and the average weight in the age range of 18 to 25 years reported by the National Association of Apparel Manufacturers³⁴ for carrying out a regression. The 14-day weights were obtained by interpolation (Table 2).

The annual probabilities of death were transformed into 14-day transition probabilities. An adjustment of the mean cycle both for costs as well as for health results was done. In the study, an average of 21 bleeds per year for patients who required OD treatment were used.²⁷ Consideration of this information is because it is a study that carried out a simulation of life expectancy with hemophilia based on a review of information from two cohort studies (Netherlands and France) during a 9-year period.

The value corresponding to the average number of rescue treatment applications in accordance with the OD approach corresponds to the reported distribution of Protocol No. 3082B2-310-WW from Wyeth²⁶ where in 74% of the patients the bleeding ceased with the first application, 18% with the second application, 4% with a third application and 2% for patients with a fourth application. Therefore, on average, 1.4 applications were required for cessation of bleeding.

The model applied a discount rate of 5% for the results in health and for costs (16-year analysis), in accordance with the guidelines for presentation of studies of economic assessment for updating the basic tables and catalogue of consumables used in the health sector in Mexico.³⁵ In the analysis, the “ability to pay” recommended by the Mexican pharmacological guidelines was used that corresponds to 1 PIB per capita,³⁵ according to the information pro-

Table 1. Parameters and costs of the model

Parameter/cost	Value (minimum-maximum)	Source
Annual number of bleeds with prophylaxis	4.91 ($\pm 20\%$)	Author, Ref. ²⁷
Annual number of bleeds under management (OD)	20.91 ($\pm 20\%$)	Author, Ref. ²⁷
Cost IU rFVIII (MX\$)	4.92	Pfizer México
Cost IU pdFVIII (MX\$)	4.92	Ref. ³⁰
Emergency consults (MX\$)	1,133	Ref. ³¹
IU/kg in rescue in patients (SD)	56 ($\pm 20\%$)	Author, Ref. ^{9,10}
Average # of infusions required to stop bleeding (OD)	1.4 ($\pm 20\%$)	Author, Ref. ²⁶
Mortality by age	Specified by age (Table 3)	Ref. ³²
Weight in children 2-18 years of age	Specified by age (Table 3)	Ref. ^{33,34}
Discounted rate	5% (3-7%)	Ref. ³⁵

OD, replacement therapy on demand; rFVIII: recombinant factor VIII; pdFVIII, factor VIII derived from plasma.

Table 2. Probabilities of death and weight of Mexican children

Age	Probability of death ³²	Average weight ³³
2	0.000653	12
3	0.000433	14
4	0.000338	16
5	0.000281	18
6	0.000255	20
7	0.000245	22
8	0.000246	24.5
9	0.000255	27
10	0.000275	30
11	0.000301	33.1
12	0.000336	36.6
13	0.000381	38
14	0.000440	42.05*
15	0.000513	46.1*
16	0.000602	50.15*
17	0.000704	54.2*
18	0.000815	58.25*
19		62.3*
20		66.35*
21		70.4**

*Estimated values correspond to interpolation among values of weight reported at 13 and 21 years of age, assuming a linear relation among the same. **Reference 34.

vided by the Bank of Mexico.³⁶ Given that Mexico had a PIB for current prices of the fourth trimester of 2012 of 16,025,000 million pesos and with a reported population for 2012 of 112,323,000 persons,³⁷ one would obtain a per capita PIB of \$142,669.9 pesos. The results of the model (costs and ICER) are expressed in Mexican pesos (2012). To verify the strength of the results estimated as baseline, a univariate sensitivity analysis was carried out with principal parameters of the model.³⁸

RESULTS

The results of the model for cost effectiveness and cost usefulness of prophylaxis with respect to OD management in patients with hemophilia A are shown in Table 3. On evaluating the results of the cost effectiveness model in health for bleeds prevented, it is noted that the alternative for OD reported for the period of 16 years was a total of 162.9 bleeds, whereas the prophylactic strategy reported 50.7 bleeds for the same time period. This represents a reduction of 112.2 bleeds (discounted) compared with the OD management.

With the strategy of OD management, a cost average of 1.67 million pesos per patient was obtained, whereas the strategy for prophylaxis for the same 16-year period reported a cost of 9.39 million pesos, which represented an incremental increase of 7.72 million between strategies.

