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Research Article

CLINICAL EFFICACY AND SERUM 25 HYDROXYVITAMIN D LEVELS OF CLONIDINE TRANSDERMAL PATCH COMBINED WITH VITAMIN D_3 DROPS IN THE TREATMENT OF TIC DISORDER IN CHILDREN

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ABSTRACT

Objectives: To investigate the clinical efficacy of clonidine transdermal patch combined with vitamin D_3 drops in the treatment of tic disorder in children and to analysis relationship between the serum 25hydroxyvitamin D level and clinical efficacy.

Methods: One hundred and twenty children with tic disorders who attended our pediatric neurology outpatient department from January 2020 to June 2022 were randomly divided into three groups: 45 cases in the clonidine transdermal patch+vitamin D_3 drops group,45 cases in the clonidine transdermal patch group, and 30 cases in the vitamin D_3 drops group. Yale General Tic Severity Scale (YGTSS) scores and serum 1-25 hydroxyvitamin D levels were compared between the three groups in 0, 4 and 12 weeks after treatment to determine efficacy and safety.

Results: Compared with pre-treatment, YGTSS scores were lower in all three groups at 4 and 12 weeks of treatment compared with pre-treatment ($P<0.05$). At 4 weeks after treatment, YGTSS scores were reduced in the clonidine transdermal patch + vitamin D_3 drops group and clonidine transdermal patch compared with the vitamin D_3 drops group($P<0.05$). At 12 weeks after treatment, YGTSS scores were lower in the clonidine transdermal patch + vitamin D_3 drops group compared with the other two groups ($P<0.05$). Serum 25 hydroxyvitamin D levels were higher in all three groups after 12 weeks of treatment compared with those before treatment ($P<0.05$).

Conclusion: Clonidine transdermal patch + vitamin D_3 drops group was more effective than other 2 groups in treating tic disorder in children, and vitamine D may be useful in the treatment of Tic disorder.

Key words: Tic disorder; Clonidine transdermal patch; Vitamin D3 drops; 25 hydroxyvitamin D

Tic disorder (TD) is a neuropsychiatric disorder that begins in childhood and is characterized by tics, and is a common developmental behavior problem in children. The main clinical features of tic disorder in children are motor tics and /or vocal tics, and more than 90% of children with tic obscura syndrome develop between the ages of 2 and 12, with a male to female prevalence of 3:1 to 5:1. According to the clinical characteristics and duration of the disease, TD is divided into three types: transient TD, chronic TD and Tourette's syndrome (TS), among which transient TD is the most common in children, with a prevalence of about 3%. Children with TD can have a variety of comorbidities, such as attention deficit hyperactivity disorder (ADHD), learning difficulties, obsessive-compulsive disorder, sleep and mood disorders, etc, among which ADHD is the most common.

The pathogenesis of tic disorder is unclear, and most scholars believe that the disease is caused by a combination of genetic, biological, psychological, immune and environmental factors. The 2017 edition of my country's expert consensus on the diagnosis and treatment of childhood tic disorders lists the alpha agonist clonidine as the first-line treatment drug. In previous studies, serum 25-hydroxyvitamin D levels in children with TD were generally deficient and significantly lower than in normal children.

This study is to investigate the clinical efficacy of clonidine transdermal patches combined with vitamin D drops and vitamin D drops alone in the treatment of tic disorders in children and to analyze the serum 25 hydroxyvitamin D level to provide an effective method for the treatment of tic disorders.

SUBJECTS AND METHODS

Patients:

One hundred and twenty children with tic disorder who attended our pediatric neurology outpatient department from January 2020 to June 2022 were selected and randomly divided into three groups: 45 cases in the clonidine transdermal patch+vitamin D_3 drops group, 45 cases in the clonidine transdermal patch group, and 30 cases in the vitamin D_3 drops group. There were 45 cases in the clonidine transdermal patch+vitamin D3 drops group, including 26 males and 17 females, aged 5-16 years, mean age 7.4±2.1 years. Duration of illness was from 6 to 25 months, mean duration of illness was 18.3±7.6 months. There were 45 cases in the clonidine transdermal patch group, including 27 males and 18 females with age from 6 to 14 years, mean age 7.8±1.9 years, duration of illness was from 5 to 28 months, mean duration of illness was 16.9±9 months. Vitamin D3 drop group was composed of 30 samples, including 19 males and 11 females with the age from 6 to 13.8 years. The average age of all samples was 7.1±2.4 years. The course of disease was 6-24 months. The average course of disease was 17.5±8.9 months. The differences in gender, age and duration of disease between the three groups were not statistically significant ($P > 0.05$). The study was approved by the Ethics Committee of the First Affiliated Hospital of Yangtze University, and the parents of the children gave informed consent.

