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Haemophilia management programme: Transformation during COVID-19

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***Background & objectives*: Haemophilia is a debilitating bleeding disorder with significant comorbidities affecting the quality of life. In India, the management of these individuals is still limited to on-demand institutional treatment with coagulant factors. In this study, we highlighted the problems faced by these patients in the COVID-19 period due to nationwide lockdown.**

***Methods*: A retrospective study was done to ascertain the trend in the number of patients with haemophilia A and B visiting the hospital, those succumbing to haemophilic complications and indications for factor requirement in the pre-COVID (October 2019-March 2020) and during the COVID-19 period (April-September 2020). Representative cases with unusual complications were described along with significant challenges faced in providing standard care of treatment to these individuals due to the COVID-19 pandemic.**

***Results*: A total of 818 and 162 individuals with haemophilia A and B, respectively, were registered with the department. The overall number of patient visits to the hospital significantly reduced from an average of 6.9 outpatient department (OPD) visits per patient in the pre-COVID-19 period to an average of 3.9 OPD visits per patient and admissions reduced to 50 per cent during the COVID-19 period. This led to a reduction in utilization of factors VIII and IX except VIIa for haemophilia with inhibitors. There was no factor utilization for elective surgeries during the COVID-19 period. A total of eight patients succumbed to haemophilia-related complications during the COVID-19 period due to delay in reaching the hospital. The challenges faced in the management of three cases with musculoskeletal bleeds, one case with scrotal haematoma and one with haemothorax during the COVID-19 period were also highlighted.**

***Interpretation & conclusions*: COVID-19 pandemic has unveiled the need for on-demand home treatment with coagulant factors and has also brought to light the existing need for primary prophylaxis, especially for younger individuals with haemophilia.**

Key words Bleeding disorder - coagulant factor - COVID-19 - emicizumab - haemophilia - management

Haemophilia A and B are prototypes of common genetic disorders. Despite significant underdiagnosis, India harbours the highest number of patients with haemophilia according to the World Federation of Hemophilia (WFH) 2020 global survey[1]. Although a great progress has been made in the last decade

with the advent of new therapeutic approaches such as long-acting coagulation factor concentrates, non-replacement therapies such as emicizumab, fitusiran and concizumab and gene therapies[2], conventional agents such as plasma-derived or recombinant FVIII/FIX concentrates still remain the mainstay of management of these individuals in India. With the availability of coagulant factors, haemophilia patients are well managed, especially for acute bleeding episodes and surgical interventions. However, these patients are mainly managed in the hospital and home therapy is usually not available. With India imposing a nationwide lockdown on March 25, 2020 due to the COVID-19 pandemic, management of such patients became challenging.

In this study, we present the data on haemophilic patients' morbidity, mortality and change in factor utilization in pre-COVID-19 period and after the start of lockdown along with the description of a few representative cases and complications that occurred mainly due to delay in hospitalization and partly contributed by lockdown and pandemic.

Material & Methods

This is a retrospective study of patients with haemophilia A and B managed in the department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, a tertiary care centre. Patients with haemophilia A with and without inhibitors received recombinant factor VIIa and VIII concentrates, respectively. Patients with haemophilia B received plasma-derived factor IX concentrates. Outpatients usually comprised those with musculoskeletal bleeds or minor mucosal bleeds. Those with severe bleeds such as iliopsoas or major organ involvement were treated on an inpatient basis. The factor dosage for different indications were provided according to the World Federation of Hemophilia (WFH) guidelines[3]. The trends in the number of visits by patients with the referral indications in the pre-COVID (October 2019-March 2020) and during the COVID-19 period (after the lockdown was declared, *i.e.* April-September 2020) were ascertained. Data of immediate six months before lockdown were taken to represent the pre-COVID-19 period. The indications were grossly divided into musculoskeletal, gastrointestinal and genitourinary, ENT (gum bleed and epistaxis), intracranial bleed, trauma and elective surgery. The factor concentrates VIII, IX and VIIa usage data for both in- and outpatients were obtained from the records maintained in the department for comparative analysis between the two periods. Data on number of patients succumbing to complications of haemophilia during the study period were ascertained through telephonic communication. Five clinical cases with unusual complications were also described where the delay in getting treatment due to the COVID-19 pandemic contributed partly to the severity of complications.

