RESULTS OF GLYCEMIC CONTROL
AMONG SEVERE STROKE PATIENTS

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ABSTRACT

Background: Hyperglycemia is a relatively common condition in stroke patients, whether they have diabetes or not, and it is associated with adverse outcomes. Achieving target blood glucose levels has a partial impact on the results, but it is not the sole determinant. Objectives: We assessed the result of glycemic control among severe stroke patients. Materials and methods: A prospective study was conducted in the Stroke Department, Can Tho Central General Hospital, from June 2020 to April 2022, with 72 severe stroke patients monitored the capillary blood glucose every 3 hours. Nineteen patients who had persistent hyperglycemia were controlled with continuous intravenous insulin. We determined the average blood glucose level for each patient, the time needed to reach the glycemic target range, the frequency of hypoglycemia, and the glycemic variability from all measured blood glucose concentration. R programming was used to analyze the data. Results: The average age of patients was 65.1±16.1. The percentage of ischemic stroke, accounting for 55.6%, was the highest, followed by cerebral hemorrhage at 34.7%, 1.4% of these patients was attributed to cerebral venous thrombosis. In admission, the median Glasgow score was 8 (IQR: 7-9), and the median modified Rankin score was 5 (IQR: 4-5). Enteral nutrition was the primary nutritional therapy. Among 53 severe strokes without persistent hyperglycemia, blood glucose levels fluctuated around the mean value of 143 mg/dL. In 19 patients with persistently elevated blood glucose concentration, the mean blood glucose levels preinfusion and post-insulin infusion were 299±117mg/dL and 165±43.2mg/dL, respectively; time to glycemic target was 8.25 hours (95% CI: 3.50-14.75 hours), the minimum was 3 hours, and the longest was 189 hours; 5.3% of these patients developed hypoglycemia, and 13.3% of persistent hyperglycemia patients did not obtain the target range. Conclusions: Blood glucose levels fluctuate within the target range among patients with non-hyperglycemia or non-persistent hyperglycemia. In patients with persistent hyperglycemia controlled with intravenous insulin, the mean blood glucose levels were achieved close to the upper limit of the glycemic target.

Keywords: hyperglycemia, insulin infusion, severe stroke.

I. INTRODUCTION

Stroke is ranked as one of the leading causes of death and disability worldwide, with a substantial economic burden on treatment and post-stroke care [1]. According to the World Stroke Organization Report 2022, one in four people over the age of 25 will have a stroke in their lifetime [2]. In Vietnam, with a population of about 98.32 million people in 2021, the incidence was estimated over 157 per 100.000 people [3]. Especially, the number of patients with severe cerebral stroke requiring intensive care can be as high as 10-30%, depending on medical resources and admission criteria in intensive care units in each country [4].

Hyperglycemia is common in diabetic and nondiabetic patients during the acute phase of stroke [5], [6]. The vivo studies have shown that hyperglycemia enhances the breakdown of the

blood-brain barrier, and promotes neuronal cell death and the progression of cerebral edema. Therefore, achieving glycemic control is one of the factors affecting the outcomes [6].

The American Society of Clinical Endocrinology and the American Diabetes Association recommended that the goal of blood glucose in critically ill patients ranges from 140 mg/dL to 180 mg/dL [7]. Intravenous insulin is often used for initial glycemic control in critically ill patients in the intensive care unit due to the ease of titration so that the insulin dose is consistent with the blood glucose levels over time. At present, many intravenous insulin protocols have been established and published. The two most important criteria to evaluate the standardization of each protocol included achieving stable blood glucose over time and the lowest rate of hypoglycemic events. These statements can only be evaluated experimentally because of the differences in responses of each patient. Accordingly, we conducted this study to investigate the mean blood glucose value, glycemic fluctuation, and the frequency of hypoglycemia in severe stroke patients with insulin infusion for glycemic control.

II. MATERIALS AND METHODS

2.1. Research Subjects

We recruited all patients with severe stroke admitted to the Stroke Department, Can Tho Central General Hospital from June 2020 to April 2022.

