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Low dose secondary prophylaxis reduces joint bleeding in severe and moderate haemophilic children: a pilot study in China

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Summary. The most common bleeding in haemophilic patients is in joints, and joint disability is the most common complications in these patients receiving inadequate treatment. Limited by economy and inadequate treatment, developing countries face huge challenge to reduce disability and improve quality of life (QoL) of haemophilic children. The aim of this study was to investigate the effect of low dose secondary prophylaxis in China. Children with moderate and severe haemophilia from the Beijing Children Hospital, Beijing, China, and with established joint disease, were followed for a 12-week observation period followed by a 12-week low dose secondary prophylaxis-study period (for haemophilia A, factor VIII concentrate 10 IU kg^{-1} twice weekly; for haemophilia B, factor IX concentrate 20 IU kg^{-1} weekly). The reduction of joint bleeding, improvement of joint function and QoL during prophylaxis were analysed. In total 34 children (median age 7.8 years) were analyzable. The number of joint bleeds decreased from a total of 337 (individual range 3–24, mean 9.9) during the observation period to 57 (range 0–6, mean 1.7) during the study period with an overall of reduction 83%. Joint function improved in 66.7% of disease joints, with 23.2% of which were considered good to moderate. School attendance improved in all subjects, sports participation and daily activity improved moderately. Low dose secondary prophylaxis significantly reduces frequency of joint bleeding; with moderate improvement in joint function, school attendance, sport participation and daily activities. Low dose secondary prophylaxis is therefore, cost-effective as applied to developing countries such as China, although there are still unresolved issues.

Keywords: children, developing countries, low dose prophylaxis, moderate haemophilia, secondary prophylaxis, severe haemophilia

Introduction

Joint bleed is the most common bleeding manifestation in persons with haemophilia. The resulting joint disability is the most common complications in these patients receiving inadequate treatment. In developed countries, with better system of haemophilic comprehensive care, joint disability is increasingly rare [1,2]. In China, as in other developing countries with economic constraint and unavailability/ill-affordability of factor concentrates, effective treatment for children with haemophilia is limited [3,4]. Haemophilic patients in developing countries therefore have a heavy burden of arthropathy, even in those with moderate severity [5–7]. In a single centre (Beijing Children Hospital, BCH) analysis, we have shown that 89% severe and moderate haemophilic children had arthropathy with the incidence increasing with age [5]. Joint disease started at an early age with rapid progression, so that chronic arthropathy was well established in 85% by age 6.

There are a large number of haemophilic children in China. With a population of 1.32 billion, the prevalence of haemophilic patients in China is estimated to be 65 000–130 000. The number of affected children that demand our care to prevent disability should therefore be correspondingly huge. In developing countries, the proportion of children among diagnosed and registered patients appears disproportionally high [8] possibly because many adult patients are either not diagnosed or

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died at young age. On observation, the proportion of haemophilic children age 14 or under in the limited 2008 Chinese National Hemophilia Registry was as high as 52.3%. [9].

Primary prophylaxis in severe haemophilic patients to prevent joint disability is considered standard for care, but the high cost is a limitation even in developed countries. In developing countries, with the poor economic condition [8], primary prophylaxis as practiced in developed countries can only be regarded as a dream far away. In developing countries, the management goal cannot be the preservation of 'perfect' joints, but should rather be decreased bleeding with improvement of quality of life (QoL) with the possibility of preventing or delaying the progression of existing joint disease. A strategy aimed at preventing future disabilities and improving the QoL of these patients is sorely needed.

This study focuses on low dose secondary prophylaxis in severe and moderate patients with joint disease in China, assessing its efficacy on improving the frequency of joint bleeding, joint function and QoL in terms of daily activity, school attendance and sport participation.

Materials and methods

Ethics

The study was approved by the Ethic Committee of BCH, and informed consents were obtained from each patient enrolled.

Definition of severe and moderate haemophilia [10]

Moderate haemophilia is defined to have baseline factor VIII (FVIII):C/factor IX (FIX):C activity 1–5%; while severe haemophilia is one with baseline FVIII:C/FIX:C activity <1%. All patients enrolled had their baseline factor levels and inhibitor status (after more than 3 days washout period) re-tested.

Definition of clinical joint disease

Clinical joint disease is defined as the presence of visible joint swelling and/or limitation of movement and/or joint deformity in the absence of an acute joint bleed.

