Original Article

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Effects of Chinese herbal medicine Ningdong Granule on regulating dopamine (DA)/serotonin (5-TH) and gamma-amino butyric acid (GABA) in patients with Tourette syndrome

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Summary **Many studies have indicated that a variety of neurotransmitters are implicated in the pathophysiology of Tourette syndrome (TS), including dopamine (DA), serotonin (5-TH), homovanillic acid (HVA), and gamma-amino butyric acid (GABA). Our previous studies found that Ningdong granule (NDG) is effective on a rat model with TS. NDG can regulate the metabolic disturbance of DA, 5-TH and HVA in the rat brain. However, the mechanisms of NDG in patients with TS are still not clear. To further evaluate the efficiency, safety, and possible mechanisms of NDG, a randomized and double-blind study was carried out. One hundred and twenty patients with TS were enrolled in thisstudy, that were randomly divided into 4 groups (NDG group, Haloperidol (Hal) group, NDG + Hal group and Control group). First, the efficiency of NDG was assessed using the Yale Global Tic Severity Score (YGTSS). Second, the concentration of DA, HVA, 5-TH, 5-hydroxyindoleacetic acid (5-HIAA) and GABA in sera were tested by ELISA. In addition, the influence of NDG on liver and renal function was recorded. We found that NDG could ameliorate tics significantly according the YGTSS score. The concentration of HVA and GABA were increased after treatment with NDG. Furthermore, we found that there was no liver or renal damage in children treated with NDG. We also found that the NDG + Hal group was more effective and safe compared with other groups. In conclusion, the current study indicates that NDG might be effective on patients with TS by regulating dopamine (DA)/serotonin (5-TH) and gamma-amino butyric acid (GABA).**

Keywords: Gilles de la Tourette-Syndrome (TS), Ningdong granule (NDG), dopamine (DA), serotonin (5-TH), gamma-amino butyric acid (GABA)

1. Introduction

Tourette syndrome (TS) is a developmental neuropsychiatric disorder, which is characterized by multiple brief, stereotypical and nonrhythmic movements, or vocalizations called tics, with a duration of at least 1 year (*1*). The prevalence of this syndrome is estimated to be four to six per 1,000 children and adolescents (*2*). Initial symptoms of TS usually occur in TS children by 7 years old (*3*). It occurs three to four times more commonly in males than in females (*4*). For some individuals, tics can cause lifelong impairment and about 5% of TS patients have life-threatening symptoms, which are defined as malignant TS (*1*). The detailed etiological and pathophysiological mechanism of TS is currently still unclear. Our previous studies showed that the metabolic disturbance of DA, and 5-TH in the brain was involved in the pathophysiology of TS (*5*). Tian *et al.* found that at least some of these GABA- and acetylcholine-related genes observed in blood that correlate with tics or are alternatively spliced are involved in the pathophysiology of TS and tics (*6*).

Haloperidol is approved by the Food and Drug Administration (USA) for treating TS. It can selectively inhibit the activity of postsynaptic DA receptors, and inhibit the excitability of the cortical motor area through

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restraining the activity of DA receptors, to weaken TS symptoms (*7*). Although Haloperidol is efficacious for the treatment of TS, a very high proportion of patients eventually discontinue the therapy because of the side effects including sedation, weight gain, extrapyramidal symptoms, and QT prolongation (*8*). Therefore, development of novel drugs for treatment of TS is urgently needed.

Traditional Chinese medicine (TCM) has been widely used in the treatment of various diseases such as nervous system disease, infectious diseases, and cancer, in China for thousands of years (*9-12*). Ningdong granule (NDG), a TCM preparation, has been revealed to tranquilize and allay excitement in TS and ADHD (*12-14*) (Table 1). It could inhibit the stereotypical behavior in TS rats, and the mechanisms might be related to the suppression of the DA system by increasing the content of HVA in sera, decreasing the content of DA and repressing the expression of DRD2 mRNA in the striatum (*13*). Besides, it also indicated that NDG was effective for ADHD children in the short term with increasing the HVA concentration in sera to regulate DA metabolism (*14*). However, the present data are limited and there is a lack of a double-blind and control trial, and the mechanism of NDG on TS patients also remains obscure. In the current study, we evaluated NDG's short-term efficacy and safety in the treatment of TS patients and explored the possible mechanism of NDG on the DA, 5-TH, and GABA system of TS patients.

