



## Observational Study

## Effect of hyperbaric oxygen on post-stroke depression

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In patients with post-stroke depression (PSD) in diabetes, the situation may be more complex, requiring simultaneous treatment of blood glucose, depressive symptoms, and neurological dysfunction. Hyperbaric oxygen (HBO) therapy can improve tissue oxygen content and improve the situation of ischemia and hypoxia, thus playing a role in protecting brain cells and restoring the function of brain cells. However, there are few studies on HBO therapy for patients with PSD. This study explores the clinical efficacy of such therapy for stroke complicated with depression and diabetes mellitus, and to provide reference and basis for clinical treatment and development through the application of relevant rating scales and laboratory test indicators.

**AIM**

To evaluate the clinical effects of HBO therapy on patients with diabetes with PSD.

**METHODS**

A total of 190 diabetic patients with PSD were randomly divided into observation and control groups (95 patients per group). The control group received escitalopram oxalate 10mg once a day for eight weeks. In addition, the observation group was also given HBO therapy, once a day, five times a week, for eight weeks. The Montgomery Depression Rating Scale (MADRS), National Institutes of Health Stroke Scale (NIHSS), hypersensitive C-reactive protein, tumor necrosis factor (TNF)- $\alpha$ , and fasting glucose levels were compared.

**RESULTS**

There were no significant differences in age, sex, or depression course between the groups ( $P > 0.05$ ). After HBO treatment, MADRS scores in both groups decreased significantly ( $14.3 \pm 5.2$ ), and were significantly lower in the control group ( $18.1 \pm 3.5$ ). After HBO treatment, NIHSS scores in both groups decreased significantly, and scores in the observation group ( $12.2 \pm 4.0$ ) decreased more than in the control group ( $16.1 \pm 3.4$ ), the difference was statistically significant ( $P < 0.001$ ). The levels of hypersensitive C-reactive protein and TNF- $\alpha$  in both groups were significantly decreased, and the observation group was significantly lower than the control group ( $P < 0.001$ ). Fasting blood glucose levels in both groups decreased significantly, and those in the observation group decreased more ( $8.02 \pm 1.10$ ) than in the control group ( $9.26 \pm 1.04$ ), with statistical significance ( $t = -7.994, P < 0.001$ ).

### CONCLUSION

HBO therapy can significantly improve depressive symptoms and neurological dysfunction in patients with PSD, and reduce the levels of hypersensitive C-reactive protein, TNF- $\alpha$  and fasting blood glucose.

**Key Words:** Hyperbaric oxygen therapy; Post-stroke depression; Diabetes; Hypersensitive C-reactive protein; Tumor necrosis factor- $\alpha$ ; Fasting plasma glucose

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**Core Tip:** Post stroke depression is one of the common complications of stroke patients. It affects stroke patients in the acute phase and also occurs in the rehabilitation phase, with an incidence rate of about 33%. However, many patients with post-stroke depression may still not be diagnosed and treated. It is currently believed that biological and psychological factors are involved in the occurrence and development of post-stroke depression. Risk factors of post-stroke depression include gender, psychiatric history, size and location of stroke, poor social support and degree of physical injury. Post-stroke depression may not only affect the emotional state and quality of life of patients, but also hinder the recovery of neurological function, and even increase the mortality of patients. Studies have shown that changes in ischemic hypoxia and brain cell damage are common mechanisms of stroke and post-stroke depression, so improving ischemic hypoxia may be an effective treatment. Diabetes is a chronic disease characterized by elevated blood sugar and other metabolic disorders. diabetes is associated with an increased risk of stroke and post-stroke depression.

