Cost and outcome: Comparisons of two alternative bypassing agents for persons with haemophilia A complicated by an inhibitor

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Summary

The development of inhibitory antibodies to factor VIII is a serious complication of haemophilia. Two haemostatic agents with different bypassing mechanisms have been used in the treatment of patients with inhibitors: activated prothrombin complex concentrate (aPCC) and recombinant factor VIIa (rFVIIa). The objective was to compare cost and outcome of aPCC and rFVIIa in the treatment of joint bleeds. The analyses were based on the FENOC (FEIBA NovoSeven Comparative Study) crossover study where 48 patients used aPCC and rFVIIa to treat two joint bleeds. Incremental cost-effectiveness ratios were calculated for three outcome measures and the variation in cost was analyzed using two alternative regression methods. Results were subjected to sensitivity analyses. Key determinants of cost were prescribed dose, bodyweight and treatment in addition to protocol. The cost of aPCC was on average lower than rFVIIa. At all but one time point, patients rated slightly higher (but not statistically significantly) percentages of treatment efficacy and stopping of the bleed by aPCC. The reported reduction in pain from start of treatment up to 48 hours varied considerably among individuals. The different relative prices in the US, Turkey and Sweden mattered, but did not reverse the main results. In conclusion, the cost per episode was significantly lower for aPCC. The large individual-level variation in reduction of pain supports decisions that consider the individual patient's experience and that accept trade-offs between cost and reduction in pain rather than focusing on cost only.

Keywords

Haemophilia A/B, factor VIII inhibitors, costs and cost analysis, bypassing agents, incremental cost-effectiveness

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Introduction

There are two alternative bypassing agents available today for the treatment of persons with haemophilia A and inhibitory antibodies to factor VIII; FEIBA (factor VIII inhibitor bypassing activity) (Baxter AG, Vienna, Austria), an activated prothrombin complex concentrate, aPCC (1); and NovoSeven (Novo Nordisk A/S, Bagsvaerd, Denmark), which consists of recombinant factor VIIa, rFVIIa (2). The two bypassing agents achieve haemostasis through different mechanisms, bypassing the factor VIII-dependent step in the coagulation cascade and promoting haemostasis by enhancing thrombin generation.

Where alternative treatment strategies exist, as in the case for persons with severe haemophilia A with inhibitors, health-economic analyses serve as a useful tool to provide input to medical decision-making. A health-economic evaluation compares costs and outcomes of alternative treatment strategies and the decision recommendation weighs the difference in cost against the difference in effects and benefits. Depending on the purpose of the evaluation and the data availability, alternative evaluation methods are applicable (3). An example of the importance of health-economic considerations along with evidence on efficacy can be found in a recent paper in this journal reviewing stroke and thromboembolism in atrial fibrillation (4).

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Regarding the two bypassing agents, FEIBA has been used in the treatment of inhibitors for more than 30 years (5, 6), and NovoSeven became available in Europe in 1996 (7). To date, most clinical research consists of case studies that establish the efficacy of either bypassing agent with no aim of actually comparing the two alternatives, see e.g. (8). Combining results from different studies, decision-analytic modelling has been used to calculate the expected cost and outcome of treatment with the products. Three recent publications (9–11) have modelled treatment with bypassing agents during one bleeding episode, but the conclusions were ambiguous.

The FEIBA-NovoSeven Comparative study (FENOC) was designed to examine the equivalence of FEIBA and NovoSeven in the treatment of joint bleeding in congenital haemophilia complicated by inhibitors. The results from the equivalence study (12) indicated that the two products exhibit a similar effect on joint bleeds, but that there is also a substantial proportion of persons who rated the efficacy of the two products differently.

In this paper we report the results from two health-economic analyses of the FENOC data. First, we explore factors associated with the individual-level variation in cost per episode. Secondly, we report the results from cost-effectiveness analyses where we have compared the incremental cost to the incremental effect measured by patient-rated efficacy, whether the bleed had stopped and the reduction in pain from baseline up to 48 hours (h) later. Both the cost and cost-effectiveness analyses were subjected to sensitivity analyses including a comparison of results based on US price level to those based on price levels in Sweden and Turkey, respectively.

