Low Dose Prophylaxis vis-a-vis on-Demand Treatment Strategies for Hemophilia: A Cost Effective and Disability Attenuating Approach

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Abstract

Aim: To assess effect of low dose prophylaxis in hemophilics in terms of bleeding, joint function, QoL and cost-effectiveness.

Methods: Analytic study done during one year among 70 adult hemophilics. In observation period (12 weeks), on-demand factor and during prophylaxis (12 weeks), low dose factor was given (Factor VIII 10 IU/KgBW biweekly for haemophilia A and Factor IX 20 IU/KgBW weekly for haemophilia B). Clinical joint assessment was done by Gilbert score and improvement by WFH definitions.

Results: Bleed reduced by 68.99% in moderate hemophilics (40 v/s 129) and 64.86% in severe hemophilics (26 v/s 74) (p<0.05). During observation in moderate hemophilics, joint, soft tissue and mucosal bleeds occurred in frequency of 120, 1 and 8. This was reduced to 39 joint bleeds, 1 soft tissue bleed and no mucosal bleed during prophylaxis. In severe hemophilics, 70 joint, 2 soft tissue bleeds and 2 mucosal bleeds occurred during observation which reduced to 26 joint bleeds without soft tissue/mucosal bleed in prophylaxis. Bleeding episodes decreased by 65.79% in joints, 66.67% in soft tissues, 100% mucosal bleeds.

After prophylaxis one joints (0.61 %) showed good improvement in joint function, thirty (18.18 %) joints showed moderate improvement and ninety two joints (55.76 %) showed mild improvement in joint function. Hospitalization reduced by 60.34% (163 v/s 411) and absenteeism by 53.73% (279 v/s 603). Factors consumption reduced by 12.33 % during prophylaxis period.

Conclusion: The low dose prophylaxis strategy significantly decreased the subsequent episodes of total bleeds including joint bleeds and improved the joint function as well as quality of life.

Introduction

In economically constraint countries like India, hemophilia is considered as a high cost disease. Total estimated prevalence of hemophilia in India based on population alone, is more than 120,000 out of which only 17,346 have been identified.1 Few of these patients have access to treatment with factors. This has lead to high morbidity (disability) and mortality among hemophilics.2

Joint bleeding is a common complication among hemophilics which leads to crippling arthropathy subsequently, if not treated properly. The frequency of joint bleeding also increase with age of the patient. The key to a long-term management of hemophilia is an efficient prophylaxis that prevents joint bleed.3,4 Many studies have demonstrated that prophylactic factor infusion reduces or prevents development of arthropathy among hemophilics.5-10

Currently, prophylactic factor infusion is considered as standard of care for hemophilics with the purpose to reduce joint related morbidity. In India, conventional prophylactic regimens used in high-resource nations, are not possible due to great economic burden on society and health care system. Therefore low dose prophylactic programs, with an aim to reduce arthropathy as well as to improve quality of life is an alternative, economically-friendly, feasible and potentially preferable strategy in India compared to on-demand care.11

Rajasthan is geographically the largest state of India with developing economy as three fourth of the state in under arid zone. A Comprehensive Hemophilia Care Program (CHP) at the SMS Medical College was started in year 2012. Factor infusions and testing are offered to haemophilia patients free by the Rajasthan state government since 2012 under the Chief Minister Free Medicine/Investigation Scheme. This scheme has lead to a dramatic sea-change from only plasma transfusion to on-demand factor therapy in hemophilia patients in Rajasthan.

The data presented here were collected in an endeavour to assess the effect of low dose prophylaxis in hemophilics in terms of frequency of bleeding, joint function, QOL (hospitalization and absenteeism from work/school) and cost-effectiveness.

Material and Methods

This hospital based observational, prospective, analytic study was conducted at a tertiary care center in Rajasthan, during April 2016 to November 2017, after obtaining due permission from Research Review Board/ Institutional Ethics Committee and informed written consent of the study participants. This study included an observation period of 12 weeks.

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and a prophylaxis period of 12 weeks. During the observation period, patients received on-demand treatment of plasma-derived factor infusion (Factor VIII for Hemophilia A and Factor IX for hemophilia B) as free supply under Chief Minister Free Medicine Scheme of Rajasthan State Government. During the prophylaxis period, factor was given in dose of Factor VIII 10 IU per kg body weight once weekly for haemophilia A and Factor IX 20 IU was given in dose of Factor VIII 10 IU during initial 12 weeks observation or more joint bleed into single joint having clinical joint disease with three scores decreased, moderate (3–4 scores decreased) or good (>5 scores decrease).Moderate haemophilia is defined to have baseline factor VIII (FVIII)/factor IX (FIX)activity 1–5%; while severe haemophilia includes baseline FVIII/factor IX activity <1%. All patients enrolled had their baseline factor levels and inhibitor status (after more than 3 days washout period) re-tested. 14

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.14

**Statistical Analysis**

Microsoft Excel® and SPSS® 20 for Windows® were used for data storage and analysis. Paired t test and McNemar’s Test were used to determine statistical difference between variables. Results were considered significant if P < 0.05.