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## INTRODUCTION

Post-stroke depression (PSD) is a common complication in stroke patients, which can affect those in the acute stage and also occur in the convalescence stage, with an incidence of approximately 33%. However, many patients with PSD may remain undiagnosed and untreated[1]. Biological and psychological factors are currently believed to be involved in the occurrence and development of PSD[2]. Risk factors include gender, history of mental illness, size and location of stroke, poor social support, degree of physical impairment, and so on[3]. PSD may not only affect patients' emotional state and quality of life, but also hinder the recovery of neurological function and even increase patient mortality[4]. Studies have suggested that changes in ischemic hypoxia and brain cell damage are the common mechanisms of stroke and PSD, so improving ischemic hypoxia may be an effective treatment[5]. Diabetes is a chronic disease characterized by elevated blood glucose and other metabolic disorders, and is associated with increased risk of stroke and PSD[6]. Therefore, in patients with PSD in diabetes, the situation may be more complex, requiring simultaneous treatment of blood glucose, depressive symptoms, and neurological dysfunction. Hyperbaric oxygen (HBO) therapy can improve tissue oxygen content and improve the situation of ischemia and hypoxia, thus playing a role in protecting brain cells and restoring the function of brain cells[7]. However, there are few studies on HBO therapy for patients with PSD. This study explores the clinical efficacy of such therapy for stroke complicated with depression and diabetes mellitus, and to provide reference and basis for clinical treatment and development through the application of relevant rating scales and laboratory test indicators.

## MATERIALS AND METHODS

### Patients

From June 2018 to June 2021, a total of 190 diabetic patients with PSD diagnosed and treated in the General Hospital of Chinese PLA were recruited, all of whom met the diagnostic criteria of PSD. Inclusion criteria: (1) Patients aged  $\geq 18$  years in line with PSD[8]; (2) The vital signs were stable, and the clinical laboratory indicators related to stroke were basically normal; (3) No serious complications or comorbidities, normal consciousness, and cognition; and (4) Diabetes was diagnosed before stroke and in line with the diagnostic criteria of the American Diabetes Association in 2018[9]. Exclusion criteria: (1) Complicated with serious dysfunction of heart, liver, kidney, and other organs; (2) Complicated with malignant tumor and coagulation diseases; and (3) Failure to cooperate with treatment or adherence. The study protocol was approved by the Ethics Committee of the General Hospital of Chinese PLA, and all patients or their families were informed and signed the consent. Among the 190 patients, there were 52 males and 43 females in the control group, with an average age of  $63.7 \pm 9.3$  years,  $49.2 \pm 14.5$  d of depression and  $5.9 \pm 3.4$  years of diabetes. There were 55 males and 40 females in the observation group, with an average age of  $62.9 \pm 6.1$  years,  $50.1 \pm 12.6$  d of depression and  $5.6 \pm 3.6$  years of diabetes. Data on the patients' age, sex, smoking history, past disease history, and disease course were collected. The patients' height and weight were measured, and their body mass index (BMI) was calculated. Their blood pressure was measured in the resting state.

### Patient grouping and treatment methods

The patients were divided into observation and control groups using the random number table method, with 95 patients in each group. Patients in both groups were given nutritional cerebrovascular application (including mecobalamin 0.5 mg), once a day, three times a week, intramuscular or intravenous injection, which can be increased or decreased according to age and symptoms, anti-platelet (thromboxane A2 inhibitor aspirin, 75-100 mg/time, Once a day), hypoglycemic [exenatide's initial dose is 5  $\mu$ g twice a day, and can be increased to 10  $\mu$ g twice a day after 1 mo of treatment according to the patient's clinical response; injections should be given within 60 min before breakfast and dinner (or before 2 main meals per day; Approximately 6 h or longer)] and other conventional treatments. The control group received oral escitalopram oxalate, 10 mg, once a day (Sichuan Kelun Pharmaceutical Co., Ltd.) for eight weeks. In addition to the oral drug regimen of the control group, the observation group received HBO therapy, once a day, five times a week, for eight weeks.

The HBO treatment was as follows: An HBO chamber (OxyHealth Europe, Vitaeris 320™) was pressurized for 20 min to reach 0.25 mpa. The patient then put on a mask and breathed pure oxygen for 40 min, breathing cabin air at 10-min intervals. Finally, patients decompressed for 30 min to normal pressure, and then left the cabin. Treatment was once a day, 10 times for a course of treatment, each course of intermittent 7-10 d, for a total of two months of observation.

