European Review for Medical and Pharmacological Sciences 2014; 18: 775-780

Clinical efficacy of montelukast sodium in treating infantile wheezing

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Abstract. – OBJECTIVES: The efficacy and safety of a single-dose of Montelukast sodium for treating virus-related infantile wheezing are investigated in this study.

PATIENTS AND METHODS: A prospective, open, randomized, controlled study was carried out on 595 cases of infants who exhibited wheezing after a respiratory syncytial virus infection. Treatment with Montelukast sodium was provided over the course of 12 weeks. The clinical efficacy of Montelukast sodium was determined based on the clinical symptom score, tidal breathing lung function, and short-acting bronchodilator usage, as well as infantile asthma diagnosis rate change at the 4th and 12th week after the administration of the treatment. The adverse reactions were also observed, and a control group was set. The mean age of the 595 patients with infantile wheezing was 10.82 months ± 4.22 months. Among these patients, 45.9% (273 out of 595) had a family history of asthma, 30.6% (182 out of 595) had allergic rhinitis, 23.9% (142 out of 595) increased peripheral blood eosinophilia, 6.1% (36 out of 595) exhibited total IgE increase, 40.0% (238 out of 595) had a recurrent history of wheezing, and 64.0% (381 out of 595) had a family history of eczema.

RESULTS: After 12 weeks of treatment, the clinical symptom scores significantly improved. Significant differences in the cough, wheezing, and motility scores were observed before and after the treatment ($p < 0.05$). TPTEF/TE and VPEF/VE significantly improved ($p < 0.05$) after the treatment. The asthma diagnosis rate was 9.6% (57 out of 595). At four weeks after treatment, various indicators correspondingly improved. Twenty-nine (4.9%) patients exhibited adverse reactions, 55.2% exhibited excitation, 20.7% suffered from insomnia, 10.3% had headaches, 3.4% had erythra, 3.4% suffered from abdominal pain, and 3.4% exhibited an increased glutamic-pyruvate transaminase level. The symptoms of eczema were relieved to some extent, and the symptoms of rhinitis became less serious. Significant differences were observed in the number of wheezing attacks, annual number of days hospitalized, annual number of days when β2AG was utilized, and lung function improvement ($p < 0.05$).

CONCLUSIONS: Montelukast sodium is clinically effective in treating virus-related wheezing, and clinical application for 4 weeks to 12 weeks can effectively relieve the symptoms of wheezing, improve lung function, and reduce the incidence rate of infantile asthma. Montelukast sodium also causes few adverse reactions.

Key Words:
Wheezing, Montelukast sodium, Infants, Treatment.

Introduction

Acute respiratory infection is the main cause of recurrent wheezing attacks in children, especially among infants. In the season of epidemic respiratory infection, acute wheezing attack is the common reason receive emergency treatment, whereas the recurrent wheezing attack after infection is closely related to the occurrence of asthma in children[1,2]. Respiratory syncytial virus (RSV) is the most common respiratory virus that causes infantile recurrent wheezing attacks. The correlation of RSV infection with asthma and wheezing has recently been confirmed. However, several controversies exist regarding the treatment of recurrent wheezing attacks after RSV infection[3,4]. The clinical efficacy of Montelukast sodium in the treatment of recurrent wheezing attack after RSV infection, its prevention and effect on the occurrence of asthma were investigated. Our team conducted an early intervention treatment with Montelukast sodium for 595 cases of child patients suffering from wheezing attacks after definite diagnosis of RSV capillary bronchitis who were hospitalized in our Hospital from September 2001 to September 2004. We observed the wheezing attacks and the changes in the lung function of the child patients before and after the treatment, as well as the symptoms of asthma after three years, to search for an effective method for the clinical treatment of virus-related wheezing.