**Results**

We included 70 hemophilics in our study out of which 58 cases were of Hemophilia A (18 severe and 40 moderate hemophilia) and 12 cases were of Hemophilia B (3 severe and 9 moderate hemophilia).

During observation period, total 129 episodes of bleeds occurred in moderate hemophilics and 74 episodes of bleeds occurred in severe hemophilics. In prophylaxis period only 40 episodes of bleeds occurred in moderate hemophilics and 26 episodes of bleeds occurred in severe hemophilics. The episodes of bleeds were decreased by 68.99% in moderate hemophilics and by 64.86% in severe hemophilics during prophylaxis period. (p<0.05) (Table 1A).

During observation period in moderate hemophilics, joint, soft tissue and mucosal bleeds occurred in frequency of 120, 1 and 8 respectively. This was reduced to 39 joint bleeds and only 1 episode of soft tissue bleed during prophylaxis period. No mucosal bleed occurred in moderate hemophilics during prophylaxis period. In severe hemophilics, 70 joint, 2 soft tissue and 2 mucosal bleeds were seen during observation period which reduced to 26 joint without soft tissue/ mucosal bleed in prophylaxis period. During prophylaxis, total decrease in bleeding episodes were 65.79% in joints, 66.67% in soft tissues and 100% in mucosal bleeds. (Figure 1).

After completion of prophylaxis period, all study participants were again evaluated for joint function including shoulder joints, elbow joints, wrist joints, hip joints, knee joints and ankle joints. Out of total 165 joints, one joints (0.61%) showed good improvement in joint function, thirty (18.18%) joints showed moderate improvement and ninety two joints (55.76%) showed mild improvement in joint function. Only forty two joints

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**Table 1A: Mean episodes of all types of bleed**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Total pts.</th>
<th>Observation period</th>
<th>After Secondary prophylaxis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>49 (70)</td>
<td>129</td>
<td>40</td>
<td>0.84±0.66 &lt;0.001</td>
</tr>
<tr>
<td>Severe</td>
<td>21 (30)</td>
<td>74</td>
<td>26</td>
<td>1.24±0.7 &lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>70 (100)</td>
<td>203</td>
<td>66</td>
<td>0.96±0.69 &lt;0.001</td>
</tr>
</tbody>
</table>

**Table 1B: Mean episodes of joint bleeds**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Total pts.</th>
<th>Observation period</th>
<th>After Secondary prophylaxis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>49 (70)</td>
<td>129</td>
<td>39</td>
<td>0.80±0.61 &lt;0.001</td>
</tr>
<tr>
<td>Severe</td>
<td>21 (30)</td>
<td>70</td>
<td>26</td>
<td>1.24±0.7 &lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>70 (100)</td>
<td>190</td>
<td>65</td>
<td>0.93±0.70 &lt;0.001</td>
</tr>
</tbody>
</table>

**Table 1C: Mean duration of hospitalization**

<table>
<thead>
<tr>
<th>Severity</th>
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<th>Observation period</th>
<th>After Secondary prophylaxis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>49 (70)</td>
<td>258</td>
<td>99</td>
<td>2.02±2 &lt;0.001</td>
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<tr>
<td>Severe</td>
<td>21 (30)</td>
<td>153</td>
<td>64</td>
<td>3.05±1.56 &lt;0.001</td>
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<tr>
<td>Total</td>
<td>70 (100)</td>
<td>411</td>
<td>165</td>
<td>2.33±1.92 &lt;0.001</td>
</tr>
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</table>

**Table 1D: Mean duration of absenteeism**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Total pts.</th>
<th>Observation period</th>
<th>After Secondary prophylaxis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>49 (70)</td>
<td>374</td>
<td>173</td>
<td>3.33±3.08 &lt;0.001</td>
</tr>
<tr>
<td>Severe</td>
<td>21 (30)</td>
<td>229</td>
<td>106</td>
<td>5.05±2.42 &lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>70 (100)</td>
<td>603</td>
<td>279</td>
<td>3.97±2.97 &lt;0.001</td>
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</tbody>
</table>

**Fig. 1: Types of bleeds occurring during observation and prophylaxis period**

Data were collected in pre-structured form at each visit regarding frequency of joint bleed, frequency of hospitalization for joint bleed and school / work attendance. At the start and at the end of study period (prophylaxis period), clinical joint assessment was done by the Gilbert score system for each joint. 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).13

**References**


2. The hemophilics patients who were followed regularly at our center and having clinical joint disease with three or more joint bleed into single joint during initial 12 weeks observation period were included in this study. Hemophilics with history of inhibitors were excluded.

