



## Short Communication

# Effect of Angong Niuhuang Pills on Positive Mental Symptoms Caused by Acute Lacunar Infarction in Patients with Mild Alzheimer

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## ABSTRACT

The aim of this study was to explore the effect of angong niuhuang pills (ANP) on positive mental symptoms caused by acute lacunar infarction in patients with mild alzheimer (MA). A total of forty patients with MA from our hospitals between December 2021 and November 2022 were assigned by the Richmond Agitation and Sedation Scale (RASS) assessment into a control group (CG) and a treatment group (TG). Both groups were given a sedative treatment scheme for on-demand use in blind method. The TG was given ANP orally or nasal feeding. Then, the duration of course disease of the two groups of patients was observed. Statistical analysis was performed on the duration of the disease (numbers of half days, half day = 12 h) and the correlation of other data between the two groups. The duration of disease in the TG was shorter than that in the CG ( $P < 0.05$ ). ANP can shorten the duration of the disease course of positive psychiatric symptoms caused by acute cerebral infarction of MA (the infarction site has no anatomical correspondence with the psychiatric symptoms), and contribute to start rehabilitation training early and improve the prognosis of the disease.

Elderly patients, especially those suffering from Alzheimer's disease, are prone to stress-induced acute psychiatric symptoms in response to unexpected events, including mental shock and severe physical injury, and most of them can be diagnosed with delirium (Liao *et al.*, 2020; Urizar *et al.*, 2021). Among them, the most common and hard to deal with are the positive manifestations of mental symptoms (Fei *et al.*, 2009). Due to acute cerebral

infarction, especially in patients with severe symptoms, there is a high rate of the incidence of panic, hallucinations, and aggressive behavior for them (Jiao, 2015). It is very difficult for these patients to carry out active rehabilitation training and passive rehabilitation training, which affects the prognosis of patients severely. Besides, physical injury (cardiovascular and cerebrovascular system damage, accidents, etc.) caused by positive mental symptoms and poor treatment cooperation will further affect the prognosis and even be fatal (Li *et al.*, 2013). Early cessation of these symptoms has positive significance for patients, medical staff, and accompanying staff. Angong niuhuang pills (ANP) are a concentrated pill made from several traditional Chinese medicines according to the classic prescription of ancient Chinese medicine. The main ingredients include bezoar, buffalo horn powder, screen fragrance, pearl, cinnabar realgar, coptis chinensis, yellow

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## Authors' Contribution

HZ and XY contributed equally to this work as co-first author. They participated in conceiving the design of the study and collecting and reviewing the data and coordination of project. YL, BX and JD participated in doing literature review, collecting the data and analysis and in preparing the manuscript. RW and SX helped in critical revision and finalizing the manuscript. All authors read, revised, and approved the final manuscript.

## Key words

Acute cerebral infarction, Positive mental symptoms, Angong niuhuang pills, CAM-CR

base, gardenia, tulip, borneol and others. This medicine is especially famous in eastern China, which is produced by Hu Qingyutang, Zhejiang, specifications: 3g per pill x 1 pill/box; batch), all according to the clinical routine dosage (1 pill of ANP, 60g/day). ANP are often used for acute cerebral apoplexy and can be used to treat reactive psychosis (Li, 2007). Therefore, when the two diseases occur at the same time, it should serve double synergistic effects. The aim of this study was to explore the influence of ANP on positive mental symptoms caused by acute lacunar infarction in patients with mild alzheimer (MA). The findings will provide new insights for the clinical treatment of patients with MA and serve as a reference for the safer use of ANP in clinical care.

### Materials and methods

A total of forty patients with MA were selected from our hospital and the medical consortium between December 2021 to November 2022. Patients in both groups were eligible to join the study if they met the following inclusion criteria: aged from 65 to 85, diagnosed with MA within 3 months before attack and diagnosed with unclassified Alzheimer, ZBI (Zarit Caregiver Burden Interview) less than 20 points, the attack time of acute cerebral infarction within 3 days (based on medical history, neurologist diagnosis, and cranial imaging evidence) and the occurrence of positive mental symptoms within 24 h, the type of cerebral infarction limited to cavity gap cerebral infarction, and patients with other major complications. Patients with organic mental diseases directly caused by the responsible lesion were excluded from the study.

Richmond Agitation and Sedation Scale (RASS) was used to determine positive psychiatric symptoms (negative symptoms were not excluded at the same time) (Boettger *et al.*, 2020), and score of +1 to +3 was included in the group.

Confusion Assessment Method-Chinese Reversion (CAM-CR) was used to evaluate the degree of disease (Gan *et al.*, 2017). The initial score greater than 20 points was included in the group. It was used to score twice a day (8AM, 8PM), and the score lower than 20 points for three consecutive times without the use of sedatives that the patient's mental symptoms were significantly relieved, and the time of the first scoring was taken as the recovery time of the patient. The evaluation time of continuous episodes of mental symptoms was terminated after 20 episodes in 10 days. If the last 3 episodes could not meet the recovery criteria sedative drugs was continued. However, CAM-CR could not be lowered than 20 points after sedative drugs are stopped. then it is evaluated as not clinically recovered, that is, it is not taken as a sample for recovery time analysis. In addition, the recovery rate of the TG and the CG was compared and explained separately.

