PROTOCOL TITLE

Comparison of Low Dose Emicizumab and Low Dose Factor VIII as a Prophylaxis in Hemophilia A patients- A Randomized Control Trail.

Place of Study	**:**	Department of Hematology and BMT Unit, Dhaka Medical College Hospital Dhaka-1000, Bangladesh.
Organization's Unique Protocol ID	**:**	ERC-DMC/ECC/2024/215
Type of the study	**:**	Experimental Study- Randomized Control Trial
Duration of study	**:**	One year
Expected time of start	**:**	01.04.2025
Last Update of the protocol submitted	**:**	01.02.2025

Introduction

Haemophilia A is an X-linked bleeding disorder that arises from mutation in factor VIII gene resulting in under production or dysfunction of coagulation factor VIII (FVIII). It affects one in 5000 live male births (CDC 2018). Patients with plasma factor VIII level <0.01IU/ml are classified as having severe Haemophilia A, those with level 0.01-0.05 IU/ml as moderate Haemophilia A and those with level >0.05-0.40 IU/ml as mild Haemophilia A [1].

Patients with severe hemophilia experience frequent spontaneous bleeding events, eighty percent of which occur in the musculo-skeletal system, while twenty percent take place in the central nervous system and other organ systems such as skin, GIT and other mucous membrane [2]. Recurrent joint bleeding is a hallmark of severe hemophilia A and a major cause of morbidity, leading to progressive irreversible joint damage and the development of hemophilic arthropathy [3].

Haemophilic bleeding events are treated with recombinant FVIII concentrate. But such episodic factor replacement therapy does not alter the natural history of spontaneous bleed leading to musculoskeletal damage and other complications due to bleeding. Therefore, Prophylaxis is recommended by the World Federation of Hemophilia as the standard of care for patients with severe hemophilia or with severe clinical phenotype, especially in young children [4]. Regular prophylaxis among patients with severe haemophilia A has clear efficacy to prevent bleeding episodes and subsequent sequelae of muscles and joints damage.

Regular prophylaxis with intravenous FVIII concentrates is considered as the standard of care in many countries especially developed countries. Factor VIII prophylaxis is 3 types- high dose prophylaxis (25-40 IU/kg 3 times/week), intermediate dose prophylaxis (15-25 IU/kg 3 times/week), and low dose prophylaxis (10-15 IU/kg 2- 3 times/week). Low dose prophylaxis approach has been adopted as an economically feasible alternative to high dose prophylaxis in resource-constrained countries because it resulted in improved outcomes compared to on-demand treatment in terms of ABR, joint bleeding and hospitalization [5].

Owing to the short half-life of about 12 hours, at least two intravenous infusions per week is required that may be burdensome for paediatric patients and their caregivers and may necessitate the use of central venous access with the risk of infection-related complications [6]. In addition, 20%–30% of patients develop inhibitors requiring immune tolerance induction (ITI) with a reported success rate of~53% to 79% [7,8]. For patients undergoing or refractory to immune tolerance induction therapy, bleeding events are controlled with bypassing agents (e.g, recombinant activated FVII [rFVIIa] or activated prothrombin complex concentrate [aPCC]). Although these treatments can be efficacious for many patients, neither of these therapies is considered as effective as FVIII replacement and there is no reliable laboratory measure of their hemostatic effect [9]. So, there is a need for alternative non-factor agent.

Emicizumab (Hemlibra®, Roche), which is a humanized, bispecific, monoclonal antibody, as one non-factor product, could bridge activated factor IX and factor X, replacing the function of FVIII and restoring hemostasis in HA patients [10]. Considering its high bioavailability and long half-life time of about 30 days, emicizumab has the potential to improve patient adherence largely, which attributes to its long interval and subcutaneous injection. As reported by previous well-designed clinical trials, emicizumab has a strong capacity to reduce bleeds compared with traditional prophylaxis using FVIII concentrates [11,12,13,14]. Owing to a complete absence of structure homology compared to FVIII, emicizumab is not suspected to induce FVIII inhibitor and can play it's role irrespective of presence of FVIII inhibitor [15]. Long-term emicizumab prophylaxis demonstrated a favorable safety profile with encouraging efficacy. However, the standard regimen, consisting of four weekly loading doses of 3 mg/kg followed by a maintenance dose at 1.5 mg/kg weekly or 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks, is costly and unaffordable for economically constrained countries limiting patient access. Any treatment protocol using a lower dose with almost equivalent efficacy will have significant impact on access to prophylaxis and the overall quality of life (QoL) of PwHA in low-or middle-income countries [16]. Low dose monthly Emicizumab with or without initial four loading doses has been found effective in reducing annualized bleeding rate significantly in few recent studies [17].