Inclusion and exclusion criteria:

All enrolled children were strictly screened for clinical symptoms, and the diagnostic criteria were screened with reference to the Expert Consensus on the Diagnosis and Treatment of Tic Disorders in Children (2017 Practical Edition) and the American Diagnostic and Statistical Manual of Mental Disorders,5th edition (DSM-5). Exclusion criteria: (1) children with epilepsy, cerebral palsy, mental retardation, autism, cardiac arrhythmia and other cardiovascular diseases were excluded; (2) children with drug allergy and intolerance (3) children who could not complete the treatment as prescribed by the doctor (4) children with other serious diseases.

	Clonidine transdermal patch + vitamin D_3 drops group	Clonidine transdermal patch group	Vitamin D_3 group	P value
Sex				0.806
Male	28	27	19	
Female	17	18	11	
age	7.5±2.2	7.3±2.1	7.1±1.2.4	0.495
Disease duration (months)	20.6±4.8	21.3±5.4	19.8±6.2	0.191

Table1: Comparison of general data among the three groups

Treatment method:

In the clonidine transdermal patch group, thiopride (China National Pharmaceutical Group Shanxi Rfl Pharmaceutical Co,Ltd,specification: 1mg/tablet) was administered according to the child's body weight,1mg/tablet for those weighing 20-40 kg and 2mg (2 tablets) for those >40kg. Vitamin D_3 group with vitamin D_3 drops alone (Sinopharm Xingsha Pharmaceuticals (Xiamen) Co,Ltd,vitamin D_3 400IU/capsule), the dose is 400U/day. The vitamin D_3 + clonidine transdermal patch group added vitamin D_3 drops on top of clonidine transdermal patch. The duration of treatment and observation was 12 weeks in all three groups.

Observation indicators:

Measurements: Yale General Tic Severity Scale (YGTSS) was administered 0, 4 , and 12 weeks after treatment. YGTSS is based on the quantitative assessment of the number, frequency, intensity, interference, and complexity of tic symptoms to obtain motor tic and vocal tic scores. The total YGTSS score is obtained by adding the motor tic and vocal tic scores. The degree of functional impairment in self-esteem, interpersonal communication, family or study life caused by tics was used to obtain the overall functional impairment score. As an evaluation index for efficacy, the higher the score, the more severe the functional impairment. And the reduction rate was calculated: (pre-treatment score - post-treatment score)/pre-treatment score×100%.
Assessment of efficacy: The clinical efficacy of the three groups of children was assessed by YGTSS before and 4 and 12 weeks after treatment.

According to the YGTSS score reduction rate as the criterion for judging the curative effect of tics, the score reduction rate ≥ 80% is clinical recovery, the score reduction rate ≥ 60% and < 80% is markedly effective,

and the score reduction rate ≥ 30% and < 60% is effective , if the deduction rate is less than 30%, it is invalid. (3) Biochemical index levels: Before treatment and 12 weeks after treatment, 2 mL of fasting venous blood was collected to detect the level of 25-hydroxyvitamin D.

Statistical methods:

SPSS 22.0 statistical software was used for data analysis, and the measurement data were expressed as mean ± standard deviation, ANOVA was used for multiple group comparisons, and SNK test was used for two-way comparisons. The χ2 test was used to compare the count data, and the difference was considered statistically significant at P<0.05.

RESULTS

Comparison of YGTSS scores in 3 child patient groups before and after treatment:

The difference in YGTSS scores between the 3 groups before and after treatment was not statistically significant (P>0.05). The YGTSS scores of children in the 3 groups were lower at 4 and 12 weeks of treatment, compared with those before treatment, and the difference was statistically significant (P<0.05). At 4 weeks after treatment, the difference in YGTSS scores between the clonidine transdermal patch + vitamin D_3 drops group compared with the clonidine transdermal patch was not statistically significant (P>0.05), but all were lower than the vitamin D_3 drops group (P<0.05). After 12 weeks treatment, YGTSS scores were lower in the clonidine transdermal patch + vitamin D_3 drops group compared with the clonidine transdermal patch and vitamin D_3 drops groups (P<0.05), and YGTSS scores were lower in the clonidine transdermal patch than in the vitamin D3 drops group (P<0.05).

Time	Clonidine transdermal patch + vitamin D_3 drops group	Clonidine transdermal group	Vitamin D_3 group
before therapy	33.52±4.26	32.69±4.78	32.135±4.38
4 weeks after treatment	22.43±5.21	23.45±3.46	25.74±3.41
12 weeks after treatment	11.23±3.57	13.64±4.23	21.85±5.33
P value	0.027	0.038	0.047

Table 2: Comparison of YGTSS scores in three groups at different time

The level of hydroxyvitamin D3 in serum of 3 groups before and after treatment:

Before treatment, the levels of hyddroxyvitamin D in serum of the 3 groups were not significant difference. After treatment for 12 weeks, the levels of hydroxyvitamin D in serum in clonidine treated child patients were significantly higher than that before treatment（P >0.05）. The difference was not statistical significance. The levels of hyddroxyvitamin D in clonidine and VD3 group and VD3 group apparently increased. The differences compared between groups had statistical significance.