According to the result of the previous combination, there is the ICER for an averted bleed or the cost by reduction of a bleed with prophylaxis over the cost of the OD treatment, which was \$68,876 pesos. The estimated ICER of an averted bleed by prophylaxis is below the "ability to pay" established by the Mexican health authorities and, therefore, is ranked as a cost-effective strategy. The results of the univariate sensitivity analysis are shown in the tornado diagram for both models (Figures 2 and 3). In the univariate analysis it was found that the prophylaxis ICER was sensitive to the variables: probability of bleed from OD management and number of IU/kg required for prophylactic management because when modifications of

$\pm 20\%$ are done, the results obtained were on the order of 26-48% and 23% in the CEIR for prevented bleed, respectively. In contrast, the remainder of the variables demonstrated to have a lesser impact on the ICER with variations in the ICER less than $\pm 20\%$.

DISCUSSION

Treatment with FVIII means survival of patients with severe hemophilia A. Also, prophylactic management has a favorable impact on the quality of life of the patients with respect to OD management. The use of the prophylactic approach reduces the number of bleeds, greatly decreasing the risk for long- or short-term joint damage.

In the model it was found that when the probability of bleeds of the group managed with OD was reduced, the ICER due to bleeds with prophylactic management increases, whereas the probability of bleeds of the OD group increases and the ICER due to averted bleeds in the prophylaxis group decreases. On the other hand, when the number of IU/kg of the prophylactic management group is increased, treatment becomes costlier and therefore the ICER increases. In this study the ICER due to averted bleeds was \$68,876 pesos. In different studies, the ICER

has been evaluated by averted bleeds, which were converted into Mexican pesos from 2012 to perform an adequate comparison.^{39,40}

When the cost of averted bleeds in this model is compared to the results obtained by Miners et al. (from \$13,024 pesos),⁴¹ there were some differences found that may explain this low ICER: a greater rate of discount of the costs (6%) and there were no discounts applied to the health results (the cost of OD management corresponds to 36.10% of the cost of the prophylactic approach), whereas in the present study they were placed at 17.7%.

Daliri et al.⁴² reported a cost of \$4,929.2 pesos per averted bleed. However, in this study a model was created with a time window of 6 months, which uses the results of a multicenter retrospective study in which some of the relevant variables were not controlled. Among these, a statistically significant difference is found in the weight of the two groups of patients, which were very low for the prophylactically managed patients. As a result, the consumption of IU/kg of the OD management represented 52.2% of the prophylactic consumption and, consequently, the cost reported with OD management is only 55% of the cost of prophylaxis, which allows one to consider that there is a possible study bias.

Table 3. Results of the deterministic analysis of cost-effectiveness in hemophilia A

Strategy	Cost	Incremental cost	Effectiveness	Incremental effectiveness	CER	ICER
Number of bleeds						
On demand	\$1,670,675		162.94		\$10,253	
Prophylaxis	\$9,398,229	\$7,727,554	50.74	112.19	\$185,209	\$68,876

CER, cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio.

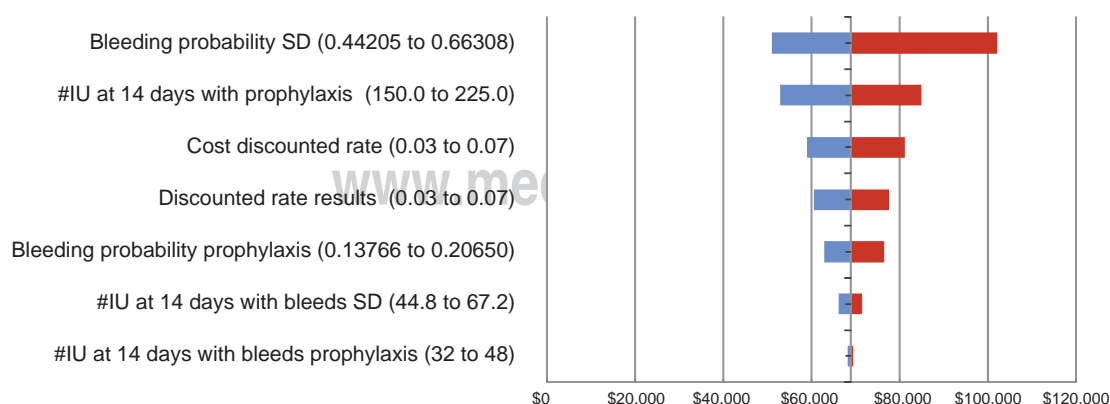


Figure 2.

Tornado diagram of the univariate analysis of on demand (OD) management vs. prophylaxis in patients with hemophilia A in Mexico (number of bleeds).