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Patients and Methods

Patients

A total of 890 child patients who were admitted in our Tianjin Children's Hospital from September 2001 to September 2004 and diagnosed with RSV capillary bronchitis were randomly selected as the subjects of the study. The diagnostic code complied with Zhu Futang's "Practical Pediatrics" (Seventh Edition)[1]. The patients were randomly divided into the treatment group and the control group at a ratio of 2:1. The treatment group had 595 cases, including 333 male cases and 262 female cases. The minimum age was six months, and the maximum age was three years and two months, with a mean age of 10.82 months ± 4.22 months. The control group had 295 cases, including 142 male cases and 143 female cases, with a mean age of 11.12 months ± 3.98 months. The wheezing attack-related factors of the two groups of patients, namely, family history of asthma, allergic rhinitis, eczema, and recurrent wheezing, as well as peripheral blood eosinophil cell and total serum IgE level are shown in Table I. The two groups of patients did not exhibit significant difference in terms of gender ($\chi^2 = 1.612$) and age ($F = 0.924$) ($p > 0.05$).

The inclusion criteria were as follows: < 2 years old, patients who had acute upper respiratory infection within the previous three weeks; patients receiving emergency treatment because of wheezing within the previous week; hospitalized patients with low respiratory RSV infection confirmed by a serology test and respiratory nasopharyngeal secretion test; and patients who were not administered with Montelukast sodium in the past. The exclusion criteria were as follows: patients with history of recurrent wheezing attacks and those who were administered with Montelukast sodium in the past.

Methods

The patients in the treatment group were administered with 4 mg/d of Montelukast sodium (Singulair, Merck, Sharp, & Dohme, Whitehouse Station, NJ, USA, 4 mg/tablet, chewable tablets) every night. The patients in the control group were administered the β2 receptor agonist (Terbutaline, manufactured by Astra Zeneca Company, Macclesfield, UK, 2.5 mg/time, inhaled from a Bary atomization pump) as required for a treatment course of 12 weeks. At the 4th and 12th week after administration, clinical symptom score, tidal breathing lung function, and short-acting bronchodilator usage, as well as infantile asthma diagnosis rate change, were recorded and observed. Tidal breathing lung function was determined through a Master Screen Paed pulmonary function instrument manufactured by Jaeger Company (Germany, Bavaria, Marktred-

Table I. General conditions included patients [n (%)].

Items		Results		χ^2	p
		Treatment group (n, %)	Control group (n, %)		
Residential area	Countryside	129 (21.7%)	64 (21.7%)	0.000	> 0.05
	City	466 (78.3%)	231 (78.3%)		
Allergic rhinitis*	–	212 (35.6%)	103 (34.9%)	0.044	> 0.05
	+	383 (46.4%)	192 (65.1%)		
Family asthma history*	–	65 (10.9%)	30 (10.2%)	0.118	> 0.05
	+	530 (89.1%)	265 (89.8%)		
Seasonal wheezing	–	114 (19.2%)	59 (20.0%)	0.089	> 0.05
	+	481 (80.8%)	236 (80.0%)		
Eczema/ atopic dermatitis	–	58 (9.7%)	24 (8.1%)	0.613	> 0.05
	+	537 (90.3%)	271 (91.9%)		
Excercise-induced wheezing	–	358 (60.2%)	172 (58.3%)	0.350	> 0.05
	+	237 (39.8%)	123 (41.7%)		
Cough after fever > 4 weeks	–	53 (8.9%)	23 (7.8%)	0.312	> 0.05
	+	542 (90.1%)	272 (92.2%)		
Total serum IgE level	–	547 (91.9%)	274 (92.9%)	0.240	> 0.05
	+	48 (8.1%)	21 (7.1%)		
Peripheral blood eosinophil cell count	–	417 (70.1%)	230 (78.0%)	0.636	> 0.05

*Allergic rhinitis was diagnosed by doctors from the otorhinolaryngology department; family asthma history referred to the first-level relative asthma history.

witz). The instrument was operated by a special technician. The Time of Peak Tidal Expiratory Flow or the Time of Expiration (TPTEF/TE) and the Volume of Peak Expiratory Flow or Tidal Volume (VPEF/VE) were obtained and considered the main observation indicators. After one treatment course, outpatient service and follow-up visits were conducted for three years.