Rationale of the study

Low dose factor VIII prophylaxis is practiced around the world. Role of standard dose Emicizumab prophylaxis is well established. Emicizumab is an expensive drug. Standard dose Emicizumab prophylaxis is very expensive for hemophilia A patients and troublesome for government to ensure continuous supply. We intend to compare low dose Factor VIII prophylaxis with low dose Emicizumab prophylaxis and compare whether low dose Emicizumab is as effective as low dose Factor VIII prophylaxis. So, we can continue prophylaxis program in hemophilia A patients with a cost-effective way in our country without risking the patient health. Moreover, Emicizumab prophylaxis reduces the chance of developing inhibitor to Factor VIII.

Hypothesis

Low dose Emicizumab prophylaxis is as effective as low dose Factor VIII prophylaxis in hemophilia A patients.

Research objectives

General objective

- To determine whether low dose Emicizumab prophylaxis is as effective as low dose Factor VIII prophylaxis in hemophilia A patient.

Specific objectives

- To assess effect of low dose Emicizumab prophylaxis in hemophilia A patient by means of determining annualized bleeding rate (ABR), annualized joint bleeding rate (AJBR), annualized spontaneous bleeding rate (ASBR), APTT.
- To assess effect of low dose Factor VIII prophylaxis in hemophilia A patient by means of determining annualized bleeding rate (ABR), annualized joint bleeding rate (AJBR), annualized spontaneous bleeding rate (ASBR), APTT.
- To compare the variables among low dose Emicizumab prophylaxis and low dose Factor VIII prophylaxis group.

Materials and Methods

Study design: Experimental study- Randomized Control Trial.

Study period: One year (July 2024 to June 2025)

Place of study: Department of Hematology and Bone Marrow Transplant Unit, Dhaka Medical College Hospital (DMCH), Dhaka, Bangladesh.

Study population: Severe hemophilia A patients attending in department of Hematology and Bone Marrow Transplant Unit, Dhaka Medical College Hospital (DMCH), Dhaka, Bangladesh.

Selection criteria

Inclusion criteria:

Low dose Emicizumab group (Case group)

1. Severe hemophilia A patient with or without inhibitor to factor VIII.

Low dose Factor VIII group (Control group)

1. Severe hemophilia A patient without inhibitor to factor VIII.

Exclusion criteria:

Low dose Factor VIII group (Control group)

1. Severe hemophilia A patient with inhibitor to factor VIII.

Sample Size: Sample size is determined by availability of drugs rather than any scientific formula. We can provide Emicizumab to 10 patients for 28 weeks as prophylaxis. So, we intend to include 10 patients in each group. [18]

Sampling technique: Block Randomization. Severe hemophilia A patients will be randomized 6:4:10 in patients with inhibitor (Emicizumab Group): Patients without inhibitor (Emicizumab Group): Patients without inhibitor (Factor VIII Group). Randomization will be generated by computer. One such plan has been added in appendix.

Variables

A. Independent variable

1. Socio-demographic variables

- Age
- Educational status
- Weight
- Occupation

2. Variables related to Hemophilia

- Severity of hemophilia A – Moderate or Severe
- Presence of Inhibitor

B. Dependent variable

1. Main outcome variables-

- Annualized bleeding rate (ABR)
- Annualized joint bleeding rate (AJBR)
- Annualized spontaneous bleeding rate (ASBR)
- APTT

2. Confounding variables-

- Development of new inhibitor to factor VIII

Study procedure

This study will be conducted in the department of Hematology and Bone Marrow Transplant Unit, Dhaka Medical College Hospital (DMCH), Dhaka for one year duration following approval from the Institutional review board (IRB), DMCH.

we will select 20 severe hemophilia A patients randomly from interested patients. we will randomize 6 patients with inhibitor to factor VIII in Low dose Emicizumab with Inhibitor group (I) and rest 14 will be randomized by block randomization in Low dose Emicizumab (without inhibitor-WI) and low dose Factor VIII group at 4:10 ratio. Patients and/or parents will be thoroughly informed about the study, drugs to be used, risk & benefits and follow up plan. Their consent for this study will be taken and they will be enrolled in the study. For Participants under 18 years, consent will be obtained from parents or legal guardian. Participants ≥18 years will give his/her own consent.

Randomization will be generated by computer. One such plan has been added in the end of protocol.

Dose- Emicizumab 0.8-1.5mg/kg weekly for 4 weeks as loading dose. Then 0.8-1.5mg/kg 4 weekly for 24 weeks. Inj. Emicizumab has 30mg in vail. Dose will be round up to 30mg, 60 mg or any dose nearest to 1 mg/kg when fractionation of vail is possible.

Factor VIII- 10-15 unit/Kg twice/thrice weekly for 28 weeks. Inj. Factor VIII is available in 250U, 500U, 750U vails. Dose will be round up to full nearest full vail strength.

If extended half-life injection is available- twice weekly. If standard half-life Factor VIII is available- thrice weekly.

Follow Up-

Participants in Emicizumab group will visit weekly for first 4 week than once 4 weekly for 24 weeks (Total 28 weeks).

Participants in Factor VIII group will visit twice/thrice weekly for 28 weeks. Information of data collection sheet will be collected once in a week.

Patient has to come physically for every dose schedule. He will be asked for number of bleeding-traumatic, spontaneous bleeding, joint bleeding, frequency of hospital visit due to hemophilia related problems in between doses and investigate for APTT.

Participants in Emicizumab group will visit weekly for first 4 week than once 4 weekly for 24 weeks.

Participants in Factor VIII group will visit twice/thrice weekly for 28 weeks. Information of data collection sheet will be collected once in a week.

Primary End Point- This study will include 28 weeks follow up of the patients. Each patient will receive 28 weeks prophylaxis. After that patients will continue prophylaxis if drugs are available but would not be included in the study. Otherwise, they will receive on demand treatment in our HTC (hemophilia treatment center). Patient would continue therapy and follow up in OPD but would not be included in the study.

Supportive care and rescue-

A Data and Safety Monitoring Board (DSMB) will be formed which will include members suggested by IRB. Any adverse event or serious adverse event (will be delt with proper medical care.

If any patient developed spontaneous or traumatic bleeding episode during prophylaxis, they will be treated with standard dose on demand treatment on priority basis.

Pharmacodynamics and pharmacokinetics of Emicizumab and Factor VIII

Pharmacodynamics and pharmacokinetics of Emicizumab and Factor VIII is attached in appendix III

Data Collection-

Data will be collected on predesigned case record form and will be collected by face-to-face interview, physical examination and collecting laboratory reports.

Data Analysis

After data collection data will be edited, cleaned and prepared for analysis at the end of the study. The statistical analysis will be conducted using SPSS (statistical package for the social science) version 25 statistical software. The findings of the study will be presented by frequency and percentage in tables. Main outcome variables- Annualized bleeding rate (ABR), Annualized joint bleeding rate (AJBR), Annualized spontaneous bleeding rate (ASBR), APTT will be compared (mean) among the groups by Anova/ Kruskal Wallis test (considering distribution of data). Where $p<0.05$ with 95% confidence level will be considered as significant.

