Clinical assessment of treatment of Tourette syndrome in Chinese children with Clonidine transdermal patch

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Tourette syndrome (TS) is a childhood-onset neuropsychiatric disorder beginning in childhood and characterized by presence of involuntary motor movements and vocalizations, called tics [1]. A prevalence of tics is around 5–100/10 000 [2] with community samples showing substantially higher rates than clinical samples, suggesting that many cases remain undiagnosed or untreated [3]. Tics range in number, frequency, and severity over the time and tend to co-occur with other psychiatric conditions such as ADD/ADHD, anxiety, learning disabilities, OCD, and mood disorders [4–7]. One half to two thirds of children with TS experience a reduction or complete resolution of tic symptoms during adolescence [8].

Tics can be classified into three subgroups: transient tics of childhood, chronic tics and Gilles de la Tourette syndrome. Tics are sudden, involuntary, stereotypic, repetitive but non-rhythmical movements or vocalizations, also frequently associated with difficulties in self-esteem, school...
performance, social acceptance and family life [9]. TS usually becomes apparent in children between ages 2 to 15 [10], with approximately 50% of patients affected by the age of 7, and it is more frequent in males than females by a ratio of 5 to 1 [1,2]. Medication should be considered when the motor tics or vocalizations interfere significantly with a child’s social and academic interactions, although behavior management and biofeedback programs have been successful for some patients [11]. Several reports implicate stimulant medications (methylphenidate) as the cause of TS. Methylphenidate may expose TS, but not cause it.

The clonidine adhesive patch is a transdermal therapeutic system (TTS) that releases clonidine at a relatively constant dose for 7 days without “peak or valley” plasma concentration changes [5]. Several days of clonidine therapy may be needed to control the vocal and motor tics. As the self-administered patch is convenient to use, has to be changed only at weekly intervals, is easy to dispose and has rapid onset of action – the patient compliance rates are high. The aim of the study was to assess the therapeutic effectiveness and adverse effects profile of the clonidine adhesive patch as compared with oral haloperidol treatment by using rigorous controlled study design.

MATERIALS AND METHODS

Studied group characteristics

The study group consisted of children with TS fulfilling CCMD-II-R on the tic disorder and TS diagnostic criteria: The symptoms appeared in most cases between 2 and 15 years. The main manifestation of the disorder included various tics and one or more involuntary vocalizations. Both symptoms appeared occasionally, but were not necessarily comorbid. The severity of the symptoms was changing over weeks and months. The course of the disease lasted at least for one year with the remission time less than 2 months. The tics and vocalizations were involuntary, and have not been explained by other diseases. This research selected 130 children who were treated at the specified hospital and fit the above diagnosis standard. We divided the patients into two group, one treated with clonidine transdermal patch and the other treated with haloperidol.

Among the 130 cases, 71 belonged to the clonidine transdermal patch group; of these, 51 were males and 20 females, with the average age 9.1. In haloperidol group were 59 cases, including 42 male and 17 female; the average age is 7.8. The average age of the symptoms appeared at the age 5.1. The subject group had male – female ratio of 2.51:1. The average duration of symptoms was 1.9 years. Data on the age of treatment, the age of onset, and the course of the disease is demonstrated in table I.

Clinical Symptoms

The main clinical manifestations are blinking, frowning, shrinking of the nose, shrugging, shaking of the head, licking the tongue, limb twitching or twisting the body, repeated clearing of the throat, etc. The location of the tic on the body is indefinite, with one or more parts having a simultaneous or alternate tic, with blinking as the most common symptom.

