

# Prospective analysis of glycemic variability in patients with severe traumatic brain injury: modified Leuven's adjustment process versus conventional adjustment process

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## Abstract

**Objective:** This study was performed to evaluate the effect of two different methods of controlling glycemic variability (GV) in patients with severe traumatic brain injury (STBI) undergoing surgery.

**Methods:** Patients with STBI were randomly grouped into a conventional adjustment process (CAP) group and modified Leuven's adjustment process (mLAP) group. Each group included 50 patients. Blood glucose levels were continuously monitored and data were recorded and analyzed.

**Results:** The mean blood glucose level was stable in both groups for 5 days postoperatively with no significant difference. The standard deviation of the blood glucose level, mean amplitude of glycemic excursions, and glycemic lability index were significantly higher in the CAP than mLAP group for the first 2 days. In the final 3 days, no significant differences were observed between the two groups. The incidence of hypoglycemia was significantly higher in the CAP than mLAP group

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on the first day. This value gradually declined during the following 4 days, but the difference between the two groups was not significant.

**Conclusion:** The mLAP produced more favorable results than the CAP for GV control in the early stage after surgery for STBI.

### **Keywords**

Severe traumatic brain injury, glycemic variability, hyperglycemia, hypoglycemia, conventional adjustment process, modified Leuven's adjustment process

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### **Abbreviations**

STBI, severe traumatic brain injury; TBI, traumatic brain injury; GV, glycemic variability; ICU, intensive care unit; CAP, conventional adjustment process; mLAP, modified Leuven's adjustment process; GCS, Glasgow coma scale; MBG, mean blood glucose; SDBG, standard deviation of blood glucose; MAGE, mean amplitude of glycemic excursions; GLI, glycemic lability index

### **Introduction**

Severe traumatic brain injury (STBI) is a common condition seen in clinical neurosurgery, and it results in a heavy burden on society and the patient's family because of its high morbidity and mortality rates. Approximately 14% of patients with traumatic brain injury (TBI) present with a high blood glucose concentration.<sup>1</sup> This rate is increased to 55.76% to 76.49% of patients with STBI.<sup>1</sup> Stress hyperglycemia is an important complication of STBI.

Glycemic variability (GV) is an important factor that reflects the efficiency of blood glucose control. It is not only a predictive factor of the patient's prognosis, but it also influences the outcome of patients with STBI.<sup>2</sup> In most Chinese health centers, practitioners in the intensive care unit (ICU) apply a conventional adjustment

process (CAP) to control the blood glucose level.<sup>3</sup> The modified Leuven's adjustment process (mLAP) was recently recommended for glycemic control,<sup>4</sup> and we have found no previous studies that compared these two types of adjustment processes. Therefore, we performed a prospective study to evaluate the efficiency of the mLAP and CAP in controlling GV. In addition, we adopted partial strategies of the two adjustment processes based on the particular characteristics of STBI. Control processes for patients with blood glucose levels below the range of 7.8 to 10.0 mmol/L were not performed.

### **Patients and methods**

#### **Patients**

This was a prospective observational study approved by the Institutional Review Board of the Affiliated Su Bei People's Hospital of Jiangsu Province with a signed waiver of informed consent. No medical decisions were based on the results. Informed consent for the blood glucose adjustment process was obtained from each patient's parent or legal guardian.

We included consecutive patients who were treated in the ICU at our institution and diagnosed with STBI by a head computed tomography scan from April 2013 to

July 2014. All selected cases conformed to the inclusion and exclusion criteria.

The inclusion criteria were as follows: (1) the patient met the criteria for STBI,<sup>5</sup> (2) the first Glasgow coma scale (GCS) score ranged from 3 to 8 upon admission to the hospital, (3) the patient was 18 to 60 years of age, (4) the random blood glucose level was  $\geq 11.1$  mmol/L, (5) the patient had no medical history that would induce hyperglycemia, and (6) the patient's family members consented to the study.