Materials and methods

Study design and population

FENOC used a prospective, open-label, randomized, crossover, clinical equivalence study design. Each participant was treated with one dose of FEIBA (75–100 U/kg body weight; target dose 85 U/kg) and two doses of NovoSeven (90–120 μg/kg body weight; target dose 105 μg/kg x 2), administered intravenously in a randomized fashion, with crossover between options for the following bleeding episode. Dosing was based on recommendations from the manufacturers and previous clinical studies (13–15) .

Patients aged 2 years or older with congenital haemophilia A, an inhibitor and the need for bypassing agents in the treatment of joint bleeding were eligible to participate. The intent-to-treat analysis included 48 persons and 96 bleeding episodes. The institutional review boards of collaborating institutions approved the FENOC study; informed consent was obtained from all participants in accordance with the Declaration of Helsinki. Further details can be found in (12) .

Data

We have used the total consumption of bypassing agents during the two treatment episodes and the use of concomitant medication and analgesics to compute the treatment cost per episode. Two binary outcome measures were used: patient-rated efficacy (treatment effective/all other ratings); and bleeding stopped (yes/no) measured at 2, 6, 12, 24, 36 and 48 h after the initial infusion (baseline); and one continuous measure of reduction in pain from initial infusion up to 48 h after, measured on visual analogue scales (VAS) ranging from 0 (no pain) to 100 (maximum pain). For the cost analysis we used individual characteristics (age, bodyweight, number of previous bleeds in the treated joint and change in inhibitor titre during the study period) and treatment characteristics (dose and whether treatment was according to protocol).

The time horizon was that of one joint bleed and no attempt was made to impute life-long consequences of the choice of bypassing agent for treatment of the single bleeds.

Prices

The price of pharmaceuticals varies among countries. To investigate the impact of the level of price and of the relative difference between the prices of the two products on cost and cost-effectiveness estimates, we have worked with three sets of prices from official sources (Table 1). The main price used in the calculations was the year 2005 US Red Book (16). For comparison, we used the national prices from Sweden (17) and Turkey (18) in sensitivity analyses. These comparators were chosen as both the level and the relative price differed between Sweden and the US Red Book, and as the Ministry of Health of Turkey has set a price ceiling which corresponds to half the level of the Red Book prices for the two bypassing agents. Moreover, reporting results on different sets of prices also provides a wider reference frame for clinicians and other readers in different countries. Throughout the paper we report costs and prices in American dollars (USD) using the exchange rates of the relevant year.

A priori, we assumed that the cost of concomitant medication and analgesics would make only a marginal contribution to the total cost per episode. For completeness, these costs were calculated using US and Swedish prices.

Evaluation methods

Cost analysis

We analyzed the patient-level variation in cost of resource use using linear regression analysis (19; Chapter 11) with robust standard errors. The cost equation

$$\text{Cost}_{\text{Product j}} = \text{f(individual characteristics, treatment characteristics)} \quad (1)$$

was estimated separately for each product. The variables in the equations were individual characteristics: age, bodyweight, pre-

Table 1: Prices. Three sets of prices used to calculate cost per episode.

	FEIBA (USD per U)	**NovoSeven** (USD per microgram)
USA*	1.68	1.48
Sweden†	1.09	0.75
Turkey‡	0.84	0.75

* US Red Book Average Wholesale Price 2005. † Pharmaceutical Benefits Board year 2006 (average exchange rate Jan-March 2006; 100 SEK = 12.86 USD; www.riksbank.se). ‡ Ministry of Health of Turkey year 2005 (exchange rate Dec 2005 100 TRY = 74.21 USD; www.tcmb.gov.tr/yeni/eng/).

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vious bleeds in the treated joint and change in inhibitor titre during the study period; and treatment characteristics: dose and whether treatment was according to protocol. In addition, we explored using the method of seemingly unrelated regressions (20; Chapter 15), which increases the statistical efficiency if there is a correlation at the individual patient level in episode costs that was not explained by the individual and treatment characteristics of our model. In general, the coefficients estimated by the regression analysis are the marginal effects of the variables in the model on the cost per episode, holding all other factors constant.