3. Seventy adults patients (58 Hemophilia A and 12 Hemophilia B) (age group 16-55 years) were included in this study after due motivation during hospitalization for acute bleeds. All of these patients reside in Jaipur city, within reachable distance from our center.

4. Data were collected in pre-structured form at each visit regarding frequency of joint bleed, frequency of hospitalization for joint bleed and school / work attendance. At the start and at the end of study period (prophylaxis period), clinical joint assessment was done by the Gilbert score system for each joint. 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).13

5. Moderate haemophilia is defined to have baseline factor VIII (FVIII)/factor IX (FIX)activity 1–5%; while severe haemophilia includes baseline FVIII/FIX activity <1%. All patients enrolled had their baseline factor levels and inhibitor status (after more than 3 days washout period) re-tested.14

6. 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.14
The duration of hospitalization (other than for factor infusion) was 411 days in observation period which reduced by 60.34% during prophylaxis period (only 163 days of hospitalization). The duration of absenteeism from work/school was also reduced by 53.73% during prophylaxis period compared to observation period (279 v/s 603). Improvement in quality of life occurred in prophylaxis period in terms of decrease in hospitalization and absenteeism from work/school (Table 1 C, D).

During observation period, all patients (70, 100%) had joint bleed which was reduced to 50 patients (71.43%) during prophylaxis period. Fifty patients (71.43%) required hospitalization and absenteeism from work/school during prophylaxis period compared to observation period (70 patients, 100%) (Table 3).

Total consumption of factors was 11,84000 Units (9,82000 Factor VIII and 2,020000 units Factor IX) during observation period which reduced by 12.33% during prophylaxis period (total consumption 10,38000 Units, FVIII 8,78000 Units and FIX 1,6000 units). Total saving of 1,46000 units (Factor VIII 104000 Units and Factor IX 42000 Units) was made by using low dose prophylaxis.

### Discussion

Hemophilic arthropathy is a disabling disease associated with recurrent joint and soft tissue bleeds. The primary prophylaxis therapy in hemophilia decrease the joint bleeds but the high cost creates implementation difficulties in economically constraint countries like India. The prophylaxis therapy with conventional dosage is also not feasible due to its high cost.

In Rajasthan state, Chief Minister’s Free Medicine Scheme was started on October 2nd, 2012 with a purpose to make available the essential medicines free of cost to the common people. With free of cost availability of Anti-Hemophilic Factor VIII, F IX and FIEBA, the treatment of hemophiliacs in Rajasthan has undergone a sea wide change from only plasma transfusions to on demand factor therapy to low-dose prophylactic factor infusion.

The effect of low dose prophylactic factor therapy is assessed in this study. In this study, the low dose prophylactic factor therapy resulted in significant decrease in subsequent episodes of total bleeds including joint bleeds. The joint function also improved after prophylaxis period. The duration of hospitalization (other than for factor infusion) also significantly reduced in patients during prophylaxis compared to on-demand therapy. The quality of life in terms of reduced absenteeism form work/school also improved significantly.

We used low dose (Factor VIII 10 IU per kg body weight twice a week for haemophilia A and Factor IX 20 IU per kg body weight once weekly for haemophilia B) during prophylaxis period which is much lesser that the dose given in previous primary prophylaxis studies. 

Rajasthan is geographically the largest state of India with estimated population of 68,548,437 with three fourth of the state is under arid zone. The estimated population of haemophiliacs in Rajasthan is approximately 7,000 and the per capita income of INR 72,156.

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### References

Introduction:
Heart Failure (HF) is predominantly a disorder of the elderly with rates increasing exponentially with time.

Materials and Methods:
The Observational and prospective study was conducted in all elderly patients admitted in emergency, medicine wards and ICU from January 2017 to December 2017. The study included all patients>60 years of age diagnosed as acute heart failure as per Boston Criteria. Patients with chronic obstructive pulmonary disease were excluded. Patients were all recruited in the study after satisfying inclusion and exclusion criteria were recruited in the study after ethical approval was obtained from Ethical committee.

Results:
Out of 56 patients 44 (78.57%) were discharged 12 (21.43%) patients expired. As per Boston score criteria, maximum patient 33 (66.07) fell into range of 8-12 while remaining had systolic dysfunction was seen in 26 patients (46.43%). As per Boston score on 2D Echocardiography Diastolic HF (EF >40%) was seen in 30 patients (53.57%) and 46.43% of study population respectively. Based on Ejection fraction there was seen diastolic dysfunction in 31 patients (55.36%) and systolic dysfunction was seen in 14 patients (25.00%).

Discussion:
The significant increase of life expectancies over the last few decades, has lead to a major change in the morbidity and mortality profile of elders. HF is predominantly a disorder of the elderly with rates improved management very less exists on heart failure in India.

Conclusion:
Annual 1 to 2% increase in the elderly population, is expected in coming decades. Therefore, there is a need for better understanding of clinical profile, etiology and outcome of heart failure in such group at tertiary care.

References: