Assessing the effectiveness and cost-effectiveness of prophylaxis against bleeding in patients with severe haemophilia and severe von Willebrand's disease

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Switching from treatment on demand to prophylaxis with clotting factor to reduce the number of bleeds in patients with severe haemophilia A and B, and severe von Willebrand's disease (vWD). Those with severe haemophilia were treated either with clotting factor on demand following a bleed, or prophylactically to prevent bleeds from occurring.

Type of intervention

Economic study type
Cost-effectiveness analysis.

Study population
Patients with severe haemophilia A and B (below 1 u/dL^-1), and severe vWD. Patients jointly registered with other haemophilia centres were excluded, as their treatment records at the study institution were only partially complete.

Setting
The setting was hospital. The economic analysis was carried out in London, UK.

Dates to which data relate
Effectiveness and resource use data corresponded to the patients treated between 1980 and 1995. The price year was not specified.

Source of effectiveness data
The evidence for final outcomes was based on a single study.

Link between effectiveness and cost data
Costing was conducted retrospectively on a sub-sample of the patient sample used in the effectiveness analysis.

Study sample
Power calculations were not used to determine the sample size. Changes in the annual number of bleeds by calendar year were assessed based on the data for 179 patients (139 with severe haemophilia A, 31 with severe haemophilia B, and 9 with severe vWD) who met the inclusion criteria. The effect of switching from treatment on demand was assessed based on the data from 47 patients: 25 adults (median age of 30 (range: 4 - 63) years at start of prophylaxis) and 22 children (median age of 4 (range: 2 - 10) years at start of prophylaxis) who had switched from treatment on demand to prophylaxis during the 16-year period, and who had experienced at least one calendar year of each
Study design
This was a before-and-after study for the part related to changes in the annual number of bleeds by calendar year and a retrospective cohort study for the part related to the effect of switching from treatment on demand. The studies were carried out in a single centre. The median duration of follow-up was 7 (range: 1 - 15) years for adults and 3 (range: 1 - 8) years for children, in the years prior to prophylaxis and 7 (range: 1 - 15) years for adults and 3 (range: 1 - 11) years for children, in the years after prophylaxis. No information was explicitly given regarding loss to follow-up. Use of clotting factors VIII and IX was grouped according to the reason for which they were given (on demand or prophylaxis). Clotting factor that had been used prior to physiotherapy, surgery or any invasive procedure was excluded.

Analysis of effectiveness
Patents were analysed in the groups to which they were initially allocated. The clinical outcome measure was the number of bleeds experienced by patients.

Effectiveness results
The median annual number of bleeds decreased from 23.5 (range: 1 - 107) in 1980, to 14 (range: 0 - 45) in 1995, (p<0.0001). Switching from treating on demand to prophylaxis reduced bleeding frequency in 41 out of 47 patients within the period of 1 year. The 25 adult patients experienced a median of 37 bleeds (range: 11 - 132) per year in the year prior to prophylaxis. During the first full calendar year on prophylaxis patients experienced a median of 13 bleeds (range: 0 - 92), representing a 65% reduction. Five patients increased bleeding after switching methods of treatment. The corresponding values for the 22 children were 21 (range: 3 - 64) in the year prior to prophylaxis and 11 (range: 0 - 49) for the year after prophylaxis.

Clinical conclusions
Prophylaxis can reduce bleeding frequency but requires more clotting factor than treatment on demand.

Measure of benefits used in the economic analysis
The benefit measure used was the number of bleeds averted by using prophylaxis instead of treating on demand, using age-adjusted patient treatment data. This was calculated based on a sub-sample of 38 patients, who could be matched by age and method of treatment up to the age of 9 years, because numbers were too small at each age above this.

Direct costs
Costs were discounted at 6% per annum. Quantities related to the amount of clotting factor used were reported separately from the costs. The unit cost of clotting factor was reported separately. Cost analysis covered the costs of clotting factors required. The cost analysis was conducted based on a sub-sample of 38 patients who could be matched by age and method of treatment up to the age of 9 years. The perspective adopted in the cost analysis appears to have been that of the purchasers and providers of haemophilia care. The source of unit cost data was the study institution and represents the purchase cost of a high-purity clotting factor. It was mentioned that the retrospective nature of the study design did not allow other relevant resource use data to be gathered. The price year was not stated.

Indirect Costs
Indirect costs were not included.

Currency
UK pounds sterling ( ).
Sensitivity analysis
A set of one-way sensitivity analyses was performed by varying the unit price of clotting factor, the discount rate, the quantities of clotting factor required and the number of bleeds patients had experienced for both methods of treatment. The highest and lowest possible values of parameters were used in the sensitivity analyses.

Estimated benefits used in the economic analysis
Whilst treating on demand patients experienced a median of 192.5 bleeds per patient. This compares to 103 bleeds per patient with prophylaxis. Benefits were not discounted.

Cost results
Costs that accrued after the first year of treatment were discounted at 6% per annum. The net discounted costs of treating on demand were 27,751 and with prophylaxis were 76,863 per patient.

Synthesis of costs and benefits
The incremental cost-effectiveness ratio for prophylaxis compared with treatment on demand was 547 per bleed avoided. However, this figure was highly sensitive to certain variables such as the unit price of clotting factor.

Authors’ conclusions
Based on evidence from this retrospective data and from other studies, prophylaxis appears successful in reducing bleeding in severe haemophilia, so there is certainly scope for it to represent a cost-effective use of resources.

CRD COMMENTARY - Selection of comparators
An implicit justification was given for the choice of the comparator. It was reasoned that despite the fact that prophylaxis was, at the time of the study, the preferred method of patient management, it requires more clotting factor than treatment on demand, and so its cost-effectiveness required assessment. You, as a database user, should consider whether the on demand treatment is a widely used health technology in your own setting.

Validity of estimate of measure of effectiveness
The internal validity of the effectiveness results cannot be guaranteed due to the before-and-after nature of the study design and the relatively small sample size. No power calculations were performed to justify the sample size adopted in the study. Given the limitations of the study design and the potential for biases the effectiveness results should be treated with some caution.

Validity of estimate of measure of benefit
The estimate of the benefit measure was derived directly from the effectiveness study. It was acknowledged that a complete cost-effectiveness analysis would consider the development of arthropathy as the long-term measure of benefit. However, it was reported that no data on this benefit measure were available in the study institution and no data were noted to exist from randomised controlled studies on the ability of prophylaxis to reduce such long-term disability.

Validity of estimate of costs
The validity of the cost results may have been positively influenced by the separate reporting of the quantities and costs of clotting factors, reporting the unit price of clotting factors and discounting the costs at a rate relevant to the UK NHS setting. In addition sensitivity analyses were performed on the resource use data and corresponding unit price value. However, the costing was conducted retrospectively, a comprehensive resource use profile was not available, and the price year was not specified. The effects of alternative procedures on indirect costs were not addressed and no
statistical analysis was performed on resource use and cost data.

**Other issues**
Given the inherent limitations of the study design, the results should be treated with some degree of caution. The issue of generalisability to other settings or countries was not directly addressed, although it may have been considered in the sensitivity analysis. Appropriate comparisons were made with other studies. The issue of the degree to which the study sample was representative of the study population was not discussed.

**Implications of the study**
More detailed proof of cost-effectiveness is likely to require the use of modelling techniques to link the information relating to joint bleeds with the development of arthropathy.

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