Cost-effectiveness analysis

We compared the difference in costs to the difference in effects for the two bypassing agents calculating the *I*ncremental *C*ost-*E*ffectiveness *R*atio, the ICER, using the formula

$$ICER = \frac{\left(\sum_i \left(Cost_{FEIBA} - Cost_{NovoSeven}\right)\right)/N}{\left(\sum_i \left(Effect_{FEIBA} - Effect_{NovoSeven}\right)\right)/N} \quad (2)$$

which is the average difference in cost of treatment of FEIBA and NovoSeven compared to the average difference in effect (21). ICERs were calculated for each point in time of measurement in the FENOC study (2, 6, 12, 24, 36 and 48 h) where cost up to each point in time was calculated and compared to the patient's assessment of the effect.

We report the average ICER along with the bias corrected 95% confidence intervals (CI) obtained by bootstrapping with 10,000 repetitions for three different definitions of effect based on patient assessments (22). Two of the measures were binary (patient considered treatment effective and that the bleeding had stopped) and one was continuous (reduction in pain from baseline, prior to first infusion of bypassing agent, up to 48 h later). For the binary measures of effect, the denominator of the ICER [Equation (2)] was equivalent to the difference in the proportion of patients who considered treatment effective/reported that the bleed had stopped. The third measure of effect, reduction in pain, was a continuous variable and calculated as the difference between the amount of pain rated at baseline and at later measurement time points. Given the continuous nature of both the cost and pain reduction, the dispersion of the individual-level ICERs could also be meaningfully illustrated in a four-quadrant diagram of incremental cost against incremental effects.

The magnitude of the ICER depends on the size of the differences, where for instance a smaller average difference in effect generates a greater ICER at a given cost difference. The sign of the ICER depends on the signs of the numerator and denominator in Equation (2). The ICER would be positive if one of the products cost more and had better effect, since both numerator and denominator would have the same sign. A negative ICER would arise if one of the products had lower average cost and on average higher effect. The less costly and more effective strategy is then in the terminology of economic evaluations defined as a *dominant strategy*.

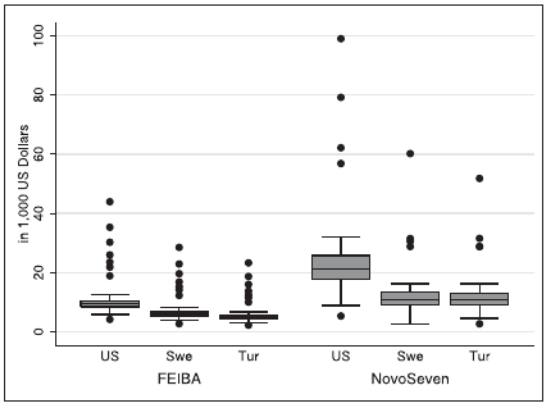

Figure 1: Cost per treatment episode. Boxplot of cost per episode using US, Swedish and Turkish prices of FEIBA and NovoSeven.

Sensitivity analyses

Prices

To explore the sensitivity of results we compared three price vectors for calculating cost: from the US, Sweden and Turkey. The US price source was the Red Book for the year 2005 (16). It is an average wholesale price reported by the manufacturer and does not necessarily reflect what a specific treatment center pays after possible discounts. The Swedish prices were negotiated national prices and equal for all treatment centres in the country (17) . The Turkish prices were also equal for all treatment centres and based on the lowest official price in the five European reference countries selected by the Turkish Ministry of Health (France, Greece, Italy, Portugal, Spain) (18) . These price sources were selected as they were uniform for the country in question; they provided a relevant basis for the sensitivity analyses of the results both in terms of the level of price and the relative price difference; and all three countries were represented in the FENOC study.

Study design

The FENOC study protocol followed the recommendations of manufacturers and of the previous literature regarding the dose and administration of the two bypassing agents. By study design, the 2-h outcome measures were reported prior to administration of the second infusion of NovoSeven. For the sensitivity analyses, we examined the pattern of change in reported pain for the two bypassing agents from baseline up to 6 h using non-parametric Wilcoxon and Mann-Whitney tests (19).

