


# Continuous Intravenous versus Subcutaneous Administration of Insulin for Glycemic Variability in Acute Ischemic Stroke

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**Background:** Continuous intravenous infusion (IV) or subcutaneous injection (SC) of insulin was widely applied to control hyperglycemia after ischemic stroke. However, the impact of different administration modes on glycemic variability was unknown.

**Methods:** Consecutive stroke patients treated with intravenous thrombolysis were screened. Subjects who received insulin treatment were included and entered into the IV or SC group according to the respective administration mode. Blood glucose was closely monitored within the first 72 hours, and the target range of glucose was from 7.7 to 10.0 mmol/L for all patients. The variabilities of glucose, assessed using standard deviation of the mean, variable coefficient and range from the maximum to the minimum value, were compared between the two groups.

**Results:** A total of 130 patients were enrolled with 66 in the IV groups and 64 in the SC group. Compared with the SC group, the IV group had higher glycemic variability evaluated as either standard deviation ( $2.7 \pm 0.7$  mmol/L vs  $2.2 \pm 0.9$  mmol/L,  $p = 0.002$ ), variable coefficient ( $0.26 \pm 0.06$  vs  $0.23 \pm 0.08$ ,  $p = 0.011$ ) or range ( $10.0 \pm 3.6$  mmol/L vs  $8.1 \pm 3.1$  mmol/L,  $p = 0.001$ ). Multivariate logistic regression analyses found that continuous intravenous infusion was associated with higher level of the standard deviation (adjusted OR 3.01, 95% CI 1.29–7.28,  $p = 0.011$ ), variable coefficient (adjusted OR 5.97, 95% CI 2.55–13.96,  $p < 0.001$ ) and range (adjusted OR 6.08, 95% CI 2.63–14.05,  $p < 0.001$ ).

**Conclusion:** Continuous intravenous infusion of insulin was associated with higher glycemic variability than subcutaneous injection in acute stroke patients receiving thrombolysis.

**Keywords:** acute ischemic stroke, insulin, continuous intravenous infusion, subcutaneous injection, administration mode

## Introduction

Hyperglycemia is a common and essential therapeutic target in acute ischemic stroke with and without premorbid diabetes.<sup>1,2</sup> Recent studies found the variability of glucose after stroke onset, or mentioned as glucose fluctuation, was an independent risk factor for poor outcomes as well as the glucose level,<sup>3–6</sup> with underlying mechanisms including increased oxidative stress, aggravated inflammation, endothelial impairment and microcirculation dysfunction.<sup>6–8</sup> It is also recommended to avoid glycemic excessive fluctuation or hypoglycemia in patients with acute ischemic stroke.<sup>9</sup>

Continuous intravenous infusion or subcutaneous injection of insulin was the main therapies to control post-stroke hyperglycemia at the acute phase.<sup>10,11</sup> However, few evidences were reported on which mode of administration was better. In the “Stroke Hyperglycemia Insulin Network Effort (SHINE)” study, intensive treatment with continuous intravenous insulin infusion was compared with standard treatment with subcutaneous injection after ischemic stroke.<sup>12,13</sup> After a 90-day follow-up, no significant difference in favorable outcome was found between the two administration strategies, while more hypoglycemia occurred in the intensive treatment group, implying a potential harm of continuous intravenous infusion for patients with acute stroke.<sup>13</sup> Considering the higher risk of hypoglycemia, we hypothesized that continuous intravenous infusion of insulin might lead to more fluctuation in blood glucose than subcutaneous administration.

## Methods

To ascertain this hypothesis, we performed a retrospective analysis based on a prospective stroke registry from the National Advanced Stroke Center of Nanjing First Hospital. Consecutive patients with ischemic stroke and hyperglycemia who received intravenous thrombolysis from January 2017 to February 2021 were screened for enrollment. The inclusion criteria were 1) received insulin via continuous intravenous infusion or subcutaneous injection within the first 72 hours after hospital admission; 2) had blood glucose monitored for 8 or more times each day within the first 72 hours. Patients entered into the continuous intravenous infusion group (IV group) or the subcutaneous injection group (SC group) according to the respective administration strategy. Baseline characteristics, medical history, treatment information, blood glucose measures and clinical outcomes were collected. Our study complies with the Declaration of Helsinki. Informed consents were obtained from all participants before enrollment, and this analysis was approved by the Ethics Committee of Nanjing First Hospital.

The treatment of insulin (Biosynthetic Human Insulin, Novolin R) via intravenous or subcutaneous was determined by the clinicians autonomously. The dose adaptations to the capillary glucose test were performed as needed every two hours in the IV group and every three hours in the SC group, respectively, according to a widely applied nomogram.<sup>14</sup> The target range of glucose was from 7.7 to 10.0 mmol/L for all patients. The variability of blood glucose was assessed using standard deviation of the mean, variable coefficient and range from the maximum to the minimum value.

