Original Article
Therapeutic effect of Biyuan tongqiao granules combined with mometasone furoate nasal spray on clinical symptoms of children with allergic rhinitis

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Abstract: Objective: To explore the clinical benefits of Biyuan Tongqiao granules (BTG) combined with mometasone furoate nasal spray (MFNS) on the symptoms of children with allergic rhinitis (AR). Methods: Seventy-eight children with AR who visited the Pediatric Department of our hospital from May 2019 to May 2020 were selected and randomly divided into the BTG group (treated with BTG alone), MFNS group (treated with MFNS alone), and combined group (children with the combined use of BTG and MFNS), with 26 cases in each group. The nasal symptoms and oculonasal symptoms were evaluated and observed at baseline and 2 months after treatment. Results: Children in the combination group had significantly lower total nasal symptom score (TNSS), total non-nasal symptom score (TNNSS) scores, and visual analogue scale (VAS) scores than those with BTG alone and MFNS alone (*P*<0.05). The overall response rate was 69.23% in children with BTG alone, 80.77% in children with MFNS alone, and 92.31% in children with the combined treatment. Conclusion: BTG combined with MFNS can improve the symptoms of sneezing and nasal congestion, which is better than single drug treatment.

Keywords: Biyuan tongqiao granules, mometasone furoate aqueous nasal spray, allergic rhinitis in children

Introduction

With improvements in living standards, people have more choice in daily eating, leading to the increasing incidence of various allergic diseases [1]. Allergic rhinitis (AR) is particularly prominent among all types of allergic reactions, with a global incidence of approximately 10-50% over the past few decades, making it a global health challenge [2]. AR in children, also known as strain rhinitis, is a non-infectious chronic inflammatory disease of the nasal mucosa mediated by immunoglobulin E (IgE), involving multiple immune factors after allergen exposure [3]. AR is one of the most common chronic diseases in pediatrics departments, with an increasing incidence and an average annual increase of 0.17% in children aged 6-7 years old and 0.18% in children aged 13-14 years old [4]. In China, AR occurs in 10% of children [5] and is a common pediatric condition with severe comorbidities, for which children are prone to complications such as otitis media and sinusitis [6]. Although AR does not cause serious events, children with acute onset typically have symptoms such as sneezing, runny

nose, nasal congestion, and nasal itching, which affect their sleep quality, learning efficiency, and quality of life, with some children even developing asthma [7].

AR is a type I allergy, which affects the serum levels of IL-17, IL-10, and other inflammatory factors. IL-17 exacerbates the inflammatory response [8] by accelerating neutrophil aggregation and promoting cell differentiation to exacerbate its pro-inflammatory effect. IL-10 suppresses the inflammatory response by inhibiting IgE production, which are then secreted by the mast cells and eosinophil differentiation [9]. IgE is a mediator of AR, and antibodies targeting it bind to basophils and mast cells to accelerate the release of interleukins and histamine, increase glandular secretion, and improve nasal hyperreactivity [10, 11].

AR is an immune disease triggered by exogenous antigens. Allergic individuals are sensitized through their first contact with the allergen, and later, re-contact with the allergen induces various nasal mucosa-related chronic inflammatory reactions. Allergens such as pol-

len and dust mites are unavoidable, and thus, exposure to known allergens can be prevented. Although specific immunotherapy is effective for AR, its long course, high cost, and unproven safety make it unfit as a first-line treatment modality for AR in children [12]. Therefore, pharmacotherapy remains the primary option for children with AR.