### Observation indicators

The following observation indexes were used to evaluate the efficacy before and after treatment: (1) Depression evaluation: The Montgomery Depression Rating Scale (MADRS) scale was used to evaluate patients' depression. The scale is divided into 10 items, with each item being rated from 1 to 6. On a scale of 0 to 60, the higher the score, the more severe the depression; (2) Neurological function evaluation: The National Institutes of Health Stroke Scale (NIHSS) scale was used to evaluate patients' neurological function. The scale includes 14 items, scored from 0 to 42. The higher the score, the more severe the neurological impairment; and (3) Measurement of hypersensitive C-reactive protein and tumor necrosis factor (TNF)- $\alpha$ : 10 mL of fasting venous blood was taken before and after treatment, and the upper serum was centrifuged after standing. Levels of the aforementioned were determined by enzyme-linked immunosorbent assay as per the manufacturer's instructions.

### Statistical analysis

Enumeration data were expressed as frequencies (percentage) and the  $\chi^2$  test was used to assess differences between the two groups. mean  $\pm$  SD was used to represent measurement data, and the difference between the two groups was assessed *via t*-test. The differences of MADRS score, NIHSS score, hypersensitive C-reactive protein, TNF- $\alpha$  and fasting blood glucose levels between the two groups before and after treatment were determined by *t*-test.  $P < 0.05$  was considered statistically significant (bilateral), and IBM SPSS 21.0 was used for statistical analysis of the data.

## RESULTS

### General patient information

This study included 190 patients with diabetes and PSD. Patients in the observation group were aged  $64.4 \pm 9.4$  years, and male patients accounted for 57.9% (55/95). The course of depression was  $50.8 \pm 15.3$

d, and the course of diabetes was  $6.2 \pm 3.6$  years. The proportion of patients with hypertension, coronary heart disease and hyperlipidemia was 54.7% (52/95), 38.9% (37/95) and 66.3% (63/95), respectively. BMI of patients in the observation group was  $25.8 \pm 3.8$  kg/m<sup>2</sup>, and systolic blood pressure was  $139.2 \pm 13.3$  mmHg. In the observation group, 57 patients (60%) had ischemic stroke and 38 (40%) had hemorrhagic stroke. In the control group, the patients were aged  $63.0 \pm 9.2$  years, 51.6% (49/95) male, the course of depression was  $47.5 \pm 13.4$  d, and the course of diabetes was  $5.7 \pm 3.2$  years. In the control group, 48.4% (46/95) had a history of hypertension, 33.7% (32/95) had a history of coronary heart disease, 54.7% (52/95) had a history of hyperlipidemia. The BMI of the control group was  $26.2 \pm 4.1$  kg/m<sup>2</sup>, and the systolic blood pressure was  $137.6 \pm 12.3$  mmHg. In the observation group, 48 patients (50.5%) had an ischemic stroke and 47 (49.5%) had a hemorrhagic stroke. There were no significant differences in these characteristics between the two groups ( $P > 0.05$ , Table 1).

### **Depressive state and neurological function scores**

Before treatment, the MADRS score of observation group ( $33.7 \pm 5.0$ ) was not statistically significant compared with the control group ( $33.0 \pm 4.0$ ,  $P > 0.05$ ). After HBO treatment, the MADRS scores in both groups decreased significantly; that of the observation group ( $14.3 \pm 5.2$ ) was significantly lower than that of the control group ( $18.1 \pm 3.5$ ), and the difference was statistically significant ( $P < 0.001$ ). Before treatment, the NIHSS score of the observation group ( $21.9 \pm 4.1$ ) was compared with the control group ( $21.0 \pm 3.9$ ), and there was no statistical significance ( $P > 0.05$ ). After HBO treatment, NIHSS scores in both groups decreased significantly; scores in the observation group ( $12.2 \pm 4.0$ ) decreased more than those in the control group ( $16.1 \pm 3.4$ ), the difference being statistically significant ( $P < 0.001$ ) (Table 2).