The stroke diagnosis was defined by the American Heart Association and the American Stroke Association [8]. The criteria for severe stroke were defined as meeting one of the following conditions, which included the need for intubation due to decreased consciousness (Glasgow Coma Scale score of ≤ 8 points), the presence of evidence of brainstem injury, any other factor causing a threatened airway, or acute respiratory failure. We excluded patients with a Glasgow Coma Scale score of ≤ 4 points, ketoacidosis, hyperosmolar hyperglycemic state, as well as patients whose guardians refused treatment.

2.2. Research methods

Study design:

A prospective study was performed with the ethical standards of the Medical Ethics Committee of the Can Tho University of Medicine and Pharmacy on medical research.

Data collection: Patients with severe cerebral stroke admitted to the hospital were tested for capillary blood glucose every 3 hours. Persistent hyperglycemia patients were defined as those with blood glucose levels elevated ≥ 180 mg/dL and prolonged for 6 hours, and they were controlled with intravenous insulin following Cleveland Clinic Intensive Care Unit insulin protocol [9]. The remaining patients were monitored for blood glucose every 3 hours for 24 hours, after which the monitoring interval was decided at the discretion of the clinician. The glycemic target range was from 140 to 180mg/dL.

All demographic and clinical variables, including the GCS (Glasgow Coma Scale), were collected for each patient on admission by the same clinician, not by the investigator. Patients were assessed for mRS (modified Rankin Scale) through questionnaires.

Operational definitions:

We calculated each patient's average blood glucose, time to achieve the glycemic target range, and the frequency of hypoglycemia; described the glycemic variability from all recorded blood glucose concentrations.

Achieving the glycemic target during intravenous insulin administration means maintaining the blood glucose within the target for 3 hours. Hypoglycemia is a condition in which blood glucose concentration falls below 70mg/dL [7].

Statistical analysis:

Data were analyzed using R programming. Categorical variables are expressed as actual numbers and percentages, whereas categorical values were assessed for normality by visual inspection of histograms. Variables with normal distribution were summarized as mean (standard deviation), and variables with non-normal distribution were summarized as median (interquartile range). A p-value less than 0.05 was considered statistically significant.

Ethical approval: A prospective study was performed with the ethical standards of the Medical Ethics Committee of the Can Tho University of Medicine and Pharmacy on medical research (No.210/HĐĐĐ-PCT 28/05/2020).

III. RESULTS

From June 2020 to April 2022, we included 72 patients with severe stroke who met the inclusion criteria and had no exclusion criteria in the final analysis. The patient's demographics are presented in

Table 1. Baseline characteristics of 72 patients with severe stroke

Characteristics	Result (n = 72)
Age (years), mean $\pm$ standard deviation	65.1$\pm$16.1
Gender, n (%)	
Men	40 (55.6)
Women	32 (44.4)
Previous medical history, n (%)	
Smoking	28 (38.9)
Atrial fibrillation	4 (5.6)
Stroke	7 (9.7)
Hypertension	59 (81.9)
Diabetes	22 (30.6)
Glasgow coma score, median (interquartile range)	8 (5-8)
modified Rankin Scale, median (interquartile range)	5 (4-5)
Enteral nutrition, n (%)	72 (100)

Men constituted the majority at 55.6%. The proportion of patients aged 50 and older was 60 patients, approximately 84%. The youngest and eldest patient was 21 years old and 96 years old, respectively. Seven patients (9.7%) had a recurrent cerebral stroke with the highest mRS score of 3 points, moderate disability, requiring some help, but still able to walk without assistance. Enteral nutrition was the primary nutritional therapy.
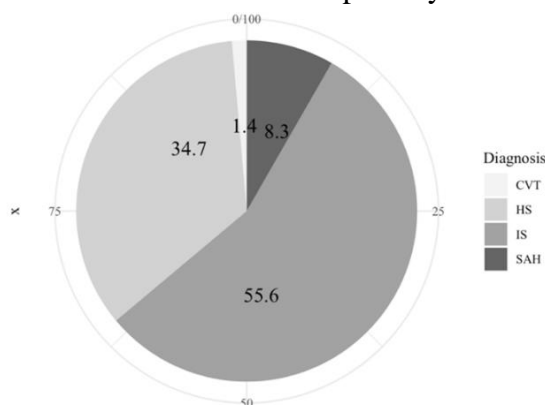
Notes: CVT – Cerebral venous thrombosis; HS – Hemorrhage stroke; IS – Ischemic stroke; SAH – Subarachnoid Stroke