According to the severity of disease, gluco-corticosteroids and antihistamines are usually administered orally, via nasal spray, or through nebulized inhalation [13]. Mometasone furoate nasal spray (MFNS) has been widely used for treating AR, and it can quickly and effectively improve clinical symptoms in children. However, in clinical practice for the management of AR in children, the recurrence rate and incidence of adverse reactions are high when using MFNS treatment alone [14]. Recent guidelines recommend combination therapy for moderate-to-severe AR, and glucocorticoid-based combination therapy is an ideal solution for symptom control [15, 16]. Traditional Chinese medicine has made significant progress in the treatment of children with AR, and this can improve the allergic state and has the advantages of low toxic side effects, long-lasting efficacy, and high safety, providing a new basis for the effective treatment of children with AR [17]. Biyuan tongqiao granule (BTG) is a compound derived from Chinese patented medicine, which has been proven effective for symptom control and immunoregulation [18]. BTG can improve the therapeutic effect of AR through various mechanisms, including the inhibition of inflammatory exudation and regulation of SP-A expression and the Th1/Th2/Th17 cell balance, making it a drug with high potential for combination therapy [17, 18]. However, there is still a lack of both foreign and domestic research on the combination of BTG and MFNS for AR in children. In this study, the combination of BTG and MFNS was administrated to treat children with AR, and the changes in symptoms were observed to evaluate its clinical efficacy, to ultimately provide a theoretical basis for improving treatment efficacy.

Materials and methods

Baseline data

Seventy-eight children who attended the pediatric department of our hospital from May 2019 to May 2020 and were diagnosed with AR according to the diagnostic criteria of Allergic Rhinitis and its Effect on Asthma (ARIA) guidelines [19] were enrolled in this study. They were selected and randomly divided into the BTG group (children treated with BTG alone), MFNS group (children treated with MFNS alone), and combined group (children treated with the combined use of BTG and MFNS) according to a random number table, with 26 cases in each group. The sample size calculation method is shown in Equation 1, with $\alpha = 0.05$ and $1 - \beta = 0.8$. The expected effective rates for BTG alone, MFNS alone, and the combination of BTG and MFNS were 65%, 65%, and 97%, respectively, with n1 = n2 = n3 = 23, an estimated dropout rate of 15%, and a final sample size for each group of 26.

$$n = \frac{(Z_{1-\alpha'/2} + Z_{1-\beta})^2 \left[p_1(1-p_1) + p_2(1-p_2) \right]}{\delta_{ij}^2}$$
$$n = \max\{n_{ij}, pairs(i,j)\}$$

(Equation 1)

The inclusion criteria were as follows: ① children aged 3-14 years old; ② children with the onset of AR upon initial diagnosis; ③ children who received no medication treatment within 1 week prior to inclusion. The exclusion criteria were as follows: ① children suffering from pneumonia, bronchitis, or asthma, among others; ② children with hematopoietic or immune system comorbidities, other primary or malignant tumors, or other wasting diseases; ③ children with a drug allergy; ④ children with psychiatric disorders; ⑤ children with low compliance. The study was approved by the Ethics Committee of Qingdao Women and Children's Hospital (No. NCT01325864), and guardians of all the children signed an informed consent form at the beginning of diagnosis for the further use of clinical records.

Methods

Children in the BTG alone group were treated with BTG (Shandong New Era Pharmaceutical Co., Ltd., Z20030071), three times daily, 15 g each time, for eight weeks. Children in the MFNS alone group were treated with MFNS (Schering-Plough Labo N.V., Belgium, H2014-0100) at 50 μg per nostril, once per day (in total, 100 μg) [15]. Children in the BTG and

MFNS combination group were treated with BTG and MFNS with the same delivery method and dosage as those in the other two groups. Children in all three groups were treated continuously for eight weeks.