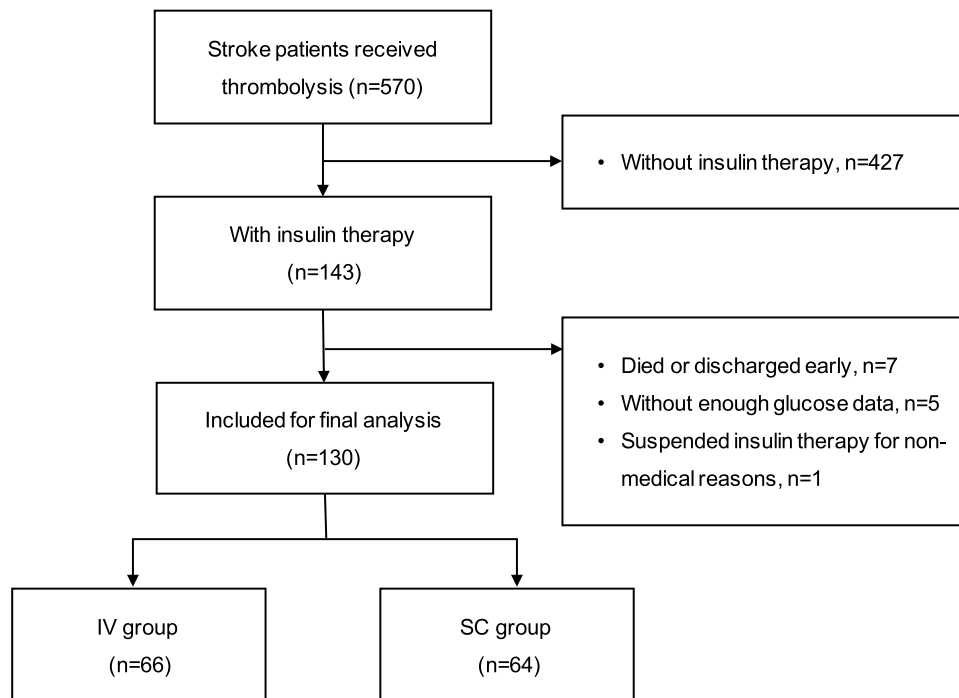
## Statistical Analysis

Baseline characteristics and the glycemic variabilities were compared between the IV and SC groups. Data were presented as mean  $\pm$  standard deviation or median (interquartile range) for continuous variables and numbers (percentage) for categorical variables. Metric and ordinal variables were analyzed by one-way ANOVA and Kruskal–Wallis test, respectively, while frequencies were compared using Fisher's exact method. Univariate and multivariate logistic regression analyses were performed to study the independent impact of different administration strategies on the variabilities. The standard deviation, variable coefficient and range were transformed into binary variables by the cutoff points of average values. Variables with  $p < 0.1$  in univariate analysis were adjusted in multivariate models. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc. Chicago, IL, USA).  $P < 0.05$  was considered statistically significant.

## Results

A total of 570 patients with acute ischemic stroke who received intravenous thrombolysis were screened and 143 cases had insulin therapy through continuous intravenous infusion or subcutaneous injection. After excluding patients who did not have enough glucose data or suspended insulin therapy for non-medical reasons, 130 participants entered into the final analysis (Figure 1). Of these included patients, 50% subjects had pre-stroke diabetes, and the average of HbA1c was  $7.0\% \pm 1.6\%$ . Among the participants, 66 (50.8%) patients entered into the IV group and 64 (49.2%) into the SC group. Patients in the IV group had higher HbA1c than in the SC group ( $7.4\% \pm 1.8\%$  vs  $6.5\% \pm 1.2\%$ ,  $p = 0.002$ ), and other baseline characteristics were comparable between the two groups (Table 1).

No hypoglycemia was reported in either group. Within the first 72 hours, the means of maximum ( $16.3 \pm 3.6$  mmol/L vs  $14.4 \pm 2.8$  mmol/L,  $p = 0.001$ ) and average glucose ( $10.3 \pm 1.7$  mmol/L vs  $9.6 \pm 1.4$  mmol/L,  $p = 0.029$ ) were higher in the IV group than in the SC group, and no difference was found regarding the minimum glucose. Compared with the SC group, the IV group had higher glycemic variability evaluated as either standard deviation ( $2.7 \pm 0.7$  mmol/L vs  $2.2 \pm 0.9$  mmol/L,  $p = 0.002$ ), variable coefficient ( $0.26 \pm 0.06$  vs  $0.23 \pm 0.08$ ,  $p = 0.011$ ), or range ( $10.0 \pm 3.6$  mmol/L vs  $8.1 \pm 3.1$  mmol/L,  $p = 0.001$ ) (Table 2). Univariate and multivariate logistic regression analyses of the glycemic variability are shown in Table 3. After adjusted for the co-variables, the IV group showed higher levels of the standard deviation (adjusted OR 3.01, 95% CI 1.29–7.28,  $p = 0.011$ ), variable coefficient (adjusted OR 5.97, 95% CI 2.55–13.96,  $p < 0.001$ ) and range (adjusted OR 6.08, 95% CI 2.63–14.05,  $p < 0.001$ ) than the SC group. The proportions of target glucose were 27% (19%–40%) in the IV group and 35% (21%–44%) in the SC group, respectively ( $p = 0.062$ ).