Mini-Mental State Examination (MMSE) was done

to assess cognitive abilities (Wang *et al.*, 2021). The third CAM-CR score is lower than 20 points, and the scale is added at the same time. It can be compared with the previous (within 3 months before the attack) MMSE scale; if there is no previous data, then comparison not to be made.

The National Institutes of Health Stroke Scale (NIHSS) was used to evaluate the effect of acute stroke on the level of consciousness, language, attention, visual field, eye movement, muscle strength, speech, sensory function, and ataxia (Kasner *et al.*, 1999). This scale is a fifteen-part rating based on neurological examination. The examiner gives the patient a score of zero to five according to the patient's answers and the ability to perform movement in each case, where zero means normal.

All data are expressed as mean±standard deviation (x±s), and spss 26.0 software is used for statistical processing. The means of the two samples were tested by t test, the mean of multiple samples was compared by one-way analysis of variance, and the non-parametric Krusral-Wallis H test with rank transformation was used for heterogeneity of variance, and P<0.05 is considered statistically significant.

### Results

Forty patients were collected in total, including twenty males and twenty females, aged 66-84 years old, of which nine were older than eighty years old, accounting for 22.5%; NIHSS score was 3-9 points, and 18 patients with more than 5 points (less than or equal to 5 points were mild patients with ischemic stroke), accounting for 45%. There were 19 cases in the TG and 21 cases in the CG. Among the nineteen patients in the TG, three patients did not recover clinically within ten days, and the recovery rate was 84.21%. Among the twenty-one patients in the CG, seven patients did not recover clinically within ten days, and the recovery rate was 66.67%. The recovery time of the TG was 8.07±2.28 (half days), and that of the CG was 12.5±2.85 (half days). The recovery time of the TG was shorter than that of the CG, and the recovery time was statistically significant (T-value=-4.64, P-value<0.001).

Whether the patients in the TG who did not recover clinically within ten days were related to the degree of

**Table I. RASS scores of each group before control enrollment.**

RASS score before enrollment	Group 1		Group 2		Total		
	N	%	N	%	N	%	
Whether the CG recovered	0	1	7.7	2	50.0	3	21.1
	1	12	92.3	3	50.0	15	78.9
Total		13	100.0	5	100.0	18	100.0

RASS score 1= mild, 2= severe, because the total number n<40, using Fisher's exact probability method, P= 0.71, which was statistically significant.

positive mental symptoms at the time of attack (RASS score +1, +2 were mild and moderate, set as group 1, RASS score +3 was severe, set as group 2). The results were not statistically significant. The CG was analyzed in the same way, and it was found that no clinical recovery was related to the severity of the RASS score, that is, patients with a score of +3 had a worse prognosis (Table I).

In the TG, the MMSE score after clinical recovery was  $21.53 \pm 1.36$ , and the MMSE score before the attack was  $22.18 \pm 1.40$ , with a P-value of 0.279, showing no statistical significance. The MMSE score of the CG after clinical recovery was  $20.93 \pm 1.59$ , and the MMSE score before the attack was  $21.79 \pm 1.42$ , with a P-value of 0.494, showing no statistical significance (Table II).

**Table II. MMSE and CAM-CR score of each group.**

Time	CG (n=15)	TG (n=15)	T-value	P-value
<b>MMSE score</b>				
Before the treatment	21.79±1.42	22.18±1.40	0.695	0.494
After the treatment	20.93±1.59	21.53±1.36	1.10	0.279
<b>CAM-CR score</b>				
Recovery time (half day)	21	14	-	0.01
CAM-CR score	19	15	-	0.01
Pearson correlation Sig. (double tail)	0.797	0.750	-	0.01

Table III shows that whether the recovery time of the TG and the CG are related to the CAM-CR score. Using the Pearson correlation test, the recovery time of the TG was significantly correlated with the CAM-CR score, and the recovery time of the CG was significantly correlated with the CAM-CR score, both P-values were 0.01, which was statistically significant.

### Discussion

After screening the patients with positive mental symptoms, the CAM-CR score was used to observe the changes of the mental symptoms of the patients, based on the following considerations: CAM-CR is an international general assessment method for delirium in my country based on the actual clinical situation and characteristics in China. CAM grades the original items, establishes detailed scoring definitions, and establishes the CAM CR with detailed quantitative scoring standards. Although CAM-CR includes the dimension of negative symptoms, mental disorders with prominent positive symptoms can be combined with negative symptoms. Therefore, it will be more objective to use comprehensive evaluation to judge the outcome, with high reliability and validity. When CAM-CR is less than 20, it is judged that the mental symptoms have improved. Because the scale has many dimensions, it is difficult to carry out qualitative analysis,

so the correlation between samples without clinical recovery and CAM-CR scores was not discussed.