Operational definitions

Severity of hemophilia-

Severe- Factor VIII level <1 IU/dL (<0.01 IU/mL) or <1% of normal

Moderate- Factor VIII level 1- 5 IU/dL (0.01- 0.05 IU/mL) or 1- 5% of normal

Mild- Factor VIII level 5- 40 IU/dL (0.05- 0.40 IU/mL) or 5- <40% of normal

Annualized bleeding rate (ABR)- ABR will be calculated as the number of reported bleeding events divided by the number of months in the reporting time window (8 weeks to 12 months) and multiplied by 12. [19]

Annualized joint bleeding rate (AJBR)- AJBR will be calculated as the number of reported joint bleeding events divided by the number of months in the reporting time window (8 weeks to 12 months) and multiplied by 12. [19]

Annualized spontaneous bleeding rate (ASBR)- ASBR will be calculated as the number of reported spontaneous bleeding events divided by the number of months in the reporting time window (8 weeks to 12 months) and multiplied by 12. [19]

Ethical consideration

- Before starting this study, the research protocol will be submitted and approved by the Institutional Review Board of DMCH, Dhaka.
- We are not exposing patient to any new drugs which safety and efficacy is not well established. Both Emicizumab and factor VIII injections are widely used among hemophilia patients.
- All participants will be informed about the objectives, methodology and purpose of the study in an easily understandable way.
- All information regarding benefits and hazards regarding the study will be delivered to the all participants & only those who agree to participate will be included in the study.
- Verbal and written consents will be obtained from all participants without any influences prior to data collection.
- Data obtained from the study will be used only for research purposes. The confidentiality of all study information will be maintained strictly.
- Participants can withdraw themselves from the study at any time even after giving consent.

Methods of maintaining confidentiality

- Research data will be coded.
- Data will be stored in a locked cabinet.
- Only research personnel will be allowed to access data.
- There is minimum physical, psychological, social and legal risk.
- Proper consent will be taken.
- Privacy of the patient will be maintained.
- No intervention will be used here.

Utilization of Results: The result of the study may help to standardized protocols of low dose prophylaxis in hemophilia A patients. Low dose prophylaxis will save money and reduce economic burden of patients and government. The result of the study will be published in national and international journals.

Facility: The study will be conducted in department of hematology and BMT unit, DMCH. Co-investigators will be responsible for maintaining patient follow up and data collection. Team of volunteer doctor and nurse will be responsible for managing any clinical emergency of the patients. The drugs will be stored in our department. APTT (investigation) will be done in our laboratory.

References

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Work schedule

Activity ↓ (months →)	1st	2nd	3rd	4th	5th	6th	7th	8th	9tth	10th	11th	12th
Literature review												
Study design and protocol writing												
IRB clearance												
Patient selection and enrollment												
Collection of data												
Data cleaning, editing,												
Data analysis												
Preparing result and writing for publication												

Budget

Total: Four lakh Taka only (Tk. /-)

Literature review and Study Design, Protocol writing and Ethical Approval	:	20,000/-
Data Collection, Data Entry	:	20,000/-
Data Cleaning and Editing	:	10,000/-
Data Analysis	:	10,000/-
Report Writing	:	10,000/-
Materials and Supplies	:	20,000/-
Internet Access	:	10,000/-
Drugs for the study	:	Government supply and WFH supported
Total	:	1,00,000/-

Consent form (English)

1. Title of the study: 'Comparison of Low Dose Emicizumab and Low Dose Factor VIII as a Prophylaxis in Hemophilia A patient- a randomized control trial'.

2. Place of the study: Department of Haematology and Bone Marrow Transplantation Unit, Dhaka Medical College & Hospital, Dhaka

3. Name of the researcher: Prof. Dr. Akhil Ranjan Biswas.

4. Purpose of the study: The study will be conducted to evaluate the comparison between low dose factor VIII prophylaxis and low dose Emicizumab of prophylaxis in preventing bleeding events in Haemophilia A.

5. Study population: Patients with Haemophilia A attending the Department of Haematology and Bone Marrow Transplant Unit, Dhaka Medical College and Hospital (DMCH), Dhaka.

6. Data provider: Patients or patient's attendants.

7. Expectation from the participants: You will be asked some questions regarding the patient and some tests will be done. Hope you will help in this process.

8. Risks & discomforts: It is to inform you that in this research you will not face any serious risk regarding the study.