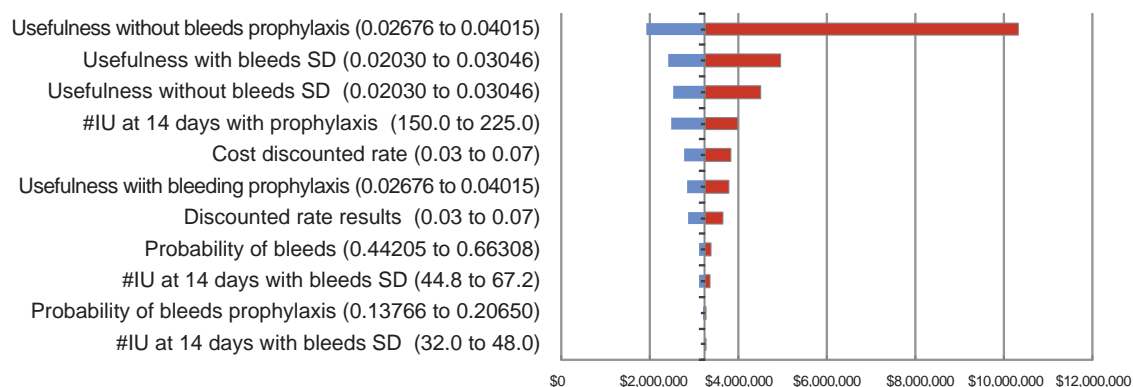


Figure 3.

Tornado diagram of the univariate analysis of OD management vs. prophylaxis in patients with hemophilia A in Mexico (AVAC).

Smith et al.⁴³ reported a cost of \$22,172 pesos for prevented bleeds in patients in the 3- to 20-year age range, which was estimated assuming a reduction in the number of bleeds for both groups as age increased. Improvement in terms of reduction of bleeds in prophylactic management is 56.37% with respect to OD. In turn, the corresponding cost of OD management with respect to prophylactic care was placed at 30%. The foregoing leads us to assume that differences in terms of the model are given by the surgical procedures that the author assumed within the model (two surgeries with an average cost of \$646,275 pesos each), which impacted directly on the increased costs of OD treatment and improved outcomes of the ICER for prophylaxis.

Lippert et al.⁴⁴ reported in their study an ICER of \$127,745 pesos for averted bleeds in patients <30 years of age in Germany and of \$271,626 pesos for older patients in Switzerland. However, the results are not directly comparable because both studies were focused on the adult population, with lower usefulness compared with found in our study. This was due in part that these are populations, in the majority, with comorbidities (such as hepatitis B, hepatitis C and HIV). In this case, costs corresponding to OD management vary from 22 to 51% of the cost of prophylactic management.

The main component of costs related to patients treated with prophylaxis corresponds to the cost of the FVIII as reported in different countries (Germany, U.S., Canada, Mexico).^{20,45,46} In some cases this represents between 72 and 96%.²¹⁻²⁵

In various studies²¹⁻²⁵ it has been identified that the cost of management of patients with hemophilia A is determined in a high percentage by the costs of the FVIII. In

this study it was decided to carry out the model only with the costs corresponding to the coagulation factors and the cost of emergency care. In this sense, the costs of hospitalization, surgical procedures, and laboratory and imaging tests were excluded because application of the coagulation factors in this study is done mainly on an outpatient basis.

The probabilities of transition for the number of bleeds in the model of the present study are based on the work of Fischer et al.²⁷ There is awareness that although one may opt to only include the results corresponding to children from the study by Manco-Johnson et al.,⁴⁷ it only reports the results up to 6 years of age. For this reason, it was considered that the reports by Fischer et al.²⁷ that combine the results of studies of an adult population may offer a better certainty according to our model, which corresponds to a population that begins in the infant stage and advances to a juvenile stage.

Within the limitations of this model are the impossibility of having studies in Mexican cohorts where one could assess the efficacy of both alternatives (OD and prophylaxis management) as well as the corresponding measurements of quality of life related to the different types of management over time in different age groups.

Another limitation of the present study is that it does not include adverse events within the model because there is controversy if any of the concentrates (rFVIII or pdF-VIII) causes a greater risk in terms of inhibitors.^{48,49} Also, joint deterioration due to bleeds and the possible surgical requirements for joint replacement were not taken into consideration. Even though there is evidence of a correlation between the number of bleeds in a joint with damage to the joint itself (Pettersson index),⁵⁰ the model does not allow for identification of the number of subsequent

bleeds in the same joint. Therefore, when these criteria are included and the assumption is made that these are present in a specific joint, one may overestimate the impact of the bleeds. In a similar sense, there is also not a well-defined type of surgical management that should be carried out for a determined number of bleeds, i.e., arthroscopy or joint replacement.

Finally, because the different sources of information used in the model are secondary sources with which there is no direct relationship that affects the patient, and because there is no judgment applied as to the cost in this disease with regard to other diseases, there were no ethical considerations related to this study.

Prophylactic treatment with rFVIII in patients with hemophilia A shows a positive impact in reducing the number of bleeds reported by patients during its use. In parallel, it leads to an improvement in the quality of life reported by these patients which, depending on budgetary constraints, may be a cost-effective alternative.

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