The exclusion criteria were as follows: (1) the patient had a medical history of diabetes or a long course of treatment with steroids, immunosuppressants, or thyroid hormones; (2) the patient still had a serious midline shift or needed a secondary operation after the first operation; (3) the inpatient stay was shorter than 24 h; (4) the patient had a history of mental illness; (5) the patient was pregnant or breastfeeding; and (6) the patient was in a terminal stage of STBI or the family members did not consent to the study.

Finally, the rejection criteria for the study were as follows: (1) interventions that caused the patients to discontinue the study and (2) adverse events, complications, or physiological changes that caused the patients to be ineligible for the study.

### *Grouping method*

The random envelope method was applied for grouping. The different intervention strategies were placed into the envelopes. The researchers successively opened the envelopes according to the patients' order of hospital admission, and the patients were thus assigned to either the mLAP group or CAP group.

### *Monitoring indices and evaluation of content*

All patients underwent peripheral blood glucose testing when they returned to the

ICU after surgery. In the CAP group, the frequency of blood glucose monitoring was adjusted according to the scope of the blood glucose level (Table 1). The frequency of monitoring in the mLAP group was every 2 hours (Table 2). All patients in the study underwent constant monitoring, and blood glucose levels were recorded for 5 days. These values were used to calculate the mean blood glucose (MBG), incidence of hypoglycemia ( $\leq 3.2$  mmol/L), standard deviation of blood glucose (SDBG), mean amplitude of glycemic excursions (MAGE), and glycemic lability index (GLI). Among these data, the MBG, MAGE, and GLI were used to estimate the GV.

### *Conventional treatment*

The blood glucose levels of all patients were strictly controlled during the first 5 days of therapy, which was the length of our study. The patients' vital signs and pupil sizes, especially when the patients were unconscious, were closely observed. In patients with STBI, the administration of 20% mannitol, furosemide, glucocorticoids, Intralipid (20% intravenous fat emulsion; Baxter, Deerfield, IL, USA), and low-molecular-weight dextran might have an effect on hyperglycemia. Therefore, in such patients, the changes in blood glucose levels should be observed and the frequency of monitoring must be reasonably adjusted when these medications are used so that the rate of abnormal hyperglycemia can be reduced. Peptison (Nutricia Pharmaceutical, Schiphol, The Netherlands), which is a type of low-sugar enteral nutritional product, was used to provide nutrition. It was continually infused to enable even absorption of the nutrition.

### *Insulin therapy for GV*

The blood glucose levels were maintained within the range of 7.8 to 10.0 mmol/L through the use of a subcutaneous pump

**Table 1.** Conventional adjustment process**Table 1.1** Treatment based on initial blood glucose level

Blood glucose level (mmol/L)	Initial intravenous insulin dose (U)	Initial rate of insulin administration via intravenous pump (U/h)
10.0–13.3	0	1
13.4–16.7	0	2
16.8–20.0	3	3
>20.0	6	6

**Table 1.2** Adjustment process based on original blood glucose level

Range of blood glucose level (mmol/L)	Variation in blood glucose level	Adjustment of insulin administration	Adjustment of monitoring frequency
<3.9		Discontinue insulin, administer intravenous injection of 20 ml of 50% glucose	Every 30 min
4.0–6.1		Discontinue insulin; if the previous blood glucose level was <6.7 mmol/L, 20 ml of 50% glucose should be intravenously injected	
6.2–7.8	Increase equal to or more than previous dose Decrease in glucose level by <0.6 mmol/L Decrease in glucose level by <0.6 mmol/L	Maintain the original dose of insulin Decrease the insulin dose by approximately 50% Discontinue insulin	
7.9–10.0	Increase in glucose level by >1.1 mmol/L Increase or decrease in glucose level by <0.6 mmol/L Decrease in glucose level by <0.6 mmol/L	Add 1 U/h to the original rate of insulin administration Maintain the original rate of insulin administration Reduce the original rate of insulin administration by 1 U/h	Every 2 h; when three consecutive blood glucose values are within the range of these values, the monitoring frequency should be changed to every 4–6 h
10.1–13.3	Increase in glucose level by >1.1 mmol/L or decrease by >0.6 mmol/L Increase in glucose level by <1.1 mmol/L or decrease by <2.8 mmol/L Decrease in glucose level by >2.8 mmol/L	Add 1 U/h to the original rate of insulin administration Maintain the original rate of insulin administration Reduce the original rate of insulin administration by 2 U/h	Every 1 h