9. The benefit of participant in the research: You can benefit from taking part in this study. The drugs can effectively reduce your bleeding events improve your quality of life. This study will also be helpful for the physicians of Bangladesh to choose more effective prophylactic agent using limited resource.

10. Alternatives: The normal treatment of you will proceed as per the general treatment procedure of the hospital, even if you do not participate in the research.pro

11. Incentives: You will not be provided any incentives to take part in this research. Your participation is likely to help us to acquire more knowledge about this disease which may be of benefit to other patients

of our country. The intervention drug will be supplied free of cost by the Govt. of the peoples' Republic of Bangladesh and the World Federation of Haemophilia (WFH) .

12. Confidentiality: The information that we will collect from this research project will be kept confidential unless permitted by you.

13. Voluntary participation: Participation in this research work is fully voluntary work. You can withdraw yourself at any stage of this research work. By signing in this informed consent form you will not be deprived from any legal rights.

14. Related questions: Please let us know if you have any question. We will try to answer your question at our level best. If you feel like throwing any question in future, then you may contact with researcher.

Prof. Dr. Akhil Ranjan Biswas: Mobile no. 01712290706.

If you agree to participate in this study, please sign the attached consent form.

INFORMED CONSENT FORM

I, Mr./Mrs./Miss ....., here by giving informed consent willingly (to allow the patient under my care) to participate in the study to be conducted by Prof. Dr. Akhil Ranjon Biswas. Professor and Head, Department of Hematology, Dhaka Medical College Hospital, Dhaka without any prejudice. I am fully convinced that during study I (or my patient) will not suffer from any serious physical or psychological problems. I am also informed that this study was carried out in the developed countries safely and my participation will bring fruitful result that will be beneficial for most patients in our country. I have right to withdraw myself (or my patient) from this study at any time. I (or the patient) will not receive any financial benefit. I have understood that the personal information, medical records and laboratory test results of mine (or the patient) will be kept strictly confidential and will be used for research purpose only.

.....	.....	.....
Signature/Thumb impression of participant/guardian	Signature/Thumb impression of witness	Signature of Researcher

Assent form (English)

Title of the study: 'Comparison of Low Dose Emicizumab and Low Dose Factor VIII as a Prophylaxis in Hemophilia A patient'

My name is Prof. Akhil Ranjon Biswas. I am head of the Department of Haematology & BMT at Dhaka Medical College Hospital, Dhaka. I am inviting you to participate in a research study titled- 'Comparison of Low Dose Emicizumab and Low Dose Factor VIII as a Prophylaxis in Hemophilia A patient'

Your guardian knows about this study, and gave permission for you to be involved. If you agree, I will ask you some of your personal data and some data about the disease you are suffering from.

You do not have obligation to participate in the study. No one will be bad at you if you decide not to participate in this study. Even if you start the study, you can stop later if you want. You may ask questions about the study at any time. If you decide to be in the study, I will not tell anyone else how you respond or act as part of the study. Even if your parents or teachers ask, I will not tell them about what you say or do in the study. Signing here means that you have read this form or have had it read to you and that you are willing to be in this study

.....	.....	.....
Signature/Thumb impression of participant	Signature/Thumb impression of guardian	Signature of Researcher

Case Record Form

Title: 'Efficacy of Low Dose Emicizumab vs Low Dose Factor VIII Prophylaxis in Severe and Moderate Hemophilia A patient'.

General Information:	**Randomization Number-**
Factor level- Date of Inves- Age of first bleeding- Age at diagnosis-	Target Joint- Number- Specify- Blood Group- Wt- Ht- Inhibitor status- Result and date of investigations-
Address: Village _ _ _ _ _ _ _ _ _ _ _ _ Upazilla _ _ _ _ _ _ _ _ _ _ _ _	Union _ _ _ _ _ _ _ _ _ _ _ _ District _ _ _ _ _ _ _ _ _ _ _ _
Educational status • Patient • Guardian	□ Illiterate □ Primary □ SSC □ HSC □ Graduate □ Postgraduate

Emicizumab Group- I and WI

	1st week	2nd week	3rd week	4th week	8th week	12th week	16th week	20th week	24th week	28th week
Episodes of bleeding										
Episodes of Joint bleeding										
Episodes of Spontaneous bleeding										
APTT										
Weight										
Dose										