Observation Indicators

On the treatment day and at the 4th and 12th week after treatment, the symptoms of wheezing, coughing, coughing and wheezing after exercise (motility) and sleep, and tidal breathing lung function of the patients were observed and recorded. The number of wheezing attacks (times per year), number of times hospitalized (mean per year), number of times β2AG (β2-adrenergic receptor agonists) was used (years), ratio of final developed asthma (%), and extent of the lung function decline (%) (TPTEF/TE and VPEF/VE) were also observed and compared. Comparisons between the two groups were carried out. The standard scoring system for the clinical symptoms is shown in Table II.

Statistical Analysis

The SPSS10.0 statistical software (SPSS Inc, Chicago, IL, USA) was used for the statistical analysis of all data. The measured data were expressed as the mean of the two samples ± standard deviation (±s) and analyzed by t/χ^2 test. According to the Shapiro-Wilk Normality Test, the symptoms and scores of the two groups of child patients and their data on hospitalization did not exhibit normal distribution. Therefore, these data were expressed as the median (4-point spacing), namely, *M* (Q). The Wilcoxon rank sum test for the comparison of the two independent samples (normal approximation) was adopted to compare the two groups. Significant difference was observed at $p < 0.05$.

Results

Clinical Efficacy

Among the 595 patients in the treatment group, 42.2% (251 out of 595) exhibited improved clinical symptoms, 44.6% (265 out of 595) exhibited improved allergic rhinitis symptoms, 64.2% (382 out of 595) exhibited improved seasonal wheezing, and 36.8% (219 out of 595) of the eczema cases improved. The use of β2AG was reduced in 67.6% (402 out of 595) of the patients, and the incidence rate of side effects was only 11% (32 out of 595). At the 4th and 12th week after treatment, significant differences were observed with regard to wheezing, coughing, coughing and wheezing after exercise (motility), and the tidal breathing lung function of the patients compared with the base values ($p < 0.05$) as shown in Table III. Significant differences were observed in the number of wheezing attacks, annual number of days hospitalized, annual number of times β2AG was used, and lung function improvement ($p < 0.05$). In the three years of follow-up visits, 63 cases in the treatment group (10.59%) and 114 cases in the control group (38.64%) were diagnosed with asthma. A significant difference exists between the two groups ($\chi^2 = 38.3967$, $p < 0.05$) (Table IV).

Adverse Reactions

During the administration of the treatment, good overall tolerance and compliance were observed, and no serious adverse reactions were reported. A total of 32 patients (5.38%) referred adverse reactions during administration. The adverse reactions were related to the following factors: 8 cases of anxiety and excitation (25.00%), 7 cases of aminotransferase increase (21.88%), 4 cases of headache (12.50%), 2 cases of diarrhea (6.25%), 2 cases of blushing (6.25%), 2 cases of abdominal pain (6.25%), 2 cases of erythra (6.25%), 2 cases of

Table II. Scoring criteria of clinical symptoms.

Items	0	1	2	3
Wheezing	None	Mild	Moderate	Severe
Cough	None	Occasional	Often	Persistent
Cough/wheezing after exercises (motility)	None	Be able to run in short distance or climb 3 steps, or in case of milk uptake	Only be able to walk or not swallow continuously	Be unable go to school/ work, or only can stay in the room, or refuse milk
Sleep	Good	Sleep well, with mild wheezing or cough	Awaken for 2-3 times, wheezing or cough	Bad, cannot sleep.

Table III. Improvement situations of clinical symptoms of the treatment group before and after treatment.

Symptom score	Basic values	After 4 weeks	t/H	p	After 12 weeks	t/H	p
Motility	1.68 ± 0.52	1.16 ± 0.39	7.8486	< 0.05	0.72 ± 0.14	8.6239	< 0.05
Wheezing	1.76 ± 0.71	1.28 ± 0.58	7.0023	< 0.05	0.92 ± 0.68	9.2316	< 0.05
Cough	1.56 ± 0.67	1.06 ± 0.61	6.9821	< 0.05	0.86 ± 0.78	9.2814	< 0.05
TPTEF/TE	0.23 ± 0.12	0.30 ± 0.14	2.1362	< 0.05	0.40 ± 0.18	2.9876	< 0.05
VPEF/VE	0.28 ± 0.20	0.32 ± 0.17	2.0216	< 0.05	0.39 ± 0.20	2.6390	< 0.05

cough aggravation (6.25%), 2 cases of dizziness (6.25%), and 1 case of costalgia (3.12%). All adverse reactions were mild, and symptoms immediately disappeared after drug withdrawal.