In the analysis of the patterns of pain reduction, we were looking for individual-level, pair wise comparisons of reduction in pain that indicated a marked shift in the pain reduction between 2 and 6 h during the NovoSeven episodes. Such a shift would suggest that the patient experienced important additional pain relief due to the second infusion. In such cases, the 2-h comparison would not be relevant in the analysis. Conversely, in the absence of a marked shift, we would present the comparisons at the 2-h measurement point keeping in mind that we were comparing outcome after administration of one-half of the NovoSeven treatment with per protocol treatment of FEIBA. This sensitivity analysis was of particular importance as the incremental cost-effectiveness ratio at the FENOC 2-h measurement point il-

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lustrated the impact of essentially halving the cost of NovoSeven (one infusion instead of two) compared to the cost of per protocol treatment with FEIBA.

Results

Cost analysis

Figure 1 illustrates the dispersion of cost per episode. The total cost includes bypassing agent, concomitant medication and analgesics where the latter two constituted 0.4 (0.1) percent of total cost during the FEIBA (NovoSeven) episode. The median (interquartile range, IQR) cost per episode in US Dollars of FEIBA was 9,603 (8,400–10,420) using US prices; 6,230 (5,450–6,761) using Swedish prices and 4,940 (4,450–5,518) using Turkish prices. The median (IQR) cost per episode in US Dollars of NovoSeven was 21,312 (17,760–25,760) using US prices; 9,000 (10,800–13,500) using Swedish prices; and 10,814 (9,012–13,067) using Turkish prices. The mean cost per episode was not equal by the paired t-test ($p<0.0001$) by the three price vectors.

Figure 2 illustrates the results of the regression analysis of the cost per episode where we have plotted actual and predicted cost per episode against age. The predicted cost of FEIBA (dashed line) is always below the cost of NovoSeven (solid line). Increasing age for children had a significant impact on cost. For example, the increase in age from 10 to 11 years old (10%) would be associated with a 13% (10%) increase in cost, all else equal, for the FEIBA (NovoSeven) episode. For adults, the age effect was only significant at conventional levels for the FEIBA episode. Increasing age from 20 to 30 years old (50%) would be associated with an increase in cost of 6%. Looking carefully, the dashed line slopes slightly upward after age 20.

While most of the observations on actual cost (symbols Δ for FEIBA and ❍ for NovoSeven) lie close to the cost predicted by the regression model (at average values of the variables), we also find a number of divergent observations. The linear regression analysis showed that four factors, in addition to age, explained the variation in cost.

First, persons who diverged from protocol as compared to those treated per protocol had 91% (57%) higher cost when treated with FEIBA (NovoSeven), all else equal. Second, increasing the dose per kg by 10% would increase cost per episode of FEIBA (NovoSeven) by 5% (9%), all else equal.

Third, while age-related differences in weight were captured by the age variables, the regression model also accounted for residual weight, which measured the impact of weighing more (or less) than the average person of the same age. For both bypassing agents, we found a significant and positive effect on cost: an increase in body weight of 10 kg would increase the cost per episode of FEIBA (NovoSeven) by 14% (19%), all else equal.

Fourth, changing levels of inhibitors over time had a small and significant association with the cost of the NovoSeven episode. The FENOC study measured inhibitor titres at enrolment and after the second event. Initial analysis of the data showed a negative and significant correlation between the logarithm of dose per kg and the logarithm of the level of inhibitors at enrolment for both bypassing agents [FEIBA –0.45 ($p<0.04$) and NovoSeven –0.41 ($p<0.04$)]. The association between dose per kg

