

Physical activity limitations in children with severe haemophilia A. does emicizumab make a difference?

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Abstract

Objective: To assess the effect of emicizumab on physical activity in children with severe haemophilia A.

Method: The prospective cohort study was conducted from October 2021 to April 2022 at the Paediatric Department of Kafrelsheikh University Hospital, Egypt, in collaboration with the Haematology out-patient clinic of the Paediatric Department, Zagazig University, Egypt, and the Paediatric Department of Cairo University Hospital, Egypt, and comprised children aged 4-18 years with severe haemophilia A who received emicizumab prophylaxis. Paediatric Haemophilia Activities List was used to assess physical activity at baseline and after six months of regular emicizumab prophylaxis. Data was analysed using SPSS 26.

Results: There were 29 children, all (100%) boys, with mean age 8.7 ± 3.51 years (range 4-15 years. Of them, 17 (58.62%) patients were negative for inhibitors. Median Paediatric Haemophilia Activities List sum score was 59.54 (interquartile range: 50.15-62.05) at baseline which moved up to 84 (interquartile range: 79.05-86.35) post-intervention ($p < 0.001$).

Conclusion: Emicizumab prophylaxis improved the level of physical activity in children with severe haemophilia A.

Keywords: Emicizumab, Haemophilia, Haematology, PedHAL. DOI: 10.47391/JPMA.EGY-S4-10

Introduction

Haemophilia A (HA) is an X-linked, recessive disorder attributed to a congenital absence or reduction in plasma clotting factor VIII (FVIII). It manifests as prolonged and severe bleeding either in spontaneous way or after traumatic events.¹ It affects about 1 in 5000 males and accounts for 80% of haemophilia cases.² In haemophilic patients, recurrent bleeding, musculoskeletal disorders and arthropathy lead to physical inactivity, which is considered the 4th major risk factor for patient mortality. Participating in sports should be allowed after getting the proper prophylactic administration of coagulation factors to lower the risk of bleeding since physical activity might lead to bleeding.³

The main line of treatment for HA is replacement therapy, either (on demand) in the case of bleeding episodes only, or with regular infusions of FVIII concentrates to avoid bleeding episodes (prophylaxis).⁴ However, many patients suffer from the development of neutralising alloantibodies, called FVIII inhibitors, in response to the infused FVIII, which leads to a variety of medical issues and a reduced quality of life (QOL).⁵

Emicizumab, a bispecific monoclonal antibody with a long half-life that is delivered subcutaneously, links activated FVIII and FX to perform the function of the missing active FVIII. It

is not known to induce FVIII inhibitors, and can work in spite of their existence.⁶

The physical activity and health-related QOL (HRQOL) of children with haemophilia are negatively affected by the disease and its treatment. Haemophilia is manifested by recurrent bleeding in joints and muscles, which leads to haemophilic arthropathy and haematomas, which, in turn, impair HRQOL,⁷ in addition to the burden of treatment, such as difficult venous access, frequent infusions, and the development of inhibitors, which affect patient's adherence to treatment, and results in the need for new treatment modalities.⁸

The current study was planned to assess the effect of emicizumab on physical activity in severe HA children.

Patients and Methods

The prospective cohort study was conducted from October 2021 to April 2022 at the Paediatric Department of Kafrelsheikh University Hospital, Egypt, in collaboration with the Haematology out-patient clinic of the Paediatric Department, Zagazig University, Egypt, and the Paediatric Department of Cairo University Hospital, Egypt. After approval from the ethics review committees of all the 3 institutions, the sample was raised using comprehensive sampling technique from among children aged 4-18 years with severe HA (FVIII < 1%) with current FVIII inhibitors and those negative for inhibitors who had a target joint or with difficult venous access. Those outside the age range, or children diagnosed with other types of haemophilia were excluded.

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After taking written informed consent from the parents of all the participants, detailed history was taken, and they were subjected to clinical examination and laboratory testing after which they received subcutaneous emicizumab in the form of 3mg/kg once weekly for 4 weeks, followed by 3mg/kg every 2 weeks. The patients were followed up for 6 months. Laboratory testing included complete blood count (CBC), liver and kidney function tests, prothrombin time (PT), activated partial thromboplastin time (APTT), internationalised normalised ratio (INR), FVIII level and FVIII inhibitors. Besides, the Paediatric Haemophilia Activities List (PedHAL)⁹ was used to assess physical activity at baseline and after 6 months of regular emicizumab prophylaxis. The PedHAL parent's version 0.12,, available in Arabic, consists of 53 items distributed over 7 domains; sitting/kneeling/standing, legs, arms, use of transport, self-care, household tasks and leisure activities, and sports. It gives the normalised score ranging from 0 to 100, with lower scores indicating worse functions.⁹

Data was analysed using SPSS 26. Paired sample t test was used for comparison of mean differences. $P < 0.05$ was considered statistically significant.

Table-1: Demographic characteristics.

| | |
|----------------------------------------|-----------------------------|
| Age: Mean \pm SD (range) years | 8.72 \pm 3.51 (4 – 15) |
| Weight: Mean \pm SD (range) kilogram | 30.97 \pm 12.97 (16 – 63) |
| Gender: | 100 % males |
| Inhibitors | |
| Positive FVIII inhibitor: N (%) | 12 (41.38%) |
| Negative FVIII inhibitor: N (%) | 17 (58.62%) |

SD: Standard deviation.