Statistical analysis: The analysis was performed using SPSS software (IBM SPSS Statistics for Windows, Version 24.0. IBM Corp. Released 2016, Armonk, NY, USA). Demographic data were presented as relative frequency in the form of mean and standard deviation. Proportions were compared using the Chi-square test.

Results

A total of 818 patients of haemophilia A and 162 patients of haemophilia B were registered with the department. Among them, 44 individuals with haemophilia A were positive for inhibitors. During the COVID-19 period, uninterrupted services were provided 24 h for the registered patients. Telephonic conversations were made and factors were issued on an outpatient department (OPD) basis. Reverse transcription–polymerase chain reaction testing for COVID-19 was also provided free of cost for these patients to prevent any hassle in the management. Despite this, the number of patient visits and patients getting admitted to hospital with haemophilia A and haemophilia B during the COVID-19 period reduced significantly as compared to pre-COVID-19 period (Table I). The overall number of patient visits to the hospital significantly reduced from an average of 6.9 OPD visits per patient in the pre-COVID period to an average of 3.9 OPD visits per patient during the COVID-19 period ($P<0.001$). The number of inpatient admissions also reduced to 50 per cent during the COVID-19 period in comparison to the pre-COVID period, thereby leading to a decrease in utilizations of factors except factor VIIa. The mean utilization of factors for a total of six months in the pre-COVID and during the COVID-19 period for factors VIII, IX and VIIa is depicted in Table II.

There were no elective surgeries performed for six months after the start of COVID-19 pandemic. The number of trauma patients requiring factors also reduced. The factor requirement for ENT, gastrointestinal or genitourinary indications and number of patient visits for musculoskeletal complications

Table I. Details of visits by outpatients and inpatient admissions for haemophilia in the pre-COVID-19 and during the COVID-19 period

Details of visits	Number of outpatient visits	Number of inpatient admissions
Number of visits by patients and admissions in pre-COVID-19 period (October 2019-March 2020)		
Haemophilia A	595	92
Haemophilia B	156	22
Haemophilia A with inhibitors	-	3
Total	751	117
Number of visits by patients and admissions during COVID-19 (April-September 2020)		
Haemophilia A	120	50
Haemophilia B	50	4
Haemophilia a with inhibitors	-	7
Total	170	61
P	<0.001	

Table II. Mean factor utilization for haemophilic patients in the pre-COVID-19 and during the COVID-19 period

Factors	Factor utilization, mean±SD		*P*
	Pre-COVID-19	During COVID-19	
VIII (units)	212,541.7±65,235	102,333±61,974.1	0.01
IX (units)	75,400±19,822.4	28,200±12,401.3	<0.001
VIIa (mg)	11.2±16.8	15.3±15.6	0.7

SD, standard deviation

reduced significantly ($P<0.03$) during the COVID period. Factor consumption for serious conditions such as intracranial bleed remained the same (Table III). A total of eight patients succumbed to haemophilia-related complications during the COVID-19 study period (musculoskeletal-related complications: 2, gastrointestinal: 1 and intracranial bleed: 3). Six of them expired before being taken to the hospital and two succumbed within one or two days of hospital admission owing to the delay in reaching a hospital.

Case 1: A 26 yr old man with haemophilia A and inhibitor positivity since 2016 (inhibitor level: 16.8 Bethesda units) was admitted with complaints of swelling of the right thigh and knee following a fall three months prior and high-grade fever for one week before presentation. Before admission, he was treated at his native place with factor VIII (factor VIIa was not available) and antibiotics. On examination, diffuse swelling involving all the compartments of the right thigh with pus discharging ulcer from the right knee was present (Fig. A). Radiological evaluation did not show any evidence of fracture, pyogenic arthritis or osteomyelitis. Ultrasonography revealed a large intramuscular haematoma involving the entire thigh. He was started on injectable antibiotics, and factor VIIa concentrates were given initially to relieve pain. While pain and pus discharge reduced after a period of two weeks, the haematoma of the right thigh started regressing slowly and caused significant restriction of movement. He was started on emicizumab (3 mg/kg subcutaneous weekly) and received four loading doses. After a total of eight weeks of admission, there was a resolution of haematoma and some improvement on mobilization with physiotherapy.