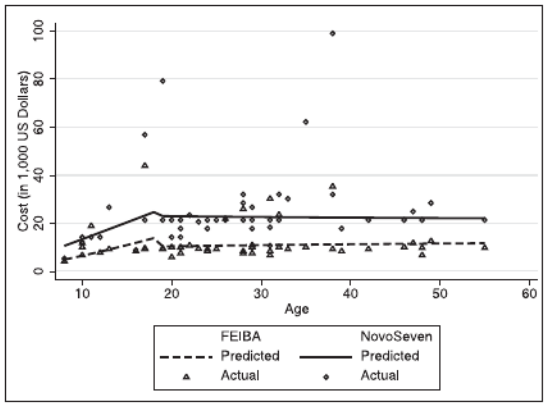

Figure 2: Cost per treatment episode plotted against age of patient. Lines show the cost predicted by the separate regression equations estimated for NovoSeven (solid) and FEIBA (dashed). The symbols Δ show actual observations for FEIBA and symbols ❍ show actual observations for NovoSeven.

and the level of inhibitor after the second event was not significant. To our knowledge, there is no evidence in the literature that the level of inhibitors would be associated with the effectiveness of either bypassing agent. Thus, the finding that an increase in the level of inhibitors of 10 units in the interval from enrolment to post second event, was associated with an increase in cost of 0.5%, could be either a spurious finding, or due to an unmeasured third factor. To further address whether this result was an artefact of sample size and number of observations per individual, longitudinal studies following individuals over time and several bleeding events are needed. Table 2 shows the detailed regression results of episode cost by FEIBA column [1] and NovoSeven column [2].

We also estimated the two cost equations jointly in order to capture the bivariate structure of data where we had two bleeding events for each individual, hence allowing the statistical model to handle unobserved individual heterogeneity using the seemingly unrelated regressions. However, the Breusch-Pagan test of independence of the two models did not indicate a bivariate structure of the data ($Chi^2 = 0.382$; $p=0.54$); that is, there was no systematic pattern at the individual level of the unexplained variation in cost for the FEIBA and NovoSeven episodes.

Cost-effectiveness analysis

Table 3 presents the incremental cost-effectiveness ratio (ICER) at FENOC assessment time points for each of the three outcome measures, columns [1]-[3]. In each column, we report the ICER based on both the US and Swedish prices. In columns [1] and [2], the ICER is predominantly negative as a consequence of FEIBA on average costing less and having slightly better average effect. The sign on the ICERs in column [3] are mixed as the average reduction in pain was initially greater during FEIBA episodes, but, at 12 h after first infusion and afterwards, it was greater during NovoSeven episodes, thus yielding positive ICERs.

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Table 2: Cost analysis. Results from linear regression analysis of factors associated with the variation in cost† per episode (based on US Red Book AWP) for FEIBA and NovoSeven, respectively. Coefficients measure the marginal effect of individual and treatment characteristics on the episode cost.

	FEIBA	NovoSeven
	Coefficient	Coefficient
Prescribed dose per kg body weight†	0.5813*	0.8933***
Age†	0.1126*	–0.0382
Child ‡	–3.1090***	–3.0581***
Interaction age† and child‡	1.1776***	1.0813***
Residual weight§	0.0140***	0.0191***
Diverge from protocol	0.9117***	0.5886***
Four or more previous bleeds in joint	–0.0524	0.1063
For event 2: Difference in level of inhibitor enrolment – after second event¶	–0.0001	–0.0005***
Constant	6.2187***	5.2258***
N	46	46
R-squared	0.9313	0.9049
Ramsey reset test where H0=no omitted variables (p-value)	0.60 (0.622)	1.23 (0.312)

*P<0.05, **P<0.01, ***P<0.001; † Natural logarithm of variable; ‡ Categorical variable = 1 if patient younger than 19 at enrolment, else=0; § residuals from a regression of weight on age; ¶ Else=0.

The same proportion of patients reported both bypassing agents effective (column [1]) at 2 h; hence it suffices to consider cost. Further analysis of the 2-h measurement point is found below under *Sensitivity analysis*. The 95% bias corrected CIs of the ICERs were wide, a fact partly explained by the relatively small sample size (N=48). In 11/34 cases in Table 3, the limits of the confidence intervals were negative.

Figure 3 illustrates the last row in column [3] of Table 3; the difference in reduction in pain at 48 h compared to the difference in cost up to 48 h. It is a four-quadrant diagram where observations above the horizontal axis (quadrants A and B) had higher cost when treated with FEIBA than when treated with NovoSeven, and vice versa for observations below. To the left of the vertical axis (quadrants A and D) lie observations representing reports of greater pain reduction when treated with NovoSeven than when treated with FEIBA, and vice versa for observations to the right.