### **Levels of hypersensitive C-reactive protein and TNF- $\alpha$**

Before treatment, there was no statistical significance in the level of hypersensitive C-reactive protein in the observation group ( $7.71 \pm 1.73$ ) compared with the control group ( $7.43 \pm 1.53$ ,  $P > 0.05$ ). After HBO treatment, the level in both groups decreased significantly, and the level in the observation group ( $2.87 \pm 1.49$ ) was significantly lower than that in the control group ( $4.52 \pm 1.42$ ); the difference was statistically significant ( $P < 0.001$ ). Before treatment, there was no significant difference in TNF- $\alpha$  between the observation group ( $57.2 \pm 13.6$ ) and control group ( $58.6 \pm 11.9$ ,  $P > 0.05$ ). After HBO treatment, TNF- $\alpha$  in both groups decreased significantly, and decreased more in the observation group ( $26.7 \pm 12.5$ ) than in the control group ( $33.9 \pm 11.1$ ), with statistical significance ( $P < 0.001$ ) (Table 3).

### **Fasting blood glucose level**

Before treatment, there was no significant difference in fasting blood glucose level between the observation group ( $10.96 \pm 0.91$ ) and control group ( $11.16 \pm 0.93$ ). After HBO treatment, the level decreased significantly in both groups, and that in the observation group decreased more than that in the control group ( $9.26 \pm 1.04$ ); the difference was statistically significant ( $t = -7.994$ ,  $P < 0.001$ , Table 4).

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## **DISCUSSION**

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We found that HBO therapy improved depressive symptoms and neurological dysfunction in patients with PSD, and reduced levels of hypersensitive C-reactive protein and TNF - $\alpha$  compared with the control group. It is worth noting that patients with diabetes and PSD who underwent HBO therapy had lower fasting glucose levels.

Stroke is an acute cerebrovascular disease with high disability and mortality rates, and PSD is a common complication that may affect nearly one-third of patients[10-12]. Importantly, PSD not only affects the patient's psychosis but may also affect the treatment effect and recovery of neurological dysfunction in patients with stroke, and even increase the incidence of recurrent stroke and all-cause mortality[13,14]. Diabetes, a chronic disease mainly characterized by elevated blood glucose, may increase the risk of stroke and PSD[15,16]. Additionally, PSD combined with diabetes may increase the risk of recurrent stroke, aggravate depressive symptoms, and even increase patient mortality[17]. Therefore, diabetes is a major cause of stroke. With the development of diabetes, patients are prone to metabolic abnormalities, cholesterol will be further increased, and thrombosis will be formed, finally leading to ischemic stroke[18]. Timely control of blood glucose is an important prevention of stroke.

Currently, escitalopram is the main first-line drug for the treatment of PSD, and the use of this drug can improve patients' emotional symptoms, but studies have demonstrated that some patients with PSD still have depressive symptoms after using escitalopram, with poor efficacy[19]. Treatment includes changing the antidepressant, adding another antidepressant, or augmenting the treatment by adding another drug, such as an atypical antipsychotic or lithium. Non-pharmacological forms of augmentation of depression treatment have also been proven to be effective, including cognitive-behavioral psychotherapy, psychoeducation, aerobic exercise, neuromodulatory treatment through vagus nerve stimulation, electroconvulsive therapy (ECT), transcranial direct current stimulation (TDCS), repetitive transcranial magnetic stimulation (rTMS) or deep brain stimulation and light therapy; however, non-pharmacological forms of biological treatment used in the treatment of treatment-resistant depression

**Table 1 Clinical characteristics of patients in two groups, n (%)**

Clinical characteristics	Observation group	Control group	<i>t/χ<sup>2</sup></i>	<i>P</i> value
Patients	95	95	-	-
Age (yr)	64.4 ± 9.4	63.0 ± 9.2	1.052	0.294
Male	55 (57.9)	49 (51.6)	0.765	0.382
Depressive course (d)	50.8 ± 15.3	47.5 ± 13.4	1.579	0.116
Smoking history	38 (40.0)	31 (32.6)	1.115	0.291
Diabetes course (yr)	6.2 ± 3.6	5.7 ± 3.2	0.941	0.348
History of hypertension	52 (54.7)	46 (48.4)	0.759	0.384
History of coronary heart disease	37 (38.9)	32 (33.7)	0.569	0.451
History of hyperlipidemia	63 (66.3)	52 (54.7)	2.666	0.103
Body mass index (kg/m <sup>2</sup> )	25.8 ± 3.8	26.2 ± 4.1	-0.676	0.500
Systolic blood pressure (mmHg)	139.2 ± 13.3	137.6 ± 12.3	0.873	0.384
Stroke type			1.724	0.189
Ischemic stroke	57 (60.0)	48 (50.5)		
Hemorrhagic stroke	38 (40.0)	47 (49.5)		