Factor VIII Group follow up

	1st week	2nd week	3rd week	4th week	5th week	6th week	7th week	8th week
Episodes of bleeding								
Episodes of Joint bleeding								
Episodes of Spontaneous bleeding								
APTT								
Weight								
Dose								

	9th week	10th week	11th week	12th week	13th week	14th week	15th week	16th week
Episodes of bleeding								
Episodes of Joint bleeding								
Episodes of Spontaneous bleeding								
APTT								
Weight								
Dose								

	17th week	18th week	19th week	20th week	21th week	22th week	23th week	24th week
Episodes of bleeding								
Episodes of Joint bleeding								
Episodes of Spontaneous bleeding								
APTT								
Weight								
Dose								

	25th week	26th week	27th week	28th week
Episodes of bleeding				
Episodes of Joint bleeding				
Episodes of Spontaneous bleeding				
APTT				
Weight				
Dose				

Interview Conducted By-

Name –

Sign-

Randomization Plan

	Group	Code	Name
1	Factor VIII Group	VJ8	
2	Emicizumab Group (with inhibitor)	QD7	
3	Emicizumab Group (without inhibitor)	XY8	
4	Emicizumab Group (with inhibitor)	VN2	
5	Factor VIII Group	AA2	
6	Factor VIII Group	HH2	
7	Emicizumab Group (with inhibitor)	JC1	
8	Emicizumab Group (without inhibitor),	NB1	
9	Factor VIII Group	QT5	
10	Emicizumab Group (with inhibitor)	RG0	
11	Factor VIII Group	MO9	
12	Factor VIII Group	AM0	
13	Emicizumab Group (with inhibitor)	KX8	
14	Factor VIII Group	CC0	
15	Emicizumab Group (without inhibitor),	CU6	
16	Factor VIII Group	XX9	
17	Factor VIII Group	PW2	
18	Emicizumab Group (without inhibitor)	EK9	
19	Emicizumab Group (with inhibitor)	KQ3	
20	Factor VIII Group	VJ8	

Put Tick sign (√) appropriate answers against each of the following statement
(If not Applicable, please write NA)

1. Source of Population:			**4. Are subjects clearly informed about:**		
(a) Ill Subject	**√Yes**	**No**	(a) Nature and purpose of Study	**√Yes**	**No**
(b) Non-ill Subject	**Yes**	**√No**	(b) Procedures to be followed including alternatives used	**√Yes**	**No**
(c) Minors or persons under guardianship	**√Yes**	**No**	(c) Physical risks	**√Yes**	**No**
2. Does the study Involve:			(d) Private questions	**√Yes**	**No**
(a) Physical risks to subjects	**√Yes**	**No**	(e) Invasion of the Body	**√Yes**	**No**
(b) Social Risks	**Yes**	**√No**	(f) Benefits to be derived	**√Yes**	**No**
(c) Psychological risks to subjects	**√Yes**	**No**	(g) Rights to refuse to participate or to withdraw from study	**√Yes**	**No**
(d) Discomfort to subjects	**√Yes**	**No**	(h) Confidential handling of data	**√Yes**	**No**
(e) Invasion of the body	**√Yes**	**No**	(i) Compensation where there are risks or loss of working time or privacy is involved in any particular procedure	**√Yes**	**No**
(f) Invasion of Privacy	**Yes**	**√No**	**5. Will signed consent form/verbal consent be required:**		
(g) Disclosure of information damaging to subject or others	**Yes**	**√No**	(a) From Subjects	**√Yes**	**No**
3. Does the study involve:			(b) From parent or guardian (if subjects are minors)	**√Yes**	**No**
(a) Use of records (hospital, medical, death, birth or other)	**√Yes**	**No**	6. Will precautions be taken to protect anonymity of subjects	**√Yes**	**No**
(b) Use of fetal tissue or abortus	**Yes**	**√No**			
(c) Use of organs or body fluids	**Yes**	**√No**			

Sign of the Principal Investigator