Project Title:

Efficacy and safety of human insulin versus analog insulin in hospitalized acute stroke patients with hyperglycemia: a randomized, open-label, single center trial

NCT ID: NCT04834362

Date: 01/Nov/2021

Project Title:

Efficacy and safety of human insulin versus analog insulin in hospitalized acute stroke patients with hyperglycemia: a randomized, open-label, single center trial

Primary Investigator

Dr. Mashfiqul Hasan
Assistant Professor of Endocrinology, NINS

Co-Investigators

Dr. Mohammad Atiqur Rahman,
Assistant Professor of Endocrinology, NINS

Dr. Sharmin Chowdhury
Medical Officer, Neurology, NINS

Advisor/Guide
Dr. Mohammad Selim Shahi
Associate Professor of Neurology, NINS

Diabetes & Endocrinology team
National institute of Neurosciences & Hospital
Dhaka, Bangladesh

Section - A

1. **Project Title:** Efficacy and safety of human insulin versus analog insulin in hospitalized acute stroke patients with hyperglycemia: a randomized, open-label, single center trial

2. Principal Investigator

SI	Name and designation	Research position
1	Dr. Mashfiqul Hasan Assistant Professor (Endocrinology) National Institute of Neurosciences & Hospital	Principal Investigator

3. Co-investigators:

SI	Name and designation	Research position
1	Dr. Mohammad Atiqur Rahman Assistant Professor (Endocrinology) National Institute of Neurosciences & Hospital	Co-Principal Investigator (1)
2	Dr. Sharmin Chowdhury Medical Officer (Neurology) National Institute of Neurosciences & Hospital	Co-Principal Investigator (2)
3	Dr. Mohammad Selim Shahi Associate Professor (Neurology) National Institute of Neurosciences & Hospital	Co-Principal Investigator/ Guide & supervisor

4. Place of the study/Institution: National Institute of Neurosciences & Hospital, Sher-E-Bnagla Nagar, Dhaka-1207.
5. Sponsoring/Collaborating Agencies: PMR Operational Plan, DGHS
6. Duration: 05 Month
7. Date of Commencement :01/02/2021
8. Date of Completion: 30/06/2021
9. Total Cost: 2,00,000/-(BDT)
10. Other Support for Proposed Research: Not required
11. Date of Submission: 18/02/2021

12. Signature of Principal Investigator:

13. Signature of Co-investigators:

14. Approval of the Head of the Institute /Principal

Name and Signature

Designation

Official Seal

Sections - B

Title: Efficacy and safety of human insulin versus analog insulin in hospitalized acute stroke patients with hyperglycemia: a randomized, open-label, single center trial

EXECUTIVE SUMMARY:

Introduction: Glycemic control in acutely ill stroke patients with hyperglycemia is vital. Although insulin is the choice of anti-diabetic agent during acute stage, it is not clear which insulin regimen is better in terms of glycemic control and prevention of hypoglycemia in hospitalized acute stroke patients who are usually on small frequent nasogastric tube feeding. The present study aims to evaluate the efficacy and safety of human insulin (regular insulin and neutral protamine hagedorn, NPH insulin) to analog insulin (basal insulin glargine and rapid acting insulin aspart) in hospitalized acute stroke patients with hyperglycemia.

Justification: Analog insulins are developed by minor alteration of the amino acid chain which alters their pharmacokinetics and make them more physiological. However, these insulins are costly and are not widely available. Conventional human insulins are more commonly used in our country. Comparison of these two regimen is necessary in our own setting to optimize optimal glycemic management of hospitalized acute stroke patients.

