Economic impact of inhibitors in pediatric hemophilia A

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Abstract

Introduction: Few studies have assessed the economic impact of inhibitors in hemophilia A in Mexico, especially in the pediatric population. **Objective:** To determine the economic impact entailed by the development of inhibitors in pediatric patients with hemophilia A. **Method:** Patients with hemophilia A under the care of a pediatric hematology department between December 2015 and November 2017 were retrospectively assessed. Direct and indirect costs were determined based on the presence or absence of inhibitors. **Results:** The cost analysis of the study population (n = 24) showed that diagnosis, follow-up, prophylaxis, treatment and hospitalization of these patients had an annual cost of \$ 6 883 187.4 per patient, out of which more than 95 % depended on the use of hemostatic factors. Annual cost per patient in the group with inhibitors was \$ 5 548 765.0 in comparison with \$ 1 334 422.4 in the group without inhibitors, 4.2 times higher. **Conclusions:** This is the first national study to show that the presence of inhibitors in pediatric patients with hemophilia A increases the cost of the disease more than four times.

KEY WORDS: Economic impact. Annual cost. Hemophilia A. Inhibitors. Mexico

Introduction

Hemophilia is a rare congenital disease, characterized by genetic abnormalities that cause factor VIII (hemophilia A) or factor IX (hemophilia type B) functional loss.¹ The prevalence of hemophilia A is estimated at approximately one case per 5000 to 7000 male births.² Patients with type A or B hemophilia, especially in the severe clinical form, experience repeated spontaneous or posttraumatic prolonged bleeding.³ Prophylaxis, especially if started early in the course of life, has been associated with better joint outcomes.⁴ Patients with hemophilia A can develop antibodies that neutralize the coagulation factor VIII they are administered.³ Currently, treatment cost is one of the most important aspects to consider in this disease;⁵ however, in our country there are few studies that have carried out a cost analysis.⁶

This research aimed to determine the direct and indirect costs of hemophilia A management, with an emphasis on the development of inhibitors.

Method

This study was carried out retrospectively at the Mother-Child Hospital of the Institute of Social Security of the State of Mexico and Municipalities, Toluca unit, in Mexico. All pediatric patients with hemophilia A who were provided care between December 2015 and November 2017 (n = 24) were assessed. This study was approved by the Institutional Ethics Committee of the hospital. A thorough recording of patient sociodemographic and clinical characteristics and bleeding events was carried out, including the type of administered factor, consultations required, laboratory tests, imaging studies and coagulation factor determinations, among others.

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Table 1. Heredofamilial and clinical characteristics of pediatric patients with hemophilia A*

Variables	Without inhibitors (n = 19)		With inhibitors (n = 5)		p
Continuous	Mean/Median*	SD/IQR	Mean/Median*	SD/IQR	
Age at diagnosis (months)	16.00	28.00	9.50	7.50	0.346
Age at the time of the study (years)	11.64	3.72	9.67	3.74	0.060
Factor VIII at diagnosis (%)	0.03	0.02	0.03	0.03	0.996
First recorded factor VIII (%)	0.01	0.03	0.04	0.41	0.354
Number of affected relatives	3.00	3.50	2.00	0.00	0.717
Categorical	n	%	n	%	
Gender					
Males	19	100.0	5	100.0	
Severity at diagnosis					0.504
Mild	2	10.5	0	0.0	
Moderate	10	52.6	4	80.0	
Severe	7	36.8	1	20.0	
Received home treatment					1.000
Yes	9	47.4	2	40.0	
No	10	52.6	3	60.0	
Home treatment**					0.058
Factor VII	0	0.0	2	66.7	
Factor VIII	10	100.0	1	33.3	
No data**	9		2		
Target joint (previous)**					0.622
No	14	77.8	5	100.0	
Yes	4	22.2	0	0.0	
No data**	1				

*Depending on the normality of the variable. Mother-Child Hospital, Institute of Social Security of the State of Mexico and Municipalities, Toluca, December 2015 to November 2017.