The observations lie mainly in quadrants C and D, illustrating that FEIBA was less costly for the majority of treatment episodes (45/48). However, the individuals were fairly evenly distributed across quadrant C and D. Twenty-five patients reported greater pain reduction with NovoSeven and 16 patients reported greater pain reduction with FEIBA. This dispersion was similar at 2 and 6 h (illustrations are available on request).

Sensitivity analysis

Price

As shown also in Figure 1, the level of the price had significant effects on overall cost per episode. While single treatment centres must take (national) prices in the specific country and year as given, the results in Figure 1 provide input to the price setting process in the long-run perspective. Here, we have focused on the total cost of bypassing agents and concomitant medication, rather than accounting for the many different cost-sharing solutions between entities that may apply in across countries.

The impact of different prices on the cost may be illustrated with relative prices. The ratio of the cost of the mean prescribed dose per kg per infusion [FEIBA (84 U)/NovoSeven (107 μg)] by the US Red Book, the Swedish and the Turkish prices were 0.89,

Table 3: Incremental cost-effectiveness ratio (ICER). ICERs by three outcome measures: patient reported [1] treatment effective; [2] bleeding had stopped and [3] reduction in pain from baseline; at the FENOC assessment time points 2–48 hours after first infusion. The ICER compares the average difference in cost to the average difference in effects between FEIBA and NovoSeven. A positive ICER indicates that the product with the best average effect also cost more. A negative ICER indicates that the product with the best average effect cost less. Bias corrected confidence intervals are in parentheses.

Hours	[1] Treatment effective		[2] Bleeding stopped		[3] Reduction in pain	
Price	US Red Book	Swedish	US Red Book	Swedish	US Red Book	Swedish
2	Cost of FEIBA lower*	Cost of Novo-Seven lower*	–81 (–1,011 - 152)	52 (–81 - 761)	–721 (–124,773 - –203)	464 (135 - 82,725)
6	–3,675 (–143,000 - –1,345)	–1,459 (–62,641 - –553)	–1245 (–30,802 - 2,040)	–494 (–11,089 - 741)	–7,301 (–1,273,168 - –2,119)	–2,899 (–468,713 - –914)
12	–1,573 (–120,000 - –323)	–610 (–44,540 - –170)	–2,736 (–111,000 - –869)	–1,060 (–33,931 - –322)	17,991 (7,731 - 25,400,000)	6,974 (3,139 - 1,822,800)
24	–977 (–29,158 - 1,495)	–357 (–8,073 - 592)	–1,606 (–56,869 - 2,667)	–587 (–21,393 - 843)	116,652 (285,097 - 23,000,000)	42,616 (89,220 - 3,786,711)
36	–1,421 (–97,742 - 770)	–549 (–33,961 - 234)	–1,756 (–56,179 - 4,457)	–678 (–25,590 - 1,600)	3,715 (–1,546 - 516,055)	1,435 (–704 - 166,534)
48	–1,359 (–53,959 - 1,015)	–491 (–20,389 - 349)	–4,900 (–294,000 - –1,494)	–1,769 (–119,000 - –536)	6,405 (1,726 - 2,617,923)	2,312 (607 - 1,537,265)

*The same proportion of patients reported FEIBA and NovoSeven effective at 2 hours, hence the ICER denominator was 0.