Figure 1. The prevalence of stroke types in patients with severe stroke

Ischemic stroke constituted the primary type of stroke, representing the majority at 55.6%, followed by cerebral hemorrhage at 34.7%, subarachnoid hemorrhage at 8.3%, and a single case of cerebral venous thrombosis at 5.3%.
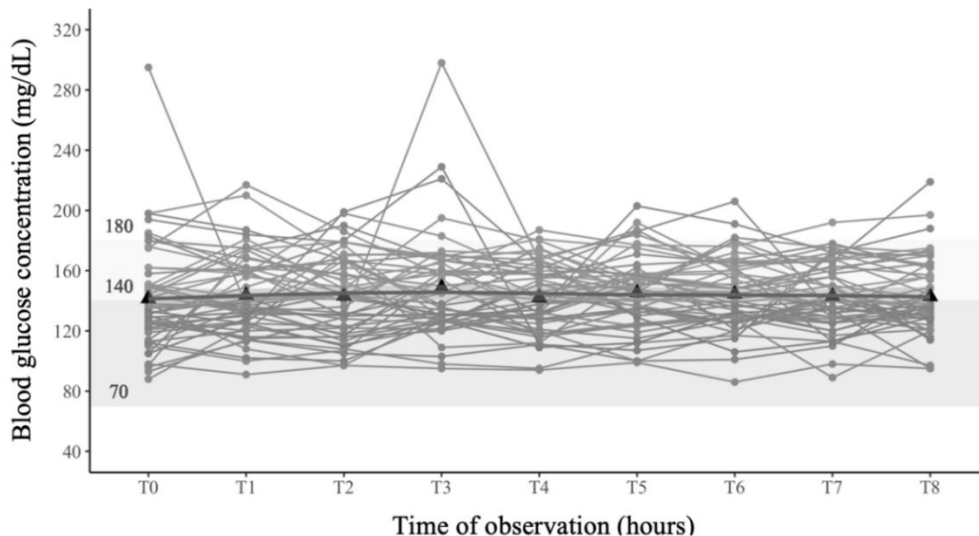

Figure 2. Blood glucose fluctuation on patients unneeded insulin infusion

Glucose fluctuations in the group that did not need to be controlled with intravenous insulin therapy were stable with mean blood glucose levels of 143±17.1mg/dL. The patient had the lowest mean blood glucose level of 95mg/dL and the highest of 208mg/dL. Approximately 75% of patients had mean blood glucose levels below 155 mg/dL.
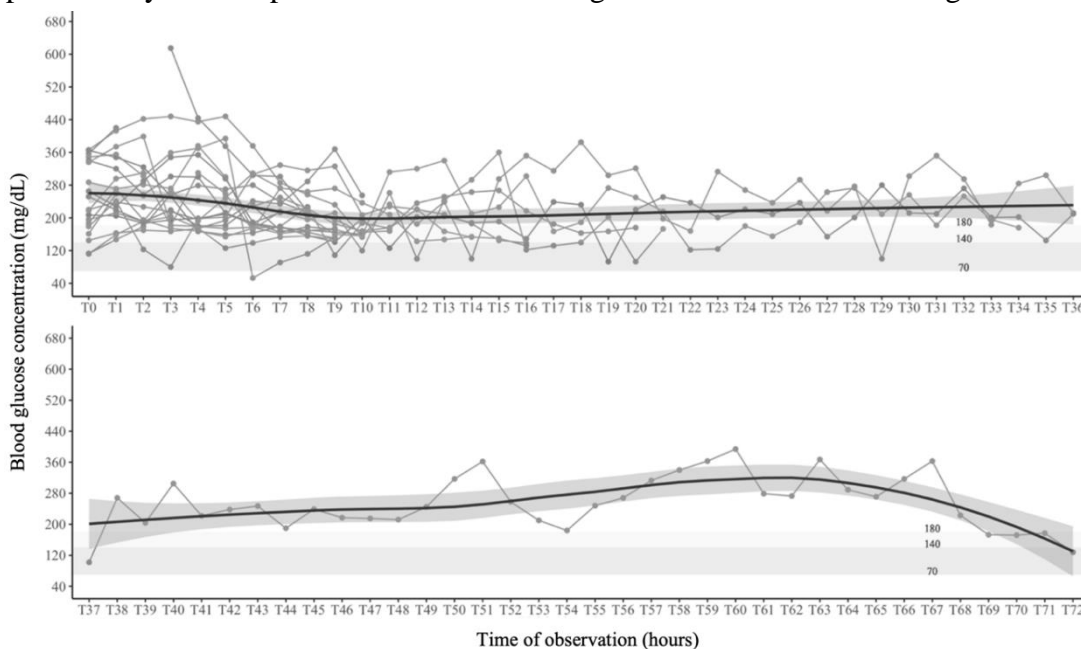