Methodology: In this single-center, open-label, randomized trial, 100 patients with acute stroke and hyperglycemia (capillary blood glucose ≥10 mmol/L on 2 or more occasions) or history of type 2 DM admitted in the in-patient Department of Neurology, National Institute of Neurosciences (NINS) & Hospital will be randomly assigned to receive human insulin or modern insulin therapy in 1:1 ratio. The study will be carried out from February to June 2021. Blood glucose (BG) will be monitored by standardized glucometer thrice a day and insulin dose will be adjusted daily. The primary outcome of the study will be the differences in glycemic control between groups, as measured by mean daily BG concentration during the hospital stay. Secondary outcomes include differences between treatment groups in any of the following measures: number of hypoglycemic events (BG <3.9 mmol/L), total daily dose of insulin, length of hospital stay, hospital complications and mortality.

Expected outcome/ result: The result will clearly show the efficacy and safety of newer insulins in comparison to conventional human insulin.

Recommendation: The study may help generating recommendations about insulin use in hospitalized acute stroke patients.

Section-C

INTRODUCTION:

It is well known that good clinical outcome in hospitalized patients with hyperglycemia cannot be expected unless target blood glucose is promptly achieved and maintained (1-3). This is also true for acute stroke patients. Hyperglycemia may affect the outcome of both ischemic and hemorrhagic stroke (4-6). Pro-oxidative and proinflammatory state imposed by hyperglycemia can cause direct neuronal toxicity. An increase of cerebral edema may be caused by hyperglycemia-mediated increase in matrix metalloproteinase-9 causing neuronal damage. Moreover, hyperglycemia may be responsible for a procoagulant state that can further compromise blood supply to the penumbral areas in acute ischemic stroke (7).

Management of hyperglycemia in acute stroke patients is particularly challenging because many of the patients cannot take their usual food and need feeding by nasogastric (NG) tube. Common practice is to feed 200 ml of liquid food (soup or milk) 2 hourly starting at morning and continue up to night (10 feeds/day). As such, insulin regimen used to control hyperglycemia in patients taking three major meals may not be appropriate in this setting. Moreover, many acute stroke patients receive corticosteroid therapy, which further deteriorates glycemic status. Dislodgement of NG tube may result in interruption of interruption of feeding, predisposing to hypoglycemia. All these challenges need to be kept in mind while choosing appropriate insulin regimen.

Hyperglycemia in hospitalized patients is defined as blood glucose levels >7.8 mmol/L. Insulin therapy should be initiated for treatment of persistent hyperglycemia starting at a threshold ≥10.0 mmol/L. Once insulin therapy is started, a target glucose range of 7.8–10.0 mmol/L is recommended for the majority of critically and non-critically ill patients (8). More stringent goals, such as <7.8 mmol/L may be appropriate for selected patients, as long as this can be achieved without significant hypoglycemia.

In most instances in the hospital setting, insulin is the preferred treatment for hyperglycemia (8). Human insulin in the form of regular insulin and intermediate acting insulin (neutral protamine hagedorn; NPH) are the most common insulin used for glycemic control in people with diabetes. However, they may not mimic the physiological insulin secretion pattern properly. As a result, tight glycemic control often leads to hypoglycemia. To improve the pharmacokinetics of the insulin, minor structural alterations are made to produce analogs insulin that have similar pharmacodynamics properties. These include long acting basal insulin like insulin detemir, glargine and degludec and rapid acting prandial insulin like insulin lispro, aspart or glulisine. These modern insulins are costlier and availability is often limited.

An insulin regimen with basal, prandial, and correction components is the preferred treatment for non-critically ill hospitalized patients with good nutritional intake (9). Clinical guidelines from

professional organizations recommend the use of subcutaneous insulin in the form of basal-bolus regimen as the preferred therapy for glycemic control in hospitalized medical and surgical patients with type 2 diabetes mellitus (T2DM) (8,10,11). Sliding scale regular human insulin regimen or premixed insulin in acute setting is strongly discouraged by current recommendations (12). These recommendations are mainly based on studies done on patients taking three major meals.

Use of regular insulin thrice a day is a common practice in our setting mainly due to its simplicity and relevance to feeding practice in acute stroke patients. Nevertheless, this regimen is associated with limited therapeutic success because of the lack of basal insulin coverage. Adding a long acting basal insulin in the form of NPH or basal insulin analogs are often not introduced in-hospital settings due to fear of hypoglycemia (9). Modern basal insulin analogs may be superior in this respect as they have more physiological pharmacokinetic properties (13).

