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ORIGINAL ARTICLE

Low dose prophylaxis in Tunisian children with haemophilia

E. GOUIDER,*† L. JOUINI,† M. ACHOUR,*† H. ELMAHMOUDI,† K. ZAHRA,*† W. SAIED*‡ and B. MEDDEB*†

**Hemophilia Center Aziza Othmana Hospital; †Tunis Medical University of Tunis, UR14ES11; and ‡Orthopedy Department, Children Hospital Bechir Hamza, Tunis, Tunisia*

Introduction: Low dose prophylaxis could be recommended in countries with limited resources. **Aim:** We report our single centre experience in children with haemophilia. **Patients:** Fifty-five children were included in our study with a weekly median dose of 30 UI kg^{-1} given once, twice or thrice a week. Age of initiation of prophylaxis is 5.32 years (0.64–11.44). Outcome assessment used were number of bleeding before and after initiating prophylaxis, haemophilia joint health score (HJHS), functional independence score in haemophilia (FISH) and quality of life with the Haemo-QoL. **Results:** Reduction of number of bleeding was clear in all patients; HJHS, FISH and Haemo-QOL were satisfactory. **Conclusion:** Low dose prophylaxis is effective and better than on-demand therapy. It should be the starting point for prophylaxis in countries with limited resources.

Keywords: functional independence score in haemophilia, haemophilia, haemophilia joint health score, low dose prophylaxis, prophylaxis

Introduction

Prophylaxis is the gold standard treatment for haemophilia [1]. It prevents bleeding and consequently joint disease [2,3]. It was initiated since the sixties [4–6]. Different protocols are used, with different doses and numbers of injections, and the optimal regimen remains to be defined. In countries with limited resources, prophylaxis regimen used should be expensive, whereas initiating prophylaxis with low dose could be recommended. We report our single centre experience with low dose secondary or tertiary prophylaxis in children.

Patients and methods

Data were extracted from patient diary and medical files of children with haemophilia.

We include all children (<15 years) receiving low dose prophylaxis with a regular follow up and outcome measurement available. The age at initiation low dose prophylaxis should be less than 15 years. Children with inhibitor were not included in the study.

The protocol of low dose prophylaxis used is illustrated in Fig. 1.

Outcome measurement was number of bleeding before and after initiating prophylaxis, in order to evaluate the efficiency.

We also performed once a year, evaluation of the joint status with the haemophilia joint health score (HJHS) version 2.2 [7] and functional independence score in haemophilia (FISH) [8]. Quality of life with the Haemo-QoL was performed one year after initiating prophylaxis [9].

SPSS 16 was used for statistical analysis, using the comparison means in paired samples with $P < 0.05$.

Results

Fifty-one children met the inclusion criteria. Forty-two were haemophilia A. Median age was 9 years (4–17) and median age at initiating the low dose prophylaxis is 5.32 years (0.64–11.44) (Fig. 2). Median follow up is 5 years (1–9).

Number of injections per week, was once, twice and three times for, respectively, 31%, 51% and 18% of children with a weekly median injection dose of 31 UI kg^{-1}. Median dose per injection is 20 UI kg^{-1} (8–50). Details of median doses used according to the

Correspondence: Emna Gouider, Hemophilia Center, Aziza Othmana Hospital, Place du gouvernement, 1008, Tunis, Tunisia.
Tel.: +21698341985; fax: +21671568228;
e-mail: emna.gouider@gmail.com

