DOI: 10.1111/hae.13892

SUPPLEMENT ARTICLE

Haemophilia WILEY

Show me the evidence: Effectiveness of low-dose prophylaxis

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Abstract

Prophylaxis is the gold standard treatment for haemophilia but requires more amount of clotting factor concentrates, than on demand therapy. Low dose prophylaxis is an alternative for countries with limited resources. There are data of evidence showing the superiority of low-dose prophylaxis than episodic treatment. Studies from China, India, Tunisia, Thailand and Indonesia reported experiences with low dose prophylaxis using outcome assessment. These studies have shown the effectiveness of various protocols regimen with once, twice or thrice injection of 10-15 UI Kg-1 per injection. These protocols allow reduction of joint bleeds and at least delay of joint damages. There is not enough long-term data nowadays, but low dose prophylaxis is certainly better than on demand therapy and should be considered as a first step of prophylaxis in some countries but not the final goal.

KEYWORDS

Low dose prophylaxis, Hemophilia, Prophylaxis, Hemophilia joint health score

Prophylaxis is the gold standard for haemophilia treatment, by reducing bleeding events and improving joint status and quality of life.[1] In fact, it does require more amount of clotting factor concentrates than for on-demand treatment, and so a higher cost, that could represent a barrier to introduce prophylaxis in countries with limited resources. In emerging countries, efficiency of prophylaxis was also demonstrated.[2]

If we consider the history of prophylaxis, low-dose prophylaxis is the first step of prophylaxis.[3] In the 1960s, Swedish started prophylaxis with low doses, and then, the evolution of the regimen led to gradually intensified prophylaxis protocols, with the aim of zero bleed, and early start.

Low-dose prophylaxis is an alternative that could be effective and recommended for countries with limited resources.[4] Is low-dose prophylaxis acceptable nowadays? In countries where on-demand therapy is the treatment option, because full-dose prophylaxis could not be applied, low-dose prophylaxis should be considered, at least for children, as a first step. There are data of evidence showing the superiority of low-dose prophylaxis than episodic treatment. Low-dose prophylaxis has positive outcomes with improvement of quality of life and reduction ofbleeding events. Moreover, Srivastava[4] reported calculations of no increase of used clotting factor concentrates.

Outcome measurements should be used in order to have objective data of the effectiveness of low-dose prophylaxis. Annual bleeding rate and Haemophilia Joint Health score are the easier and cost effective tools.

Many countries such as China,[5] India,[6] Tunisia,[7] Thailand,[8] Indonesia,[9] Algeria and Egypt practise low-dose prophylaxis as a primary, secondary or tertiary prophylaxis.

Published studies on low-dose prophylaxis have shown superiority of such protocol over episodic treatment in terms of bleed reduction, and quality of life, with improved physical activity, independent functioning, school attendance and community participation. Various protocols were used, once, twice or thrice injection regimen, with 10-15 UI kg^{-1} per injection (Table 1).

We will review the reported data and outcome measurements used to demonstrate the effectiveness of low-dose prophylaxis.

What is needed to start a low-dose prophylaxis? Countries with 0.5-1 UI per capita can start to introduce prophylaxis with low doses.

It is mandatory to understand the benefits of prophylaxis and have a regular supply of clotting factor concentrate. A multidisciplinary team, with close relationship to people with haemophilia, is also a required condition.[4]

TABLE 1 Low-dose prophylaxis studies

Author & country	Cohort size	Median dose	Outcomes assessed	Duration of therapy	Results
Wu (2011) Prospective haemophilia A & B China	34	FVIII 10 IU kg^{-1} twice a week for haemophilia A or FIX IU kg^{-1} once haemophilia B	Joint bleed, Gilbert score, School attendance and Daily activity	12 wk	Good response with significant improvement in the frequency of joint bleeding
Verma (2016) Randomized study haemophilia A India	11	10 IU kg^{-1} twice weekly	Joint bleed	11.5 mo	Safe method of preventing joint bleeds
Gouider (2016) Retrospective study haemophilia A & B Tunisia	51	10-15 IU kg^{-1} 2 or 3 times weekly for haemophilia A 25-35 IU kg^{-1} once or twice weekly for haemophilia B	Bleeding events HJHS FISH	Median follow-up 5 y [1-9]	Effective and better than on-demand therapy
Chuansumrit (2018) Prospective study haemophilia A Thailand	50	8-10 IU kg^{-1} once to twice weekly	Bleeding events	3 mo	Efficacy of low fixed-dose prophylaxis regimen
Chozie (2019) Randomized study haemophilia A Indonesia	25	10 IU kg^{-1}, twice a weekly	HJHS and HEAD-US scores	12 mo	Effective in reducing joint bleeding episodes and improvement of HJHS compared with on-demand FVIII treatment in severe haemophilia A children

This low-dose prophylaxis regimen certainly improves the physical activity, but we should bear in mind that there is still a limitation as the level of factor VIII is not optimal for enhanced activities.

Brekkan et al[10] reported a model-based evaluation of low-dose factor VIII prophylaxis in haemophilia A. Based on simulations, a promising low-dose prophylaxis regimen was identified as decreasing treatment costs compared with standard high-dose prophylaxis at a small increase in bleeding risk. The results indicate that low-dose prophylaxis is advocated where the standard of care is on-demand treatment; however, the results should be considered in the context of any limitations of the applied models.

To conclude, low-dose prophylaxis is cost effective, efficient and a safe method for preventing joint bleeds and at least delay joint damages. We do not have enough long-term data today, and we should carefully document basic outcome data for as long as possible. Main goals are improved quality of life and reduced bleeding events, rather than zero bleed. It is better than on-demand therapy. It can be considered as the first step of prophylaxis in some countries, but not the final goal.

DISCLOSURES

The author has no competing interests.

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How to cite this article: Gouider E. Show me the evidence: Effectiveness of low-dose prophylaxis. *Haemophilia*. 2019;26:9–10. https://doi.org/10.1111/hae.13892