2. Materials and Methods

2.1. *Participants*

One hundred and twenty patients (6~18 years) were recruited from the outpatient department of integrative medicine in pediatrics, Provincial Hospital Affiliated to Shandong University. All participants clearly met the DSM-IV diagnostic criteria for TS (*15*), and participated in the clinical trial from May 2009 to June 2010. No participants had taken anti-TS medication before being recruited for the research. In addition, we excluded patients who had a past history of seizures, cardiovascular disease, organic brain disorder, current abuse or dependence on drugs within 6 months. After a detailed explanation of the process of our study, both the patients and their parents gave their informed consent. All research procedures were permitted by the medical ethics committee of the Provincial Hospital Affiliated to Shandong University.

2.2. *Study design*

The study was performed using a randomized, and double-blind, 8-week trial. The patients were equally divided into NDG group (n = 30), Haloperidol group (n = 30), NDG + Hal (n = 30) and Control group (n = 30) by a randomized computer-generated code. The NDG group were assigned to receive NDG 5 mg/kg/day (No. 20090412, 999 Co. Ltd., Shenzhen, China) and one kind of placebo with similar appearance and taste with Haloperidol for 8 weeks. Patients in the Haloperidol group were started at a dose of 0.75 mg/day and increased by 1.5~3.0 mg/day increments every 2 weeks to a maximum tolerated dose of 4.5 mg/day and one kind of placebo with similar appearance and taste with NDG (*16*). The NDG + Hal group were assigned both of them at the same dose. The control group were assigned to receive the above two kinds of placebo. These two kinds of placebo were provided by 999 Co. Ltd., Shenzhen, China. All of the medicines were filled by a pharmacist in charge who mastered the data of treatment assignment and the weight and number of the subjects in the trial.

2.3. *The Yale Global Tic Severity Score analysis*

As previously noted, the Yale Global Tic Severity Score (YGTSS) (*17*), used as a Chinese-translated version in the study, is a semi-structured clinical interview designed to assess current tic severity. This scale yields three summary scores, including total motor, total vocal, and total tic scores. We rated the scores at the first clinic visit as the baseline scores and then every 2 weeks vocal for a total of 8 weeks of follow-up. The clinical rating at each visit was recorded by the same clinicians to avoid personal bias in severity evaluation.

Table 1. Composition and active ingredients of Ningdong granule (NDG)

Components	Voucher specimens No.	Part used	Amount used (g)
Uncaria rhynchophylla (Miq.) Jacks	0706011	Ramulus	20
Gastrodia elata Blume	0705081	Root	6
Ligusticum chuanxiong Hort	0704081	Rhizome	6
Buthus martensii Karsch	0704021	Dried body	3
Scolopendra subspinipes mutilans L. Koch.	0707021	Dried body	Single band
Haliotis diversicolor Reeve.	0701041	Shell	20
Haliotis diversicolor Reeve.	0701041	Shell	20
Dried human placenta	0708021	Dried placenta	3
Glycyrrhiza uralensis Fisch.	0706011	Rhizome	3

Table 2. Baseline of case data

Items	Control (n = 28)	Control (n = 28)	Haloperidol (n = 30)	NDG + Hal (n = 30)	Statistical significance
Year (yr)	10.3 ± 1.9	10.2 ± 1.7	10.4 ± 2.1	10.3 ± 2.0	NS
Gender	22:6	22:7	23:7	24:6	NS
weight (kg)	33.2 ± 3.0	33.4 ± 3.2	33.1 ± 3.3	33.2 ± 2.8	NS

Data are expressed as mean ± S.D. NS: not statistically significant ($p > 0.05$).