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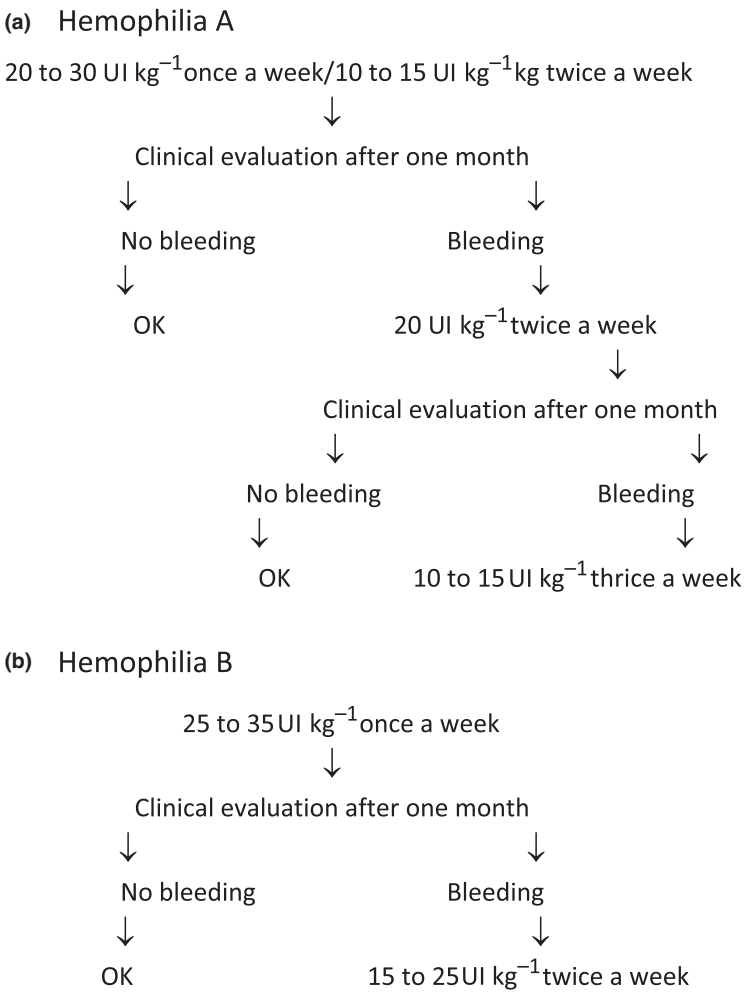

Fig. 1. Protocol adapted for haemophilia A and B.

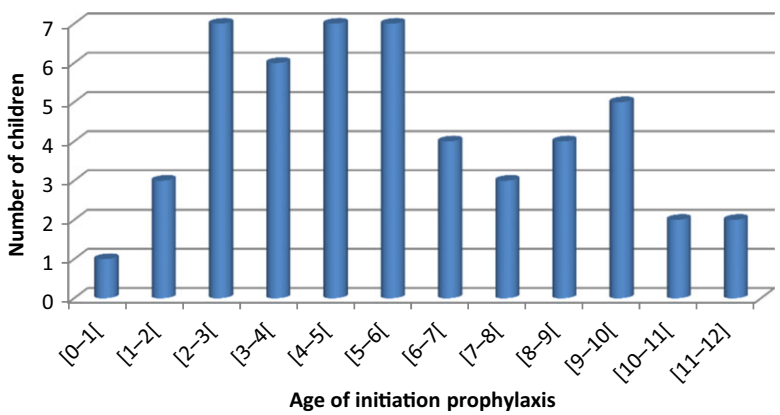

Fig. 2. Age of initiation prophylaxis.

type of haemophilia and the number of injections per week is illustrated in Table 1 and Fig. 3.

Twenty children did not need escalation in the regimen of prophylaxis (number of injection per week and/or the dose per injection).

The number of bleeding was significantly reduced after initiating the prophylaxis, with no bleeding in some cases. Median number was 7 in on-demand therapy compared to 0.5 with low dose prophylaxis. This is illustrated in the Fig. 4.

Functional independence score in haemophilia

It was achieved in 50 children. It was equal to 32/32 in 40 children, 31/32 in four children and between 20 and 25 in six children. It was stable during the

Table 1. Median doses per week and per injection used.

	Weekly median dose UI kg^{-1} w^{-1}		Median dose per injection UI kg^{-1} inj^{-1}	
Once a week				
HA (n = 12)	27.7 (16–50),	27.7 (16–50)	27.7 (16–50)	27.7 (12.5–50)
HB (n = 4)	27.5 (20–35.71)		27.5 (20–35.71)	
Twice a week				
HA (n = 22)	35.35 (20–66.66)	34.5 (20–66.66)	17.67 (10–33.33)	17.25 (10–33.33)
HB (n = 4)	28.12 (22.22–55.4)		14.06 (11.11–27.7)	
Thrice a week				
HA (n = 8)	42.75 (24–64.37)	48 (24–90)	14.25 (8–21.45)	16 (8–30)
HB (n = 1)	90		30	