Discussion

RSV infection is closely related to asthma. Several studies have confirmed that about 30% of infants suffer from at least one wheezing attack in the first year after birth. The main reasons are viral respiratory infection and exposure to a smoky environment. About 20% of infants suffer from lower respiratory system diseases accompanied with wheezing attacks at least once in the first year after birth. Among these instances, 60% are induced by viral infection. RSV is one of the primary causes of infantile lower respiratory system infection, especially for child patients less than six months old[1,5-7]. Sigurs et al[8] conducted a prospective study for seven years among infants of less than one year old who required hospitalization because of lower respiratory RSV infection. The researchers reported that the prevalence rates of recurrent wheezing and asthma were 68% and 30%, respectively. Both rates were significantly higher than those of the control group. However, researchers as well as doctors continue to debate whether the effects of RSV infection on the occurrence of wheezing after infection are consistent in all infected persons, and whether the occurrence of persistent asthma after infection can be controlled. A clear agreement has been not reached on whether a treatment should be conducted and how the treatment should be conducted. Therefore, we conducted a prospective, open, randomized controlled study of 890 infants diagnosed with RSV infection in the lower respiratory system to understand and investigate the clinical characteristics of wheezing after RSV infection. The efficacy and safety of a single dose of Montelukast sodium for the treatment of infantile virus-related wheezing were also investigated. A significant difference in the RSV infection rate among the different populations was observed. Among the 890 patients diagnosed with RSV infection, those with atopic traits (eczema and/or atopic dermatitis) in the treatment and control groups accounted for 90.3% (537 out of 590) and 91.9% (271 out of 295), respectively. The history of asthma among the same first degree relatives relatives also showed a higher prevalence rate. The prevalence rate was 89.1% (530 out of 595) in the treatment group and 89.8% (265 out of 295) in the control group. This particular result indicates that the population with atopic traits is susceptive to RSV, which is in accordance with previous reports[9]. However, some articles reported that RSV infection has no significant correlation with atopic traits. This conclusion can be further confirmed by conducting strict birth cohort studies.

Singulair was utilized in this study to provide intervention therapy for 595 patients with RSV capillary bronchitis who continuously manifested

Table IV. Clinical comparative analysis of the treatment group and the control group.

	Treatment group (595 cases)	Control group (295 cases)	H/χ^2	p
Wheezing attack times (times/year)	2.23 ± 0.67	10.26 ± 1.32	13.9274	< 0.05
Hospitalization times number (mean/year)	1.34 ± 0.22	4.96 ± 1.11	10.1960	< 0.05
β2AG use day number (years)	7.35 ± 1.28	30.65 ± 4.12	21.9253	< 0.05
Lung function decline (%)	4.32 ± 1.41	48.52 ± 10.23	52.6395	< 0.05
	7.62 ± 2.39	30.48 ± 9.82	47.2390	< 0.05
Ratio of developing into asthma (%)	63 (10.59%)	114 (38.64%)	38.3967	< 0.05

the early symptoms of wheezing attack for 12 weeks (wheezing at least once daily, chewing before sleep). Singulair effectively relieved 42.2% (251 out of 595) of the clinical symptoms in the acute stage, 44.6% (265 out of 595) of the allergic rhinitis symptoms, 64.2% (382 out of 595) of the seasonal wheezing attacks, and 36.8% (219 out of 595) of the symptoms of eczema. In addition, Singulair effectively reduced β2AG consumption (number per year) up to 67.6% (402 out of 595). The prevalence rate of the adverse reactions was 11% (32 out of 595). At the 4th and 12th week after treatment, significant differences were observed with regard to wheezing, coughing, coughing and wheezing after exercise (motility), and the tidal breathing lung function of the child patients compared with the base values ($p < 0.05$). Two hundred and ninety-five patients in the control group inhaled β2 AG as a receptor agonist either by oral administration or atomization only when a wheezing attack occurred; no intervention treatment was provided. The two groups showed no significant differences with regard to the number of wheezing attacks, annual mean of hospitalization days, annual mean of β2AG use, and lung function improvement ($p < 0.05$). In the three years of follow-up visits, 63 patients in the treatment group (10.59%) and 114 patients in the control group (38.64%) were diagnosed with asthma. No significant difference existed between the two groups ($p < 0.05$). Therefore, Singulair can effectively prevent recurrent wheezing attacks after RSV acute infection and reduce the incidence rate of infantile persistent asthma.