2.4. *Contents of DA, HVA, 5-TH, 5-HIAA and GABA in sera detected by ELISA*

The serum levels of DA, HVA, 5-TH, 5-HIAA and GABA were measured using a sandwich enzyme-linked immunosorbent assay (ELISA) according to the instructions of the manufacturer (R & D, Shanghai, China). Patient's blood was centrifuged for 10 min at 20,000 × g at 4°C and the serum was used for testing. Briefly, antigen standards and serum samples were added to each well of 96-well plates pre-coated with primary antibodies. After adding biotin conjugate reagent and enzyme conjugate reagent into each well, the plates were incubated at 37°C for 30 min. The plates were then rinsed four times with distilled water. After a chromogenic reaction, the absorbance was measured at 450 nm by a microtiter plate reader within 15 min.

2.5. *Routine analysis and liver and renal function tests*

All of the subjects' blood samples were collected and sent for liver and renal function tests to the Department of Clinical Laboratory, Provincial Hospital Affiliated to Shandong University at end of the trial.

2.6. *Statistical analysis*

All analyses were performed using the SPSS statistical software package (Version 13.0, SPSS Inc. Chicago, IL, USA), and $p < 0.05$ was considered statistically significant. The Yale Global Tic Severity Score from baseline to week 8 was performed using a rank-sum test. The values of routine analysis and liver and renal function week 8 were compared using a paired Student's t-test. Analyses of side effects between the protocols were performed by Fisher's exact test. The levels of DA, HVA, 5-TH, 5-HIAA and GABA in sera were analyzed by repetitive-measure analysis of variance (ANOVA).

3. Results

3.1. *Study population*

No significant difference was identified between NDG group, Haloperidol group, NDG + Hal group and Control group with regard to basic demographic data including age, gender, and weight (Table 2).

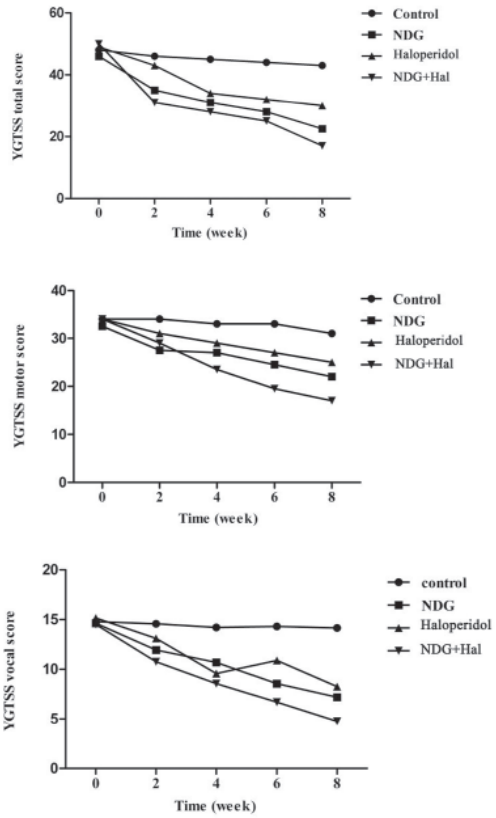

Figure 1. YGTSS score at (0, 2, 4, 6, and 8) week time points. (A) YGTSS total score; **(B)** YGTSS motor score; **(C)** YGTSS vocal score.

3.2. *Assessment of Yale Global Tic Severity Scores*

After treatment, patients in the control group had no significant change in YGTSS motor tic score and YGTSS vocal tic score as well as YGTSS total tic score, at each time point (Compared with the baseline score, $p > 0.05$). However, at the two week time point, patients in the remaining three treatment groups, the YGTSS total tic score, YGTSS motor tic score and as well as YGTSS vocal tic score were significantly reduced ($p < 0.05$), the scores of NDG + Hal group were more significantly reduced ($p < 0.01$) (Figure 1).