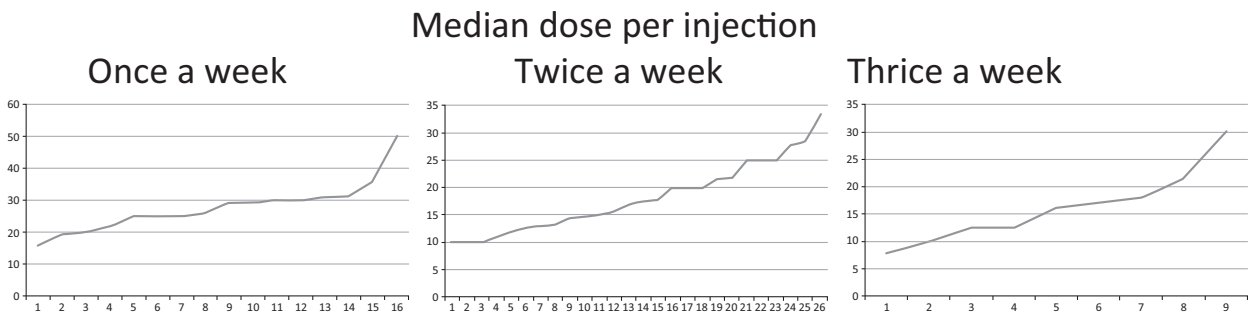

Fig. 3. Doses per injection according to the number of injection per week.

follow-up period. It was correlated with the number of bleeding before initiating low dose prophylaxis (P = 0.028).

Haemophilia joint health score

It was performed in all children. The median score is 4 (0–24) SD 3.11. It was less than 10 in 41/52 children. Comparing the score with the previous one, one year before, for 36 children, we found that it is quite stable (Fig. 5); it increases for one patient from 10 to 21 because of lack of compliancy. It also increases for 5 other children but remains less than 10. No correlation was observed between the age of initiating low dose prophylaxis and HJHS.

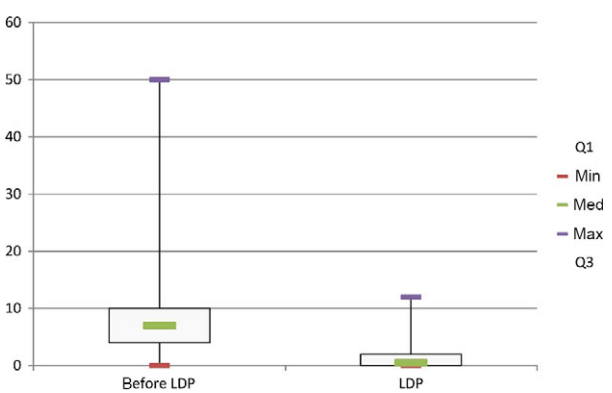

Fig. 4. Bleeding per year before and during low dose prophylaxis. The median (Q1–Q3) values for number of bleeding per year before and after LDP were 7 (0–50) and 0.5 (0–12) respectively.

Haemo-QoL

It was performed once in 21 children after the first year of initiating prophylaxis. Median value of the transformed scale score of the Haemo-QoL for the different items varies from 14.28 to 50. It was, respectively, 25, 14.28, 24.37, 45, 34.06, 29.68, 21.87, 33.33, 30.70, 50, 25 for physical health, feeling, attitude, how you see yourself, family, friends, help, other person, sport and school, coping with haemophilia, treatment and health in general.

Discussion

It is well established nowadays that prophylaxis is the gold standard treatment for haemophilia. On the other side, prophylaxis requires more clotting factor concentrates than on-demand therapy, and so more economical resources. This is a big challenge in developing countries.