Case 2: A 50 yr old male with haemophilia A, who was treated at his native place for right thigh swelling and pain for 15 days was admitted to our hospital due to the progression of his symptoms. Inhibitor screening done twice was negative. He was infused factor VIII, 50 units per kg. Ultrasound revealed a large haematoma of the right thigh. Packed red blood cells were transfused in view of anaemia. With the frequent infusion of factor VIII concentrates, there was a clinical response. He was advised factor infusions for cover for a few weeks but took discharge and could not come for regular infusions. He was again admitted twice within a span of 7-14 days with worsening of thigh swelling. In the last admission, ultrasound revealed a large, loculated fluid collection in the right thigh for which drain was inserted. Intravenous antibiotics were started and around 2500 ml of serosanguineous fluid was drained over a period of 14 days (Fig. B). Factor therapy was continued and drain was removed after 14 days. With ultrasonography showing a small residual collection, he was subsequently discharged. There was no repeat collection on follow up.

Case 3: A 47 yr old male with haemophilia A developed scrotal swelling. However, due to financial constraints and COVID-19 situation, he did not visit the hospital. After one month of progressive increase in the size of swelling followed by ulcerative lesion, he came to our hospital. On examination, there was a large diffuse swelling involving the entire scrotum

Table III. Comparison of factor usage in haemophilic patients for various indications during the pre-COVID-19 and COVID-19 periods

Indications	Pre-COVID-19 (n)		During COVID-19 (n)		*P*
	OPD	IPD	OPD	IPD	
ENT	13	13	5	3	<0.001
Gastrointestinal and genitourinary	22	27	0	9	0.03
Musculoskeletal	74	61	43	43	0.03
Intracranial bleed	0	7	0	5	0.4
Trauma	0	6	0	1	0.2
Elective surgery	0	3	0	0	0.2
Total	109	117	48	61	0.008

OPD, outpatient department; IPD, inpatient department; ENT, ear, nose and throat

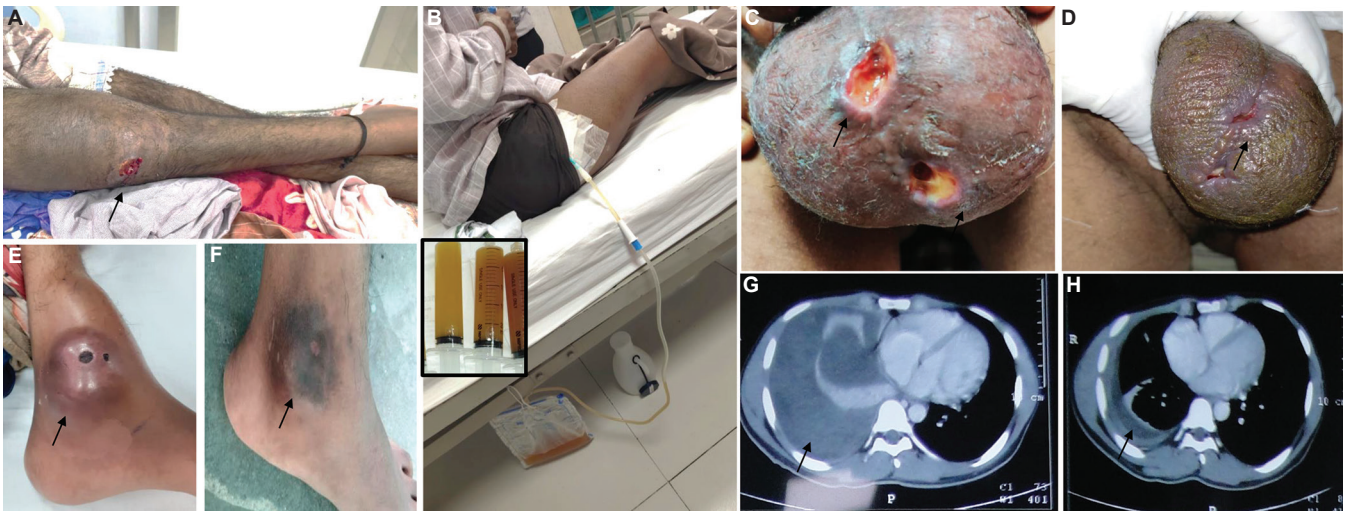

Figure. (**A**) Case 1 with right lower-limb swelling; (**B**) Case 2 with a large collection in the right thigh with drain; (**C** and **D**) Case 3 with scrotal haematoma and ulcer pre-treatment and healed wound post-treatment; (**E** and **F**) Case 4 with left ankle hemarthrosis pre- and post-treatment; (**G** and **H**) Case 5 with CT chest showing gross haemothorax of the right lung before treatment and repeat CT after two months showing significant resolution of haemothorax and expansion of the lung.

and necrotic ulcer with pus discharge from the anterior aspect of the scrotum (Fig. C). Intravenous antibiotics were started. Ultrasonographic evaluation was suggestive of loculated haematoma with echogenic debris and normal testis. Factor VIII concentrate was administrated and inhibitor screening was negative. He was discharged after a period of 14 days on oral antibiotics following the healing of the wound (Fig. D).