In different countries, basal-bolus therapies with insulin analogs are being used more commonly. But intermediate-acting and regular human insulin are also observed to have almost similar efficacy and safety (12,14). No inpatient trials have been conducted in our region to determine optimal treatment regimens for hospitalized patients with T2DM in special situation like acute stroke. As there are significant differences in patient demographics, admission cause, feeding practice and availability of hospital resources between patients of developed and developing countries, the choice of agents may not be similar (15,16). In this background, the present study aims to compare the efficacy and safety of conventional human insulin (regular insulin and intermediate acting NPH insulin) to newer analog insulin (basal insulin glargine with rapid acting insulin aspart) in acute stroke patients with hyperglycemia admitted in a referral tertiary neuroscience institute of Dhaka.

RATIONALE:

One in five patients hospitalized for acute stroke has hyperglycemia. For optimum outcome of these patients, proper glycemic control is essential. Acute stroke patients, who need hospitalization, are usually unable to take food normally and they are fed through nasogastric tube with small frequent feeding (200 ml, 2-hourly, 10 feed/day). It is not clear which insulin regimen will suit better to these type of feeding practice. Moreover, corticosteroids (dexamethasone) are often used in these patients as treatment adjunct which further challenges glucose homeostasis. Different insulin regimens are used in such patients but none is validated in clinical trials. Episodes of hypoglycemia may cause further neurological deterioration in acute stroke patients. So regimen with less chance of hypoglycemia needs to be identified. Although analog insulins are observed to have less chance of hypoglycemia, they are costly and had not been well studied in our setting. It is essential for us to know the efficacy and safety of analog insulin regimen in comparison to human insulin, so that appropriate management decision can be made

OBJECTIVES:

General objective:

- To compare the efficacy and safety of human insulin (regular insulin and intermediate acting NPH insulin) to analog insulin (basal insulin glargine and rapid acting insulin aspart) in hospitalized acute stroke patients with hyperglycemia

Specific objectives:

In hospitalized acute stroke patients with hyperglycemia -

- To evaluate the efficacy and safety of human insulin (regular insulin and intermediate acting NPH insulin)
- To assess the efficacy and safety of insulin analog (basal insulin glargine and rapid acting insulin aspart)
- To compare the efficacy and safety of two insulin regimen
- To evaluate the socio-demographic and clinical characteristics of the patients included in two treatment arms

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METHODOLOGY:

Type of study: Single-center, open-label, randomized trial

Place of Study: Department of Neurology, National Institute of Neurosciences & Hospital, Dhaka.

Study Period: February to June, 2021

Study population: Patients admitted in the Department of Neurology with acute stroke and hyperglycemia

Sample Size:

Sample size was calculated according to following formula for non-inferiority trial (17):

$$N = 2 \times \left(\frac{z_{1-\alpha} + z_{1-\beta}}{\delta_0} \right)^2 \times s^2$$

Here, N= sample size per group

α= 0.05

β= 0.20

δ0= a clinically acceptable margin (assumed as 3 mmol/L of blood glucose)

S2= Pooled standard deviation of both comparison group= 8

So,

$$N_{\text{non-inferiority}} = 2 \times \left(\frac{1.645 + 0.845}{3} \right)^2 \times 6^2 = 50$$

As a result, 50 patients will be randomly assigned to two treatment groups (50 human insulin regimen, 50 analog insulin regimen).