**Figure 1** Flow chart of patient inclusion.

There was no difference in clinical outcomes between the two groups, regarding modified Rankin Scale (mRS) score at 90 days [1(0–3) vs 1(0–3),  $p = 0.666$ ], proportion of a mRS score of 0 to 2 (60.6% vs 68.8%,  $p = 0.363$ ) and symptomatic intracranial hemorrhage within 24 hours (6.1% vs 4.7%,  $p = 0.517$ ) (Table 2).

**Table 1** Baseline Characteristics

|                               | <b>Total<br/>(n = 130)</b> | <b>IV Group<br/>(n = 66)</b> | <b>SC Group<br/>(n = 64)</b> | <b>p</b> |
|-------------------------------|----------------------------|------------------------------|------------------------------|----------|
| Age, years                    | 69.9 ± 12.7                | 69.4 ± 14.5                  | 70.4 ± 10.6                  | 0.635    |
| Sex, male (%)                 | 77 (59.2%)                 | 41 (62.1%)                   | 36 (56.3%)                   | 0.593    |
| Medical history               |                            |                              |                              |          |
| Hypertension (%)              | 95 (73.1%)                 | 51 (77.3%)                   | 44 (68.8%)                   | 0.325    |
| Diabetes before onset (%)     | 65 (50.0%)                 | 35 (53.0%)                   | 30 (46.9%)                   | 0.599    |
| Atrial fibrillation (%)       | 26 (20.0%)                 | 16 (24.2%)                   | 10 (15.6%)                   | 0.275    |
| Systolic blood pressure, mmHg | 151.2 ± 22.7               | 149.6 ± 21.6                 | 152.8 ± 23.8                 | 0.425    |
| Laboratory test               |                            |                              |                              |          |
| HbA1c, %                      | 7.0 ± 1.6                  | 7.4 ± 1.8                    | 6.5 ± 1.2                    | 0.002    |
| Serum creatinine, umol/L      | 77.4 ± 51.3                | 78.3 ± 66.3                  | 76.6 ± 30.7                  | 0.853    |
| Platelet, ×10 <sup>9</sup> /L | 195.8 ± 61.7               | 195.5 ± 63.6                 | 196.0 ± 60.1                 | 0.962    |
| Admission NIHSS score         | 5 (3–13)                   | 6 (3–13)                     | 4 (3–12)                     | 0.230    |
| Door-to-thrombolysis, min     | 25 (15–30)                 | 25 (17–30)                   | 25 (15–30)                   | 0.883    |
| Endovascular treatment (%)    | 35 (26.9%)                 | 16 (24.2%)                   | 19 (29.7%)                   | 0.555    |

**Abbreviation:** HbA1c, glycated hemoglobin.

**Table 2** Blood Glucose Variables and Clinical Outcomes Between Groups

|   | <b>IV Group<br/>(n = 66)</b> | <b>SC Group<br/>(n = 64)</b> | <b>p</b> |
|---|------------------------------|------------------------------|----------|
| Blood glucose within 72 hours             |                              |                              |          |
| Maximum, mmol/L                           | 16.3 ± 3.6                   | 14.4 ± 2.8                   | 0.001    |
| Minimum, mmol/L                           | 6.3 ± 1.2                    | 6.3 ± 1.4                    | 0.868    |
| Average, mmol/L                           | 10.3 ± 1.7                   | 9.6 ± 1.4                    | 0.029    |
| Standard deviation, mmol/L                | 2.7 ± 0.7                    | 2.2 ± 0.9                    | 0.002    |
| Variable coefficient                      | 0.26 ± 0.06                  | 0.23 ± 0.08                  | 0.011    |
| Range, mmol/L                             | 10.0 ± 3.6                   | 8.1 ± 3.1                    | 0.001    |
| Proportion of target glucose <sup>a</sup> | 27% (19%–40%)                | 35% (21%–44%)                | 0.062    |
| Clinical outcomes                         |                              |                              |          |
| mRS at 90 days                            | 1 (0–3)                      | 1 (0–3)                      | 0.666    |
| mRS 0–2 at 90 days (%)                    | 40 (60.6%)                   | 44 (68.8%)                   | 0.363    |
| sICH with 24 hours (%)                    | 4 (6.1%)                     | 3 (4.7%)                     | 0.517    |