(continued)

**Table 1.2** Continued

13.4–16.7	Decrease in glucose level by >2.8 mmol/L	Maintain the original dose of insulin	
	Decrease in glucose level by >2.8 mmol/L or increase beyond the previous reading	Add 2 U/h to the original rate of insulin administration	
>16.7	Decrease in glucose level by >4.4 mmol/L	Reduce the original rate of insulin administration by 1 U/h	Every 30 min; when three consecutive blood glucose levels are >16 mmol/L
	Decrease in glucose level by >4.4 mmol/L	Maintain the original rate of insulin administration	
	Increase beyond the previous reading	The initial insulin dose for intravenous injection should be determined according to Table 1.1, and 4 U/h should be added to the original rate of insulin administration	

that provided continuous insulin. During therapy, our researchers monitored the dose of insulin and its effect on blood glucose control. Each group of patients underwent a different blood glucose control protocol. In the CAP group, we applied the guidelines of glucose detective and work standards from the book entitled *ICU: Standard; Process; Practice*<sup>3</sup> (Table 1); in the mLAP group, the mLAP protocol was performed (Table 2). These methods were not suitable for patients with STBI who had blood glucose levels lower than 7.8 to 10.0 mmol/L. For these patients, we only applied partial methods to avoid hypoglycemia. During the control of blood glucose, electrolyte disturbances and other adverse reactions were observed and resolved in a timely manner.

**Statistical analysis**

Statistical analyses were performed with SPSS 17.0 (SPSS Inc., Chicago, IL, USA). To assess the differences in patient characteristics between the two groups, t-tests (for comparisons of the MBG, SDBG, MAGE,

and GLI) and chi-square tests were used with a level of significance of  $p < 0.05$ .

**Results**

*Clinical characteristics*

Our prospective investigation included 100 patients with STBI (50 patients in each group) according to the inclusion and exclusion criteria. The patient population consisted of 63 males and 37 females, with ages ranging from 27 to 61 years (mean age,  $46.22 \pm 3.59$  years). No significant differences in age or sex were found between the two groups. The differences in the interval from trauma to admission between the CAP group ( $3.29 \pm 1.39$  h) and the mLAP group ( $3.06 \pm 1.60$  h) and the first GCS score at admission were not significant. Multiple complex cerebral trauma (more than 2 types of TBI) was the most common type of TBI in both the CAP group (24 patients, 48.0%) and mLAP group (27 patients, 54.0%). The difference between the groups was not significant. The different types of operations that were

**Table 2.** Modified Leuven's adjustment process

**Table 2.1** Treatment based on initial blood glucose level

Blood glucose level (mmol/L)	Initial intravenous insulin dose (U)	Initial rate of insulin administration via intravenous pump (U/h)
8.3–9.9	0	2
10.0–12.1	0	3
12.2–14.4	0	4
≥14.5	4	6

**Table 2.2** Adjustment process based on original blood glucose level\*

Blood glucose level (mmol/L)	Variation in blood glucose level	Adjustment processes of insulin
≤3.9		Discontinue insulin; intravenous injection of 20 ml of 50% glucose
4.0–5.5		Discontinue insulin
5.6–8.3	Increase or decrease in glucose level by <1.7 mmol/L	Maintain original insulin dose
	Decrease in glucose level by >1.7 mmol/L	Decrease insulin dose by approximately 50%
8.4–11.0	Increase or decrease in glucose level by <1.7 mmol/L	Add 1 U/h to the original rate of insulin administration
	Increase or decrease in glucose level by >1.7 mmol/L	Decrease rate of insulin administration by approximately 50%
≥11.1	Increase in glucose level	Add 2 U/h to original rate of insulin administration

\*The frequency of monitoring blood glucose was every 2 hours.

performed according the evaluations of the patient conditions in each group were not significantly different. The patient characteristics are summarized in Table 3.