Inclusion criteria

- Patients admitted to adult neurology ward with acute stroke with
- Patients having hyperglycemia (capillary blood glucose ≥10 mmol/L in 2 or more occasions or having history of treatment for DM)
- Patients with age of 18-80 years of both sexes
- Patients or their attendants giving consent to take part in the study

Exclusion Criteria

- Patients with hyperglycemic emergencies (hyperglycemic hyperosmolar state or diabetic ketoacidosis)
- Pregnant patients
- Those not giving consent to participate in the study

Study Procedure

Patients will be randomly assigned to receive either a human insulin regimen (starting with regular insulin three times a day with NPH insulin twice a day) or analog insulin regimen (basal insulin glargine once daily and insulin aspart three times a day) following a computer-generated randomization table. All oral antidiabetic drugs will be discontinued on admission.

For a patient who is known to have diabetes but were not getting insulin previously (or previous insulin dosage is not known), insulin therapy will be started at a total daily dose of 0.3-0.4 units/kg/day for an admission BG between 10-15 mmol/L or 0.5-0.6 units/kg/day for a BG >15 mmol/L. In previously insulin treated patients, ongoing total daily dose of insulin will be started. If there is history of poor glycemic control with ongoing insulin dose, then 10-20% increase of daily dose of insulin will be considered.

For a patient who is not known to have diabetes, insulin therapy will be started if admission BG is >10 mmol/L in two or more occasions. A total daily dose of 0.3-0.4 units/kg/day will be started if admission BG is 10-15 mmol/L and 0.5-0.6 units/kg/day for a BG >15 mmol/L.

Patients treated with human insulin regimen will receive 50% of total daily dose as NPH insulin at around 6 am and 6 pm, while the rest 50% regular human insulin three times a day in 3 equally divided doses at around 6 am, 12 pm and 6 pm.

Patients treated with modern insulin regimen will receive 50% of total daily dose as basal insulin glargine at the same time of day and 50% as insulin aspart given in 3 equally divided doses at 6 am, 12 pm and 6 pm.

In both groups, insulin dosage will be adjusted daily to a target fasting and premeal BG 7.8-10.0 mmol/L in the absence of hypoglycemia. Insulin dosage will be adjusted daily according to BG values. If the fasting and/or premeal BG is 10-15 mmol/L in the absence of hypoglycemia, the total daily dose will be increased by 10% every day. If the fasting and/or premeal BG is >15 mmol/L, the insulin daily dose will be increased by 20% every day. If a patient develops hypoglycemia (BG <3.9 mmol/L), the insulin daily dose will be decreased by 20%. Supplemental regular insulin will be given in addition to scheduled mealtime insulin for BG >10 mmol/L using a supplemental insulin protocol.

BG will be measured before each bolus insulin injection (at 6 am, 12 pm and 6 pm). Glycated hemoglobin (HbA1c) will be measured after hospital admission if not done within last three months.

Except anti-diabetic treatment, other treatments will be continued as per the decisions of the treating physicians. If NG feeding is discontinued and patient is kept NPO, conventional group will receive neutralizing insulin with any dextrose containing fluid along with low dose NPH insulin, if needed. Modern insulin group will receive neutralizing insulin with any dextrose containing fluid with glargine insulin as before.

After recruitment, each recruited patient will be visited daily (even in holidays according to a predefined schedule) by one of the investigators and insulin dose will be adjusted according to glucose profile of previous day. Insulin injection and capillary blood glucose monitoring by glucometer will be done by trained nurses as part of their routine patient care. Doctors and nurses on duty will be provided with cell number of the investigators who will receive call on 24/7 basis for any emergency or uncertainty regarding management of hyperglycemia.

Hypoglycemia is regarded as the only short-term adverse event of insulin. As both treatment arms will use established and recognized insulin regimen, no compensation will be provided to the patient or his/her attendants in case of any adverse event. As most of the hospitalized patients have severe stroke with case fatality rate around 20%, death will not be regarded as parameter of primary treatment outcome.

During discharge, last in-hospital insulin dose will be continued with education to the caregiver regarding insulin injection and glucose monitoring technique. No follow up visit is included in the study.