Case 4: A 14 yr old male with haemophilia A presented with left ankle haemarthrosis. With progressive increase in size of swelling, the patient was advised for admission for full workup and continuous factor therapy. However, due to travel restrictions, he could not get admitted and could not afford factor therapy from outside. The swelling further worsened causing severe pain and restriction of movements. He was admitted thereafter, and on examination, the swelling which was initially involving the medial malleolus became diffuse and extended into the medial and anterior aspect of the calf muscles of the left leg with necrotic skin ulcer (Fig. E). Factor VIII and antibiotics were administered. He required factor administration for a total period of 11 days. This resulted in a 50 per cent reduction in swelling with no signs of inflammation. However, due to financial constraints, parents took discharge. He was advised for continuous factor therapy on an outpatient basis. A telephonic follow up after two months revealed complete healing of swelling (Fig. F).

Case 5: A 22 yr old male with haemophilia A presented with complaints of right-sided chest pain with dry cough for a period of one week. There were no signs of infection. Radiograph of the chest was initially normal. His pain continued and thus he came for factor infusions irregularly for a week. He was advised hospitalization. However, due to fear of COVID-19 infection, he delayed admission for two weeks. On admission, examination revealed stable vitals and absent breath sounds on the right side. Chest X-ray revealed gross haemothorax on the right side. Post-factor activated partial thromboplastin time (APTT) after maximal factor administration showed no evidence of correction. Factor VIII inhibitor levels were 26.4 BU. In view of deranged APTT, intercostal drainage was deferred, but therapeutic tapping was done twice draining 100-200 ml of serosanguineous fluid. Computerized tomography revealed gross haemothorax with post-contrast enhancement of the pleural wall (Fig. G). Activated factor VII for four days was administered which prevented further worsening of bleed in the pleural cavity. However, he started developing high-grade fever spikes on day five of admission and was started on intravenous antibiotics. Long-term antibiotics were provided. The patient could not afford for alternative treatment with long-acting bypassing agents. He was admitted for almost a period of one month. With no signs of infection, he was discharged on request and was advised for chest physiotherapy. A repeat computed tomography scan after two months showed significant resolution of haemothorax and expansion of the lung (Fig. H).

Discussion

The last decade has seen a remarkable change in haemophilia care in India. However, COVID-19 pandemic has posed serious challenges in managing these individuals and brought out the underlying lacunae in management and emphasized the need to update the government-supported haemophilia management programme. Our results showing a decrease in factor usage and patients visits after the spread of COVID-19 pointed towards difficulties in travelling and reluctance to visit the hospital by patients during the lockdown period.

While haemophilia societies were started all over India with tremendous efforts of the Hemophilia Federation of India[4], home therapy and prophylaxis are not available to most of these patients. The pandemic situation also had a negative impact on the on-demand institutional factor therapy. The five illustrative cases showed how the delay in receiving the factors after the start of bleed led to further worsening of bleeding episodes and secondary complications. This, in turn, increased the cost of treatment in the form of increased need of factors and supportive treatment in addition to the sufferings and period of hospitalizations. The decrease in patient visits, especially for musculoskeletal problems, highlighted the morbidity endured by these patients during COVID-19 lockdown. These scenarios highlighted the lacunae in the management of these individuals and emphasized the need for home therapy and prophylaxis to prevent mortality and morbidity and also for overall cost-effectiveness.

There were certain limitations in this study. Data were not collected by surveying all the patients under follow up and were limited to a patient visiting the hospital. Furthermore, information about deaths was restricted to those who were in contact with us. We could not contact all the patients registered with us to assess the actual magnitude of difficulties faced by them.

To conclude, this study highlighted the hardships encountered by the haemophilic patients. This necessitates the availability of on-demand home therapy and subsequently primary prophylaxis therapy not exclusively for the prevention of disastrous complications but to improve the quality of life of these individuals.

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***Conflicts of Interest*:** None.

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