Outcome measurements

Primary indicators

Treatment efficacy: The treatment efficacy was evaluated before treatment and two months after treatment. The score of clinical symptoms and signs was used as the efficacy index to judge the treatment efficacy. An efficacy index ≥66% was considered markedly effective, 26-66% was considered effective, and <26% was considered ineffective, and the overall response rate was the sum of the effective and markedly effective scores [20]. The calculation was as follows: efficacy index = (pre-treatment score - post-treatment score)/pre-treatment score × 100%. The clinical symptom scoring standard was as follows: at least 1 consecutive sneeze number <5, daily runny nose <4 times, nasal congestion on conscious inhalation, intermittent itchy nose and other symptoms, scored as 1 point; at least 1 consecutive sneeze number 6-10, daily runny nose 5-9 times, intermittent or interactive nasal congestion, bearable itchy nose and other symptoms, scored as 2 points; at least 1 consecutive sneeze number ≥11, daily runny nose ≥10 times, mouth breathing almost all day, unbearable itchy nose and other symptoms, scored as 3 points. The physical sign scoring standard was as follows: mild swelling of the turbinate, with the nasal septum and middle turbinate still visible, scored as 1 point; the inferior turbinate and nasal septum (or nasal base) were close, with a small gap remaining between the inferior turbinate and the nasal base (or nasal septum), scored as 2 points; the inferior turbinate was close to the nasal base and nasal septum, with invisible middle turbinate or polypoid changes and polyp formation in the mucosa of the middle turbinate, scored as 3 points.

Nasal symptoms

The total nasal symptom score (TNSS) scale was used to evaluate the nasal symptoms in the children. The TNSS scale was used to rate the severity of symptoms, including sneezing, runny nose, nasal congestion, and nasal itching, with 0 indicating no symptoms and 4 indicating extremely severe symptoms [21]. The total non-nasal symptom score (TNNSS) scale was used to evaluate the concomitant nasal symptoms in the children. The TNNSS scale was used to rate the concomitant symptoms other than total nasal symptoms, such as nasal reflux, itching of the eyes and nose, and lacrimation, with 0 indicating no symptoms and 1 indicating the presence of symptoms [22].

Improvement of ocular and nasal symptoms

The visual analogue scale (VAS) score was used to evaluate the improvement in ocular and nasal symptoms in children before treatment and after treatment. The VAS scale was evaluated using a score of 0-10 points on a 10 cm long straight line, with 0 points indicating no symptoms and 10 points indicating very severe symptoms. Patients made a mark [23] on the horizontal line to indicate symptom perception.

Secondary indicators

Adverse effects: The adverse effects were observed and recorded in the follow-up period, including nausea, vomiting, chest distress, hot flush, nasal bleeding and rash.

Statistical methods

Statistical analysis was performed with SPSS 22.0 software. The measurement data were expressed as the mean ± SD ($\overline{x}\pm s$), and the enumeration data were indicated as [n (%)] and compared by a Chi-square test. A paired sample t-test was used for intra-group comparisons and an independent sample t-test was used for comparisons between groups, whereas ANOWA was used for multiple group comparisons. $P<0.05$ indicated a statistically significant difference.

Results

Differences in baseline data

There were no statistically significant differences in baseline data such as gender, age, disease duration, disease gradation, and body mass index (BMI), indicating comparability among groups ($P>0.05$, **Table 1**).

Comparison of treatment efficacy

The overall response rate was found to be 69.23% in children treated with BTG alone, 80.77% in children treated with MFNS alone,

Table 1. Comparison of baseline data ($\bar{x}$±s)/[n (%)]

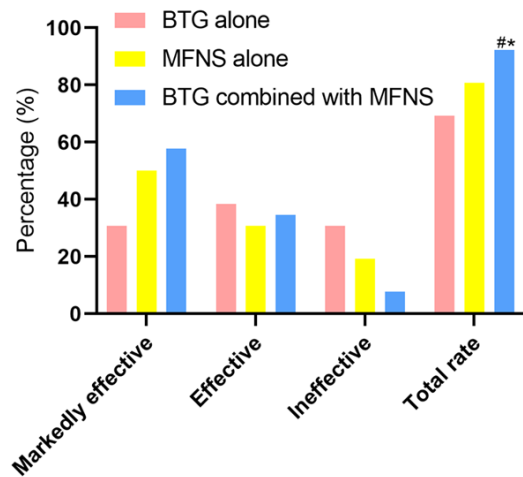| Clinical data		BTG alone (n = 26)	MFNS alone (n = 26)	BTG combined with MFNS (n = 26)	P-value
Gender	Male	16	13	14	0.696
	Female	10	13	12	
Mean age (years)		6.25±1.72	6.05±1.26	6.17±1.52	0.891
Duration (years)		1.48±0.38	1.53±0.43	1.58±0.49	0.711
Condition	Mild	19	20	18	0.962
Classification	Moderate-severe	7	6	8	
Body mass index (kg/m^2)		15.00±1.25	15.25±1.38	15.19±1.29	0.733