Figure 3. Blood glucose fluctuation in patients needed insulin infusion therapy

For hyperglycemia requiring control with intravenous insulin, the mean pre-control and post-control blood glucose concentrations were 299±117mg/dL and 165±43.2mg/dL, respectively. The median rate of time blood glucose levels were in the target range was

30.0%. The median time to target blood glucose was 15 hours, the minimum was 3 hours, and the longest was 189 hours (Figure 3). There were 15 patients (78.9%) who achieved the target range. Hypoglycemia occurred in one patient, three patients died before completing the protocol, and one did not achieve the target blood glucose concentration during the control period.

IV. DISCUSSION

According to the history of critical care, many studies have been conducted to find the most appropriate blood glucose targets for critically ill patients. However, the results obtained from these studies vary due to the heterogeneity of the study population, especially in terms of disease severity, the types of diseases, and the presence or absence of diabetes in the patients. Therefore, it is difficult to conclude the optimal common goal. The evidence from studies on glycemic targeting in stroke patients shows that the brain has a specialized glucose metabolism, different from many other organs in the body, with high energy needs and limited glucose reserves. Tight glycemic control is associated with an increased risk of decreased cerebral metabolism and adverse events [4], [10]. Furthermore, tight glycemic control has shown no benefit on functional or survival outcomes but may reduce the risk of infection [10]. The NICE-SUGAR study also revealed that attaining target blood glucose levels in critically ill patients poses a challenge. Furthermore, the more one attempts to lower blood glucose goals, the greater the likelihood of an increased risk of hypoglycemia [4].

The research by Gibson et al. assessed the effectiveness of a continuous insulin infusion protocol on 170 critically ill patients in the intensive care unit [9]. The median age was 63.5 (interquartile range: 54-71), and men accounted for 49%. This study recorded that the average blood glucose concentration before insulin infusion was 244mg/dL, whereas our study found it to be 299mg/dL. In Gibson's study, the median time to achieve glycemic control with intravenous insulin was 11.1 hours (interquartile range: 4.5-28.6), while in our study, it was 42 hours. Gibson's median time to goal blood glucose was 4.2 hours, compared to 15 hours in our study. Our longer time to reach the glycemic target is likely due to our patients having higher baseline blood glucose levels. Although our time to goal and Gibson's differed, our median post-control glycemic scores were similar, with a median of 168 mg/dL (interquartile range: 147.5-199.5) and 168 mg/dL (interquartile range: 156.0-175.0), respectively. The rate of hypoglycemia that Gibson noted was 1.2%, and 15% of the patients did not achieve the glycemic target [9]. In our study, the rate of achieving the target blood glucose was 78.9%, one patient experiencing hypoglycemia, accounting for 5.3%. One patient did not reach the target during the control process, also with a rate of 5.3%, and three patients died before discontinuing the regimen.

