Prophylaxis therapy with bypassing agents in patients with haemophilia A and inhibitors undergoing surgery: A cost analysis in Spain

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Abstract
Objectives: This study estimated the cost of prophylaxis with activated prothrombin complex concentrate (aPCC) and recombinant activated factor VIIa (rFVIIa) in surgical patients with haemophilia A and inhibitors in Spain.

Methods: A decision-analytic model was developed to estimate the cost to the Spanish National Health System of providing haemostatic coverage in this haemophilia population, with age distribution and average weight derived from the literature, and the annual number of surgeries (0.33 per patient) from local data. Drug costs were calculated from official ex-factory prices with a 7.5% mandatory deduction and recommended dosing regimens.

Results: The estimated average costs per patient were €10,100.73 (aPCC) and €14,265.89 (rFVIIa) for dental extraction, €24,043.88 (aPCC) and €62,301.08 (rFVIIa) for minor surgery and €126,595.81 (aPCC) and €347,731.09 (rFVIIa) for major surgery. Assuming an estimated 23 annual surgeries in this population (N = 69), distributed as 19% dental extraction, 50% minor surgery and 31% major surgery, the total annual cost of prophylaxis was €1,209,682.35 with aPCC and €3,221,929.28 with rFVIIa.

Conclusions: aPCC costs were 62.5% lower than rFVIIa. Assuming potential clinical equivalence, aPCC is a potentially cost-saving option for surgical patients with haemophilia A and inhibitors.

KEYWORDS
cogulation disorders
1 | INTRODUCTION

Haemophilia is a hereditary condition characterised by a deficiency of blood clotting factor VIII (FVIII) or factor IX (FIX). Recent prevalence estimates suggest that there are approximately 400,000 patients with haemophilia globally. These patients experience repeated bleeding episodes, especially in the joints and muscles, which are associated with long-lasting clinical consequences, including loss of joint range of motion, musculoskeletal disorders and chronic joint diseases, profoundly impacting quality of life.

The initial therapeutic approach to the management of haemophilia is primarily based on the replacement of the deficient factor. However, approximately 15%-35% of patients can develop neutralising antibodies, which complicate the management of their haemophilia; this occurs mainly in those with severe haemophilia A.

Patients with haemophilia and inhibitors experience a greater incidence of orthopaedic complications, recurrent bleeding episodes and joint pain than those without inhibitors and are more likely to develop permanent disabilities. Accordingly, haemophilia in patients who develop inhibitors is associated with greater severity, more complications and increased treatment costs.

In Spain, the average cost per bleeding episode has been estimated to be €2,998.52 in patients with haemophilia A and inhibitors, imposing a substantial economic burden on both the patient and the healthcare system. Elective surgery for orthopaedic problems is usually required in this population, and patients may also require intervention for a wide range of other general surgical and dental procedures over their lifetime. The problem most frequently encountered during surgical interventions in these patients is bleeding and the potential difficulties related to bleeding control.

Currently in Spain, there are two bypassing agents approved for the prevention of bleeding episodes in patients undergoing surgery or invasive procedures: activated prothrombin complex concentrate (aPCC; FEIBA NF®; Baxalta US Inc, a Takeda Company) and recombinant factor VIIa (rFVIIa; NovoSeven®, Novo Nordisk). The perioperative use of bypassing agents (before, during and after surgery) can successfully control haemostasis in these patients, so it is advisable to use specific prophylactic measures prior to surgery. However, there is limited information on perioperative management. Several consensus recommendations for prophylactic therapy in these patients have been reported, but a lack of evidence regarding precise doses and regimens for specific surgical procedures is apparent. In 2016, Spanish Consensus Guidelines were published on prophylactic therapy with bypassing agents in patients with haemophilia and inhibitors and provided recommendations for dosing regimens.

The main objective of the present study was to evaluate the total cost of the bypassing agents aPCC and rFVIIa as a prophylactic strategy for surgery in patients with haemophilia A and inhibitors in Spain using these recommended dosing regimens.

Plain Language Summary

What is the new aspect of your work?

• In patients with haemophilia A and inhibitors to factor VIII who were undergoing a surgical operation, we estimated the costs to the Spanish National Health System to prevent bleeding or to help stop bleeding. Bleeding was treated using either activated prothrombin complex concentrate (aPCC) or recombinant activated factor VIIa (rFVIIa).

What is the central finding of your work?

• aPCC was estimated to cost 62.5% less in a year than rFVIIa, based on how many patients with haemophilia A and inhibitors were expected to need a surgical operation and on the doses of aPCC and rFVIIa that are recommended for different types of operations.

What is (or could be) the specific clinical relevance of your work?

• Our research suggests that aPCC is a cost-saving option compared with rFVIIa to prevent or treat bleeding in people with haemophilia A and inhibitors who are undergoing surgical operations.