Protocol deviation and protocol violation:

Deviation to protocol will be recorded and reported to ethical committee as soon as possible. Failure to obtain informed written consent, use of incorrect insulin regimen, not fulfilling inclusion and exclusion criteria will be regarded as protocol violation and will be reported to ethical committee immediately. In case of protocol violation, the data of related participant will be discarded.

Outcome variables

The primary efficacy outcome of the study will be the differences in glycemic control between groups, as measured by mean daily BG concentration during the hospital stay.

The primary safety outcome will be the frequency of hypoglycemic events (BG <3.9 mmol/L).

Secondary outcomes include differences between treatment groups in any of the following measures: total daily dose of insulin, length of hospital stay, hospital complications, and mortality.

Data collection technique

Data will be collected in a predesigned questionnaire by the research team. The researchers will recheck randomly and blindly to verify the collected data.

Data management

All data will be compiled and edited meticulously by thorough checking and rechecking. All omissions and inconsistencies will be corrected and will be removed methodically.

Statistical analysis

Computer based statistical analysis will be carried out with appropriate techniques and systems by SPSS 22.0. Quantitative data will be expressed as mean and standard deviation or median and inter-quartile range; and qualitative data will be expressed as frequency and percentage. Continuous variables, analysis will be made by the Students T-test or Mann-Whitney *U* test. Categorical variables will be analyzed by the χ^2 test. All probabilities will be 2-tailed. Statistical significance will be accepted at $p \leq 0.05$.

Utilization of results

The result of study will be helpful for the physicians to choose appropriate insulin regimen in patients hospitalized with acute stroke having hyperglycemia. It will also help the policy makers in ensuring adequate supply of appropriate insulin that may help improve the outcome of patients.

FLOW CHART

Sl. No.	Job Title	Feb'21	Mar'21	Apr'21	May'21	Jun'21
1.	Questionnaire Validation	√				
2.	Data Collection	√	√	√		
3.	Data Analysis				√	
4.	Report writing and Printing				√	√
5.	Submission					√

ETHICAL IMPLICATIONS:

Prior to the commencement of this study, approval of the institutional review board (IRB) of National Institute of Neurosciences & Hospital, Dhaka will be sought. The aims and objectives of the study along with its procedure, risks and benefits of this study will be explained to the patients or attendants of the patients in easily understandable local language and then written consent will be taken from each. It will be assured that all information and records would be kept confidential.

Role of funding agency

The funding agency will have no role in protocol development, data collection, analysis, interpretation or writing the report. The authors will have full access to all study data and will have the final responsibility for the decision to submit for publication.

REFERENCES:

1. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab. 2002;87:978-982.

2. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. JAMA. 2003;290: 2041-2047.

3. Van den Berghe G, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. Crit Care Med. 2003;31:359-366.

4. Levetan CS. Effect of hyperglycemia on stroke outcomes. Endocrine Practice. 2004 Mar 1;10(Supplement 2):34-9.

5. Skafida A, Mitrakou A, Georgiopoulos G, Alevizaki M, Spengos K, Takis K, Ntaios G, Thomadakis C, Vemmos K. In-hospital dynamics of glucose, blood pressure and temperature predict outcome in patients with acute ischaemic stroke. European Stroke Journal. 2018 Jun;3(2):174-84.

6. Rosenthal J, Lord A, Ishida K, Torres J, Czeisler BM, Lewis A. Highest In-Hospital Glucose Measurements are Associated With Neurological Outcomes After Intracerebral Hemorrhage. Journal of Stroke and Cerebrovascular Diseases. 2018 Oct 1;27(10):2662-8.

7. O'Connell JE, Hildreth AJ, Gray CS, Garg R, Chaudhuri A, Dandona P, Munschauer F. Hyperglycemia, insulin and acute ischemic stroke. Stroke. 2006 May 1;37(5):1150-1.

8. Moghissi ES, Korytkowski MT, DiNardo M, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Care. 2009;32: 1119-1131.

9. Cefalu WT, Berg EG, Saraco M, Petersen MP, Uelmen S, Robinson S. Diabetes Care in the Hospital: Standards of Medical Care in Diabetes-2019. DIABETES CARE. 2019 Jan 1;42:S173-81.