**Not included in frequency distribution.

***Target joint was defined as the presence of a joint that bleeds at least three times in a period of 1 to 3 months.

SD = standard deviation. IQR = Interquartile range.

For direct cost analysis (those derived from the care of the disease), the year 2016 was taken as the basis, considering institutional costs for that year, with the calculation being carried out in Mexican pesos. For indirect costs (those that do not directly depend on the underlying disease) averages of income per worked hour and hours worked per week in the employed population during 2016 for Mexico, as determined by the National Institute of Statistics and Geography, including lost days due to hospitalization and the days used for care in the visits required during the study period by patient parents or legal guardians.^{7,8} Data were analyzed with the R® software (R Project for Statistical Computing, CRAN, The Comprehensive R Archive Network, Vienna).

Results

Patient family, hereditary and clinical characteristics, both in patients with and without inhibitors, are

shown in Table 1. Details of the hemorrhagic events are shown in Table 2.

Direct costs

The cost for medical appointments per patient per year in the group without inhibitors was \$ 757.1 (0.06 % of total annual cost per patient), in comparison with \$ 548.0 in the group with inhibitors (0.01 %). Regarding laboratory tests, the estimated cost per patient per year for this item was \$ 357.0 in the subgroup without inhibitors (0.03 % of total annual cost per patient) and \$ 131.8 in the subgroup with inhibitors (0.01 %). Regarding imaging studies, the estimated cost for this item per patient per year was \$ 722.4 (0.05 % of total annual cost per patient) in the group without inhibitors, in comparison with \$ 669.5 (0.05 %) in the group with inhibitors. The detailed cost of medical appointments, with the recorded laboratory and imaging tests, are shown in Table 3.

Table 2. Hemorrhagic events in pediatric patients with hemophilia A[†]

Characteristics	Without inhibitors (n = 19)			With inhibitors (n = 5)			Total by category
	Events (n)	%	Events per patient (n)	Events (n)	%	Events per patient (n)	
Type of bleeding							
Articular	73	64.60	3.84	21	75.00	4.20	94
Mucosal	26	23.01	1.37	5	17.86	1.00	31
Muscular	8	7.08	0.42	2	7.14	0.40	10
Traumatic brain injury	4	3.54	0.21	0	0.00	0.00	4
Hemorrhage due to direct trauma	1	0.88	0.05	0	0.00	0.00	1
No data	1	0.88	0.05	0	0.00	0.00	1
Subtotal	113	100.00	5.95	28	100.00	5.60	141
Anatomical site							
Lower limbs	41	36.28	2.16	12	42.86	2.40	53
Upper limbs	28	24.78	1.47	8	28.57	1.60	36
Mucosal	27	23.89	1.42	5	17.86	1.00	32
Muscular	6	5.31	0.32	1	3.57	0.20	7
Unknown	6	5.31	0.32	0	0.00	0.00	6
Central Nervous System	2	1.77	0.11	0	0.00	0.00	2
Other	3	2.65	0.16	2	7.14	0.40	5
Subtotal	113	100.00	5.95	28	100.00	5.60	141
Patients with target joint*							
Yes	4	83.34	0.21	0	79.17	0.00	4
No	15	16.66	0.79	5	20.83	1.00	20
Subtotal	19	100.00	1.00	5	100.00	1.00	24
Hemorrhagic events that received hemostatic factor**							
Yes	101	89.38	5.32	28	100	5.60	129
No	3	2.65	0.16	0	0.0	0.00	3
No data	9	7.96	0.47	0	0.0	0.00	9
Subtotal	113	100.00	5.95	28	100.00	5.60	141

[†]Mother-Child Hospital, Institute of Social Security of the State of Mexico and Municipalities, Toluca, December 2015 to November 2017.

*Defined as the presence of a joint that bleeds at least thrice in a period of 1 to 3 months.

**Number of factor VIII administrations in the study period and in all evaluated patients. ISSEMYM (*Instituto de Seguridad Social del Estado de México y Municipios*) = Institute of Social Security of the State of Mexico and Municipalities.