Researches suggest that cysteinyl leukotrienes (CysLTs) are an important medium of the viral infection-related wheezing attack. Therefore, a leukotriene regulator is assumed to have a preventive effect on infection-related wheezing. Bisgaard et al[10] investigated the preventive effect a CysLT receptor on chronic airway changes with recurrent and persistent symptoms caused by virus-induced wheezing. The study was a randomized, double-blind, placebo-controlled study. In this work, infants aged 3 months to 36 months who were hospitalized due to RSV capillary bronchitis were randomly divided into two groups. Montelukast sodium and a placebo treatment were successively administered for a total of 28 days; one treatment at a time. The results showed that the number of no-symptom days in the Montelukast group was significantly higher than that of the control group, indicating that CysLT as an antagonist can effectively prevent recurrent wheezing attacks after RSV acute infection. This finding is in accordance with our research result. Most infantile wheezing attacks are related to viral respiratory infection. Several infants experience only one mild wheezing attack continuously for 2 days to 3 days, which is usually brought about by acute bronchitis caused by the initial RSV infection. For other infants, especially for those with RSV infection accompanied by eczema and/or atopic dermatitis, the wheezing attacks occur immediately after a cold or a fever; these infants require hospitalization every month. Among the patients in this present study, those who experienced persistent wheezing developed into patients with infantile asthma[11,12]. The pathological basis of wheezing is the constriction of the airway caused by airway inflammation, myxedema, and thick sputum embolism. Leukotriene has an important role in capillary bronchial wheezing caused by expectoration difficulty among infants and the usual coexistence of coughing and wheezing. Therefore, leukotriene receptor as an antagonist can effectively reduce virus-induced wheezing attacks[13].

Compared with glucocorticoid and other common clinical wheezing-control drugs, Singulair is safer. In this study, 32 cases (5.38%) reported adverse reactions. These adverse effects were related to the following factors: 8 cases of anxiety and excitation (25.00%), 7 cases of aminotransferase increase (21.88%), 4 cases of headache (12.50%), 2 cases of diarrhea (6.25%), 2 cases of blushing (6.25%), 2 cases of abdominal pain (6.25%), 2 cases of erythra (6.25%), 2 cases of cough aggravation (6.25%), 2 cases of dizziness (6.25%) and 1 case of costalgia (3.12%). All these adverse reactions were mild and their symptoms immediately disappear after drug withdrawal, which agrees with literature[14].

Conclusions

This was an open clinical study, and a variety of treatment methods were conducted for comparative observation. A certain degree of deviation was revealed by the comparative analysis of the treatment and the control groups. A double-blind, randomized, controlled clinical work should be conducted in the future to compare the inhaled corticosteroid (ICS) treatments with the treatment observation group and obtain the clinical difference between hormonal therapy and non-hormonal therapy. Such study will have a more significant clinical applica-

tion value[4,15]. In the current report, the ICS-induced leukotriene level of sputum specimens of asthma patients receiving ICS treatment for asthma paracmasis is still significantly higher than that of the normal control group. This result suggests that the airway of asthma patients generate leukotriene, and leukotriene generation cannot be inhibited by ICS[16-18]. Clinics that protect the health of wheezing children need to investigate the changes in airway inflammation and the clinical sequelae of patients with virus-related wheezing, and prepare a safe and effective therapeutic regimen. Considering that a leukotriene regulator has a complementary and anti-inflammatory effect on ICS, and that the efficacy and safety of ICS treatments for infantile patients vary greatly[19,20], the treatment effects of the drugs other than ICS should be given focus.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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