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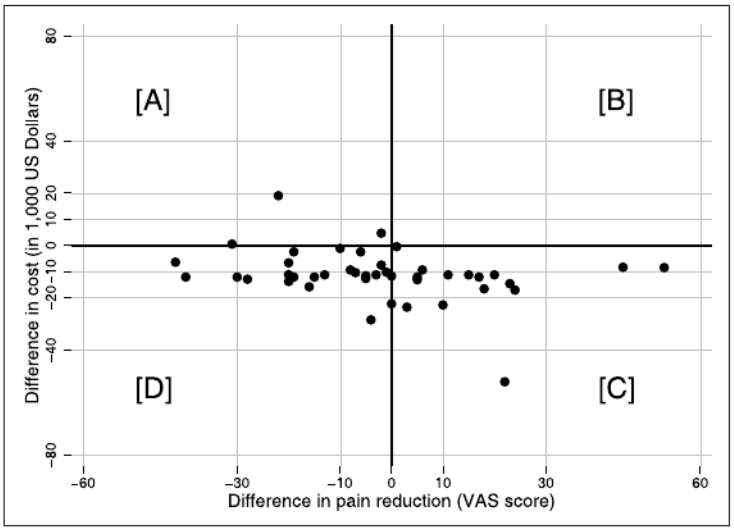

Figure 3: Difference in reduction in pain from baseline to 48 hours later against the difference in cost. Differences defined as FEIBA–NovoSeven. Observations in quadrants A-D have the following characteristics (clockwise): [A] Higher cost and lower effect when treated with FEIBA; [B] higher cost and higher effect when treated with FEIBA; [C] lower cost and higher effect when treated with FEIBA; [D] lower cost and lower effect when treated with FEIBA.

1.14 and 0.88. In other words, cost of the mean dose per kg of FEIBA was 89% of that of the mean dose of NovoSeven by the US Red Book prices, while the same cost in Sweden was 114% and in Turkey 88%.

The difference in relative prices between the US and Sweden, essentially reducing the cost difference found at the US price level, was sufficient to flip the sign of the ICERs in only one case: 2 h after the first infusion (Table 3). By US prices, the average cost in USD up to 2 h was 8,939 (10,043) for FEIBA (NovoSeven); by Swedish prices 5,800 (5,090) and by Turkish prices 4,469 (5,089). As FEIBA was on average more costly at the Swedish price level, the ICER was positive implying that the slightly higher proportion of patients reporting that the bleeding had stopped at 2 h or the slightly bigger average reduction in pain at 2 h came at a price. As similar changes in the sign of the ICER were not seen at later measurement points, the difference in relative prices did not change the main conclusions on cost efficiency from the FENOC study.

Study design

The pattern of pain reduction between assessment time points did not differ between the two products; the null hypothesis of no difference could not be rejected by the Wilcoxon and Mann-Whitney non-parametric tests. Thus, measuring outcome prior to the second infusion does not seem to have been a disadvantage to NovoSeven.

Discussion

The FENOC study was the first head-to-head randomized investigation designed to evaluate and compare two alternative bypassing agents in the treatment of haemophilia with inhibitors. Based on the FENOC clinical data and price vectors from three countries (the US, Sweden and Turkey) we have addressed two health-economic questions: 1) What individual and treatment characteristics were associated with variation in cost per episode in FENOC?; and 2) How did the two bypassing agents compare in a cost-efficiency analysis where we used three alternative measures of patient-assessed outcome? Here we discuss the results on the cost-efficiency first.

Overall, we found that the average cost per treatment episode was significantly lower for FEIBA, but 3/48 patients had lower cost for the NovoSeven episode. For the two binary patient assessments "patient considered treatment effective" and "bleeding stopped", the lower average cost per episode for FEIBA together with the slightly higher percentage efficacy yielded negative ICERs.

The main finding in the clinical study based on FENOC data (12), where the criteria for clinical equivalence was defined according to a modified version of the McNemar test (23), was that the criterion for declaring the two products equivalent was infrequently met, probably related to a lack of statistical power. The ICER on the other hand is based upon sample averages and we obtained confidence intervals by bootstrapping. We found that the ICERs relating the average difference in cost to the average difference in outcome were negative in 24/34 cases (Table 3). The 95% CIs were wide and included zero in 23/34 cases, which may in part be explained by the relatively small sample, and thus the potential influence of the estimates from single individuals.

The third outcome measure was the reduction in pain from baseline to the study assessment points. Whereas the difference in pain reduction between the two products tended to be small for many patients, shown by a clustering close to the vertical axis in Figure 3, one third did experience differences in pain reduction exceeding 20 VAS units. The variation was also evident from the calculated ICERs in column (3), Table 3, where only 3/12 cells provided a negative ICER with a negative confidence interval. The positive ICERs were a result of on average slightly greater

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reported pain reduction by NovoSeven. For instance, at 48 h, the ICER was 6,405, which means that the extra cost per one VAS unit greater pain reduction by NovoSeven was 6,405 USD.