**Table 2 Depressive state and neurological function scores of the two groups**

Group	Patients	MADRS scores		NIHSS scores	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	95	33.7 ± 5.0	14.3 ± 5.2 <sup>a,d</sup>	21.9 ± 4.1	12.2 ± 4.0 <sup>a,d</sup>
Control group	95	33.0 ± 4.0	18.1 ± 3.5 <sup>a</sup>	21.0 ± 3.9	16.1 ± 3.4 <sup>a</sup>

<sup>a</sup>*P* < 0.001 vs before treatment in this group.

<sup>d</sup>*P* < 0.001 vs control group after treatment.

MADRS: Montgomery Depression Rating Scale; NIHSS: National Institutes of Health Stroke Scale.

**Table 3 The levels of hypersensitive C-reactive protein and tumor necrosis factor-α in the two groups**

Group	Patients	Hypersensitive C-reactive protein (mg/L)		Tumor necrosis factor-α (ng/L)	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	95	7.71 ± 1.73	2.87 ± 1.49 <sup>a,d</sup>	57.2 ± 13.6	26.7 ± 12.5 <sup>a,d</sup>
Control group	95	7.43 ± 1.53	4.52 ± 1.42 <sup>a</sup>	58.6 ± 11.9	33.9 ± 11.1 <sup>a</sup>

<sup>a</sup>*P* < 0.001 vs before treatment in this group.

<sup>d</sup>*P* < 0.001 vs control group after treatment.

also do not show substantial efficacy. Despite the improvement achieved during electroshocks, ECT has no lasting effect, and despite continued pharmacotherapy, relapses are observed in a large (37%) proportion of patients[20]. TDCS has been used with a moderate effect on depression, similar to rTMS, which also has moderate and short-term efficacy in improving mood and cognitive function in people with depression[21]. Light therapy has proven to be ineffective in enhancing the effects of antidepressants in both seasonal and recurrent depression[22]. Currently, HBO therapy is known to be an effective and safe method for treating PSD, which has been the subject of numerous studies. This study found that HBO therapy can improve depressive symptoms and neurological dysfunction in patients with PSD, specifically improving the blood supply to the lesion and facilitate the blood supply to the focal point of the stroke. Under the action of HBO, the phenomenon of counter-stealing blood will appear in the tissue, which is conducive to the blood supply to the ischemic lesion. Increase vertebro-basilar artery blood flow: Under HBO, the vertebrobasilar artery system is the only blood vessel that

**Table 4 Fasting blood glucose levels of the two groups**

Group	Patients	Before treatment	After treatment	t value	P value
Observation group	95	10.96 ± 0.91	8.02 ± 1.10	20.177	< 0.001
Control group	95	11.16 ± 0.93	9.26 ± 1.04	13.256	< 0.001
t value	-	-1.475	-7.994	-	-
P value	-	0.142	< 0.001	-	-

does not contract but dilates, thus increasing the blood supply and oxygen supply to the brain stem and reticular structure, which is conducive to the improvement of the patient's wakefulness and mood. HBO therapy was found to improve depressive symptoms and neurological dysfunction in patients with PSD. Similar to this study, a meta-analysis established that HBO treatment reduced NIHSS scores (mean difference = 2.77 points, 95%CI from 3.57 to 1.98 points,  $P < 0.001$ ) and improved Hamilton Depression Scale scores (mean difference = 4.33 points, 95%CI from 4.82 to 3.84 points,  $P < 0.001$ )[7].

Ischemic anoxic injury may be a common initiating factor of stroke and PSD, and inflammatory processes may also be involved in the occurrence and development of depression. It has been suggested that patients with PSD had higher levels of TNF- $\alpha$  compared with non-depressed patients ( $25.65 \pm 9.24$  vs  $17.29 \pm 4.27$ ,  $P < 0.001$ )[23]. In this study, diabetic PSD patients in the observation group had lower levels of hypersensitive C-reactive protein and TNF- $\alpha$  compared with the control group. This suggests that inflammatory factors can be used as biomarkers of PSD in patients with diabetes and may be effective early treatment targets[24]. Interestingly, the present study found that patients with PSD and diabetes who underwent HBO therapy had lower fasting glucose levels. Previous studies have suggested that HBO therapy can promote insulin secretion in patients with diabetes and enhance glucose uptake by brain cells[25].