Regarding the pace of glycemic decrease, which rate of blood glucose reduction will provide the optimal benefit is currently open to question. Our study found that the rate of blood glucose reduction closely correlated with the initial blood glucose concentration with $r = 0.71$ and $p < 0.001$. Specifically, in patients with high blood glucose concentration at the beginning of control, the faster the rate of blood glucose reduction and vice versa.

Briefly, we have identified several key findings in our study. Firstly, the homogeneity of the study population stands out because the need for glycemic control is heterogenous in different patients. Secondly, the blood glucose control process is greatly influenced by nutrition so ensuring that all patients requiring intravenous insulin receive continuous enteral feeding helps to minimize the glucose fluctuation caused by diet. Thirdly,

we do not only focus on blood glucose levels at any one time or average blood glucose levels but also consider glycemic variability over time. Despite its many advantages, our study does have several limitations. The determination of glycemic concentration based on capillary blood glucose measurement can introduce bias in critically ill patients with low blood pressure.

V. CONCLUSION

In patients with no or persistent hyperglycemia, blood glucose levels fluctuate and stabilize within the target range. Among patients with hyperglycemia managed by continuous insulin infusion following this protocol, mean blood glucose levels reached close to the upper limit of the blood glucose target.

REFERENCES

1. Donkor E. S. Stroke in the 21st Century: A Snapshot of the Burden, Epidemiology, and Quality of Life. *Stroke Research and Treatment*. 2018. 1-10. https://doi.org/10.1155/2018/3238165.
2. Organization World Stroke. Global Stroke Fact Sheet 2022. 2022. https://www.world-stroke.org/news-and-blog/news/wso-global-stroke-fact-sheet-2022.
3. Mai Duy Ton, Dao Xuan Co, Luong Ngoc Khue, Nguyen Trong Khoa, Nguyen Huy Thang, et al. Current State of Stroke Care in Vietnam. *Stroke Vasc Interv Neurol*. 2022. 2(2), 1-5. https://doi.org/10.1161/SVIN.121.000331.
4. McCall S. J., Alanazi T. A., Clark A. B., Musgrave S. D., Bettencourt-Silva J. H., et al. Hyperglycaemia and the SOAR stroke score in predicting mortality. *Diab Vasc Dis Res*. 2018. 15(2), 114-121. http://doi.org/10.1177/1479164117743034.
5. Capes S. E., Hunt D., Malmberg K., Pathak P., Gerstein H. C. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: A systematic overview. *Stroke*. 2001. 32, 2426-32. https://doi.org/10.1161/hs1001.096194.
6. Snarska K. K., Bachórzewska-Gajewska H., Kapica-Topczewska K., Drozdowski W., Chorąży M., et al. Hyperglycemia and diabetes have different impacts on outcome of ischemic and hemorrhagic stroke. *Arch Med Sci*. 2017. 13(1), 100-108. http://doi.org/10.5114/aoms.2016.61009.
7. Association American Diabetes. Diabetes Care in the Hospital: Standards of Medical Care in Diabetes—2022. *Diabetes Care*. 2022. 45(1), S244–S253. https://doi.org/10.2337/dc22-S016.
8. Sacco R. L., Kasner S. E., Broderick J. P., Caplan L. R., Connors J. J., et al. An Updated Definition of Stroke for the 21st Century: A Statement for Healthcare Professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013. 44(7), 2064-89. http://doi.org/10.1161/STR.0b013e318296aeca.
9. Gibson G. A., Militello M. A., Guzman J. A., Bauer S. R. Evaluation of an updated insulin infusion protocol at a large academic medical center. *AJHP Residents Edition*. 2016. 73(11), 88-93. http://doi.org/10.2146/ajhp150383.
10. Vespa P., McArthur D. L., Stein N., Huang S.-C., Shao W., et al. Tight glycemic control increases metabolic distress in traumatic brain injury: a randomized controlled within-subjects trial. *Crit Care Med*. 2012. 40(6), 1923-9. http://doi.org/ 10.1097/CCM.0b013e31824e0fcc.