At 48 h after first infusion, 18 patients reported pain exceeding 10 units on the VAS scale (6 in both episodes, 8 only when treated with FEIBA and 4 only when treated with NovoSeven). The reason for the discordance in the latter two cases is not fully understood (1, 2, 12) and we cannot from these data rule out that it is a matter of chance. However, one hypothesis is that there is a genuine difference between individuals in response to the products; a hypothesis that could be investigated with several observations per individual on each bypassing agent.

The health-economic regression analysis on the cost data revealed an interesting relationship between cost per episode and the patients' body weight. Relatively heavier persons consumed more of both products. For example, 10 kg higher body weight was associated with 14% (19%) higher episode cost for FEIBA (NovoSeven). Further exploring the data, we found a significant positive correlation between (residual) bodyweight and total number of infusions during the FEIBA episode for adults ($p<0.05$). For NovoSeven, this correlation was positive and significant for children and adolescents ($p<0.05$). Hence it appears that the higher costs were due both to a greater number of units used because of bigger body size, and to extra infusions. A candidate for future research would then be a further individualized treatment, for instance increasing the span of the dose per kg body weight.

For obvious reasons, the price paid for the products did affect the cost per treatment episode. Firstly, the size of differences in cost per episode depended on the price of each of the products. The results reported in Table 3 show that the level of the ICER was affected by the difference in relative price between the US and Sweden. The relative cost advantage of FEIBA was reduced by a factor 2.5–2.8 when applying Swedish prices rather than the US Red Book prices for the 15/17 pairs of ICERs of US and Swedish prices where the sign did not change. Secondly, differences in the relative-price, if sufficiently great, may flip the sign of the ICER when the difference in consumption of, in this case units of FEIBA and micrograms of NovoSeven, is close enough to start with. Here the sign of the ICER flipped in 2/17 pairs, at 2 h after first infusion and before the second infusion of NovoSeven. In addition, at 2 h the two bypassing agents had the same proportion of patients who rated them effective, and in this case comparing cost would be sufficient. As FEIBA was less costly by the US price and NovoSeven by the Swedish price, the result was in line with the flipping sign of the ICER by the two alternative outcome measures at 2 h.

Throughout the analyses we have referred to the US Red Book average wholesale prices, knowing that prices of products actually paid by centers, insurers and patients in the US are much more heterogeneous. Presenting the actual national prices from Sweden and Turkey then offer relevant points of reference. In an experiment of thought, treating a patient with the median FENOC consumption of the two products and assuming that the price of FEIBA was actually USD 1.68 per unit as in the Red Book, equality of cost per episode would be reached at a price of USD 0.67 per µg of NovoSeven, a price slightly below the Swedish and Turkish levels. Hence, US clinicians mindful of cost-effectiveness need not only consider inter-individual variation in dosage and efficacy, but also the inter-individual variation in prices of the two products and the difference in the relative price and costs of treatment. The results on different relative prices presented in this article will hopefully provide some guidance.

Besides the difference in cost, the incremental cost-effectiveness depends on the difference in efficacy. The reported efficacy of bypassing therapies varies substantially. The efficacy rate found for FEIBA in the FENOC study concords e.g. with figures reported by Hilgartner et al. (24) (88%) and by Negrier et al. (25) (81%). It is true that lower efficacy rates have been reported for FEIBA than seen in FENOC (6) but that is also the case for recombinant factor VIIa (26).

Finally, the results from the health-economic analyses of FENOC data reveal the need for further research into factors explaining the individual-level variation in outcome measures including pain and the patients' quality of life. A future study, following individuals longitudinally over several bleeding episodes treated with either product would shed further light on factors associated with variation at the individual level in the FENOC study. In the meantime, the results here support clinical decisions that take the individual patient's experiences into account, and decisions that make trade-offs between cost and reduction in pain.

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