The first reported studies on prophylaxis in the beginning of the sixties [10] used less clotting factor

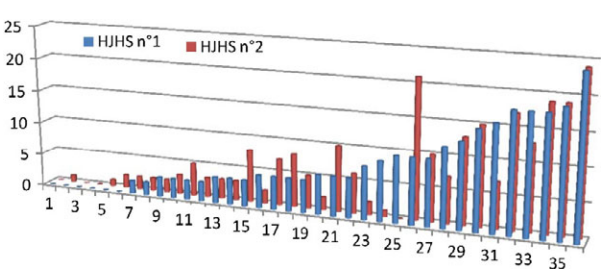

Fig. 5. Haemophilia joint health score and evolution after one year.

concentrates than used nowadays. The improvement of the different regimen of prophylaxis leads to the use of big amount of clotting factor concentrates [11,12]. It is well established that prophylaxis is superior to on-demand therapy [2], but the big challenge is to define the most economical regimen. Fisher K *et al.* compared the intermediate dose vs. high dose prophylaxis in outcome and costs. They conclude that quality of life is equivalent in the two regimens with a small reduction of bleeding in high dose, although the high dose is more expensive [13].

China experience reported a clear reduction of bleeding with secondary and tertiary low dose prophylaxis, respectively, in children and adult [14,15].

In emerging countries, efficiency of prophylaxis was also demonstrated [16]. One hundred and eighty-six patients from 11 countries were enrolled in 24-month, prospective, non-interventional study. Mean annual rate of treated bleeds on prophylaxis was significantly lower than on the on-demand group. Joint status was also better in the prophylactic group.

In Tunisia, where the economic resources are limited, and the amount of clotting factor concentrates are limited, we progressively introduce prophylaxis with low doses. The idea initially rises for children who bled frequently. National consumption of clotting factor concentrate was 0.25 UI capita^{-1}. Calculated doses for on-demand therapy and that for low-dose prophylaxis regimen were comparable, that leads us to initiate prophylactic treatment for those children. Then, the experience was spread to all children going to school. It was secondary or tertiary prophylaxis according to the International Society on Thrombosis and Haemostasis (ISTH) definitions [17]. National consumption has progressively increased to 1 UI capita^{-1}. Our experience demonstrates the efficiency of such regimen with clear reduction in number of bleeding, satisfactory joint status which should be regularly evaluated. Education of families was also one important key of the efficiency of such protocol of treatment.

Number of reported bleeding is an objective assessment tool, and must be also used for monitoring patient according to our protocol, even if some subclinical bleeds may occur.

HJHS is a cheap method to evaluate the joint disease. It only requires a trained physiotherapist, involved in the care of haemophilia but its time consuming. Ultrasound could be also another tool to be used for assessment. It was used for some children (data not shown). Combining the two tools, we could improve the evaluation of joint status. Results some years later will be more informative. We will be able to compare data of adults receiving on-demand therapy to those who received low dose prophylaxis during their childhood.

We did not find a correlation with the age at initiating prophylaxis and HJHS as it was reported in the literature [13]. This could be explained by the fact that we started prophylaxis later for the majority of children.

We observed a satisfactory quality of life which is well appreciated by the families especially those having experience with haemophilia. Quality of life was assessed by the HaemoQoL questionnaire. The scores of this scale ranged from 0 to 100, with higher values representing lower QOL. It is not always easy to evaluate quality of life in children as it is not funny to answer questions, and sometimes, answering is not evident. Although HJHS and FISH were regularly done, and now admitted in clinical practice in our centre, HaemoQol is not.

These results are reflecting a real life experience of low dose prophylaxis.

If we compare the ABR to the results reported by Fisher K comparing high and intermediate dose of prophylaxis [13], even if the median age of our cohort is smaller, the results are similar. HJHS of our cohort is also similar to that of the intermediate dose prophylaxis, but we need more time in order to conclude such comparison.

Prospective larger cohorts of children with haemophilia receiving low dose prophylaxis could be collected from different centres and countries, for better data analysis.

Low dose prophylaxis should be the starting point for prophylaxis. It is certainly not enough, but it is better than on-demand treatment. We were able to reduce the number of bleeding, which is one of the first aims. In order to be more efficient and prevent joint disease, we should certainly now start earlier and introduce primary prophylaxis [18].

Introduction of prophylaxis regimen leads to increase progressively the consumption of CFC, but on the other hand, money will be saved in terms of transport to hospital, absence from school and then work. Prevention of joint disease with no need of surgery later will also contribute to save money.

Limited economical resources must not be a barrier to start prophylaxis. Low dose prophylaxis could be the first step of prophylaxis.

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Disclosures

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

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