Table-2: Baseline and post-intervention values for the Paediatric Haemophilia Activities List (pedHAL).

| Domain | Baseline | | After 6 months of prophylaxis | | p-value |
|-----------------------------|----------------------|---------------|-------------------------------|---------------|----------|
| | Median (IQR) | Range | Median (IQR) | Range | |
| Sitting/kneeling/standing | 55.6 (44.4 – 61.25) | (28 – 80) | 82 (76.7 – 86.7) | (60 – 95.6) | <0.001** |
| Function of legs | 48.9 (44.7 – 58.9) | (26 – 71.1) | 78 (72.2 – 85.2) | (62 – 93.3) | <0.001** |
| Functions of arms | 70 (60 – 78.35) | (50 – 90) | 93.3 (86.7 – 96.7) | (73.3 – 100) | <0.001** |
| Use of transportation | 60 (50 – 70) | (50 – 80) | 90 (80 – 100) | (60 – 100) | <0.001** |
| Self-care | 66.7 (55 – 70.55) | (50 – 82.5) | 93.3 (88.9 – 95.3) | (72.5 – 100) | <0.001** |
| Household tasks | 60 (48.35 – 66.7) | (26.7 – 73.3) | 86.7 (71.65 – 90) | (60 – 100) | <0.001** |
| Leisure activity and sports | 40 (36.7 – 45) | (20 – 55) | 66.7 (60 – 72.65) | (44 – 80) | <0.001** |
| Sum score | 58.5 (50.15 – 62.05) | (38.5 – 76) | 84 (79.05 – 86.35) | (67.7 – 90.4) | <0.001** |

$p < 0.05$ is considered significant. IQR: Interquartile range, SD: Standard deviation.

Table-3: Sum score comparison between baseline and post-intervention values related to patients with and without inhibitors.

| Domain | Baseline | | After 6 months of prophylaxis | | p-value |
|-----------------------------|-----------------------|---------------|-------------------------------|---------------|----------|
| | Median (IQR) | Range | Median (IQR) | Range | |
| FVIII Inhibitors N = 12 | 53.45 (43.67 – 60.57) | (38.5 – 69.5) | 79.75 (73.95 – 88.025) | (69.4 – 90.2) | <0.001** |
| Non FVIII inhibitors N = 17 | 61.5 (54.3 – 62.2) | (39.5 – 76) | 84.4 (80.25 – 86.35) | (67.7 – 90.4) | <0.001** |

$p < 0.05$ is considered significant. IQR: Interquartile range.

Results

There were 29 children, all (100%) boys, with mean age 8.7 ± 3.51 years (range 4-15 years). All 29(100%) patients were receiving 'on demand' therapy during episodes of bleeding, and were shifted to emicizumab prophylaxis. Of them, 12(41.38%) patients had FVIII inhibitors, and 17(58.62%) were negative for inhibitors. Median PedHAL sum score was 59.54 (interquartile range [IQR]: 50.15-62.05) at baseline which moved up to 84 (IQR: 79.05-86.35) post-intervention ($p < 0.001$) (Table 1).

Baseline pedHAL activity list domain scores were low, with leisure activity and sport scoring the lowest 40 (IQR: 36.7-45) and the function of arms scoring the highest 70 (IQR: 60-78.35). After 6 months of prophylaxis, there was a significant improvement in all PedHAL domains, with the highest improvement in self-care and the functions of arms, and the lowest in leisure activity and sports domains (Table 2).

PedHAL scores improved significantly in cases with and without FVIII inhibitors (Table 3).

Discussion

The study found a positive impact of emicizumab on physical activity in children with severe HA. The baseline PedHAL sum score was lower than those reported from Romania,¹⁰ which may be attributed to the fact that all the included cases in the current study had severe HA and most of them were with target joints.

Though the PedHAL sum score improved significantly in the current study, it was lower than the score among Dutch

children who received early intensive factor replacement.¹¹

A study showed improvement in PedHAL score in 4 patients who were given emicizumab prophylaxis as an initial experience in children with inhibitors.¹²

In PedHal, some redundant items are not usually needed, and the list may be shortened as a study showed that decreasing of the pedHAL list items by more than half is expected to keep the most important items while representing all domains of the original PedHAL.¹³

Physical activity domains improved significantly in both patients with and without inhibitors in the current study, which is an advantage for emicizumab prophylaxis. It also overcomes other obstacles related to traditional therapies, such as difficult venous access and frequent transfusions, that affect adherence to treatment.

Significant improvement in all domains of PedHal were noted in the current study, but leisure activity and sports domains scored on the lower side which may be attributed to the fear of parents related to contact sports and school activities. This fear may decrease gradually with time, and the patients are needed to be followed up for a longer period.

In terms of limitations, the current study did not calculate the sample size, which could have influenced the power of the study.

Conclusion

Emicizumab prophylaxis improved physical activity in children with severe HA.

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Conflict of Interest: None.

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