HEMOSTATIC FACTOR CONSUMPTION FOR PROPHYLAXIS AND BLEEDING EVENTS

Annual cost per patient for the use of factor VIII for prophylaxis was \$ 1,141,240.9 (85.52 % of total annual cost per patient) in the group without inhibitors and \$ 1,783,375.2 (32.12 %) in the group with inhibitors. Prophylaxis annual cost, including factors VII and VIII, was \$ 36,407,522.3, with an annual cost of \$ 1,141,240.9 per patient for the group without inhibitors, in comparison with \$ 2,944,788.9 in the group with inhibitors, which represents a 2.6-fold higher cost for prophylaxis associated with the presence of inhibitors. The cost for the use of hemostatic factors for prophylaxis, detailed by patient and throughout the study period, is shown in Table 4.

Annual cost per patient for the use of factor VIII for the care of hemorrhagic events was \$ 187,851.0 (14.08 % of total annual cost per patient) in the group without inhibitors and \$ 37,422.0 (0.67 %) in the group with

inhibitors. The cost of using factor VIII for the care of hemorrhagic events, detailed by patient, as well as the cost throughout the study period and individual annual cost are shown in Table 5. Annual cost per patient for the use of Factor VII as prophylaxis was \$ 1,161,413.7 (20.92 % of total annual cost per patient) and for the care of hemorrhagic events, \$ 2,560 105.4 in the group with inhibitors (46.11 %). Factor VII was not administered to patients without inhibitors.

IN-HOSPITAL CARE

The percentages of in-hospital care events, reason for hospitalization and factor VIII requirements for each group (without and with inhibitors) are shown in Table 6.

Indirect costs

Two-hundred and sixty days lost by the cohort were quantified. Annual cost per patient for the days of work

Table 3. Resources consumed by pediatric patients with hemophilia A*

Variables	Without inhibitors (n = 19)				With inhibitors (n = 5)				Total by category (\$ MXN)
	Events (n)	Individual cost** (\$ MXN)	Total cost in the study** (\$ MXN)	Annual cost per patient (\$ MXN)	Events (n)	Individual cost** (\$ MXN)	Total cost in the study** (\$ MXN)	Annual cost per patient (\$ MXN)	
Medical appointments	147	195.7	28 767.9	757.1	28	195.7	5 479.6	548.0	34 247.5
Laboratory tests									
Blood count	3	150.0	450.0	11.8	1	150.0	150.0	15.0	600.0
Coagulation factor VIII determination	8	1 240.0	9 920.0	261.1	2	1 240.0	2 480.0	65.3	12 400.0
Coagulation times	6	309.0	1 854.0	48.8	2	309.0	618.0	16.3	2 472.0
Hepatitis B and C	1	1 341.0	1 341.0	35.3	1	1 341.0	1 341.0	35.3	2 682.0
Subtotal	18	3 040.0	13 565.0	357.0	6	3 040.0	4 589.0	131.8	18 154.0
Imaging studies									
Computed axial tomography	3	1 937.0	5 811.0	152.9	5	1 937.0	9 685.0	254.9	15 496.0
Radiograph	10	292.5	2 925.0	77.0	0	292.5	0.0	0.0	2 925.0
Magnetic resonance imaging	2	7 878.0	15 756.0	414.6	2	7 878.0	15 756.0	414.6	31 512.0
Ultrasonography	1	708.0	708.0	18.6	0	708.0	0.0	0.0	708.0
Electroencephalogram	3	751.0	2 253.0	59.3	0	751.0	0.0	0.0	2 253.0
Subtotal	19	11 566.5	27 453.0	722.4	7	11 566.5	25 441.0	669.5	52 894.0
Subtotal			83 350.9	2 193.4			40 098.6	1 055.2	123 449.5

*Cost of each event (medical appointment, laboratory test, etc.). Mother-Child Hospital, Institute of Social Security of the State of Mexico and Municipalities, Toluca, December 2015 to November 2017.

**Includes the costs of all events throughout the study period.

\$ MXN = Mexican pesos.

