Original Article

Effectiveness of polyvalent bacterial lysate for pediatric asthma control: a retrospective propensity score-matched cohort study

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Background: Previous studies showed bacterial lysates were effective for pediatric asthma. However, evidence of polyvalent bacterial lysate Qipian is lacking.

Methods: In this real-world retrospective cohort study, data of children with asthma, aged six months to 14 years old, attending to Jiangxi Provincial Children's Hospital from January 2021 to April 2022, prescribed routine treatment for asthma plus Qipian (Qipian group) or not (control group) were extracted. To minimize the impact of confounders on the outcomes, baseline characteristics were utilized to perform propensity score matching through a multivariable logistic regression model. After matching, asthma control, exacerbation, etc. were compared.

Results: Totally, 795 patients were included (337 in the Qipian group and 458 in the control group), with 278 pairs (556 patients) matched. Most baseline characteristics were well-balanced. The proportion of males were 68.3% and 70.1% in the two groups. The Qipian group favored better asthma control, with more "controlled" [3-month: 257 (92.4%) *vs.* 240 (86.3%); 6-month: 246 (88.5%) *vs.* 235 (84.5%)], and fewer "poorly/very poorly controlled" patients, compared with the control group (P=0.004 and 0.025, respectively). Patients in the Qipian group had lower risks of exacerbation. Incidence rate ratios (IRR) for any exacerbation were 0.56 [95% confidence interval (CI): 0.33 to 0.93] in the 3-month period and 0.83 (95% CI: 0.55 to 1.26) in the 6-month period. IRR for severe exacerbations were 0.09 (95% CI: 0.01 to 0.71) in the 3-month period and 0.20 (95% CI: 0.06 to 0.70) in the 6-month period (compared to the control group). Qipian significantly reduced the cumulative dose of short-acting beta-agonist (3-month: 3.22±10.37 *vs.* 8.08±16.71 mg; P<0.001; 6-month: 6.56±16.23 *vs.* 11.81±24.41 mg; P=0.002). There was no difference in incidences of respiratory tract infection or fever due to respiratory tract infection between the two groups. Numbers of antibacterial agent prescription were fewer in the Qipian group compared to the control group (3-month: 0.67±1.16 *vs.* 1.04±1.45; P=0.001; 6-month: 1.14±1.69 *vs.* 1.51±2.12; P=0.023).

Conclusions: According to this retrospective study, Qipian may be effective for improved pediatric asthma control. Safety profile and mechanisms of action of Qipian need further investigation. Further randomized controlled trials are warranted to confirm our results.

Keywords: Pediatric asthma; Qipian; polyvalent bacterial lysate; real-world retrospective cohort study; propensity score matching (PSM)

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Introduction

In 2019, according to the Global Burden of Disease, there were estimated to be 262 million people affected by asthma with 455,000 deaths (1). The prevalence of asthma varies among different countries. A nationwide survey in 2010 showed that the prevalence of pediatric asthma was 3.02% in China (2). In European countries, rates have ranged from 1.2% to 26.7% (3). Asthma was identified as one of the leading causes of hospitalization in children according to a national surveillance in the United States between 1980 and 2004 (4). Treatment of exacerbation, which is usually triggered by respiratory tract infection (RTI), accounts for approximately 80% of the direct costs of asthma (5).

Airway inflammation and hyper-responsiveness are features of asthma, and T helper 2 (Th2) inflammation plays an important role in asthma (5-7). Inhaled corticosteroids (ICS) and bronchodilators have been recommended as the preferred treatment (8). In addition to routine treatment, use of bacterial lysates can improve symptom control and reduce exacerbation of asthma and is relatively safe without reports of associated serious adverse events (9-11). The efficacy of additional bacterial lysates in RTI prevention has also been confirmed (12). It is speculated the mechanism of action of bacterial lysates is regulating immune response by shifting Th2 to Th1 activity (9-12).