Methods

The dosage of the clonidine transdermal patch was given to patients according to their weight respectively large, medium and small doses. The patients with weight between 20~40kg were given 1.0mg/film; patients with weight between 41~60 were given 1.5mg / film and those with weight of more than 60kg were given 2.0mg / film. For maximum benefit patches were affixed to the skin of the lower subscapular corner, and replaced once per week, for a total of four weeks. Each new patch was also switched to a new location, usually to the contralateral scapula. The haloperidol group was given a small dose of combination of Haloperidol-Antin (Artane/trihexyphenidyl) treatment. Both doses were 0.5 ~ 0.7mg / time, twice a day (morning and evening), applied orally. If the relief of symptoms was not obvious, the dose was increased by 0.25mg, with the maximum dose being 1mg / times. Both groups of patients were followed up once a week for a total of four weeks. Before each application of the medicine we conducted an assessment using the Yale Global Tic Severity Scale(YGTSS) and the Clinical General Impressions Scale (CGI). At the same time we educated parents about TS, warned them that the children should avoid watching television, playing computer games for long periods of time, and that they should increase outdoor activities. Parents were told not to pay much attention to the tic symptoms of the child and to avoid emotional stimulation or corporal punishment in response to the behavior. Before and after treatment, the liver and kidney function were examined as well as electrocardiogram examination was conducted.

Efficacy Assessment Standards

Using the YGTSS measure, changes in the rating scale scores and a reduction rate indicate a change in symptoms. Affected patients who came to the hospital for the first time were assessed by specially trained doctors, screening for motion tics, vocalization tics and functional impairment level, the sum of the three scores indicating the total twitch score. After 12 weeks of treatment, the doctors carried out

Table I. Characteristics of the compared groups of patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Numbers</th>
<th>Age (Years)</th>
<th>Gender</th>
<th>Duration of Illness (Years)</th>
<th>Age of Illness Onset (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (haloperidol)</td>
<td>59</td>
<td>7.8±1.5</td>
<td>42</td>
<td>1.8±0.8</td>
<td>6.2±1.8</td>
</tr>
<tr>
<td>Treatment (clonidine)</td>
<td>71</td>
<td>9.1±0.8</td>
<td>51</td>
<td>2.0±0.6</td>
<td>6.8±1.9</td>
</tr>
</tbody>
</table>
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the YGTSS again to assess the score. The assessment index for the treatment is determined by the reduction in the value of the scores, divided by the base score.

Reduction Rate = (total score before the treatment – total score after the treatment)/total score before the treatment *100%.

The treatment is considered effective when the reduction rate is ≥ 50% and ineffective when the reduction rate is < 50%.

Statistical Analysis Method
Count data was analyzed using a χ2 test and measurement data using an independent sample t test. SPSS13.0 was used to conduct statistical analysis.

RESULTS

Comparison of the Reduction Rate in YGTSS Between Two Groups
The YGTSS score in both groups decreased after 4 weeks of treatment, but the clonidine transdermal patch group showed a higher reduction in the overall tic symptom scores (61.7 ± 7.3%) than that in the haloperidol group. (40.8 ±6.5%; P<0.05) (table II).

Table II. Two Groups YGTSS Reduction Rate Comparison

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline score</th>
<th>Score after 4 Wk Treatment</th>
<th>Reduction Rate</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group (haloperidol)</td>
<td>36.13+/−3.82</td>
<td>20.05+/−2.73</td>
<td>40.8+/−6.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Treatment Group (clonidine)</td>
<td>40.02+/−3.72</td>
<td>14.15+/−3.84</td>
<td>61.7+/−7.3</td>
<td></td>
</tr>
</tbody>
</table>

Comparative Efficacy in Two Treatment Groups
In the clonidine transdermal patch group, there were a total of 71 cases, with 58 cases in which treatment proved effective. The rate of efficacy is 81.7%. In the haloperidol control group, there were 59 cases, in which 39 cases were assessed as effectively treated, with an efficacy rate of 66.1%. The difference was not statistically significant (P<0.05).

ADVERSE REACTION
In the clonidine transdermal patch group, one of 71 patients experienced a decrease in blood pressure and dizziness; the adverse reaction disappeared after drug withdrawal. In the haloperidol group, 6 cases of 59 had adverse reactions: 2 had mild cervical muscle tension and 4 had mild drowsiness and fatigue. There were no severe extrapyramidal reactions. Neither the conventional blood tests, electrocardiogram nor other tests of liver and kidney function showed obvious abnormality.