Study design

The study consists of an observation period of 12 weeks and a study period (secondary prophylaxis period) of 12 weeks.

During the observation period, patients receive on-demand treatment of plasma-derived (pd) intermediate purity factor concentrates or cryoprecipitate for haemophilia A and prothrombin complex concentrate (PCC) or plasma for haemophilia B, which the parents could afford to use [as below]. The cost of concentrate or cryoprecipitate is shared 70% by Government Medical Insurance for Beijing residents and 30% by patients.

During the study period, prophylaxis was fulfilled by FVIII 10 IU kg^{-1} twice a week (every Tuesday and Friday) for haemophilia A or FIX 20 IU kg^{-1} once weekly (Tuesdays or Fridays) for haemophilia B. For all haemophilia A patients, pd intermediate purity concentrates were used for prophylaxis for the first 17 children enrolled. The subsequent 11 children enrolled after November 2008 received recombinant FVIII (rFVIII, Kogenate FS®; Bayer Healthcare Co., Ltd, Tarrytown, NY, USA). All haemophilia B patients used PCC.

The cost of pd intermediate concentrate and PCC purchased at 1.2 RMB/IU was shared as follows: study budget 50%, Government medical insurance for Beijing residents 35%, patient 15%. rFVIII was donated by Bayer Healthcare China at no cost.

All infusions are provided by the haemophilia clinic nurse at Beijing Children's Hospital.

Inclusion/exclusion criteria. (i) Inclusion criteria: Two to 18 years age severe and moderate haemophilia A and B patients followed at our clinic, with clinical joint disease as defined earlier, as well as three or more joint bleeds into one single joint during the initial 12 weeks observation period. (ii) Exclusion criteria: history of inhibitors.

Data collection

a. Patients log on bleeding/daily activity/sport participation.
b. Nurses treatment record maintained after each infusion (on Tuesdays/Fridays).

During the prophylaxis period: data from patient bleeding log and treatment record for each subject were extracted once every 4 weeks during patient's clinic visits.

Outcome measurements

The following outcome measurements during the observation and study period were obtained and compared.

a. Frequency of joint bleed as recorded in patient bleed log.
b. Clinical joint assessment as measured by the Gilbert score system for each joint, at the beginning and end of prophylaxis period. Improvement attributable to prophylaxis was based on WFH definitions as: poor (no score decreased), mild (1–2 scores decreased), moderate (3–4 scores decreased) or good (≥5 scores decrease) [11].
c. Activity and participation measurement at the beginning and end of prophylaxis period.

- School attendance (number of days absent from school in each period).
- School activity participation was scored based on BCH definition: 0 (unable to have activities beyond classes), 1 (able to walk around in school yard), 2 (participation in exercise drill and stretching), 3 (participation in non-contact sports such as swimming or jogging) or 4 (participation in contact sport such as basketball, but not in competition).

Improvement in school activity participation attributable to prophylaxis was scored as poor (no change), mild (≤2 scores increase), moderate (>2 scores increase) or good (full increase from score 0–4).

- Daily activity was scored (based on BCH definition) as 0 (wheelchair bound), 1 (can work slowly), 2 (walking plus one activity such as swimming or jogging), 3 (walking plus two or more additional activities), 4 (no activity limitation).

Improvement in daily activity attributable to prophylaxis is scored as poor (no change), mild (≤2 scores increase) moderate (>2 scores increase) or good (full increase from score 0 to 4).

Statistics

Statistics Package for Social Science (SPSS; SPSS Company, Chicago, IL, USA) 13.0 for Windows was used for data analysis. We used Rank-test to determine the significance of data difference between the observation and study period. $P < 0.05$ is considered statistically significant.

Results

The study was completed over a 2-year period (1 March 2007 – 1 March 2009). Of the 40 children enrolled, one developed inhibitors during the observation period, five did not complete the 12 weeks prophylaxis for personal reasons.

The 34 analyzable patients include 28 haemophilia A (11 severe, 17 moderate), and six haemophilia B (two severe and four moderate) patients with a median age of 7.5 (range 2.5–17.5) years. Among moderate haemophilia, six patients had 1% FVIII:C or FIX:C activity, five had >1–2% activity and 10 had >2–5% activity.