Figure 1. Comparison of treatment efficacies. The overall response rate in MFNS group was higher than that in the BTG group, and the overall response rate in the combination group was significantly higher than that in BTG or MFNS group (*P*<0.05). * compared with BTG alone, # compared with MFNS alone. BTG, Biyuan Tongqiao granules; MFNS, mometasone furoate nasal spray.

and 92.31% in children treated with the combination of BTG0 and MFNS. The combined use of BTG and MFNS showed an increased overall response rate compared to that with BTG alone and MFNS alone (*P*<0.05). These results suggested that BTG combined with MFNS was more effective for children with AR than BTG or MFNS alone (**Figure 1**).

Comparison of nasal symptoms

TNSS and TNNSS scores of children in the three groups were significantly lower after treatment than before treatment (*P*<0.05). Children treated with MFNS alone and with BTG combined with MFNS showed decreased TNSS and TNNSS scores compared to those of indi-

viduals treated with BTG alone (*P*<0.05), and the TNSS scores of children treated with BTG and MFNS were significantly lower than those of children treated with MFNS alone (*P*<0.05), suggesting that BTG combined with MFNS could improve nasal symptoms (**Figure 2**).

Comparison of improvements in ocular and nasal symptoms

The children in the three groups showed decreased VAS scores after treatment relative to those before treatment (*P*<0.05). The VAS scores of children treated with MFNS alone and with BTG combined with MFNS were significantly lower than those of children treated with BTG alone (*P*<0.05), and the VAS scores of children treated with BTG combined with MFNS were significantly lower than those of children treated with MFNS alone (*P*<0.05). These results suggested that BTG combined with MFNS could improve the ocular and nasal symptoms and show higher efficacy (**Figure 3**).

Adverse effects

The incidence of adverse effects in the BTG, MFNS, and BTG combined with MFNS groups were 3.85% (1/26, nausea), 7.69% (2/26, 1 hot flush and 1 nasal bleeding), and 11.54% (3/26, 2 hot flush and 1 rash), respectively, with no statistical difference (*P*>0.05). All adverse effects in each group subsided spontaneously.

Discussion

MFNS is a glucocorticoid preparation and an effective anti-inflammatory agent. It is often used clinically for treating AR and seasonal rhinitis, but the disease is prone to relapse after discontinuing the medication. BTG comprises
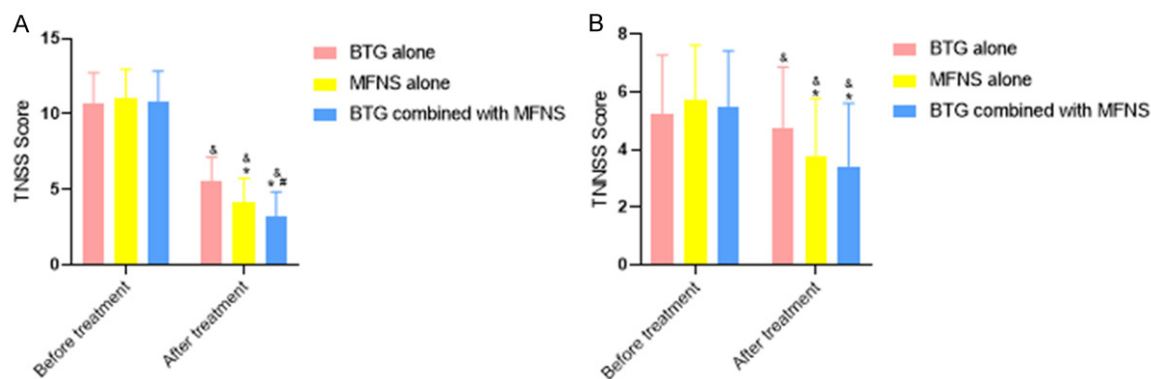
Figure 2. Analysis of nasal symptoms. The total nasal symptom score (TNSS) and total non-nasal symptom score (TNNSS) of children in all three groups after treatment were significantly lower than those before treatment ($P<0.05$). The TNSS and TNNSS scores for children in the MFNS group and combination group were significantly lower than those in the BTG group ($P<0.05$), and the scores for children in the combination group were significantly lower than those in the MFNS group ($P<0.05$). & compared with before and after treatment, * compared with BTG alone, # compared with MFNS alone. BTG, Biyuan Tongqiao granules; MFNS, mometasone furoate nasal spray.