3.3. *Levels of DA and HVA in sera detected by ELISA*

The content of DA in sera was not significantly different in the four groups ($p > 0.05$). After treatment the HVA content in the NDG + Hal (67.07 ± 12.01 ng/mL), NDG (64.25 ± 12.88 ng/mL) and Haloperidol

group (60.88 ± 11.71 ng/mL) were increased to a different degree as compared to the control group (47.13 ± 7.58 ng/mL) ($p < 0.05$), The HVA content was higher in the NDG + Hal group than in the NDG ($p < 0.01$) and Haloperidol ($p < 0.05$) group (Figure 2).

3.4. *Levels of 5-TH and 5-HIAA in sera detected by ELISA*

The content of 5-TH and 5-HIAA in sera were not significantly different in the four groups ($p > 0.05$) (Figure 3).

3.5. *Levels of GABA in sera detected by ELISA*

After treatment, the GABA content in the NDG + Hal (166.22 ± 41.91pmol/mL), NDG (123.69 ± 38.47 pmol/mL) and Haloperidol group (113.97 ± 36.23 pmol/mL) were increased to a different degree as compared to the control group (85.63 ± 33.69 pmol/mL) ($p < 0.05$), The content of GABA was higher in the NDG + Hal group than in the NDG ($p < 0.01$) and Haloperidol ($p < 0.05$) group (Figure 4).

3.6. *Analysis of side effects*

No serious adverse effects were detected during the study, while eight kinds of side effects, which were mild and tolerable for the children, were observed as presented in Table 3. In Haloperidol group and NDG + Hal group, the incidence of sedation, extrapyramidal and QT prolongation reactions were higher than that in the NDG and control group ($p < 0.05$). The incidence of nausea and headache reactions in the NDG + Hal group was higher than that in the control group ($p < 0.05$). The incidence of anxiety in the NDG + Hal group was higher than that in the NDG group ($p < 0.05$).

3.7. *Liver and renal function monitoring*

As shown in Table 4, in the NDG + Hal group and Hal group, although the content of alanine in sera were higher than the control group ($p < 0.05$), it was still within the normal range in the Haloperidol group.

4. Discussion

In our previous studies, we found that NDG has the effect of tranquilizing and allaying without obvious side or toxic effects on rats with TS (*12-14*). NDG can regulate the metabolic disturbance of DA, 5-TH and HVA in the rat brain (*13*). However, the mechanisms of NDG in Children with TS are still not clear. To further evaluate the efficiency, safety, and possible mechanisms of NDG, a randomized and double-blind study was carried out in the current study. We found that the effect of NDG was similar to Hal in reducing tic symptoms and NDG might have a synergistic effect on treating TS. The NDG + Hal group was more effective and safe compared to the NDG group and the Hal group. We also found that there was no liver or renal damage in children treated with NDG.

TS is associated with multiple neurotransmitter systems within the basal ganglia-thalamo-cortical circuits (*19,20*). Previous studies showed that the metabolic disturbance of DA, 5-TH and GABA in the brain is involved in the pathophysiology of TS (*21-23*). DA is a key monoamine neurotransmitter in the brain, and numerous studies have shown its regulatory role for motor and limbic functions (*24*), movement (*25*),

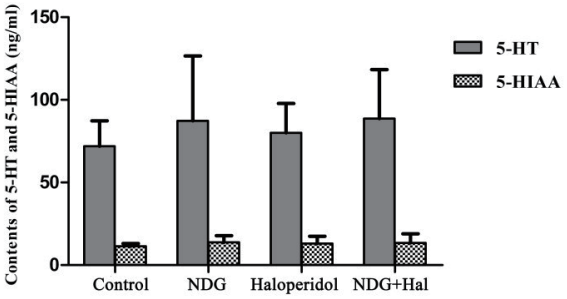

Figure 3. Content of 5-TH and 5-HIAA in sera after treatment with NDG or Hal for 8 weeks. Data are expressed as mean ± S.D.