2 | MATERIALS AND METHODS

A decision-analytic model was developed to estimate the cost to the Spanish National Health System of providing haemostatic coverage with bypassing agents for patients with haemophilia A and inhibitors undergoing surgery. The two alternative prophylactic options considered in the analysis were aPCC and rFVIIa.

The model aimed to estimate an average cost per patient with neutralising antibodies undergoing surgery, which required defining the population profile. A hypothetical cohort of patients was used to generate the decision tree (Figure 1). On the basis of data from a local epidemiological study from a Spanish national registry, it was assumed that the haemophilia population consisted of 77.2% adults (≥14 years) and 22.8% children (<14 years). Drug consumption was calculated using the average weight of adults (72.9 kg) and children (27.6 kg), which was derived from the same haemophilia study cohort.

The time horizon comprised the duration of prophylactic regimens defined by each surgery and was restricted to one year for the population analysis. No discount rate was applied owing to the short period of time assessed. In the model, the potential surgical procedures were grouped into three categories: dental extraction, minor surgery and major surgery. The definitions of minor surgery and major surgery followed the criteria established in the Spanish
Data collected by haematology units at four referring hospitals in Spain, for patients with haemophilia A and inhibitors undergoing dental extraction, minor surgery or major surgery over 5 years, were used to estimate the proportion of surgery types and the annual number of surgeries per patient. An expert panel of three local haematologists experienced in haemophilia management validated these data as being representative of the Spanish patient population with haemophilia A and inhibitors. The distribution of surgeries was 19% for dental extraction, 50% for minor surgery and 31% for major surgery. The annual number of surgeries was 0.33 per patient. The duration of regimens considered for each of the surgeries (taking into account the surgery only and not the rehabilitation period) was 1 day for dental extraction, 4 days for minor surgery and 15 days for major surgery, in accordance with the information provided by the expert panel.

Only pharmaceutical costs pertaining to the bypassing agent were included in the model. Other healthcare costs were not included based on the assumption that these interventions would be similar between both alternatives. The pharmaceutical costs were calculated based on the ex-factory price of the two drugs assessed. Drug costs were calculated based on the typical dosages used in clinical practice by haematologists and in line with those recommended in the respective summaries of product characteristics (Tables 1 and 2).23,24 Drug prices were obtained from the catalogue of the Spanish General Council of Official Pharmaceutical Colleges,25 and the 7.5% mandatory deduction established by the Royal Decree-Law 8/2010 for Spanish National Health System reimbursed drugs was applied.26 Cost calculations considered the mean unit cost (aPCC—cost per U, and rFVIIa—cost per µg) for the available formulations of each bypassing agent. All costs included in the model were expressed in euros (€) at their value in the year 2018.
2.1 | Population analysis

A population analysis was performed to evaluate the total budget for prophylaxis with bypassing agents in patients with haemophilia A and inhibitors undergoing surgery in Spain. A total of 69 patients with haemophilia A and inhibitors were considered based on estimations derived from a local epidemiological study of this population. Considering an average of 0.33 interventions per patient-year, the annual number of surgeries was 22.74 per year.

2.2 | Sensitivity analysis

One-way sensitivity analyses were carried out to evaluate the robustness of the model and the uncertainty of outcomes of the base case. The following individual modifications were conducted: the number of annual surgeries per patient was modified in a range of ±40%.

3 | RESULTS

3.1 | Population analysis

The estimated average costs per patient were €10 100.73 (aPCC) and €14 265.89 (rFVIIa) for dental extraction, €24 043.88 (aPCC) and €62 301.08 (rFVIIa) for minor surgery and €126 595.81 (aPCC) and €347 731.09 (rFVIIa) for major surgery. Assuming an estimated 23 annual surgeries for 69 patients in Spain and the proportions of surgery types (19% dental extraction, 50% minor surgery and 31% major surgery), the total annual cost of prophylaxis was €1 209 682.35 with aPCC and €3 221 929.28 with rFVIIa.
The results of the model showed that, compared with rFVIIa, prophylactic treatment with aPCC was cost-saving for patients with haemophilia A and inhibitors undergoing surgery in Spain.

Based on our model, the estimated cost per patient for each surgery showed a difference of costs for aPCC prophylaxis therapy versus rFVIIa of €4 165.16, €38 257.20 and €221 135.28 for dental extraction, minor surgery and major surgery, respectively. This difference between alternatives (€2 012 246.93) resulted in a 62.5% lower total cost for aPCC than rFVIIa (Figure 2). Detailed results are shown in Table 3.

3.2 | Sensitivity analysis

Regarding the annual number of surgeries per patient, the one-way sensitivity analysis showed that an increase of 40% in the annual number of surgeries per patient (ie 0.46 interventions per patient-year) resulted in total annual costs of prophylaxis of €1 693 555.28 with aPCC and €4 510 700.99 with rFVIIa, whereas when the annual number of surgeries per patient was decreased by 40% (ie 0.26 interventions per patient-year), total annual costs were €725 809.41 with aPCC and €1 933 157.57 with rFVIIa.