Staphylococcus and Neisseria tablet (Qipian; Qilu Pharmaceutical Co., Ltd., Jinan, China) is a polyvalent bacterial lysate of *Staphylococcus epidermidis*, *Moraxella (Neisseria) catarrhalis*, and *Bacillus subtilis*. Several studies have indicated that Qipian add-on treatment can prevent recurrent RTI in children (13,14). For pediatric asthma, one study has investigated the efficacy of Qipian add-on treatment *vs.* routine treatment on children with recurrent RTI complicated with asthma (15). Another compared Qipian plus montelukast add-on treatment *vs.* routine treatment for pediatric asthma (16). There was no study comparing Qipian add-on *vs.* routine treatment on children with asthma.

To evaluate the effectiveness of Qipian add-on treatment for pediatric asthma control, we conducted this retrospective propensity score (PS)-matched cohort study. We present the following article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-489/rc).

Methods

Study design

This was a retrospective PS-matched cohort study. The data of children with asthma attending to Jiangxi Provincial Children's Hospital (Nanchang, China) from January 2021 to April 2022 were extracted from the health information system. Patients were divided into the Qipian group and the control group according to whether they had been administered with Qipian or not for asthma. Baseline characteristics were used to perform propensity score matching (PSM) to minimize the impact of confounders on the outcomes. Effectiveness of Qipian added to routine treatment was compared with routine treatment alone after matching. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Ethics Committee of Jiangxi Provincial Children's Hospital (Approval No. JXSETYY-YXKY-20220119). Informed consent was waived due to the retrospective nature of the study.

Eligibility criteria

The inclusion criteria were: (I) age six months to 14 years old; (II) diagnosed with asthma [according to International Classification of Diseases (ICD)-10 code in the health information system]; (III) prescribed routine treatment for asthma [e.g., ICS, long-acting beta-agonist (LABA), leukotriene receptor antagonist (LTRA), or combination inhaler] plus Qipian (Qipian group) or not (control group); (IV) complete baseline data; and (V) ≥6 months follow-up, defined as the time from initiation of routine asthma treatment plus Qipian (Qipian group) or not (control group) to last encounter between January 2021 and April 2022.

Patients were excluded if they had participated any interventional study, had other severe respiratory diseases (e.g., tuberculosis), or other diseases requiring systemic corticosteroids (e.g., rheumatic conditions).

Baseline characteristics and outcomes

Baseline characteristics included age (<2, 2–5, 6–14 years old), sex, medical insurance, concurrent RTI, allergic rhinitis, or not, prescription of ICS, LABA, LTRA, and combination inhaler.

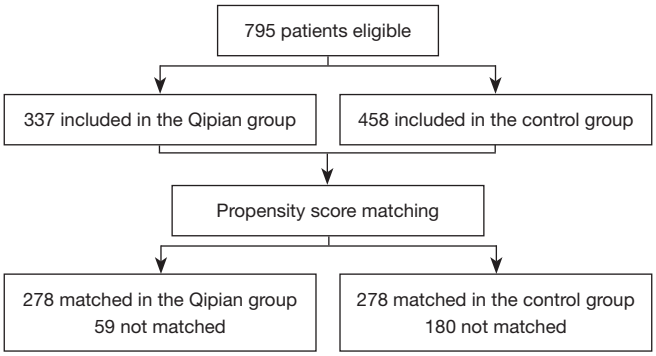

Figure 1 Trial flow chart.

