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SHORT COMMUNICATION

Intermediate Dose Prophylaxis in Adults with Haemophilia: A Clinical Audit from a Resource Limited Setting

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Abstract To address the scarcity of real world data on adult prophylaxis from developing world, a short term intermediate dose prophylaxis in adult haemophilia A patients was initiated. A total of eight patients aged > 18 years with moderate/severe haemophilia A were given an average dose of 23 IU/kg recombinant factor VIII (rFVIII) concentrate twice weekly for 2 months. A clinical audit was done on completion of four months. The mean age of the participants was 31.63 (± 6.98) years. The mean bleed rate during two months of episodic versus prophylactic regimen was 5.13 versus 0.63 (p = 0.01) and that of work days lost, hospital visits for hemophilia care were 30.63 (± 24.69) versus zero days, 20.63 (± 16.19) versus zero days respectively. The mean of factor VIII consumed during prophylaxis was 13,500 IU/month (i.e., 23 IU/kg/dose).The median time gap between prophylactic infusion to trough level was 67.50 h (60–74 h) and the median trough level observed was 2.50% (range 1–5%). The results of our clinical audit show that Intermediate dose prophylaxis with rFVIII concentrates in young adult patients with moderate/severe haemophilia A appears to be effective in reducing the frequency of bleeds.

Keywords Hemophilia · Intermediate dose · Prophylaxis · Adults

Introduction

Haemophilia being a congenital lifelong disease needs perpetual medical and personal care [1]. The clinical manifestations of the condition depend on the severity of the disease. Revolution in clotting factor concentrate (CFC) replacement and improvement in clinical care over the last few decades have contributed immensely in extending the life expectancy of persons with haemophilia (PwH) from early adolescence to nearly 80 in developed world [2]. The existing two treatments for haemophilia are episodic treatment (ET) and prophylaxis treatment (PT). An evidence based analysis was done on formal assessment of comparing the benefits of prophylaxis and episodic treatment in all age groups of PwH by applying outcomes hierarchy from haemophilia value frame work. The interpretation was, compared to ET, primary and secondary PT has more clinical benefits in terms of health status achieved/retained, process of recovery and sustainability of health [3–5]. Episodic therapy is the widely practiced treatment policy across the developing world [6]. Even though prophylaxis is accepted as the standard of care in all age groups, it has been practiced more in children with severe haemophilia only [7]. Robust data regarding secondary prophylaxis in adolescents and adults are quite less. Evidence on the duration and dose of adult prophylaxis is also under the process of evolution [6–8].

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The majority of adult PwH in India are not under any prophylaxis treatment. High cost, difficulty in accessing the treatment centres, poor adherence to the treatment and poor venous access are the crucial barriers identified [9–11]. However even for younger adults PT could not be initiated because of limited resources and lack of real world data. To address this challenge we initiated a short term secondary/tertiary intermediate dose prophylaxis in adult PwH with moderate/severe haemophilia A.

Methodology

After getting ethical approval from the institution adult PwH (age > 18 years) with moderate/severe Haemophilia A were briefed about prophylaxis. Those who were willing to participate in the prophylaxis regimen for a period of two months were initiated with the same. The prophylaxis group were given recombinant factor VIII (rFVIII-Novoeight) concentrate in a dose of 23 IU/kg/dose twice weekly for a period of two months. Inhibitor screening was done at the end of prophylaxis. Measurement of factor VIII trough level was performed in all patients. Data regarding number of bleeds per month, number of work days lost and number of hospital visits were collected for ET and PT. A clinical audit was done on completion of four months. The inclusion criteria were Factor VIII inhibitor status negative, more than 50 exposure days to cryoprecipitate/plasma/CFCs and established joint disease. Factor level was assessed with APTT based one stage clotting factor assay and all except one had factor level < 1% but he had clinically severe disease. The inhibitor testing was done with Bethesda inhibitor assay and done at baseline and at two months of completion of PT. The initial dose was taken at the treatment centre and the rest of the doses were taken as home therapy twice weekly for two months. The episode of bleed was defined as per ISTH and was explained to PwH for documentation [12]. Statistical analysis was done in SPSS-21. The continuous variables were expressed in mean with standard deviation and categorical variables as frequency with percentage. Wilcoxon signed rank test and paired *t* test were used to compare the outcome variables. A *p* value of < 0.05 was considered as significant.

