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Haemophilia

A survey of the outcome of prophylaxis, on-demand or combined treatment in 20–35 year old men with severe haemophilia in four European countries

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For children with severe haemophilia, prophylaxis is recognized as the optimum standard of care [1] [2]. It is also one of the principles of Haemophilia care espoused by the European Association for Haemophilia and Allied Disorders (EAHAD) [3]. However, the continuation of prophylactic therapy into adulthood is being more closely scrutinized on the grounds of benefit and cost. This study was carried out to examine the long-term effects of prophylaxis and the continuing benefit of the therapy in adulthood. National Haemophilia patient organizations in Ireland, UK, France and Sweden were asked to participate by randomly selecting 20 severe haemophilia patients between 20 and 35 years from their database. Of the total of 80 questionnaires, 58 (72.5%) responses were received either by mail or by phone interview. Ireland provided 19, UK provided nine, France provided 10 and Sweden provided 20 responses. The four countries were chosen based on their access to treatment for patients with severe haemophilia. Swedish patients with severe haemophilia have been treated with prophylaxis since the late 1970s. Ireland, France and the UK introduced prophylaxis in the mid 1990s. The study examined the differences in medical outcomes and quality-of-life in patients who had full access to primary prophylaxis, entirely on-demand or combinations of therapies. Information on age, country and employment status and responses to an EQ5D questionnaire were collected. Medical data was also collected on type and severity of haemophilia, treatment regime (prophylaxis vs. on-demand), bleeds per year, target joints, major bleeds (e.g. ilio-psoas or intercranial) and days missed from work/college per year. The primary analysis evaluated the differences between the four countries, and the secondary analysis examined the differences as a proportion of life spent on prophylaxis in comparison to on-demand therapy. The mean age was 27.5 ± 4.7 years. In the primary analysis of the individual countries (Table 1a), patients in Sweden have spent a significantly higher percentage of their life on prophylaxis ($P \leq 0.05$), showed the lowest number of bleeds/year, lowest presence of target joints ($P \leq 0.001$) and major bleeds ($P \leq 0.005$), lowest number of days missed from work/college, higher scores in Mobility (EQ5D) ($P \leq 0.05$) and highest utility value. The secondary analysis (Table 1b) confirmed these findings. Patients always treated with prophylaxis reported significantly lower number of bleeds/year than patients treated entirely or primarily on-demand ($P \leq 0.05$), significantly lower presence of target joints ($P \leq 0.001$) and higher score in mobility ($P \leq 0.005$). Of the respondents who had received prophylaxis all of their lives, five reported major bleeds at some point, and five reported target joints without specifying that most bleeds occur in these joints. Three of each of these reported both target joints and major bleeds. No information on lifestyle or compliance was collected. Patients treated on-demand reported significantly higher number of days missed from work than all other groups ($P \leq 0.05$) and significantly lower score in EQ5D dimension Self-care ($P \leq 0.05$). The reported average number of bleeds/year for Sweden and France of 3.2 and 20.1, respectively, are broadly consistent with previous studies [4,5]. The results in the primary analysis for France, UK and Ireland and in the secondary analysis for the on-demand group are also similar to other published work [6, 7]. Hence, the results in this study support the view that prophylaxis started at a young age and continued into adulthood is an extremely effective treatment for patients with severe haemophilia. Four patients who were treated using prophylaxis switched to on-demand therapy and subsequently reverted to prophylaxis. Nine patients (22%), who had been treated primarily with on-demand therapy have now changed to prophylaxis treatment. Respondents in both of these groups reported that this change took place due to increased bleeding episodes and/or joint problems that were developing when treated with on-demand therapy. When asked about days missed from work, there was a significant difference between countries. Swedish respondents reported a mean 0.5 days missed/year from work or college for reasons related to haemophilia. In Ireland and the UK, the days missed were 5 and 6.6 days respectively. With the French respondents, the mean time missed from work or college for reasons related to haemophilia was 15 days. This number was dramatically increased by two patients in the group not being able to attend work or college for 6 months following orthopaedic operations. For adults who have been treated with on-demand therapy, a requirement for orthopaedic surgery or joint replacement is not uncommon. This is further supported when the treatment regime was examined. Patients on prophylaxis missed a mean of 0.7 days per year and patients on-demand missed 19.2 days. The results from the EQ5D demonstrate the clear benefits of long-term prophylaxis over on-demand therapy. A number of studies on cost effectiveness [8–10] have reported the difference in utility values between prophylaxis and on-demand of 0.03 and 0.09. This study has shown that the benefit of prophylaxis continued into adulthood increases the utility value by a more significant 0.16–0.20. Overall, on-demand treatment results in a lower utility value in relation to quality-of-life for people with severe haemophilia. Prophylaxis started at an early age and continued into adulthood results in less bleeding, less damage to joints and less time missed at work. Prophylaxis increases mobility and the ability to do everyday activities and improves the health-related quality of life of people with severe haemophilia. It would be beneficial to extend this survey in the future to gather data on a larger number of people with Haemophilia from a larger number of countries and the authors plan to do this. It would be interesting to extend this survey to countries where distinctly different prophylaxis regimes are used and to countries that use low levels of FVIII per capita to assess what may well be, in effect, a baseline utility figure.

Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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Table 1. (a) Individual country results and (b) Results by treatment regime.

	Reported mean number of bleeds per year (*n*)	Presence of target Joints (%)	Occurrence of major bleeds (%)	Mean days missed per year (*n*)	Mean EQ5D utility value
(a)					
France	20.1	100	80	15.0	0.74
Ireland	16.5	94*	68	5.0	0.68
Sweden	3.2	25	20	0.5	0.93
UK	17.5	100	44	6.6	0.76
(b)					
Group 1 (100% on prophylaxis)	3.2	26.3	26.3	0.9	0.88
Group 2 (50–99% on prophylaxis)	11.5	81.0	59.1	3.6	0.77
Group 3 (1–50% on prophylaxis)	20.1	93.8	56.2	3.6	0.79
Group 4 (0% on prophylaxis)	26.5	88.9	48.5	19.2	0.72

*Of respondents from Ireland, UK and France only one person (20 years old) does not report target joints. He was on prophylaxis until he was 18 and has now switched to on-demand.

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Mutations in coagulation factor XIII subunit A in severe factor XIII deficiency patients: five novel mutations detected

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Congenital factor XIII (FXIII) deficiency is a rare autosomal recessive disorder affecting one in 1–5 million individuals, the prevalence of which is higher in countries where consanguineous marriages are common [1]. It is a serious bleeding diathesis, the common symptoms being bleeding from the umbilical stump, prolonged bleeding postinjury, menorrhagia, poor healing of wounds, intra cranial bleed and spontaneous abortions. FXIII deficiency is usually attributed to mutations in the factor *13A* (*F13A*) gene which is located in chromosome 6, at p24-25 [2]. It spans 160 kb and consists of 15 exons separated by 14 introns. Sixty-nine unique mutations (34 missense, 21 deletions/insertions, 9 splice site and 5 nonsense) in *F13A* gene have been reported in the Factor 13 mutation database (*http://www.f13-database.de/*). Detection of these mutations is important to study the molecular basis of FXIII deficiency and also for genetic diagnosis in affected families.

In this report, we have studied mutations in seven FXIII-deficient patients who were so diagnosed on the basis of their clinical history, normal screening coagulation values and clot solubility assays [3]. Five of seven patients had history of first degree consanguinity among parents. Genomic DNA of the patients was extracted from citrated blood samples by the standard phenol chloroform method. *F13A* gene was screened for mutations by PCR and direct sequencing using ABI 3130XL sequencer. The amino acid positions were reported according to Ichinose *et al.* [4]. The deleterious effect of the novel mutations was confirmed by studying degree of conservation of the mutated amino

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