Table 4. Days in which factor VIII was received and units administered for prophylaxis in pediatric patients with hemophilia A (n = 24)*

Patient	Days received (n)	Average daily IU received	Total IU received during the study	Cost per unit (\$ MXN)	Cost per patient (\$ MXN)	Individual annual cost (\$ MXN)
Without inhibitors						
1	719	591.7	425 408.3	13.9	5 896 159.5	2 948 079.8
2	547	1 163.5	636 413.5	13.9	8 820 690.6	4 410 345.3
3	482	455.4	219 482.1	13.9	3 042 022.5	1 521 011.3
4	377	631.3	237 981.3	13.9	3 298 420.1	1 649 210.1
5	598	167.0	99 866.0	13.9	1 384 142.8	692 071.4
6	633	250.0	158 250.0	13.9	2 193 345.0	1 096 672.5
7	148	143.0	21 164.0	13.9	293 333.0	146 666.5
8	612	625.0	382 500.0	13.9	5 301 450.0	2 650 725.0
9	644	192.9	124 251.8	13.9	1 722 129.3	861 064.6
10	552	476.6	263 062.5	13.9	3 646 046.3	1 823 023.1
11	572	189.6	108 472.0	13.9	1 503 421.9	751 711.0
12	564	250.0	141 000.0	13.9	1 954 260.0	977 130.0
13	489	461.3	225 592.0	13.9	3 126 705.1	1 563 352.6
14	21	750.0	15 750.0	13.9	218 295.0	109 147.5
15	279	250.0	69 750.0	13.9	966 735.0	483 367.5
Subtotal	7 237	6 597.2	3 128 943.4		43 367 156.0	
With inhibitors						
1	238	600.0	142 800.0	13.9	1 979 208.0	989 604.0
2	313	1 250.0	391 250.0	13.9	5 422 725.0	2 711 362.5
3	628	690.8	433 815.8	13.9	6 012 686.8	3 006 343.4
4	429	462.6	198 455.4	13.9	2 750 591.8	1 375 295.9
5	207	581.6	120 385.3	13.9	1 668 540.1	834 270.0
Subtotal	1 815	3 585.0	1 286 706.5		17 833 751.7	

*Mother-Child Hospital, Institute of Social Security of the State of Mexico and Municipalities, Toluca, December 2015 to November 2017.

IU = international units, \$ MXN = Mexican pesos.

Table 5. Days in which factor VIII was received and administered units for the care of hemorrhagic events in pediatric patients with hemophilia A (n = 24)*

Patient	Days Received (n)	Average IU received daily	Total IU received during the study	Cost per unit (\$ MXN)	Cost per patient (\$ MXN)	Annual individual cost (\$ MXN)
Without inhibitors						
1	3	608.3	1 825.0	13.9	25 294.5	12 647.3
2	6	2 333.3	14 000.0	13.9	194 040.0	97 020.0
3	6	500.0	3 000.0	13.9	41 580.0	20 790.0
4	3	916.7	2 750.0	13.9	38 115.0	19 057.5
5	76	2 220.5	168 754.5	13.9	2 338 938.0	1 169 469.0
6	1	500.0	500.0	13.9	6 930.0	3 465.0
7	3	750.0	2 250.0	13.9	31 185.0	15 592.5
8	32	1 103.9	35 325.1	13.9	489 605.8	244 802.9
9	5	1 450.0	7 250.0	13.9	100 485.0	50 242.5
10	21	500.0	10 500.0	13.9	145 530.0	72 765.0
11	3	625.0	1 875.0	13.9	25 987.5	12 993.8
12	2	500.0	1 000.0	13.9	13 860.0	6 930.0
13	47	583.3	27 416.7	13.9	379 995.0	189 997.5
14	26	571.4	14 857.1	13.9	205 920.0	102 960.0
15	7	2 000.0	14 000.0	13.9	194 040.0	97 020.0
16	39	921.9	35 953.1	13.9	498 310.3	249 155.2
17	26	937.5	24 375.0	13.9	337 837.5	168 918.8
18	24	1 291.7	31 000.0	13.9	429 660.0	214 830.0
19	222	533.3	118 400.0	13.9	1 641 024.0	820 512.0
Subtotal	552	18 846.8	515 031.6		7 138 337.6	
With inhibitors						
1	2	750.0	1 500.0	13.9	20 790.0	10 395.0
2	2	5 000.0	10 000.0	13.9	138 600.0	69 300.0
3	31	500.0	15 500.0	13.9	214 830.0	107 415.0
Subtotal	35	6 250.0	27 000.0		374 220.0	

*Mother-Child Hospital, Institute of Social Security of the State of Mexico and Municipalities, Toluca, December 2015 to November 2017.