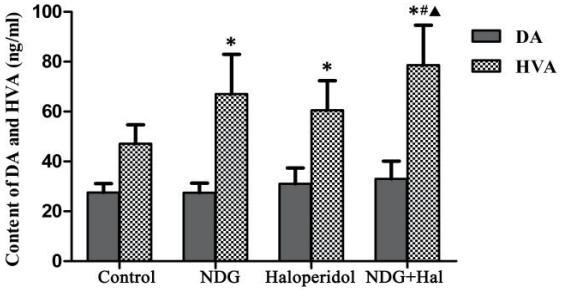

Figure 2. Content of DA and HVA in sera after treatment with NDG or Hal for 8 weeks. Data are expressed as mean ± S.D. * $p < 0.05$ *vs.* Control, # $p < 0.01$ *vs.* NDG, ▲ $p < 0.05$ *vs.* Hal.

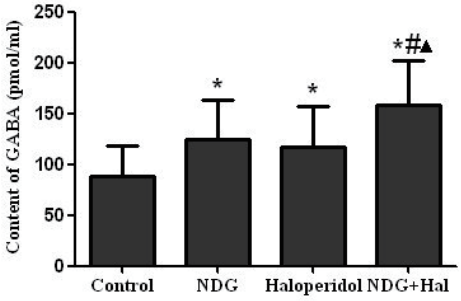

Figure 4. Content of GABA in sera after treatment with NDG or Hal for 8 weeks. Data are expressed as mean ± S.D. * $p < 0.05$ *vs.* Control, # $p < 0.01$ *vs.* NDG, ▲ $p < 0.05$ *vs.* Hal.

Table 3. Clinical complications and side effects

Items	Control (%) (n = 28)	NDG (%) (n = 29)	Hal (%) (n = 30)	NDG + Hal (%) (n = 30)	Statistical significance
Sedation	1 (3.5%)	3 (10.3%)	10 (33.3%)*#	12 (40%)*#	*#
weight gain	2 (7%)	2 (6.9%)	4 (13.3%)	5 (16.7%)	
Extrapyramidal	0	0	5 (16.7%)*#	5 (16.7%)*#	*#
QT prolongation	0	0	5 (16.7%)*#	5 (16.7%)*#	*#
Nausea	0	3 (10.3%)	4 (13.3%)	4 (13.3%)	
Headache	0	1 (3.4%)	4 (13.3%)	6 (20%)*	*
Anxiety	1 (3.5%)	0	6 (20%)#	4 (13.3%)	#
Increased appetite	0	4 (13.8%)	4 (13.3%)	7 (23.3%)*	*

* $p < 0.05$ *vs.* control, # $p < 0.05$ *vs.* NDG.

Table 4. Measure of liver or renal function

Items	Control	NDG	Haloperidol	NDG + Haloperidol	Statistical significance
ALT	24.03 ± 4.43	25.34 ± 5.43	29.87 ± 6.17*	30.23 ± 6.17*	*
AST	24.57 ± 6.53	26.17 ± 5.37	25.90 ± 4.33	26.58 ± 4.98	NS
BUN	24.04 ± 4.43	25.34 ± 5.43	29.87 ± 6.17	30.23 ± 6.17	NS
Cr	75.94 ± 11.18	76.83 ± 10.49	76.64 ± 9.76	77.41 ± 9.79	NS

ALT: alanine transferase, AST: aspartate transaminase, BUN: blood urine nitrogen, NS: not statistically significant ($p > 0.05$), * Significant difference ($p < 0.05$) *vs.* Control.