Prophylaxis reduced the frequency of joint bleeds

The total number of joint bleeds during the observation period was 337 (individual range 3–24, mean 9.9). This decreased to a total of 57 (range 0–6, mean 1.7) during the prophylaxis period. Overall reduction was 83.1%. Figures 1 and 2 show the improvement seen in all severe and moderate patients. In severe haemophilia (left panels), joint bleeds decreased from observation (total 156, mean 12, range 4–24) to prophylaxis (total 24, mean 2.6, range 0–6) period by a total of 87.3%. In moderate haemophilia (right panels), joint bleeds decreased from observation (total 181, mean 8.6, range 3–20) to prophylaxis (total 24, mean 0.9, range 0–3) period, by a total of 78.2%.

Improvement in joint clinical function (Gilbert score)

Change in clinical joint function could be assessed in 69 disease joints (11 left elbows, five right elbows, 16 left knees, 13 right knees, 14 left ankles and 10 right ankles) in the 34 analyzable patients.

As indicated in Table 1, overall, 46 (66.7%) of the disease joints showed improvement and 23.2% of which were considered good to moderate during the prophylaxis period.

Improvement in quality of life

School attendance and sport participation in school (Table 2). School attendance: Only 15 of the 34 analyzable patients were available for this evaluation as seven were of preschool age, eight had dropped out of school before enrollment and four living out of city did not attend school in Beijing. As indicated in Table 2, 10 of 15 patients in the observation period had school

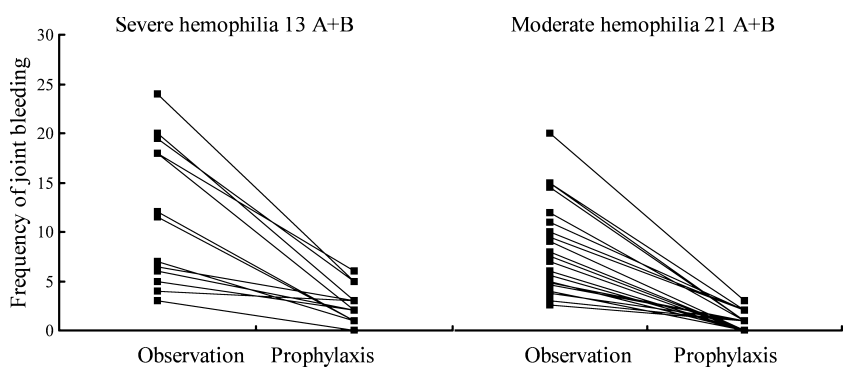

Fig. 1. Reduction of joint bleeds in individual patient from observation to prophylaxis period for 13 severe haemophilia A and B (left panel) and 21 moderate haemophilia A and B patients (right panel).

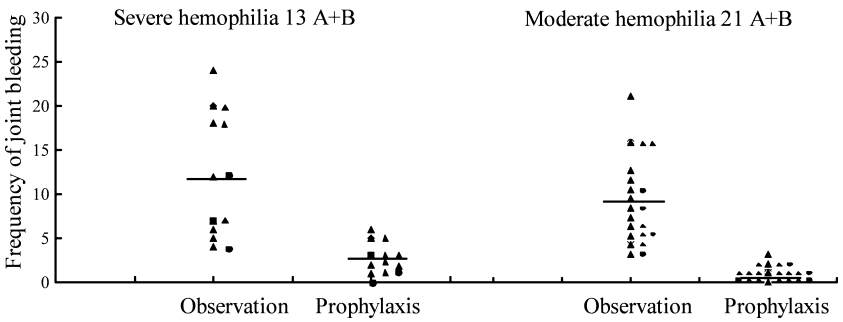

Fig. 2. Aggregate reduction of joint bleeds from observation to prophylaxis period in 13 severe haemophilia A and B (left panel) and 21 moderate haemophilia A and B (right panel) (▲ haemophilia A, ● haemophilia B, — mean).

Table 1. Improvement in joint clinical function.

Type	Patients (*n*)	Joint (*n*)	Joint function improvement (*n*) Poor	Mild	Moderate	Good
Severe VIII	11	25	11	10	3	1
Moderate VIII	17	32	11	12	5	4
Severe IX	2	2	0	2	0	0
Moderate IX	4	10	1	6	0	3
Total	34	69	23 (33.3%)	30 (43.5%)	8 (11.6%)	8 (11.6%)

Table 2. School attendance and school sport participation for 15 severe and moderate haemophilia A and B patient during observation and prophylaxis periods.

