MaHTAS
Malaysian Health Technology Assessment Section

MANAGEMENT OF HAEMOPHILIA

Executive Summary

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Background

Haemophilia is an inherited bleeding disorder that results from a low level of proteins needed for normal blood clotting. There are two main types of haemophilia, haemophilia A, which is caused by a lack or decrease of clotting factor VIII (FVIII); and haemophilia B, which is caused by a lack or decrease of clotting factor IX (FIX). The occurrence of haemophilia A and B is approximately one per 5000 and one per 50,000 male births respectively, with no racial predilection. The mean prevalence of haemophilia A for high income countries was 12.8 ± (SD6.0) per 100,000 males whereas it was 6.6 ± 4.8 per 100,000 males for the rest of the world. The mean prevalence of haemophilia A in Malaysia has increased from 5.6 per 100,000 males in 1998 to 6.6 per 100,000 males in 2006, the mean was 5.9 ± 0.4 per 100,000 males. As for Haemophilia B, for the highest income country, the prevalence was 2.69 ± 1.61 per 100,000 males whereas the prevalence for the rest of the world was 1.20 ± 1.33 per 100,000 males. The reported prevalence for Malaysia was 1.00 ± 0.11 per 100,000 males.

Haemophilia arthropathy due to repeated joint bleeds is the major cause of morbidity in persons with haemophilia. In patients with severe form of the disease, bleeding episodes may occur as frequently as 20-30 times per year, and life-threatening bleedings such as intracranial haemorrhage may occur. The basic treatment to stop or prevent bleeding in haemophilia patients is by giving clotting factor replacement therapy. The optimal approach is by giving factor replacement in such a way that bleeds and chronic joint damage are prevented, short and long-term complications avoided and there is full integration of the patient into society.

Replacement therapy for haemophilia is usually given either prophylactically or on-demand approach. Prophylaxis is the regular continuous treatment started after the first joint bleed and before the age of two years, or before the age of two years without previous joint bleed whereas on-demand factor infusion, also known as episodic therapy is defined as therapy to abrogate an acute haemorrhage.

Unfortunately, some patients developed neutralising antibodies (inhibitors) to replacement factors (factor VIII (FVIII) or factor IX (FIX)) rendering such treatment ineffective. The development of inhibitors is one of the challenging complications of treatment in haemophilia patients resulting in increased morbidity and significant economic burden. Although several factors are known to influence the risk of inhibitor development, the source of factor concentrate for replacement therapy, namely recombinant or plasma-derived factor concentrates may also have an effect on inhibitor development.

Inhibitor eradication by immune tolerance induction (ITI) is generally accepted as the most preferred treatment option. However, in about 30% of haemophilia A patients and a larger proportion of patients with haemophilia B, who undergo ITI, failure to eradicate the inhibitor is observed. In these patients, in those waiting for ITI to start, as well as in those undergoing ITI, acute bleeding episodes are generally managed by preparations containing activated coagulation factors. These products known as bypassing agents are able to bypass factor VIII and factor IX dependent steps in the coagulation cascade and promote haemostasis by enhancing thrombin generation. Currently there are two bypassing agents available namely activated recombinant factor VII (rFVIIa) and activated prothrombin complex concentrate (aPCC).

The history of comprehensive care of haemophilia, embracing diagnosis, treatment and multidisciplinary support has evolved over the past 60 years. It is defined as a

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continuing supervision of all medical and psychosocial factors affecting the haemophilia patients and their family. In many developed countries, comprehensive care were made possible because of the advanced economic condition of these countries, provide comprehensive services including haemophilia care, orthopaedic and dental services and education, as well as psychosocial support.

Policy Question
Should a national haemophilia program be introduced in Malaysia?

Objective

1. To assess the efficacy and resource implications of prophylaxis treatment when compared to on-demand treatment for patients with haemophilia
2. To assess the safety, effectiveness and cost-effectiveness of recombinant factors compared to plasma derived
3. To assess the efficacy and resource implications of rFVIIa when compared to aPCC and the resource implications
4. To assess the effectiveness of comprehensive care including non-pharmacological management for haemophilia and other rare bleeding disorders patients

Methods
Major electronic databases such as Medline, Embase, and Cochrane Database of Systematic Review were searched up to August 2012. Studies were reviewed separately according to the research questions. Retrieved records were screened for relevance. Potentially relevant papers were retrieved and independently checked against predefined criteria for inclusion by two reviewers. Included reviews and primary papers were critically appraised and data were extracted and narratively presented

Result and conclusion
Fifty-one studies met the inclusion and exclusion criteria.