10. Schnipper JL, Magee M, Larsen K, Inzucchi SE, Maynard G. Society of Hospital Medicine Glycemic Control Task Force summary: practical recommendations for assessing the impact of glycemic control efforts. J Hosp Med. 2008;3(suppl 5):66-75.

11. Seley JJ, D'Hondt N, Longo R, et al. Position statement: inpatient glycemic control. Diabetes Educ. 2009;35(suppl3):65-69.

12. Bueno E, Benitez A, Rufinelli JV, Figueredo R, Alsina S, Ojeda A, Samudio S, Cáceres M, Argüello R, Romero F, Echagüe G. Basal-bolus regimen with insulin analogs versus human insulin in medical patients with type 2 diabetes: a randomized controlled trial in Latin America. Endocrine Practice. 2015 Jul;21(7):807-13

13. Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. US Study Group of Insulin Glargine in Type 1 Diabetes. Diabetes care. 2000 May 1;23(5):639-43.

14. Umpierrez GE, Hor T, Smiley D, Temponi A, Umpierrez D, Ceron M, Munoz C, Newton C, Peng L, Baldwin D. Comparison of inpatient insulin regimens with detemir plus aspart versus neutral protamine hagedorn plus regular in medical patients with type 2 diabetes. The Journal of Clinical Endocrinology & Metabolism. 2009 Feb 1;94(2):564-9.

15. Leite SA, Locatelli SB, Niece SP, Oliveira AR, Tockus D, Tosin T. Impact of hyperglycemia on morbidity and mortality, length of hospitalization and rates of re-hospitalization in a general hospital setting in Brazil. *Diabetol Metab Syndr.* 2010;2:49.

16. Torres-Torres N, Maldonado-Rodríguez MA, Pérez-López S, Sierra-Martínez K, García AJ. Glycemic control and the outcomes of Hispanic patients with diabetes admitted to the general ward of a community hospital in Puerto Rico. *P R Health Sci J.* 2011;30:43-50.

17. Zhong B. How to calculate sample size in randomized controlled trial?. Journal of thoracic disease. 2009 Dec;1(1):51.

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Section - D

BUDGET

Total Budget: 2,00,000/- (BDT)

Detailed Budget:

1. Personnel Cost: 40,000/-(BDT)

   Time spent by the persons

Sl. No	Category of the Persons	Percentage of time spent
1	Professional Scientific Staff	70%
2	Technical	20%
3	Other Staff	10%

2. Field Expenses/Laboratory Cost: 25,000/-(BDT)
3. Supplies and Materials (Ten glucometers with strips):25,000/-(BDT)
4. Patient Cost: Not Applicable
5. Travel Cost (Internal travel cost only): 15,000/-(BDT)
6. Transportation of Goods: 10,000/-(BDT)
7. Office Stationery (Items & quantity to be specified):10,000/-(BDT)
8. Data Processing/Computer Charges (If applicable):30,000/-(BDT)
9. Printing and Reproduction:25,000/-(BDT)
10. Contractual Services (Other than manpower): Not Applicable
11. Administrative Overhead /Dissemination:20,000/-
12. Miscellaneous 5,000/-

Section - E

Directorate General of Health Services
Planning, Monitoring and Research
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Application for Ethical Clearance

Principal Investigator:
Dr. Mashfiqul Hasan, Assistant Professor of Endocrinology, National Institute of Neurosciences and Hospital, Sher-e-Bangla Nagar, Dhaka

Co-investigators:
Dr. Mohammad Atiqur Rahman, Assistant Professor of Endocrinology, National Institute of Neurosciences and Hospital, Sher-e-Bangla Nagar, Dhaka
Dr. Sharmin Chowdhury, Medical Officer, National Institute of Neurosciences and Hospital, Sher-e-Bangla Nagar, Dhaka