sesses antibacterial activity and can relieve a stuffy nose, alleviate pain, and exert anti-allergic effects by stabilizing the mast cell membrane, regulating the imbalance of Th cell immunity, and inhibiting the release of inflammatory transmitters, thus playing the role of improving human immune function. *Angelica dahurica* has a warm-pungent property and fragrant smell, has analgesic and anti-inflammatory effects, and can open the nine orifices of the human body. It can also inhibit mast cell degranulation to block the inflammatory response, reduce IgE production, regulate immune functions, and improve allergic constitution [24-26]. It has different degrees of inhibitory effects on *Streptococcus*, *Staphylococcus aureus*, *Penicillium*, and *Typhoid* bacilli [27].

Scutellaria baicalensis Georgi. has anti-inflammatory and anti-allergic activity and contains glycosides polysaccharide, amino acids, and trace elements, which can elevate the levels of cyclic adenosine monophosphate, IgE, and immunoglobulin M in the blood, increase the ability of white blood cells to induce interferon produc-
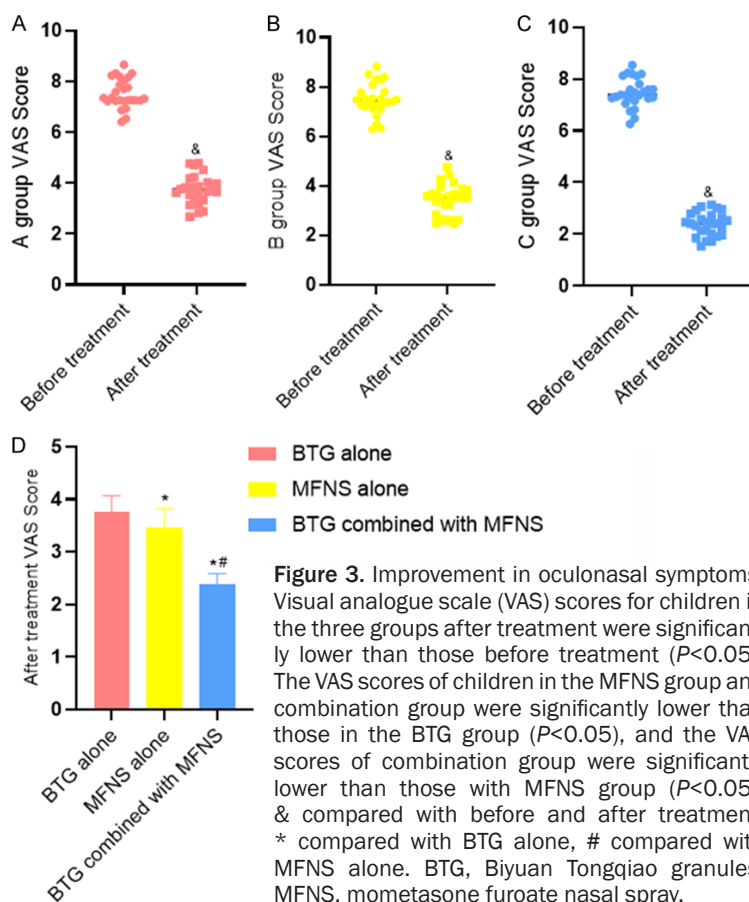
Figure 3. Improvement in oculonasal symptoms. Visual analogue scale (VAS) scores for children in the three groups after treatment were significantly lower than those before treatment ($P<0.05$). The VAS scores of children in the MFNS group and combination group were significantly lower than those in the BTG group ($P<0.05$), and the VAS scores of combination group were significantly lower than those with MFNS group ($P<0.05$). & compared with before and after treatment, * compared with BTG alone, # compared with MFNS alone. BTG, Biyuan Tongqiao granules; MFNS, mometasone furoate nasal spray.