**Comparison of monitoring indices**

During the first 5 days postoperatively, the MBG level was controlled within a limited scope ranging from approximately 7.8 to 10.0 mmol/L, and the MBG values between the two groups were not significantly different on any of the days.

During the first 2 days, the SDBG, MAGE (Figure 1), and GLI in the CAP group (day 1:  $4.7 \pm 1.2$  mmol/L,  $0.86 \pm 0.41$  mmol/L, and  $255.9 \pm 213.7$ ; day 2:  $4.0 \pm 1.7$  mmol/L,  $0.63 \pm 0.38$  mmol/L,

and  $112.7 \pm 92.8$ ) were significantly higher than those in the mLAP group (day 1:  $1.1 \pm 0.68$  mmol/L,  $0.51 \pm 0.25$  mmol/L, and  $255.9 \pm 213.7$ ; day 2:  $1.2 \pm 0.44$  mmol/L,  $0.41 \pm 0.17$  mmol/L, and  $93.1 \pm 72.7$ ,  $p < 0.05$ ). These values showed a decreasing trend over the next 3 days in both groups with no significant differences between the groups.

The incidence of hypoglycemia in the CAP group ( $15.2\% \pm 3.7\%$ ) was significantly higher than that in the mLAP group ( $10.4\% \pm 1.8\%$ ) on the first day postoperatively ( $p < 0.05$ ). During the next 4 days, this rate began to decrease in both groups, but the downward trend was not significantly different between the two groups (Table 4).

**Table 3.** Comparison of general information between the CAP and mLAP groups

Characteristics	CAP group	mLAP group	P value
Age (years)	49.52 ± 2.79	47.97 ± 4.13	0.129
Sex			
Male	34	29	0.768
Female	16	21	
Etiology			
Industrial accident	11	18	0.481
Motor vehicle traffic incident	17	13	
Fall	9	8	
Violent attack	13	11	
Admission GCS score	5.81 ± 2.76	4.95 ± 3.19	0.334
Interval from trauma to admission (h)	3.29 ± 1.39	3.06 ± 1.60	0.215
CT findings			
Position of STBI			
Left	14	17	0.801
Right	17	15	
Bilateral	19	18	
Location of STBI			
Frontal	20	20	0.918
Temporal	21	23	
Parietal	18	17	
Occipital	13	12	
Basal	11	16	
Type of STBI			
Single cerebral contusion	1	2	0.527
Multiple cerebral contusions	3	2	
Ventricular hemorrhage	2	3	
Traumatic acute subdural hematoma	3	4	
Traumatic acute epidural hematoma	7	4	
Traumatic acute subarachnoid hemorrhage	4	5	
Traumatic intracerebral hematoma	6	3	
Multiple complex cerebral trauma	24	27	
Type of operation			
Intracranial hematoma evacuation	15	12	2.131
Unilateral decompressive craniectomy	8	7	
Bilateral decompressive craniectomy	9	11	
Extraventricular drainage	7	6	

Data are presented as n or mean ± standard deviation.

CAP, conventional adjustment process; mLAP, modified Leuven's adjustment process; GCS, Glasgow coma scale; CT, computed tomography; STBI, severe traumatic brain injury

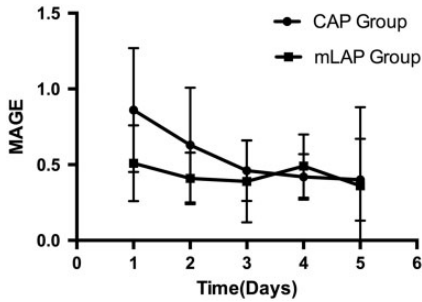
## Discussion

### *Stress hyperglycemia in patients with STBI*

Stress hyperglycemia is a physiological phenomenon involving an increase the in blood

glucose level due to infection, trauma, or hemorrhage and can lead to the development of a neuroendocrine disorder. This type of hyperglycemia only occurs in patients without diabetes. STBI includes intracerebral hemorrhage, brain stem