IU = international units, \$ MXN = Mexican pesos.

Table 6. Hospital care events in pediatric patients with hemophilia A with and without inhibitors (n = 24)*

Events	Total (n)	Without inhibitors (n = 19)		With inhibitors (n = 5)		p
		Events (n)	%**	Events (n)	%**	
Hospital care events	59	46	100.00	13	100.00	
Visit to the emergency department	49	37		12		0.043
Care at emergency room without hospitalization	33	28	75.68	5	41.67	
Care at emergency room with hospitalization	9	4	10.81	5	41.67	
Hospitalization by hematology department	7	5	13.51	2	16.67	
Reason for hospitalization						< 0.001
Prophylaxis	22	22	47.83	0	0.00	
Hemorrhage	10	1	2.17	9	69.23	
Infection	5	5	10.87	1	7.69	
Trauma	2	2	4.35	0	0.00	
Surgery	1	1	2.17	0	0.00	
Other	8	5	10.87	2	15.38	
Unknown	11	10	21.74	1	7.69	
Need for factor VIII during hospitalization						0.0148
Yes	35	30	83.33	5	41.67	
No	13	6	16.67	7	58.33	
Unknown	11	10		1		

*Mother-Child Hospital, Institute of Social Security of the State of Mexico and Municipalities, Toluca, December 2015 to November 2017.

**With regard to total events.

Table 7. Cost of the care of pediatric patients with hemophilia A*

	Total cost in the study period (\$ MXN)	Cost per patient in the study period (\$ MXN)	Annual cost (\$ MXN)	Annual cost per patient (\$ MXN)	%**
Without inhibitors (n = 19)					
Medical appointments	28 767.9	1 514.1	14 384.0	757.1	0.06
Laboratory tests	13 565.0	713.9	6 782.5	357.0	0.03
Imaging studies	27 453.0	1 444.9	13 726.5	722.4	0.05
Factor VIII					
Prophylaxis	43 367 156.0	2 282 481.9	21 683 578.0	1 141 240.9	85.52
Hemorrhagic events	7 138 337.6	375 702.0	3 569 168.8	187 851.0	14.08
Factor VII					
Prophylaxis	0.0	0.0	0.0	0.0	0.00
Hemorrhagic events	0.0	0.0	0.0	0.0	0.00
Visit to the emergency department	14 911.0	784.8	7 455.5	392.4	0.03
Hospitalization	58 936.8	3 101.9	29 468.4	1 551.0	0.12
Indirect costs	58 923.0	3 101.2	29 461.5	1 550.6	0.12
Total	50 708 050.3	2 668 844.8	25 354 025.2	1 334 422.4	100.00
With inhibitors (n = 5)					
Medical appointments	5 479.6	1 095.9	2 739.8	548.0	0.01
Laboratory tests	4 589.0	263.6	2 294.5	131.8	0.01
Imaging studies	25 441.0	1 339.0	12 720.5	669.5	0.05
Factor VIII					
Prophylaxis	17 833 751.7	3 566 750.3	8 916 875.9	1 783 375.2	32.12
Hemorrhagic events	374 220.0	74 844.0	187 110.0	37 422.0	0.67
Factor VII					
Prophylaxis	11 614 136.8	2 322 827.4	5 807 068.4	1 161 413.7	20.92
Hemorrhagic events	25 601 054.3	5 120 210.9	12 800 527.2	2 560 105.4	46.11
Visit to the emergency department	4 836.0	967.2	2 418.0	483.6	0.01
Hospitalization	42 864.1	8 572.8	21 432.0	4 286.4	0.08
Indirect costs	12 517.3	658.8	6 258.7	329.4	0.02
Total	55 518 889.9	11 097 530.0	27 759 444.9	5 548 765.0	100.00

*Mother-Child Hospital, Institute of Social Security of the State of Mexico and Municipalities, Toluca, December 2015 to November 2017.

