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A cohort study of the usefulness of primary prophylaxis in patients with severe haemophilia A in our hospital

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【Introduction】

In Japan, the primary treatment for haemophilia in the 1990s was on-demand therapy, and no institutions were administering primary prophylaxis at that time. In 1999, our institution was the first to introduce primary prophylaxis with the intention of treating all patients with severe haemophilia.

【purpose】

The purpose of this study was to evaluate the usefulness of primary prophylaxis in patients with severe haemophilia A in our hospital.

【Patients and methods】

- This study included 15 patients with haemophilia A who received primary prophylaxis at our hospital for a minimum of 5 years.
- We analysed the annualized bleeding ratio (ABR) of joints or other sites, current joint function and X-ray, and MRI at the age of 6 years.
- This study was approved by the St. Marianna University School of Medicine ethics committee (approval No. 2982).

【Result】

1. Patient characteristics

The patients were aged 6.2–16.8 years at the end of October 2014, with a median age of 12.1 years. The observation periods ranged from 5.2 to 15.2 years, with a median period of 8.8 years.

2. Method of introducing primary prophylaxis

- Factor VIII concentrates (25–40 units·kg^{-1}·dose^{-1}) were administered 3 times/week or every other day, according to the Swedish protocol.
- When therapy was first introduced, injections were given once per week, and then twice a week after whoever was giving the injections became skilled at the procedure, and then this was increased further to 3 times/week depending on bleeding symptoms and activity levels.
- Weekly primary prophylaxis began when patients were aged 0.8–2.4 years (mean 1.3 ± 0.4 years, median 1.3 years).
- The number of injections was increased to 2 times/week when patients were aged 1.3–2.7 years (mean 1.8 ± 0.41 years, median 1.8 years).
- The number of injections was increased to 3 times/week when patients were aged 0.9–9.0 years (mean 3.3 ± 2.08 years, median 2.9 years).
- Six patients with high activity levels were transitioned to alternate-day regimens when aged 7.0–12.8 years (mean 10.2 ± 2.6 years, median 10.4 years).
- Injections were usually administered to peripheral blood vessels.

3. ABR after introducing primary prophylaxis

The mean joint and non-joint ABR values were 0.49 ± 0.5 and 1.54 ± 1.69, respectively, for the objective 3 times/week and alternate-day regimens.

4. Functional evaluation of joints

All patients displayed a normal range of motion for both elbows, knees, and ankles. Gilbert scores[1)] for these joints were 0 for all patients. In radiographs also evaluated in October 2014, Pettersson scores[2)] for the elbows, knees, and ankles were 0 for all patients. In MRI findings at age 6, all patients scored 0 on the compatible MRI scale[3)] for the knees and ankles.

Table1 Joint and non-joint ABR after introducing primary prophylaxis

Case	Joint ABR (no./participant/year)				Non-joint ABR (no./participant/year)			
	1 time/week	2 times/week	3 times/week	Alternate-day	1 time/week	2 times/week	3 times/week	Alternate-day
1	0	0.57	0.42	–	0	3.8	1.28	–
2	0	0.25	0	–	0	3.5	1.8	–
3	0	–	0.9	1	1	–	2.4	2
4	1	0.57	0.2	2	3	2.28	1.7	0
5	0	0	0.9	0.75	1	0.3	1.5	3.4
6	0	0.3	0.12	–	3	2.3	0.12	–
7	–	–	0.1	–	–	–	0.55	–
8	–	–	–	1.5	–	–	–	1.8
9	0	0	1.5	0.5	6	0	6.8	6
10	0	0	1	1	0	3.4	2.4	2
11	0	0	0	–	0	0	3.3	–
12	0	0	0.6	0	0	0	1	0
13	0	0	0	–	4	0	0.75	–
14	1	0	0.25	–	1	0	0.75	–
15	0	0.5	1	–	2	2.5	0	–
Mean ± SD	0.15 ± 0.37	0.18 ± 0.20	0.5 ± 0.48	0.96 ± 0.65	1.6 ± 1.89	1.50 ± 1.6	1.7 ± 1.7	2.17 ± 2.07
Median	0	0	0.335	1	1	1.3	1.39	2
Observation periods Mean ± SD Median (months)	3.82 ± 3.34 3	20.6 ± 23.4 14	84.6 ± 78.0 78	21.1 ± 13.0 16	3.82 ± 3.34 3	20.6 ± 23.4 14	84.6 ± 78.0 78	21.1 ± 13.0 16

5. Incidence of inhibitor detection

Low-responder inhibitors were detected in two patients, but the inhibitor was promptly disappeared in immune tolerance induction therapy of short-term.