	Clonidine transdermal patch + vitamin D_3 drops group	Clonidine transdermal group	Vitamin D_3 group
25 hyddroxyvitamin D level（ng/ml）（ng/ml）			
Before treatment	22.58±3.97[a]	24.31±4.43[a]	23.683±4.23[a]
Treatment after 12 weeks	38.53±4.23 [ab]	25.61±2.98	37.58±3.64 [b]

Table 3: Levels of hydroxyvitamin D in 3 groups at different time

Comparison of clinical efficacy in 3 groups of child patients:

After 12 weeks of treatment, the total effective rate of clonidine transdermal patch+vitamin D3 drops group was 91.1%, the total effective rate of clonidine transdermal patch was 84.4%, the total effective rate of vitamin D_3 drops group was 50%, and the difference of total clinical efficiency between the three groups was statistically significant (P<0.05). The total effective rate of clonidine transdermal patch + vitamin D_3 drops group and clonidine transdermal patch were both higher than that of vitamin D_3 drops group, and the differences were statistically significant (P<0.05). The total clinical effective rate of clonidine transdermal patch + vitamin D_3 drops group was higher than that of vitamin D_3 drops group, and the difference was not statistically significant (P=0.065).

grouping	Clonidine transdermal patch + vitamin D_3 drops group	Clonidine transdermal patch group	Vitamin D_3 group
例数	*45*	45	30
get well	27	24	3
efficient	14	14	12
invalid	4	7	15

Table 4: Comparison of clinical efficacy

DISCUSSION

Tic disorder is a chronic neuropsychiatric disease that begins in childhood. In severe cases, it will seriously affect their daily learning and life, and the proportion is as high as 1%[1]. The pathogenesis of tic disorder is not yet fully clarified, and its etiology may be the result of a variety of factors[2-4].

Clonidine was identified as the first-line drug in my country's Expert Consensus on Diagnosis and Treatment of Tic Disorders in Children.· Clonidine is an α2 receptor agonist, which can directly stimulate the α2 receptors of the central post-synaptic membrane of the hypothalamus and oblongata to activate inhibitory neurons, reduce the outflow of central sympathetic nerve impulses, and thereby inhibit peripheral sympathetic

nerve activity. Clonidine can also stimulate α2 receptors on the presynaptic membrane of peripheral sympathetic nerves, enhance its negative feedback, reduce the release of norepinephrine from peripheral nerves, reduce peripheral vascular and renal vascular resistance, slow down heart rate, and lower blood pressure. Vitamin D comes from vitamin D_2 in food or from subcutaneous 7-dehydrocholesterol to synthesize vitamin D_3, both of which are metabolized in the liver to 25-hydroxyvitamin D. Insufficient intake or insufficient sunlight can easily cause vitamin D deficiency. Studies have found that vitamin D deficiency is relatively common worldwide[5]. In addition to regulating calcium and phosphorus metabolism and promoting bone health, vitamin D also plays an important role in the development and function of the nervous system[6], such as nourishing neuronal cytokines, regulating cell proliferation and differentiation, and promoting neuronal development And regulating the synthesis of neurotransmitters and other functions[7-8]. 25-hydroxyvitamin D can promote the proliferation and differentiation of neurons, synaptic connection, and play an important role in the balance of the neurotransmitter system. If it is lacking or insufficient, it will have an adverse effect on the normal development of the dopamine system, thereby participating in the occurrence of tics.

The present study showed that after 12 weeks of treatment, the serum 25-hydroxyvitamin D levels in the three groups were higher than those before treatment, and the 25-hydroxyvitamin D level in the clonidine transdermal patch + vitamin D_3 drops group was higher than that in the clonidine transdermal patch The above research results suggest that clonidine transdermal patch combined with vitamin D_3 has a more significant clinical effect in the treatment of tic disorders. It can increase the expression of the rate-limiting enzyme tyrosine hydroxylase of dopamine production and reduce the excitability of nerve cells, so as to effectively improve the symptoms of tics. Vitamin D_3 alone has a certain clinical effect in the treatment of children with tic disorders. At the same time, our group found that the incidence of adverse reactions was comparable between the clonidine transdermal patch + vitamin D_3 drops group and the clonidine transdermal patch group, while the vitamin D_3 alone group had a higher safety and lower incidence of adverse reactions. Adverse effects of clonidine include sedation, dry mouth, headache, dizziness, dizziness, irritability, change in heart rate, decrease in blood pressure, change in electrocardiogram, etc. For some children with mild to moderate tic disorder and some children's families considering the side effects of long-term use of clonidine, vitamin D_3 drops can be used for treatment.

However, for children with moderate to severe tic disorders, treatment with clonidine transdermal patches combined with vitamin D_3 drops is recommended and is more effective. However, it is important to note that tic disorders are psychologically related to the child, and necessary psychological support and cognitive interventions should be provided during the pharmacological treatment to improve the efficacy. In conclusion, clonidine transdermal patches combined with vitamin D_3 drops are more clinically effective than vitamin D_3 drops alone in the treatment of tic disorders in children, and have a higher safety profile, providing a potential new approach for the diagnosis and treatment of children with tic disorders.

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