**Figure 1.** Graph of the MAGE in the CAP and mLAP groups. The differences in the MAGE between the CAP and mLAP groups were not significant during the last 3 days postoperatively. MAGE, mean amplitude of glycemic excursions; CAP, conventional adjustment process; mLAP, modified Leuven's adjustment process

injury, and a midline shift induced by diffuse brain white matter injury, which results in damage to the hypothalamic-pituitary-adrenal axis. Damage to the structure and function of the brain can also overstimulate the sympathoadrenomedullary system, which induces an imbalance of insulin, catecholamines, and glucagon, leading to hyperglycemia. Meanwhile, the abnormal release of cytokines and the occurrence of insulin resistance induce hyperglycemia.<sup>6</sup> Nutritional support also influences hyperglycemia.

The mechanism of hyperglycemia after STBI, its negative effects, and its control programs have recently received increasing attention.<sup>7</sup> Hyperglycemia is regarded as a factor that can influence the prognosis<sup>7-10</sup> as well as the development of hypoxia and hypotension.<sup>11</sup> One observational study showed that STBI was associated with an increase in the blood glucose level during admission; the mean increase in the glucose level was based on the presence of isolated STBI, and the study showed that further surgical intervention may not change the blood glucose level.<sup>7</sup> Hyperglycemia can change the plasma osmotic pressure

(which can impact cell shape and function), retrain immune cell function, induce the upregulation of proinflammatory cytokines, induce mitochondrial dysfunction, and increase oxygen free radicals, thus negatively impacting the entire organism.<sup>12</sup> Appropriate management of stress hyperglycemia is therefore closely related to the outcome of STBI.

### Damage induced by GV

GV is a wide fluctuation of the blood glucose level,<sup>12-14</sup> but the fluctuation range and frequency have not yet been defined. Egi et al.,<sup>15</sup> who performed a case-control study involving 7,034 patients with STBI in 4 institutions in 2006, concluded that GV was the main target in blood glucose control. Larger GV is an important risk factor for increased mortality.<sup>14-16</sup> Another study conducted in China showed that GV in the early stage is an independent factor that could influence the prognosis of patients with STBI.<sup>17</sup> Bagshaw et al.<sup>18</sup> retrospectively analyzed 66,184 patients with STBI and concluded that GV and hypoglycemia in the early stage can predict the mortality rate. Yoder<sup>19</sup> reported that hypoglycemia could induce a metabolic energy disorder and lead to an increase in lactate, which would increase hypoxic/ischemic brain damage. However, hyperglycemia associated with TBI could increase the lactate/pyruvate ratio, which would result in dramatic alkalization. These processes will result in nerve cell death.<sup>20</sup> From our viewpoint, strict glycemic control includes two aspects: decreasing the MBG and decreasing the GV. The SDBG, MAGE, and GLI may reflect the GV, which is a significant factor that influences the prognosis of the patient.

### Advantages of the mLAP

Strict glycemic control is not an easy task; it requires high-frequency glycemic monitoring