The outcomes of interest included asthma control, numbers of times of any exacerbation and severe exacerbation, cumulative dose requirement of short-acting beta-agonist (SABA), and numbers of times of RTI, fever due to RTI, and antibacterial agent prescription for RTI in the 3- or 6-month period. Asthma control was divided into four categories according to the Pharmacoepidemiologic Pediatric Asthma Control Index (PPACI) (17): (I) controlled: mean number of SABA doses <4 per week, and no oral corticosteroid (OCS) prescription, emergency department (ED) visit, or hospitalization for asthma; (II) partly controlled: mean number of SABA doses ≥4 and <7 per week, and no OCS prescription, ED visit, or hospitalization for asthma; (III) poorly controlled: mean number of SABA doses ≥7 per week, OCS prescription, or ED visit, but no hospitalization for asthma; and (IV) very poorly controlled: any hospitalization for asthma, irrespective of number of SABA doses, OCS prescription, and ED visit. Any exacerbation was defined as ED visit, need for systemic corticosteroid, or hospitalization for asthma. Severe exacerbation was defined as hospitalization for asthma.

Statistical analysis

To minimize the impact of confounders on the outcomes, patients in the two groups were 1:1 PS-matched. The PS was calculated using multivariable logistic regression model with independent variables of all baseline characteristics as described above. Matching was performed with the nearest-neighbor methods within a caliper width of 0.02. The balances between the two groups before and after PSM were assessed based on standardized differences. A standardized difference <0.1 was considered well-balanced between the two groups (18).

After PSM, asthma control was compared using Wilcoxon signed-rank test between the two groups. For any exacerbation and severe exacerbation, simple negative binomial regression was used. Incidence rate ratio (IRR) and 95% confidence intervals (CI) were also calculated. The other outcomes were compared using paired-t test or Wilcoxon signed-rank test.

All statistical analyses were performed with the software SPSS 25.0 (IBM Corp., Armonk, NY, USA). A two-sided P<0.05 was considered statistically significant. Continuous data were presented as mean ± standard deviation. Categorical data were presented as number (percentage).

Results

Patients

A total of 795 patients were included (337 in the Qipian group and 458 in the control group). Before PSM, the Qipian group had more concurrent RTI. Prescriptions of routine treatment were also different between the two groups. Fewer patients received ICS and LABA, and more were administered LTRA in the Qipian group.

After PSM, there were 556 patients (n=278 each; *Figure 1*). The baseline characteristics were well-balanced, except undetermined medical insurance (Qipian: 1.4% *vs.* control: 0.4%) and ICS prescription (Qipian: 55.4% *vs.* control: 62.2%). Most patients were male (Qipian: 68.3% *vs.* control: 70.1%) and had concurrent RTI (Qipian: 64.0% *vs.* control: 65.8%). Nearly 25% had allergic rhinitis in the entire matched cohort. The prescription rates of LABA, LTRA, and combination inhalers were approximately 55%, 73%, and 6%, respectively (*Table 1*).

Table 1 Baseline characteristics before and after PSM

Characteristics	Before PSM, n (%)			After PSM, n (%)		
	Qipian (n=337)	Control (n=458)	StdDiff	Qipian (n=278)	Control (n=278)	StdDiff
Age, years						
<2	28 (8.3)	43 (9.4)	–0.04	27 (9.7)	28 (10.1)	–0.01
2–5	241 (71.5)	334 (72.9)	–0.03	195 (70.1)	188 (67.6)	0.05
6–14	68 (20.2)	81 (17.7)	0.06	56 (20.1)	62 (22.3)	–0.05
Sex						
Male	229 (68.0)	324 (70.7)	–0.06	190 (68.3)	195 (70.1)	–0.04
Female	108 (32.0)	134 (29.3)	0.06	88 (31.7)	83 (29.9)	0.04
Medical insurance						
Yes	26 (7.7)	48 (10.5)	–0.10	24 (8.6)	28 (10.1)	–0.05
No	307 (91.1)	407 (88.9)	0.07	250 (89.9)	249 (89.6)	0.01
Unknown	4 (1.2)	3 (0.7)	0.05	4 (1.4)	1 (0.4)	0.11
Concurrent RTI	232 (68.8)	284 (62.0)	0.14	178 (64.0)	183 (65.8)	–0.04
Concurrent AR	87 (25.8)	127 (27.7)	–0.04	76 (27.3)	69 (24.8)	0.06
Prescription of						
ICS	162 (48.1)	284 (62.0)	–0.28	154 (55.4)	173 (62.2)	–0.14
LABA	157 (46.6)	287 (62.7)	–0.33	157 (56.5)	150 (54.0)	0.05
LTRA	263 (78.0)	269 (58.7)	0.42	204 (73.4)	202 (72.7)	0.02
Combination inhaler	17 (5.0)	25 (5.5)	–0.02	16 (5.8)	19 (6.8)	–0.04