Patients (number)	Days absent from school (day) Observation	Prophylaxis	Improvement of sport participation in school (BCH score)* None	1–2	>2
Severe (6)	120	0	1	4	0
Moderate (9)	187	22	2	5	0
Total (15)	307	22			
Mean	20.4	1.4	3	9	0
Median	9	0			
P value	0.005		Improvement 60%		

*Three patients reach to degree 4 in observation period and don't calculate in.

absence for a total of 307 days (mean for all 15 patients 20.4 days, mean 9 days). During prophylaxis, only three of the patients had school absence to a total 22 days (mean for all 15 patients 1.4 days, median 0 days), $P = 0.005$, showing significant improvement during the prophylaxis period.

School sports participation: During the observation period, 12 patients were unable to participate in any school sport, of whom nine (75%) had only mild improvement (≤2 scores increased) during the prophylaxis period.

Daily activities. During the observation period, 29 of 34 patients were unable to participate in any daily activity and improvements were observed during prophylaxis in 20 (69%). Improvement was mild in most patients ($n = 17$) but in a smaller number of patients, moderate ($n = 1$) and good ($n = 2$) improvement were seen.

Discussion

Primary prophylaxis successful in significantly reducing joint bleeding and preventing joint abnormality [12] is at present not feasible in developing countries because of the high cost. Furthermore, in developing countries such as China, many haemophilic children, whether they have severe or moderate disease, already have significant abnormalities in joint structure and function because of frequent joint bleeding. The under-treatment results in an increased likelihood of repeated bleeding. An affordable management strategy is urgently needed to arrest the vicious cycle of bleeding and joint function deterioration.

The present pilot study showed that patients with established joint abnormalities can have good response to relatively low dose secondary prophylaxis totalling 20 IU kg^{-1} $week^{-1}$ with significant improvement in the frequency of joint bleeding. In these children, the resulting improvement in clinical joint function is associated with significant improvement in the QoL, with greatly improved school attendance and school sports participation, although improvement in daily activity was mild.

Clotting factor used in the present low dose prophylaxis was approximately 900–1000 IU kg^{-1} $year^{-1}$. This is much less compared to the high amount used in the Canadian Hemophilia Escalating Dose Primary Prophylaxis Study (CHPS, 3656 IU kg^{-1} $year^{-1}$) [13] and the full dose primary prophylaxis (Malmo regimen) used in the Joint Outcome Study (JOS, 6000 IU kg^{-1} $year^{-1}$) [14,15]. Our secondary prophylaxis protocol therefore used a relatively small quantity of clotting factor that is more affordable in developing countries with an objective to improve joint function and QoL rather than to totally prevent joint dysfunction.

The number of bleeding during low dose secondary prophylaxis in this study remains relatively high with a mean of 2.6 joint bleeding over the 12 weeks prophy-

laxis period (12–15 year^{-1}) in severe haemophilia and a mean of 1 (4–5 year^{-1}) in moderate haemophilia. Thus, although we showed low dose secondary prophylaxis could improve joint function and QoL in the short term (12 weeks), whether longer term low dose secondary prophylaxis will prevent progression of existing joint disease remains unknown.

In addition, several limitations exist in this study. (i) As a result of economical constraint, the on-demand treatment of the joint bleeding of patients in the observation period was not uniform. The improvement attributed to our secondary prophylaxis regime may have been more modest had the on-demand treatment during the observation period be more controlled. Our results are none-the-less valid, given the treatment as represented in the observation period is a reality of haemophilia management in our patients. The treatment in the observation period illustrates the problem of treatment in developing countries, i.e. poor economics and lack of medical insurance, [9] corroborating the observation that low factor usage is common among developing countries [16]. (ii) Our moderately affected patients had relatively severe clinical manifestations in terms of frequency of bleeding and joint disabilities. We believe this is not related to accuracy of diagnosis of moderate haemophilia because inclusion of the 11 patients with factor level between 1% and 2% into severe category for re-analysis (data not shown) did not change the relative frequency of bleeding between the two groups. It is possible that these patients with moderate disease were not recognized during earlier bleeding episodes so that treatment were not provided. Delayed diagnosis, delayed treatment and inadequate treatment related to economic situations almost certainly will set up a vicious cycle resulting in recurrent bleeding, target joint development and joint disability [17,18], another reality of haemophilia management in developing countries. (iii) Even in study setting, our patients could not be on supervised home infusion programme, so that the infusions could only be given on fixed Tuesday and Friday each week with 3 and 4 days intervals between factor infusions. In future, if home care and home infusions become feasible, a study on infusion every 3 days should be performed to access any better control in bleeding.