**Table 4.** Comparison of glycemic variability between the CAP and mLAP groups

	Day 1			Day 2			Day 3			Day 4			Day 5		
	CAP	mLAP	P value	CAP	mLAP	P value	CAP	mLAP	P value	CAP	mLAP	P value	CAP	mLAP	P value
MBG (mmol/L)	11.6 ± 2.3	9.1 ± 1.7		10.9 ± 2.8	10.2 ± 1.1		10.3 ± 1.02	10.1 ± 0.94		9.7 ± 2.01	10.1 ± 1.9		10.2 ± 1.0	9.5 ± 0.98	
P value		0.194			2.519			0.116			0.769			3.273	
SDBG (mmol/L)	4.7 ± 1.2	1.1 ± 0.68		4.0 ± 1.7	1.2 ± 0.44		2.1 ± 1.4	1.6 ± 0.82		1.9 ± 0.8	2.1 ± 0.72		1.7 ± 0.98	1.4 ± 0.59	
P value		0.0064			0.0021			0.429			7.153			0.894	
MAGE (mmol/L)	0.86 ± 0.41	0.51 ± 0.25		0.63 ± 0.38	0.41 ± 0.17		0.46 ± 0.20	0.39 ± 0.27		0.42 ± 0.15	0.49 ± 0.21		0.40 ± 0.27	0.36 ± 0.52	
P value		0.019			0.013			1.742			0.525			6.792	
GLI	255.9 ± 213.7	112.7 ± 92.8		202.7 ± 163.5	93.1 ± 72.7		113.8 ± 69.4	95.2 ± 61.6		92.2 ± 53.1	90.9 ± 47.1		89.4 ± 55.7	93.1 ± 42.6	
P value		0.022			0.0083			3.354			2.964			0.593	
IH(%)	15.2 ± 3.7	10.4 ± 1.8		10.2 ± 2.5	9.4 ± 1.3		7.9 ± 2.6	8.0 ± 2.1		6.9 ± 1.7	6.6 ± 1.4		3.7 ± 2.1	3.3 ± 1.9	
P value		0.001			0.324			0.724			0.226			0.430	

Data are presented as mean ± standard deviation.  
CAP, conventional adjustment process; mLAP, modified Leuven's adjustment process; MBG, mean blood glucose; MAGE, mean amplitude of glycemic excursions; GLI, glycemic liability index IH, incidence of hypoglycemia

and management of complicated insulin injections. Previous studies have shown that these two procedures highly influence glycemic fluctuation.<sup>20</sup> Studies have shown that the time spent by doctors to maintain blood glucose levels within a normal level, according to their own experience, is 27.4% of a day.<sup>21</sup> Doctors and nurses should cooperate to better control blood glucose levels.<sup>22</sup>

In this prospective study, comparison of the mLAP with the CAP showed that the latter protocol required more complicated procedures than the former protocol. Using the CAP, investigators found several problems such as delayed monitoring and mismatch between the application of insulin and the change in blood glucose. These problems occurred because the process required a higher number of professional medical workers. In contrast, the mLAP protocol has the advantages of early adjustment, relatively simple procedures, and a simple operation. In addition, the complication rate associated with the mLAP was high for the different investigators. Finally, our series showed that GV under the CAP was higher than under the mLAP during the first 3 days postoperatively. The differences in GV between the two groups were not significant from days 3 to 5 postoperatively because of the gradual improvement of patients who were managed by the CAP. TBI and craniotomy can damage the glyce-mic self-adjustment process, which would make glycemic control difficult. In contrast, the mLAP was more beneficial for patients with TBI because of the well-controlled glucose level. These factors would be beneficial for improvement of the prognosis of patients with STBI.

### **Limitations**

This study was performed to estimate the effect of the CAP and mLAP on GV of patients undergoing surgery for STBI.

However, several limitations should be mentioned. First, it was necessary to strictly obey the inclusion and exclusion criteria to ensure safety and effectiveness in this study. As a result, the number of patients in the two groups was small and the patients' characteristics differed, restricting the application of multiple statistical analyses. Thus, bias could not be avoided. Second, the study was performed during a 5-day period, which may have been too short. A longer study duration could provide more useful information about the advantages and disadvantages of the two blood glucose adjustment processes (however, ensuring patient safety is still the most important factor in such studies). In addition, because of the short observation time, the relationship between the two blood glucose adjustment processes and complications such as deep vein thrombosis, intracranial infection, and pressure sore development could not be evaluated. Third, the study only included two types of blood glucose adjustment processes. This may have reduced the strength of our study conclusion to some degree. Finally, STBI is a complex disease involving different types of cerebral hematomas and contusions, which may have different effects on the blood glucose level and GV. This may also lead to biased results. Therefore, we are planning to perform a multicenter prospective randomized study involving a larger sample and longer observation time, more types of blood glucose adjustment processes, and stricter inclusion and exclusion criteria to verify the therapeutic effects of these processes in patients with STBI.

### **Conclusion**

Overall, the mLAP exhibited benefits such as early regulation, easy access, and a simple operation. The results were superior

to those of the CAP during the early stage of recovery.

### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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