Guide/Supervisor:
Dr. Mohammad Selim Shahi, Associate Professor of Neurology, National Institute of Neurosciences and Hospital, Sher-e-Bangla Nagar, Dhaka

Place of the Study/institution: National Institute of Neurosciences & Hospital, Sher-E-Bangla Nagar, Dhaka-1207

Title of Study: Efficacy and safety of human insulin versus analog insulin in hospitalized acute stroke patients with hyperglycemia: a randomized, open-label, single center trial

Type of Study: Clinical trial

Duration: 5 months

Total Cost: 2,00,000/-

Funding Agency: DGHS

Circle the appropriate answer to each of the following
(If not Applicable wife *NA)*

(b) Non* Ill Subjects Yes No

(c) Minors or persons under guardianship Yes No

2. Does the study involve:

(a) Physical risks to the subjects Yes No

(b) Social Risks Yes No

(C) Psychological risks to subjects Yes No

(d) Discomfort to subjects Yes No

(e) invasion of the body Yes No

(fl Invasion of Privacy Yes No

(g) Disclosure of Information damaging to subject or others Yes No

(a) Nature and purposes of study Yes No

(b) Procedures to be followed including alternatives used Yes No

(c) Physical risks Yes No

(d) Private questions

(e) Invasion of the Body Yes No

(‖) Benefits to be derived Yes No

Yes No

(g) Right to refuse to participate or to withdraw from study Yes No

(h) Confidential handling of data Yes No

(i) Compensation where there are risks or loss of workng time or privacy is involved in any particular procedure Yes No

3. Does the study involve:

Use of records. (Hospital, medical, death, birth or other) Yes No

Use of fetal tissue or abort us Yes No

Use of organs or Body fluids Yes No

4. Are subjects clearly informed about

5. Will signed consent form/verbal consent be required

Yes No

From Subjects

Yes No

From parent or guardian (if subjects are minors)

6. Will precautions be taken to protect anonymity of subject Yes No

Section -F

Abstract for IRB/Ethical Committee:

Glycemic control in acutely ill stroke patients with hyperglycemia is vital. Although insulin is the choice of anti-diabetic agent during acute stage, it is not clear which insulin regimen is better in terms of glycemic control and prevention of hypoglycemia in hospitalized acute stroke patients who are usually on small frequent nasogastric tube feeding. The present study aims to evaluate the efficacy and safety of human insulin (regular insulin and neutral protamine hagedorn, NPH insulin) to analog insulin (basal insulin glargine and rapid acting insulin aspart) in hospitalized acute stroke patients with hyperglycemia. In this single-center, open-label, randomized trial, 100 patients with acute stroke and hyperglycemia (capillary blood glucose ≥10 mmol/L on 2 or more occasions) or history of type 2 DM admitted in the in-patient Department of Neurology, National Institute of Neurosciences (NINS) & Hospital will be randomly assigned to receive human insulin or modern insulin therapy in 1:1 ratio. The study will be carried out from February to June 2021. Blood glucose (BG) will be monitored by standardized glucometer thrice a day and insulin dose will be adjusted daily. The primary outcome of the study will be the differences in glycemic control between groups, as measured by mean daily BG concentration during the hospital stay. Secondary outcomes include differences between treatment groups in any of the following measures: number of hypoglycemic events (BG <3.9 mmol/L), total daily dose of insulin, length of hospital stay, hospital complications and mortality. Computer based statistical analysis will be carried out by SPSS 22.0. Quantitative data will be expressed as mean and standard deviation or median and inter-quartile range; and qualitative data will be expressed as frequency and percentage. Continuous variables will be compared by the Students T-test or Mann-Whitney *U* test. Categorical variables will be analyzed by the χ^2 test. All probabilities will be 2-tailed. Statistical significance will be accepted at $P \leq 0.05$. Prior to the commencement of this study, approval of the institutional review board (IRB) of NINS will be sought. The aims and objectives of the study along with its procedure, risks and benefits of this study will be explained to the patients or attendants of the patients in easily understandable local language and then written consent will be taken from each. The result of the study may help us to choose appropriate insulin regimen for hospitalized acute stroke patients in our setting.