**Note:** <sup>a</sup>Target glucose is defined as a range from 7.7 to 10.0 mmol/L.

**Abbreviations:** mRS, modified Rankin Scale; sICH, symptomatic intracranial hemorrhage.

**Table 3** Univariate and Multiple Logistic Regression of Blood Glucose Variation

|                                   | <b>Crude OR (95% CI)</b> | <b>p</b> | <b>Adjusted OR (95% CI)</b> | <b>p</b> |
|-----------------------------------|--------------------------|----------|-----------------------------|----------|
| Standard deviation <sup>a</sup>   |                          |          |                             |          |
| IV vs SC                          | 4.10 (1.97–8.51)         | <0.001   | 3.01 (1.29–7.28)            | 0.011    |
| variable coefficient <sup>b</sup> |                          |          |                             |          |
| IV vs SC                          | 5.53 (2.60–11.76)        | <0.001   | 5.97 (2.55–13.96)           | <0.001   |
| Range <sup>c</sup>                |                          |          |                             |          |
| IV vs SC                          | 3.33 (1.62–6.84)         | 0.001    | 6.08 (2.63–14.05)           | <0.001   |

**Notes:** <sup>a</sup>OR for standard deviation was adjusted by hypertension, HbA1c and combined thrombectomy. <sup>b</sup>OR for variable coefficient was adjusted by sex, hypertension, HbA1c and combined thrombectomy. <sup>c</sup>OR for range was adjusted by HbA1c and combined thrombectomy.

## Discussions

In this study, we found that continuous intravenous infusion of insulin for hyperglycemia was associated with higher glycemic variability than subcutaneous injection in patients with acute stroke. Despite closer monitoring and adaption, patients in the IV group seemed to had lower proportion of target glucose than in the SC group.

The underlying mechanisms of different variabilities in two administration routes were not entirely clear. The primary explanation might be the different absorption rates of insulin.<sup>10</sup> In the SC group, insulin is injected into subcutaneous tissue and enters into circulation through blood and lymph capillaries. Subcutaneous tissue consists of fat lobules and extracellular matrix, which constitutes a physiological barrier to insulin delivery and keeps a steady increase in insulin concentration in circulation.<sup>15–17</sup> In the IV group, insulin is directly injected into the venous system, which might lead to a steep change in plasma concentration, especially at the time points of start, stop and dose adjustment. Another possible

explanation is that the IV strategy needed more doses of insulin than the SC group under the same glycemic level according to the nomogram.<sup>14</sup> A larger dose might lead to greater change in blood glucose.

By comparing the glycemic variabilities of different insulin therapies, our findings were in accordance with the SHINE study in regard to revealing harmful effects of continuous insulin infusion on patients with acute ischemic stroke. Unlike the SHINE study which was stopped early for high risk of hypoglycemia, no patients in our cohorts experienced such adverse event, and the average blood glucose was similar in the two groups. This might be due to different glycemic targets, which were 4.4–7.2 mmol/L and 4.4–9.9 mmol/L in the intensive and standard groups of the SHINE study, respectively,<sup>13</sup> and 7.7 to 10.0 mmol/L in both groups of ours. Furthermore, our objective was to compare the two administration strategies, instead of exploring the relative effect of “intensive glycemic control” over “standard control”.

Our study added evidences of different effects of continuous intravenous and subcutaneous injection of insulin on the glycemic variability. However, some limitations should be mentioned. First, as a single-center and hospital-based retrospective study with a small sample size, the selection bias must exist. We only enrolled patients who had records of blood glucose for 72 hours, and patients died or be discharged early would had been excluded. Second, as a case–control study, the stroke severities and HbA1c levels were not balanced and patients in the IV groups tended to be severer and had a higher glucose level before stroke, which possibly impacted our results. Although we used regression analysis to adjust the confounding factors, the statistical power might be weakened. Third, we chose patients receiving intravenous thrombolysis as participants because glycemic control could be initiated quickly and within the first few hours after stroke onset in these patients.<sup>1</sup> Whereas, the interactive effect of thrombolytic agents on glycemic variability was not known, and it was still unclear whether insulin administration modes would affect glycemic variability in patients who did not perform thrombolysis. Fourth, the glycemic variability was calculated based on capillary glucose at different time points. However, continuous glucose monitoring might provide more and accurate measurements. Further studies with prospective design and large sample size are needed.

## Conclusion

Continuous intravenous infusion of insulin for glycemic control might be associated with higher glycemic variability than subcutaneous administration in patients who had acute stroke and received thrombolysis. For controlling hyperglycemia smoothly and avoiding high fluctuation, the mode of subcutaneous injection might be preferred to continuous intravenous infusion in clinical practice.

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## Disclosure

The authors report no conflicts of interests in this work.

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