Chinese herbal ingredients such as *Magnolia denudata* Desr., prepared *Xanthium sibiricum* Patr., Herba Ephedrae, *Angelica dahurica*, and *Scutellaria baicalensis* Georgi. Prepared *X. sibiricum* Patr. is characterized by sweet and bitter taste and a mild property. It also pos-

tion, increase the activity of natural killer cells, enhance the non-specific immune function, and regulate humoral immunity [28, 29]. The anti-inflammatory effects of prepared *X. sibiricum* Patr., *A. dahurica*, and *S. baicalensis* Georgi. can reduce inflammatory reactions and the degree of swelling of nasal mucosa and effectively relieve the symptoms of nasal congestion; its anti-allergic and regulatory effects on immune functions of the body can effectively relieve the symptoms of sneezing and runny nose. *Magnolia denudata* Desr. and Herba Ephedrae have astringent effects, which can improve local blood circulation, reduce capillary vascular permeability, relieve nasal mucosal edema, and promote the absorption of secretions, and the aqueous extract of Herba Ephedrae can inhibit the release of allergy transmitters [30], effectively relieving the symptoms of nasal congestion and runny nose. Jiang showed that BTG can act on multiple components of the inflammatory reaction, thus reducing the symptoms of inflammatory reactions and exerting good anti-inflammatory effects, which might be related to enhancing specific and non-specific immune functions [31].

Kong conducted research to observe the clinical value of BTG combined with MFNS, and the results showed that the levels of IgE in the study group treated with BTG and MFNS were significantly lower than those in the control group treated with MFNS [32]. This indicated that a combination of the two drugs could significantly improve inflammatory injury and the hyperreactive nasal mucosa in children with AR. This might be related to the fact that topical glucocorticoids, such as MFNS, can accelerate the apoptosis of inflammatory cells, lead to the secretion of adjustable inflammatory factors, and improve airway reactivity in children [33-35].

In this study, we found that TNSS, TNNSS, and VAS scores in the combination group were significantly lower than those with BTG or MFNS alone, which proved that BTG combined with MFNS could improve the symptoms of sneezing and nasal congestion, and the clinical efficacy of BTG combined with MFNS was significantly better than that with BTG and MFNS alone, indicating that the combination was more effective than single drug for the treatment of children with AR. The response rates with BTG alone, MFNS alone, and BTG combined with MFNS were 69.23%, 80.77%, and 92.31%, respectively. The overall efficiency of the combination of the two drugs was higher, which could be attributed to the multifaceted comprehensive effects of the pharmacological components of BTG on immune organs, immune cells, and inflammatory mediators, among others. The addition of BTG accelerates the transdermal absorption of the drug of MFNS, resulting in a significant increase in the bioavailability of the drug.

In conclusion, BTG combined with MFNS can improve the clinical symptoms of children with AR and improve the therapeutic efficacy. The novelty of this study is the comparison of the therapeutic effect of BTG or MFNS treatment alone with that of the combined use of a BTG and MFNS regimen. The shortcomings of this study are the lack of molecular mechanistic research, lack of long-term follow-up after treatment, and lack of a further understanding of the recurrence of AR. In the next step, the molecular mechanism will be investigated, and a long-term follow-up study will be carried out after treatment, to obtain more representative and scientific conclusions, thereby providing a more detailed theoretical basis for clinical treatment.

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Disclosure of conflict of interest

None.

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