Data are presented as number (%) except for StdDiff. PSM, propensity score matching; StdDiff, standardized difference; RTI, respiratory tract infection; AR, allergic rhinitis; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LTRA, leukotriene receptor antagonist.

Outcomes

For asthma control, Qipian add-on treatment showed better results than routine treatment in the 3- and 6-month periods. The results in the 3-month period were "controlled": 257 (92.4%) versus 240 (86.3%); "partly controlled": two (0.7%, each); "poorly controlled": 18 (6.5%) versus 25 (9.0%); and "very poorly controlled": one (0.4%) versus 11 (4.0%; P=0.004). The results in the 6-month period were "controlled": 246 (88.5%) versus 235 (84.5%); "partly controlled": 0, each; "poorly controlled": 29 (10.4%, each); and "very poorly controlled": three (1.1%) versus 14 (5.0%; P=0.025; *Table 2*).

Patients in the Qipian group experienced fewer times of any exacerbation and severe exacerbation. The risks of exacerbation were significantly lower for Qipian add-on treatment, except for any exacerbation in the 6-month period. The IRR for any exacerbation were 0.56 (95% CI: 0.33 to 0.93; P=0.026) in the 3-month period and 0.83 (95% CI: 0.55 to 1.26; P=0.374) in the 6-month period. The IRR for severe exacerbation were 0.09 (95% CI: 0.01 to 0.71; P=0.022) in the 3-month period and 0.20 (95% CI: 0.06 to 0.70; P=0.012; *Table 2*) in the 6-month period.

Qipian significantly reduced the cumulative dose requirement of SABA (3-month period: 3.22±10.37 *vs.* 8.08±16.71 mg; P<0.001; 6-month period: 6.56±16.23 *vs.* 11.81±24.41 mg; P=0.002). There was no difference in the incidence of RTI or fever due to RTI between the two groups. In the 3- and 6-month periods, the number of antibacterial agent prescriptions were fewer in the Qipian group than the control group (3-month period: 0.67±1.16 *vs.* 1.04±1.45; P=0.001; 6-month period: 1.14±1.69 *vs.* 1.51±2.12; P=0.023; *Table 2*).

Table 2 Outcomes after propensity score matching in the 3- and 6-month periods

Outcomes	Qipian (n=278)	Control (n=278)	P value
In the 3-month period			
Asthma control			
Controlled	257 (92.4)	240 (86.3)	0.004
Partly controlled	2 (0.7)	2 (0.7)	
Poorly controlled	18 (6.5)	25 (9.0)	
Very poorly controlled	1 (0.4)	11 (4.0)	
Times of any exacerbation	0.09±0.35	0.16±0.46	
IRR (95% CI)	0.56 (0.33 to 0.93)		0.026
Times of severe exacerbation	0.00±0.06	0.04±0.20	
IRR (95% CI)	0.09 (0.01 to 0.71)		0.022
Cumulative SABA dose, mg	3.22±10.37	8.08±16.71	<0.001
Times of RTI	1.31±1.66	1.40±1.77	0.623
Times of fever due to RTI	0.13±0.44	0.18±0.55	0.412
Times of antibacterial agent prescription for RTI	0.67±1.16	1.04±1.45	0.001
In the 6-month period			
Asthma control			
Controlled	246 (88.5)	235 (84.5)	0.025
Partly controlled	0	0	
Poorly controlled	29 (10.4)	29 (10.4)	
Very poorly controlled	3 (1.1)	14 (5.0)	
Times of any exacerbation	0.17±0.54	0.21±0.56	
IRR (95% CI)	0.83 (0.55 to 1.26)		0.374
Times of severe exacerbation	0.01±0.10	0.05±0.24	
IRR (95% CI)	0.20 (0.06 to 0.70)		0.012
Cumulative SABA dose, mg	6.56±16.23	11.81±24.41	0.002
Times of RTI	2.41±2.78	2.31±3.00	0.389
Times of fever due to RTI	0.23±0.63	0.30±0.76	0.269
Times of antibacterial agent prescription for RTI	1.14±1.69	1.51±2.12	0.023