moods (*26*), neurobehavioral abilities (*27*), and problem solving (*28*). Convergent evidencegave us the signal that dopamine is the final common neurobiological pathway for the expression of TS symptoms (*29*). After reuptake by DA transporters, the DA was transformed into HVA in neurons, and released into the blood, and its concentration in plasma has been widely used to study the function of central DA in psychiatric disorders (*13,30-32*). Therefore, HVA is regarded as the major indicator of DA activity (*13,31*). The current study also revealed that the content of HVA increased in TS patients' sera, while there was no statistical difference in the content of DA after treatment with NDG and Hal. In contrast, neither DA nor HVA concentrations greatly changed for an 8-week period of medication in the placebo group. Based on the hypoactivity of dopamine systems in the brain involved in the pathophysiology of TS, we inferred that NDG could improve the symptoms of TS by enhancing the metabolism of DA *in vivo* and increasing the HVA content in sera. As a dopamine D2 receptor blocker, the mechanism fit for Hal. However, neither NDG nor Hal had an effect on the concentration of DA in sera, which suggested that DA outside the brain has no direct link to the pathophysiological changes in TS.

The research indicates generally that the neurotransmitter serotonin has an inhibitory action in the brain (*33,34*) and it is deeply involved in the regulation of emotion and behavior, including the inhibition of aggression (*35,36*). Serotonergic dysfunction has been reliably associated with the pathology of TS (*18*). As the main metabolite of 5-TH, 5-HIAA is released back into the blood after the metabolism of 5-TH in the central neural system, and 5-HIAA, and therefore, is also regarded as the major indicator of 5-TH activity (*22*). In this research, the results revealed that there was no statistical difference in the content of 5-TH and 5-HIAA after treatment in three groups. So we are unable to infer that NDG improves the symptoms of TS by enhancing metabolism of 5-TH.

From a developmental perspective, many GABAergic interneurons of the cerebral cortex clearly migrate tangentially from the same embryonic regions in the ganglionic eminence that also give rise to the GABAergic medium spiny projection neurons of the striatum (*37*). Could adverse events arising at a specific point in development, the differential loss of medium spiny projection neurons in the matrix compartment – account for the striatal imbalance and intracortical deficits in inhibition seen in some patients with Tourettesyndrome (*38*)? Because of the reported GABA abnormalities in the TS brain, and the possible immune abnormalities in blood and brain of TS subjects (*39*), we postulated that GABA might be involved in the pathophysiology of TS. In this study, we demonstrated that NDG and Hal could increase the level of GABA in sera and improve the symptoms in TS children.

The present study indicates that the symptoms of TS were alleviated and the content of HVA/GABA in sera was increased, but the DA, 5-TH, and 5-HIAA concentrations changed little after treatment with NDG or Hal on TS patients. Based on the above results, it could be inferred that NDG was effective on TS by regulating the DA and GABA system while increasing the content of HVA and GABA in sera, which is valuable for potential pharmacological findings in the clinical application of NDG.

GTSS was widely used to assess the severity of TS, which can be easily mastered for the symptoms

of TS children. For short-term effectiveness, both NDG and Hal can improve the clinical symptoms for TS children by YGTSS at different time points. However, Haloperidol had more side effects than NDG in the form of sedation, weight gain, extrapyramidal symptoms, QT prolongation, Nausea, Headache, and Anxiety. The results suggest that NDG is safe for TS children. NDG is promising to be a safe and effective medication as an alternative therapy for TS.

However, the present study has some limitations as follows. First, only short-term outcomes and adverse effects were observed for 8 weeks, which was limited for NDG as a synthetic therapeutic option pending further study on long-term outcomes. Second, we measured the contents of DA, HVA, 5-TH, 5-HIAA and GABA in sera to deduce the metabolism of neurotransmitters *in vivo*, which was indirect evidence for explaining the metabolism of neurotransmitters in brain. Furthermore, we did not analyze the metabolism of some other kinds of neurotransmitters beyond DA and 5-TH, which might also participate in the pathophysiological course of TS. Therefore, it is a great necessity to explore more meaningful evidenceof pharmacology for an effective and safe alternative treatment.

Acknowledgements

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