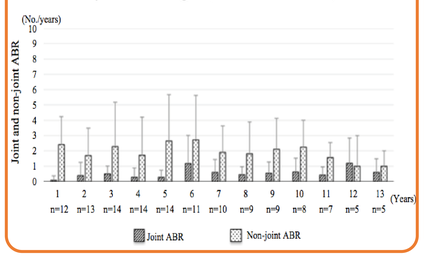
6. Life-threatening bleeding

Life-threatening bleeding events occurred in 2 of the 15 patients during the observation period. Patient 11 sustained an occipital bone fracture and subdural hematoma from a blow to the head. Patient 12 sustained a subgaleal hematoma from a blow to the head.

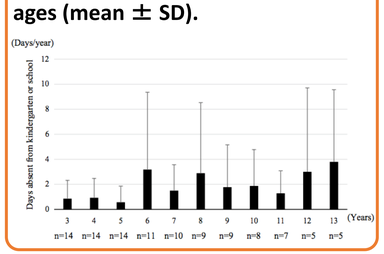
7. Number of bleeding-related hospitalizations

Six of the 15 patients were hospitalized to treat bleeding after beginning primary prophylaxis. Five of these patients were hospitalized only once. Patient 3 was hospitalized 5 times starting at age 8, and on 4 of these occasions it was due to a sports-related traumatic joint injury or muscle bleeding. Of the 10 total hospitalizations, half were for traumatic bleeding due to sports.

8. Changes in joint and non-joint ABR with respect to age (mean ± SD)



9. Days absent from kindergarten or school due to bleeding at different ages (mean ± SD).



10. Sports participation

It was revealed that about 90% of patients who introduced the primary prophylaxis are belong to the extracurricular activities of the movement after elementary school enrollment, and are working in sports aggressively.

11. Trough levels

Primary prophylaxis regimens and trough levels

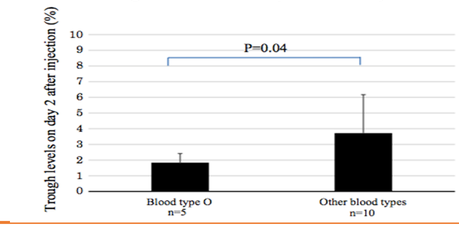
On day 3 after injection in 3 times/week regimens, 43 % of patients exhibited trough levels less than 1 % at some point. All patients exhibited trough levels of 1 % or higher on day 2 after injection in 3 times/week or alternate-day regimens.

11. Trough levels

Relationship between trough levels and age

Positive correlations were observed between age and trough levels on days 2 and 3 after injection (r = 0.74 and r = 0.85, respectively; both p = 0.01).

Relationship between trough levels on day 2 after injection and blood type



【Discussion】

- In our institution, primary prophylaxis for patients with severe haemophilia A had good adherence, was performed safely, reduced the number of bleeding events, and prevented progression to arthropathy.
- Additionally, primary prophylaxis reduced the number of bleeding-related hospitalizations and absences from kindergarten and school, showing that primary prophylaxis can improve the quality of life of haemophilia patients.
- The inhibitor was only observed in 2 patients (overall 13 %) in our study, which is lower than the previously reported 21–30 % rate of inhibitor appearance in previously untreated patients with severe haemophilia.
- Traumatic bleeding did occur in some patients who became highly active. It was considered that it is necessary to regularly evaluate of joints using MRI and reconsider the regimen of prophylaxis for such patients.
- In the future, it may be necessary to maintain trough levels at higher than 1 % depending on the patient's exercise or activity levels. Regimens could also be modified to fit the individual, for example by attempting to make peak and trough levels coincide with club activities.
- Since trough levels tend to be low in younger and blood type O patients, these individuals must be monitored appropriately.
- Since this study was conducted in a single, small facility, it is desirable to examine the utility of primary prophylaxis in a large, multicentre study in Japan in the future.

【Conclusion】

Overall, primary prophylaxis for patients with severe haemophilia A was performed safely, reduced the number of bleeding events, and prevented progression to arthropathy.

【References】

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Conflict of Interest (COI) of the Principal Presenter: No potential COI to disclose.

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Prophylaxis
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