In spite of the limitations, the current pilot study forms the basis for a larger scale multicentre study for a longer prophylaxis period with proper controls.

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Disclosures

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

References

1 Manco-Johnson MJ, Riske B, Kasper CK. Advances in care of children with hemophilia. *Semin Thromb Haemost* 2003; **29**: 585–94.
2 Steen Carlsson K, Hojgard S, Glomstein A *et al.* On demand vs. prophylactic treatment for severe hemophilia in Norway and Sweden: differences in treatment characteristics and outcome. *Haemophilia* 2003; **9**: 555–66.
3 Zhang L, Li H, Zhao H, Zhang X, Ji L, Yang R. Retrospective analysis of 1312 patients with hemophilia and related disorders in a single Chinese institute. *Haemophilia* 2003; **9**: 696–702.
4 Guo Ye, Zhang L, Zhu X, Yang R. The retrospective survey of 429 children hemophilia in China. *Chin J Pract Pediatr* 2006, **21**: 293–5 (in Chinese).
5 Wu RH, Wu XY, Zhang NN, Zhang JS, Sui Y. Evaluation clinical data and current condition of children hemophilic patients in China. *Chin J Thromb Haemost* 2008; **14**:116–20 (in Chinese).
6 Chuansumrit A, Krasaesub S, Angchaisuksiri P, Hathirat P, Isarangkura P. Survival analysis of patients with haemophilia at the International Haemophilia Training Centre, Bangkok, Thailand. *Haemophilia* 2004; **10**: 542–9.
7 Kulkarni ML, Nanda G. Hemophiliacs – a picture from a developing country: Karnataka, a south Indian state. *Southeast Asian J Trop Med Public Health* 1993; **24**(Suppl. 1): 270–3.
8 Evatt BL. Demographics of hemophilia in developing countries. *Semin Thromb Haemost* 2005; **31**: 489–94.
9 Poon MC, Luke KH. Haemophilia care in China: achievement of a decade of World Federation of Hemophilia treatment centre twinning activities. *Haemophilia* 2008; **14**: 879–88.
10 World Federation of Hemophilia. *Guidelines for the Management of Hemophilia*, 2005. Available at http://www.wfh.org/2/docs/Publications/Diagnosis_and_Treatment/Guidelines_Mng_Hemophilia.pdf or http://www.wfh.org/index.asp?lang=EN.
11 Gilbert MS. Prophylasxis: musculoskeletal evaluation. *Semin Hematol* 1993; **30**(Suppl. 2): 3–6.
12 Carcao MD, Aledort LM. Prophylaxis in the hemophilia population-optimizing therapy. *Haemophilia* 2007; **13**: 227–32.
13 Feldman BM, Pai M, Rivard GE *et al.* Tailored prophylaxis in severe hemophilia A: interim results from the first 5 years of the Canadian Hemophilia Primary Prophylaxis Study. *J Thromb Haemost* 2006; **4**: 1228–36.
14 Nilsson IM, Berntorp E, Lofqvist T, Pettersson H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. *J Inst Med* 1992; **232**: 25–32.
15 Manco-Johnson MJ, Abshire TC, Shapiro AD *et al.* Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med* 2007; **357**: 535–44.
16 O'Mahony B. Global haemophilia care: future challenges and opportunities. *Haemophilia* 2002; **8**: 515.
17 Jansen NW, Roosendaal G, Bijlsma JW, Degroot J, Lafeber FP. Exposure of human cartilage tissue to low concentrations of blood for a short period of time leads to prolonged cartilage damage: an *in vitro* study. *Arthritis Rheum* 2007; **56**: 199–207.
18 Aledort LM, Haschmeyer RH, Pettersson H. A longitudinal study of orthopaedic outcomes for severe factor VIII deficient haemophiliacs. The Orthopaedic Outcome Study Group. *J Intern Med* 1994; **236**: 391–9.