4 | DISCUSSION

To our knowledge, this is the first study to estimate costs of prophylaxis based on expert recommendations for prophylaxis with bypassing agents in patients with haemophilia A and inhibitors undergoing surgery in Spain. The clinical benefit of following the recommendations for prophylaxis in patients with haemophilia and inhibitors undergoing surgeries is well understood.2,27,28 However, despite recent evidence reporting the efficacy of bypassing agents as prophylactic therapy,29-32 surgical procedures in patients with haemophilia and inhibitors have often been avoided owing to the greater associated risk of complications.15

A single report comparing aPCC and rFVIIa use in the treatment of joint bleeding concluded that both bypassing agents appeared to have similar efficacy33; however, we are not aware of a study that reports a direct comparison between both bypassing agents when administered prophylactically to provide haemostatic coverage in surgery. Due to the lack of direct comparisons between the assessed strategies, the present study was designed to follow a conservative approach, in the form of a cost analysis. The available evidence does suggest that both alternatives could be selected for the achievement of maximum clinical benefit in the targeted population, given similar prophylactic efficacy in patients with haemophilia and inhibitors undergoing surgical procedures.14,17,18,34-37 However, in real-world clinical practice, other factors such as frequency of dosing and resultant nursing requirements, as well as a patient’s preferential response to one of the bypassing agents, may influence treatment selection.

The results of this analysis showed that aPCC is cost-saving compared with rFVIIa in providing haemostatic coverage for patients with haemophilia A and inhibitors undergoing surgery and is consistent with a previous cost comparison study.38 The observed cost savings derived from aPCC use could potentially enable more surgeries to be performed in patients with haemophilia A and inhibitors, without increasing resource use in the healthcare system.38 Our findings may contribute to more efficient allocation of limited resources and facilitate increased sustainability of the Spanish healthcare system.

Several limitations should be considered when interpreting these findings. The main limitation is the absence of specific dosages for prophylaxis with bypassing agents, due to the range of possible dosages stated in the guidelines. An expert panel was consulted to determine appropriate dosages, and the data applied to the cost analysis were considered reliable and representative of the treatment used in the Spanish population. Expert consensus can be used as a validated approach, especially in rare diseases, such as haemophilia, where sufficient data are lacking.39 Other limitations concern the annual number of surgeries per patient and distribution of each type of surgery, which were derived from four local hospitals. Although these hospitals are reference centres for haemophilia management and cover a substantial number of patients with haemophilia in Spain, some bias could be inadvertently introduced when assuming that they represent the entire Spanish population. To address the potential uncertainty surrounding these data, a sensitivity analysis was carried out for the population analysis by increasing and decreasing the annual number of surgeries per patient. The results of the sensitivity analyses were robust and showed that aPCC remained a cost-saving option versus rFVIIa, with a 40% increase or decrease in the number of annual surgeries per patient.

It should also be acknowledged that the estimated costs and estimated level of cost savings between aPCC and rFVIIa cannot be extrapolated to other countries due to the high inter-country variability in the costs of these pharmaceutical agents. In addition, the future regulatory approval and use of treatments for patients with haemophilia and inhibitors such as replacement therapy with antihaemophilic factor VIII (recombinant) and porcine sequence (suctocog alfa, OBI-1, BAX 801, OBIZUR®; Baxalta US Inc, a Takeda Company) will affect the outcomes of pharmacoeconomic modelling studies of inhibitor bypass therapy.

Finally, only pharmaceutical costs associated with prophylaxis with bypassing agents were considered. The cost of antifibrinolytic agents, adjunct therapies commonly used with rFVIIa and aPPC,40 were not included in the model. The effect on the estimates of adding these costs into the model would have been minor given the relatively low price of antifibrinolytic agents. Additional direct healthcare costs, including visits and diagnostic tests, hospitalisations and rehabilitation care, as well as indirect costs, were not considered in our study. This approach was based on the assumption that similar interventions could be anticipated for both assessed alternatives, and so, no relevant differences are expected. However, it is possible that indirect costs could be considerably higher with rFVIIa than with aPCC due to the frequency of administration23 and potential requirement for related enhanced nursing support or care in a critical care unit. Inclusion of these costs...
would be expected to widen the disparity in costs between the two agents assessed.

5 | CONCLUSIONS

Based on this analysis using Spanish reference data, prophylactic therapy with aPCC was associated with a 62.5% lower cost than rFVIIa. Assuming potential clinical equivalence in providing haemostatic coverage in surgery, aPCC may be a cost-saving treatment option for prophylaxis in patients with haemophilia A and inhibitors undergoing surgery in Spain.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

María Mareque and Itziar Oyagüez designed the study, analysed and interpreted the data, and prepared the manuscript. María Eva Mingot Castellano, María Fernanda López-Fernández and María Teresa Álvarez-Román designed the study, validated the data utilised in cost analysis model, interpreted the study findings and prepared the manuscript. All authors reviewed the manuscript drafts, revised it critically for important intellectual content, approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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