Data are presented as number (%) or mean ± standard deviation unless otherwise specified. Data were analyzed using Wilcoxon signed-rank test, except that simple negative binomial regression was used for any exacerbation and severe exacerbation. IRR, incidence rate ratio; CI, confidence interval; SABA, short-acting beta-agonist; RTI, respiratory tract infection.

Discussion

In the present study, there was a higher proportion of unmatched patients with concurrent RTI in the Qipian group, indicating that physicians tended to prescribe Qipian for children with RTI in the real-world setting. After PSM for control of confounders, effectiveness of Qipian add-on treatment and routine treatment for pediatric asthma were compared. The results showed that Qipian may improve asthma control, reduce exacerbation risk, cumulative SABA dose, and number of antibacterial agent prescriptions.

The Th2 type airway inflammation plays a central role in asthma (5). Previous studies have revealed that bacterial lysates regulate immune response by shifting Th2 to Th1 (i.e., increasing Th1 cells and decreasing Th2 cells) (11). Additionally, bacterial lysates can promote anti-inflammatory cytokine [interleukin (IL)-10] and Th1-specific cytokines interferon gamma, IL-2, and IL-12 secretion, as well as reduce Th2-specific cytokines IL-4 and IL-5 (9-11). A RTI event is the major cause of asthma exacerbation. Bacterial lysates may also lower the RTI risk through increasing secretory IgA, serum IgA, IgG, and IgM (12).

In the present study, PPACI developed by Després *et al.* (17) was used to assess asthma control. The PPACI categorized asthma control according to number of SABA dose, OCS prescription, ED visit, and hospitalization. The results showed that there were significantly more "controlled", and fewer "poorly/very poorly controlled" patients in the Qipian group. Qipian administration also reduced risks of any and severe exacerbation, and cumulative SABA dose. These results suggested that Qipian add-on may be an effective treatment and an ideal treatment option for pediatric asthma. The add-on treatment significantly decreased antibacterial agent prescription, indicating that Qipian may have a prophylactic or symptom-relief effect against bacterial RTI. Generally, these results from the present study were similar to those of studies of other bacterial lysates (9-11).

This study has some limitations. First, even though PSM was used, there were several minor unbalanced baseline characteristics. Some bias was inevitable because of the retrospective design. Secondly, there was a lack of data in lung function, toxicity, and tolerability of Qipian in the present study. Lastly, immunocyte, cytokine, and immunoglobulin levels were not measured. The effect of Qipian on immunity could not be analyzed. Thus, the mechanisms of action of Qipian for asthma need to be further investigated.

In conclusion, Qipian add-on treatment may be effective for improved asthma control. Qipian can be considered as an option for add-on therapy in pediatric asthma. Safety profile and mechanisms of action of Qipian need further investigation. Randomized controlled trials are also warranted to confirm the efficacy.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-22-489/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-22-489/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-22-489/coif). VS serves as an unpaid editorial board member of *Translational Pediatrics* from March 2022 to February 2024. LL received the funding of Science and Technology Program of Jiangxi Provincial Health Commission (No. SKJP220210802). MDN serves as the advisory member for Eurosets Srl. Medolla Modena Italy. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Ethics Committee of Jiangxi Provincial Children's Hospital (Approval No. JXSETYY-YXKY-20220119). Informed consent was waived due to the retrospective nature of the study.

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