Prophylaxis compared to on-demand approach
This review included 26 studies which met the inclusion and exclusion criteria including two systematic reviews. There were only two randomised controlled trials (RCT) identified and these studies have been combined in one of the systematic review and meta-analysis. The other studies were non-randomised controlled trials, retrospective cohort studies and cross-sectional studies. Most of these studies were conducted in European countries and United States of America but there were two studies conducted in Asian countries namely in Iran and Taiwan. These studies were heterogeneous, thus the results were not pooled.

There was good level of evidence from systematic reviews of randomised controlled trials supported by numerous observational studies that the used of prophylaxis approach in haemophilia treatment was effective in decreasing the frequency of joint bleeds and preventing or slowing down the development of haemophilic arthropathy. However, the evidence showed that the cost of treatment was high and mainly contributed by the cost of factor concentrates. Prophylaxis approach was shown not to increase the risk of inhibitor development and there was no increase risk of infection.

Recombinant compared to plasma-derived factors
Nine studies met the inclusion and exclusion criteria. There were two systematic reviews identified which summarised non-randomised and observational studies. One randomised controlled trial, three prospective non-randomised studies and two retrospective cohort studies were also included. No study on cost-effectiveness was retrieved. However, the studies included have high risk of bias, thus the results were not pooled.

There was insufficient evidence to answer the research question on the efficacy and safety of recombinant factor compared to plasma-derived factor concentrates. Only fair level of evidence with high risk of bias was available for Haemophilia A. The evidence showed inconsistent results for recovery of rFIX and pdFIX. Limited good level of evidence showed that recovery of rFIX was lower compared to pdFIX. As for safety, it cannot be concluded that plasma-derived factors has lower risk of inhibitor development due to inconsistency of the results.

There was no retrievable evidence on cost-effectiveness from the available scientific databases. Only the costs of the factors were available from Pharmacy Department of Hospital Ampang and Hospital Kuala Lumpur. There were other factors that may affect the cost such as the risk of inhibitors, infection rate, efficacy, hospitalisation and other adverse events which should be calculated into the cost.

Treatment of patient with inhibitors

Twelve studies were included to address research question 3 on the effectiveness and cost effectiveness of rFVIIa when compared to aPCC for haemophilia patients with inhibitors. One meta-analysis, four systematic reviews, two RCTs, three cost-minimisation analyses and two costing studies were selected which met the inclusion criteria.

Two RCTs compared head to head the rFVIIa and aPCC. These two RCTs however were included in three of the systematic reviews included in this review. Eight of the primary studies and reviews included were sponsored by industries.

Good level of evidence showed that rFVIIa and aPCC had similar efficacy and both can be administered as single intravenous bolus (270 µg/kg of rFVIIa, 75-100 IU/kg of aPCC). There was no higher risk of adverse events reported in rFVIIa compared to aPCC. Fair level of evidence suggested that rFVIIa is more cost-effective compared to aPCC.

Comprehensive care

There were three observational studies and one guidelines retrieved that reported the benefits of comprehensive care. All the studies were from United States.

Fair level of evidence showed that comprehensive care reduced the mortality rate in haemophilia patients, reduced the hospitalisation days and reduced the number of days lost from school or work. There was insufficient evidence on cost effectiveness, however the fair level of evidence suggested that comprehensive care leads to cost saving.

Recommendation

Based on the good level of evidence retrieved, prophylaxis therapy is recommended in haemophilia patients to improve their quality of life and prevent complications. Since the cost of factor concentrates is high, a low or intermediate dose prophylaxis may be considered.

No specific recommendation can be made with regards to recombinant and plasma-derived factors. There was insufficient evidence to address this decision problem. More primary research in the form of well-designed and adequately powered RCTs is required.

The use of bypassing agents either rFVIIa or aPCC is recommended for treatment of any kind of bleeds in haemophilia patients with inhibitors since the limited good level of evidence showed that both the bypassing agents had similar efficacy. Further well designed, high quality research is needed to study the relative effectiveness of rFVIIa compared to plasma-derived aPPC. A study among our

population is strongly encouraged to provide better insight on the response to these bypassing agents.

Based on the available evidence and the current practice of haemophilia management worldwide, comprehensive care for haemophilia patients is recommended and seemed to be the way forward to improve the quality of care and prevent complications.

A national haemophilia program should be introduced in Malaysia to address several issues pertaining to management of haemophilia patients such as care delivery, medical expertise and treatment products. World Federation of Haemophilia steps to set up a national haemophilia program may be used as a guide. A registry which is an important component of comprehensive care should be incorporated in the national program. A registry enables centres to monitor their performance and use of resources both at a local and national level.

A local economic evaluation should be conducted to assess the best model of treatment for haemophilia patients in Malaysia that will not only improve the outcome of the patients but also be cost effective.