The recovery time of the TG was shorter than that of the CG, and it was statistically significant. It shows that the addition of ANP can shorten the course of positive mental symptoms in patients with MA caused by acute lacunar infarction. Elderly patients, especially those suffering from dementia, are prone to stress-induced acute mental disorders. There are many inducing factors, and they cannot be evaluated by ordinary people's cognition and experience of stress factors (Liao *et al.*, 2020; Urizar *et al.*, 2021) considering ANP's effect of treating acute cerebral apoplexy simultaneously, so it cannot be inferred that the intervention effect of the positive mental symptoms caused by other reasons and aggravated by dementia patients has similar effects. The subjects of this experiment are patients with acute lacunar infarction, and there is no anatomical responsibility relationship between the location of the infarction and the mental symptoms. At present, it is believed that the proportion of post-stroke mental illness is as high as 70%, and the mechanism is still inconclusive (Kliem *et al.*, 2021). Early diagnosis and early intervention of post-stroke mental illness can improve the prognosis as soon as possible. This study provides a treatment option for specific psychiatric symptoms. However, for ischemic stroke whose infarction site is the focus of mental symptoms, the prognosis often takes longer, and even becomes sequelae (Wei *et al.*, 2019). The pathogenesis of mental symptoms is different from that discussed in this study (Sheng *et al.*, 2007), so the conclusion of this study cannot be used to infer that it can improve the mental symptoms of all patients with cerebral infarction.

There were cases in both groups that did not recover clinically within the prescribed event. Although the recovery rate of the TG was 26.3% higher than that of the CG, the number of samples is too small, so it cannot be considered that the use of ANP has a decisive effect on the treatment results. However, multi-center research can be used to expand the sample size and further evaluate the use of ANP. Association of pills with treatment success. In the CG, patients who did not recover clinically were associated with RASS scores and were statistically significant. That is, the more severe the illness at the beginning of the attack of positive mental symptoms, the greater the chance of not recovering. If the TG and the CG are combined, similar results can be obtained. For patients with Alzheimer's disease who develop acute stress syndrome and do not improve significantly within a limited period of time, it is often considered to be a residual mental symptom, and the cognitive function further declines, irreversible to the state before the attack (Sheng *et al.*, 2007). Therefore, it is relatively reasonable to set an observation period of 10 days. Of course, setting a longer observation period may still have room for improvement in a small number of patients, but the treatment plan can

be more open, and the variables of the study will increase. But in any case, the more severe the mental symptoms at the time of attack, the worse the prognosis, which is also in line with the empirical conclusions in clinical work.

After the acute mental symptoms of the patients in the TG and the CG disappeared, there was no statistically significant decline in cognitive function (evaluated by MMSE score), but this is only the result of an event study. It cannot be inferred that repeated delirium will not affect the cognitive ability of patients with Alzheimer's disease. From the point of view of P value, the patients who took ANP seemed to retain better cognitive ability. It is expected to increase the sample size to prove the feasibility of this treatment in improving cognition.

ANP is a prescription in Wu Tang's detailed analysis of epidemic warm diseases. It is traditionally used in clinic to clear heat and detoxify, calm convulsion and open the mind, and mainly treat such diseases as heat entrapment, high fever caused by pericardial infection, restlessness, delirium, turbid phlegm, and infantile convulsion (Cui, 2012). In recent years, with the deepening of basic research on traditional Chinese medicine and clinical practice of traditional Chinese medicine, the pharmacological effects of ANP have been clarified, and the scope of clinical application has also been expanded. From the pharmacological analysis of its mechanism, according to modern pharmacological research, the drug can improve brain circulation, scavenge free radicals, and can inhibit the excessive response of the central nervous limbic system, acting as a sedative and hypnotic (Zeng *et al.*, 2020). It has achieved good curative effect and positive results in clinical research on the treatment of stroke and reactive psychosis. Inspired by this, this study was designed, and in the course of clinical treatment, it did effectively shorten the course of positive mental symptoms caused by acute cerebral infarction in patients with MA and recover early. Waiting for multi-center, larger sample size and introduction of more evaluation parameters, the drug users and the course of treatment can be more clearly defined.

#### Conclusion

ANP had a significant impact on positive mental symptoms caused by acute lacunar infarction in patients with MA. The findings showed that ANP can shorten the duration of the disease course of positive psychiatric symptoms caused by acute cerebral infarction of MA and contribute to start rehabilitation training early and improve the prognosis of the disease.

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#### IRB approval

This study was approved by the Advanced Studies Research Board of Zhejiang Chinese Medical University, Zhejiang Province, China.

#### Ethical approval

The study was carried out in compliance with guidelines issued by Ethical Review Board Committee of Zhejiang Chinese Medical University, China. Official letter would be available on request to corresponding author.

#### Statement of conflict of interest

The authors have declared no conflict of interest.

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