Results

A total of eight adults with moderate (n = 1, 12.5%) and severe haemophilia (n = 7, 87.5%) were incorporated in the audit. Among them 7 (87.5%) were taking prophylaxis for the first time.

The mean age of the participants was 31.63 (± 6.98) years.

The educations of the PwH were Middle school-1 (12.5%), High school-2 (25%), Higher secondary-2 (25%) and Graduation-3 (37.5%). The working status was PwH under regular job were 5 (62.5%), with no job-2 (25%) and as student 1 (12.5%).

The mean consumption of CFCs was 13,500 IU/person/month for prophylaxis treatment (PT). The mean dose during PT was 23 IU/kg/dose.

The mean days covered under prophylaxis were 76.63 (± 5.68) days. The median time gap between prophylactic infusion to trough level was 67.50 h (60–74 h) and the median trough level observed was 2.50% (range 1–5%).

The mean bleed rate during episodic therapy was 5.13 (± 2.51) /month and that of prophylaxis was 0.63(± 0.74)/month with a *p* value 0.01. The difference in the bleed rates between the two treatment options was statistically significant. The mean work days lost during ET was 30.63 (± 24.69) days. The work days lost during PT was zero. The mean days of hospital visits for hemophilia care during ET were 20.63 days (SD ± 16.19). During PT the hospital visit days were zero.

The factor VIII inhibitors were reported as absent at the base line and also at the end of prophylactic treatment.

Discussion

The aim of our clinical audit was to create evidence about intermediate dose adult prophylaxis in moderate/ severe haemophilia.

The mean consumption of CFCs was 23 (± 4.74) IU / kg/dose twice weekly for prophylactic treatment (PT) in our study. Miners et al. and Collins study used FVIII concentrate in a dose of 20–40 IU/kg thrice weekly for severe Haemophilia A [6, 13].

When bleed rate was compared between the two treatment strategies in this study, a statistically significant reduction in bleed rate was observed (5.13 vs. 0.63, *p* 0.01). In Collins study they had 19 adults with a mean age of 36.4 years and 16 target joints. On prophylaxis they had significant reduction in joint bleeds (15 in episodic therapy vs. 0 in prophylaxis therapy, $p < 0.001$) [13]. In Miners study the median annual bleed rate during ET was 23.5 (range 1–107) and that of PT (range 0–45) was 14 with $p < 0.0001$ [6].

In the current study, the mean work days lost during ET was 30.63 (± 24.69) days. The work days lost during PT was zero. Tagliaferri et al. [9] had shown a significant reduction in work days lost in his study (32 0.4 in ET to 3 in PT).

The number of bleeds occurred in a patient during PT is believed to be related to the time/week spent with FVIII < 1 IU/dL^{-1}. Our patients were maintained at a

trough level $>$ 1–5 IU/dL^{-1} which was above the threshold. This would have resulted in reduction in bleed rates. The age and health of the patients also could contribute to the clinical benefits [10, 11]. The ideal adult prophylaxis dose is still in evolving phase compared to that of children.

It has been proved that prophylaxis at any age reduces the morbidity and mortality associated with the disease and thereby increasing the quality of life of PwH. Studies revealed even though PT consumed more CFCs and resulted in higher costs was balanced by the better clinical outcomes and the improvement in well being [7, 12, 13]. The ambiguity in adult prophylaxis are optimal dose, dosing interval, duration, lack of consensus in the management of PT, reduction of adherence to PT with increasing age, determinants of variability in phenotype of PwH, the financial and logistics burden to the patient [1, 2, 11, 14, 15].

Conclusion

The results of our clinical audit show that Intermediate dose prophylaxis with rFVIII concentrates in young adult patients with moderate/ severe haemophilia A appears to be effective in reducing the frequency of all type of bleeds as well as help to save their productive work days.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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