DISCUSSION
TS occurred mostly in 5 to 15-year-old school-age children. It is estimated that about 15% of children will face this problem. The incidence rate is very high, about 1% ~ 7% [12]. The disease is more common in boys [1,2]. Its manifestations are varied including muscle twitching, cramps and other so-called “exercise-induced tics,” as well as the sounds of the “vocal tic.” The primary symptoms include repeated, rapid motor tics of one type or more, as well as vocal symptoms; these can be associated with inattention, hyperactivity, forced movements and thinking, as well as other behavioral symptoms. Some reports show that the intelligence structure of TS patients is limited as compared to that of other children [13]. There is a certain gap between TS patients and healthy children in terms of general knowledge, comprehension, logical thinking, abstract conceptualization, non-structured visual practice and visual-motor ability, etc. These children may have some degree of memory impairment, which will affect their learning process; meanwhile, personality and sleep problems are also more prominent, leading to a lower quality of life than in the healthy population [14–17] For this reason, it is concluded that an early intervention will help to improve their quality of life [18]. The cause of the disease remains unclear. Its incidence is associated with genetic factors [19–20], nervous imbalance [21,22], psychological and environmental factors [23], etc. In recent years with the development of biochemistry, neurochemistry and neuropharmacology, it was revealed that the cause of TS might be due to the hyperactivity of the basal ganglia of the central nervous system neurotransmitter dopamine, or due to dopamine receptor hypersensitivity [24–28].

At present, clinicians always use oral haloperidol, tiapride, topiramate and other drugs together with psychological treatment [29]. The oral drugs, however, lead readily to drowsiness, fatigue, emotional temper, akathisia and an acute dystonia extrapyramidal reaction to light. Tiapride can cause hyperthyroidism leading to obesity, as well as memory loss, sleep disorders and other adverse reactions. Because of these adverse reactions and taking medication orally twice per day (which was skipped easily), the therapy was often discontinued, which influenced the overall efficacy of the treatment. Clonidine is a selective α-2 adrenergic receptor agonist, originally used for the treatment of high blood pressure. It can act on the locus coeruleus to inhibit noradrenergic activity. The noradrenergic pathway plays an important role in regulation of the arousal state, directly affecting dopamine, 5-HT, endogenous opioids and nerve growth factor activity. The mechanisms of clonidine as the medicine for the treatment are: low-dose application with the stimulation of inhibitory pre-synaptic α-2 receptors, blocking norepinephrine into the brain, but then reducing the release of norepinephrine, working together to suppress symptoms such as the tic [30]. The controlled-release of clonidine delivers treatment to the skin surface, using the clonidine concentration gradient between the drug reservoir and the skin surface. The drug enters the human body through the layers of skin from the controlled-release membrane at constant speed within 7 days. This produces the therapeutic effect of circulating...
CONCLUSIONS
This form of drug administration helps to avoid many common adverse reactions. The drug needn’t run through the digestive tract, thus the impact of pH, digestion and other factors on the potency of the drug, as well as the stimulation of the digestive tract is avoided. There are also the following advantages:
1. The externally bonded drug is easily accepted by children and only needs to be changed once a week in an easy-to-facilitate administration;
2. The patch rarely causes drowsiness, slow reaction, memory loss or other adverse reactions, thus bringing the children less interference with their learning and life. This allows for better compliance with the treatment;
3. It causes no increase in appetite, therefore the patch can be used for obese children;
4. There are no adverse effects on liver and renal functions;
5. Extrapyramidal side effects are very few, while a decline in blood pressure and local erythema only appeared on some cases;
6. Although there is not much difference on efficacy of the two groups, the YGTSS score of the clonidine transdermal patch group is apparently decreased and there were fewer side effects. Therefore, clonidine transdermal patch treatment has obvious advantages for children with TS. However, the efficacy for a large number of people, as well as the long-term efficacy remains to be assessed.

REFERENCES
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