Case record form – insulin trial

Reg. No.		Ward		Bed	
Name		Age (yr)		Gender	M/F
Address					
Phone	(1) 01_____	(2) 01_____			
Date and time of admission	_____/_____/_____, _____ am/pm				
Date and time of stroke event	_____/_____/_____, _____ am/pm				
Assigned group					

Presenting features on admission (Circle or underline the appropriate options)

Chief complaints	Unconsciousness, Hemiparesis Rt/Lf, Headache, Vomiting, Seizure		
Duration of symptoms	_____ days, _____ hours		
Past history	HTN, DM, IHD, CKD, Stroke, Others:		
Drug history			
Family history		Smoking	Never/ Ex / Current smoker
GCS	E_____V_____M_____	NIHSS score	
Pulse (beats/min)	_____, regular/irregular	BP (mm of Hg)	_____/_____
Any remarkable findings			

Investigation Profile

CT findings	Hemorrhage	Site: GT/Lobar/Brain stem/Cerebellar/SAH/IVH Volume:_____ml Ventricular Extension: Present/Absent				
	Infarct	Large vessel infarct/Perforator infarct; Anterior circulation/Posterior circulation/Water shade zone infarct				
MRI/MRV/MRA/CTA						
CBG on admission		Chest X-ray				
Creatinine (mg/dL)		ECG				
Sodium (mmol/L)		Echo				
Potassium (mmol/L)		Hemoglobin (g/dL)		Total Cholesterol		
Cloride (mmol/L)		ESR (mm)		HDL		
Troponin-I		WBC (10^9/L)		LDL		
HbA1c (%)		DC of WBC (N,L%)		TG		
RBS		Platelet (10^9/L)				
SGPT (U/L)						
Urine R/E						

In-hospital events/diagnosis

Pneumonia	Yes, No	Treatment needed for hypertension	Yes, No

Pressure sore	Yes, No	Treatment needed for hyperglycemia	Yes, No
UTI	Yes, No	≥2 blood glucose >10 mmol/L	Yes, No
Thrombolytic therapy	Yes, No	Cardiac event	Yes, No
Neurosurgical procedure (specify)	Yes, No	Electrolyte imbalance (Specify)	Yes, No
Any other event/diagnosis:			

Outcome

Hospital outcome	Discharged to home/ Referred to other hospital/ Death
Date of outcome	
mRS at discharge	

For hyperglycemic patients

Date	**7 am**	**1 pm**	**7pm**			**Insulin**	**Feeding**	**Steroid**

Section - H

PRINCIPAL INVESTIGATOR INFORMATION SHEET

1. (i) Name : Dr. Mashfiqul Hasan
   (i) Designation : Assistant Professor (Endocrinology)
   (ii) Official Address with telephone: National Institute of Neurosciences & Hospital, Sher-E-Bangla Nagar, Dhaka-1207. Telephone: +88029137305
   (iii) Present Residential Address with telephone: Kha-42/1, Shahjadpur, Gulshan, Dhaka-1212.

Academic Qualification

Degree	*Institute/University*	*Field of study*	*Year*
Postgraduate:			
MD	Bangabandhu Sheikh Mujib Medical University (BSMMU)	Endocrinology	**Jan 2016**
MCPS	Bangladesh College of Physicians and Surgeons (BCPS)	Medicine	**Jul 2009**
Ggraduate:			
MBBS	Dhaka Medical College (University of Dhaka)	Medical Sciences	**May 2005**
Undergraduate:			
HSC	Dhaka College, Dhaka Board		**1999**
SSC	Banani Bidya Niketon, Dhaka Board		**1997**

(a) Research Experience: 10 years Teaching: 4 Years

(b) Other Experience : Administration

Others :

Percentage of time to be devoted to this Project : 50%

Number of Scientific Publications: 27