**Annual cost percentage per patient. \$ MXN = Mexican pesos.

absenteeism in the group without inhibitors was \$ 1,550.6 (0.12 % of total annual cost per patient), in comparison with \$ 329.4 (0.02 %) in the group with inhibitors.

Total costs

Estimated total cost for the care of patients with hemophilia A during the study period was \$ 106,226,940.2, with an annual cost of \$ 53,113,470.1 for all 24 included patients, which represented a cost of \$ 13,766,374.7 per patient for the entire study period and an average annual cost per patient of \$ 6,883,187.4. Annual cost per patient in the group without inhibitors was \$ 1,334,422.4 in comparison

with \$ 5,548,765.0 in the group with inhibitors, which represents a cost 4.2 times higher in the group with inhibitors. As observed in Table 7, more than 95 % of annual cost depended on the use of coagulation factors (factors VIII and VII), mainly for prophylaxis (\$ 61,200,907.8 throughout the study period for factor VIII and \$ 11,614,136.8 for factor VII), but also for the treatment of hemorrhagic events, and it was different between both subgroups, with 99.6 % for the use of factor VIII in the subgroup without inhibitors, in comparison with 32.8 % in the group with inhibitors. However, the cost in the group with inhibitors for the use of factor VII corresponded to 67 % of annual cost per patient, while in the group without inhibitors it was not required.

Discussion

In this study, hemophilia A was found to be associated with high levels of morbidity, in addition to having an important economic impact, which increases 4.2 times in the presence of inhibitors. All potential sources of cost in hemophilia A were included and were described in detail (medical appointments, laboratory or imaging studies, care of hemorrhagic events, indirect costs, etc.) for a holistic analysis of the economic impact of hemophilia (type A, since no cases of hemophilia B were recorded) and of the presence of inhibitors in a pediatric population.

This research is a continuation of the academic work that our group has developed with regard to the costs of hemophilia in Mexico.⁹ The cost analysis showed that more than 95 % of costs depend on the use of coagulation factors, which is consistent with the findings reported by multiple international publications.⁸⁻¹⁰ It is important pointing out that most patients (> 90 %) received hemostatic factors for the treatment of the disease, and a considerable percentage of them, prophylactic treatment. This suggests that, in Mexico, in spite of economic limitations, carrying out treatment protocols similar to those recommended by the World Federation of Hemophilia and the Mexican Clinical Practice Guidelines for the Diagnosis and Treatment of Hemophilia in the Pediatric Population is being sought.^{11,12} These interventions have a substantial impact with regard to a decrease in the frequency of hemorrhagic events and in associated morbidity, as well as to long-term disability.^{13,14} This study also showed a high frequency of bleeding in the mucous membranes, which might be related to low reporting of this type of bleeding, given its low impact on patient morbidity.

Given the elevated costs of treatment with coagulation factors, indirect costs would appear to be low (0.02 % of total cost); however, this can have considerable implications for the families of affected patients. The present study explores all potential sources of costs within the process of care of patients with hemophilia based on the review of individual medical records. Other analyses have tried to recreate an outlook of the repercussions and the economic impact with more subjective quantifications (surveys to specialists),¹¹ but that contribute to a better understanding of the national impact of this disease.

This study has important limitations; for example, it corresponds to patients cared for in a single institution; notwithstanding, it provides valuable information,

given that hemophilia continues to be a rare disease, in addition to characterizing in detail 24 pediatric cases, out of which approximately 20 % developed inhibitors. The low number of cases also limited multivariate statistical approaches, which are essential for determining independent associations, and thus, clinical conclusions are still limited.

Our research shows, from the perspective of a national public institution, that the development of inhibitors in the pediatric population with hemophilia A substantially increases the costs of the disease.

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