This study has some limitations. Owing to the small sample size, fewer variables were collected, and the observation time was short. Large randomized controlled clinical trials are required to validate the role of HBO therapy in patients with diabetes and PSD.

## CONCLUSION

In conclusion, HBO therapy can significantly improve depressive symptoms and neurological dysfunction in patients with PSD, and reduce the levels of hypersensitive C-reactive protein, TNF- $\alpha$  and fasting blood glucose, which is worthy of clinical promotion.

## ARTICLE HIGHLIGHTS

### Research background

This study explores the clinical efficacy of such therapy for stroke complicated with depression and diabetes mellitus, and to provide reference and basis for clinical treatment and development through the application of relevant rating scales and laboratory test indicators.

### Research motivation

Changes in ischemic hypoxia and brain cell damage are common mechanisms of stroke and post-stroke depression, so improving ischemic hypoxia may be an effective treatment. Diabetes is a chronic disease characterized by elevated blood sugar and other metabolic disorders. diabetes is associated with an increased risk of stroke and post-stroke depression.

### Research objectives

This study explores the clinical efficacy of such therapy for stroke complicated with depression and diabetes mellitus, and to provide reference and basis for clinical treatment and development through the application of relevant rating scales and laboratory test indicators.

### Research methods

Patients in both groups were given nutritional cerebrovascular application, once a day, three times a week, intramuscular or intravenous injection, which can be increased or decreased according to age and symptoms, anti-platelet, hypoglycemic and other conventional treatments. The control group received oral escitalopram oxalate, 10 mg, once a day for eight weeks., In addition to the oral drug regimen of the control group, the observation group received hyperbaric oxygen (HBO) therapy, once a day, five times

a week, for eight weeks. The HBO treatment was as follows: an HBO chamber was pressurized for 20 min to reach 0.25 mpa. The patient then put on a mask and breathed pure oxygen for 40 min, breathing cabin air at 10-min intervals. Finally, patients decompressed for 30 min to normal pressure, and then left the cabin. Treatment was once a day, 10 times for a course of treatment, each course of intermittent 7-10 d, for a total of two months of observation.

### **Research results**

There were no significant differences in age, sex, or depression course between the groups. After HBO treatment, Montgomery Depression Rating Scale scores in both groups decreased significantly, and were significantly lower in the control group. After HBO treatment, National Institutes of Health Stroke Scale scores in both groups decreased significantly, and scores in the observation group decreased more than in the control group, the difference was statistically significant. The levels of hypersensitive C-reactive protein and tumor necrosis factor (TNF)- $\alpha$  in both groups were significantly decreased, and the observation group was significantly lower than the control group. Fasting blood glucose levels in both groups decreased significantly, and those in the observation group decreased more than in the control group, with statistical significance.

### **Research conclusions**

HBO therapy can significantly improve depressive symptoms and neurological dysfunction in patients with post-stroke depression, and reduce the levels of hypersensitive C-reactive protein, TNF- $\alpha$  and fasting blood glucose.

### **Research perspectives**

The future research direction is mainly to study the influence of depression in diabetes patients.

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## **FOOTNOTES**

**Author contributions:** Guo H and Ge YR conceived the study; Guo H, Dong YB and Zhao XC collected the data; Guo H, Zhao XC, Wang JC and Ge YR contributed to the formal analysis; Guo H and Zhao XC contributed to the investigation; Guo H, Zhao XC and Su GL contributed to the methodology; Guo H, Zhao XC, Su GL and Dong YB supervised the study; Zhao XC validated the study; Guo H and Ge YR contributed to the visualization of the study; Guo H and Wang JC originally drafted the manuscript; Guo H, Ge YR, Wang JC and Dong YB reviewed and edited the manuscript.

**Institutional review board statement:** The study was reviewed and approved by The First Medical Center, Chinese PLA General Hospital Institutional Review Board (Approval No. 20180068).

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