Montelukast for Postinfectious Cough: A Systematic Review of Randomized Controlled Trials

S Dong[1], Y Zhong[2], W Lu[3], H Jaing[1], B Mao[1]

ABSTRACT

Objectives: *To systematically assess the efficacy and safety of montelukast for postinfectious cough (PIC) and to propose a recommendation via a systematic review of all available randomized controlled trials (RCTs).*

Methods: *Electronic databases and relevant journals were searched for RCTs from inception to July 2014. In addition, some unpublished literature was also searched. All studies included in the systematic review met the same inclusion criteria. Methodological quality and evidence quality were examined according to Cochrane handbook. The data were extracted and trial quality was assessed independently by two reviewers.*

Results: *Fourteen RCTs involving 1372 patients were included in our review. The methodological quality of the included trials was poor because one or more biases were observed in these studies. The quality of evidence was low to moderate levels. All trials reported better effect favouring montelukast treatment. Findings suggested that compared with other Western medication and Chinese medicine, montelukast showed significant effects in shortening cough relief time, increasing the clinic obvious effective rate, decreasing coughing frequency and severity, and improving quality of life. Adverse events were mentioned in six studies, but no serious adverse effects were reported in any of them.*

Conclusions: *Montelukast demonstrated potential positive efficacy and safety for PIC; however, we could not come to a firm conclusion on the efficacy and safety of montelukast for PIC. More high quality randomized controlled trials are required to confirm the efficacy and safety of montelukast for PIC.*

Keywords: Montelukast, postinfectious cough, systematic review

El montelukast para la tos postinfecciosa: una revisión sistemática de ensayos controlados aleatorios

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RESUMEN

Objetivos: *Evaluar sistemáticamente la eficacia y seguridad del montelukast para la tos postinfecciosa (TPI) y proponer una recomendación a través de una revisión sistemática de todos los ensayos controlados aleatorizaron (ECA) disponibles.*

Métodos: *Se realizó una extensa búsqueda de EAC en datos electrónicas y revistas pertinentes desde los inicios hasta julio de 2014. Además, la búsqueda se extendió también a fuentes de literatura inédita. Todos los estudios incluidos en la revisión sistemática reunieron los mismos criterios de inclusión. La calidad metodológica y la calidad de la evidencia fueron examinadas según el Manual Cochrane. Se extrajeron los datos y la calidad de los ensayos se evaluó de forma independiente por dos revisores.*

Resultados: *Catorce ensayos ECA que comprendían 1372 pacientes se incluyeron en esta revisión.*

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La calidad metodológica de los ensayos incluidos fue pobre se observaron una o más predisposiciones en estos estudios. La calidad de las pruebas tuvo niveles de bajos a moderados. Todos los ensayos reportaron mejores efectos a favor del tratamiento con montelukast. Los resultados sugirieron que, en comparación con otros medicamentos occidentales y la medicina china, el montelukast mostró efectos significativos en cuando a acortar el tiempo de alivio de la tos, aumentando la tasa de efectividad clínica de forma obvia, disminuyendo la frecuencia y severidad de la tos, y mejorando la calidad de vida. Eventos adversos fueron mencionados en seis estudios, pero no se reportaron efectos adversos graves en ninguno de ellos.

Conclusiones: *El montelukast demostró poseer potencial eficacia positiva y seguridad para la TPI. Sin embargo, no pudimos llegar a una conclusión firme sobre la eficacia y seguridad del montelu-kast para TPI. Se requieren ensayos controlados aleatorios de más alta calidad para confirmar la eficacia y seguridad del montelukast frente a la TPI.*

Palabras claves: montelukast, tos postinfecciosa, revisión sistemática

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INTRODUCTION

Patients who complained of a persistent cough lasting more than three weeks but not beyond eight weeks after experiencing acute symptoms of an upper respiratory tract infection (URTI), with normal chest radiograph findings, were considered to have a postinfectious cough [PIC] (1). Postinfectious cough, a self-limited disease, is a common and important respiratory symptom that can produce significant complications for patients and a diagnostic and therapeutic challenge for physicians (2). In retrospective studies, the frequency has ranged from 11% to 25% in non-PIC patients with a history of URTI (3–6), which increased to 25 to 50% in PIC (1, 7). The pathogenesis of PIC may be multifactorial (8, 9). The extensive disruption of epithelial integrity and widespread airway inflammation of the upper and/or lower airways with or without transient airway hyper-responsiveness and other possible potential pathogenesis have been regarded as the reasons (10–13).

Although PIC is a self-limited disease, persistent cough and financial burden were suffered among patients. For PIC patients, the optimal treatment is not known. Therapy with antibiotics has no role except bacterial sinusitis or B pertussis infection, as the cause is not bacterial infection. The use of inhaled ipratropium or glucocorticoids may be helpful, but this might do more harm than good.

Montelukast, an orally active cystenil leukotriene type-1 receptor antagonist of leukotriene D4 with high selectivity, has been commonly used in upper and lower respiratory tract diseases. The Allergic Rhinitis and its Impact on Asthma (ARIA) 2010 revision proposed the use of oral leukotriene receptor antagonist in seasonal allergic rhinitis (AR) in both adult and paediatric patients (14). David *et al* recommended leukotriene receptor antagonists as the first-line or add-on asthma controller therapy (15). Montelukast was thought to be effective for PIC in clinical practice, and has been commonly used in PIC so far. Increasing efforts have been directed toward seeking relevant scientific evidence, and an increasing number of clinical trials on montelukast in the management of PIC have been performed, but the findings have not yet been systematically summarized. So this systematic review was conducted to provide more evidence-based information for clinical practice.

METHODS

Research protocol: All methods were performed according to a predefined protocol, which consisted of the search databases, search strategies, inclusion criteria and exclusion criteria. The search strategies, following the PICO approach, included study design, patient characteristics, intervention, comparison and outcome.

Search strategy: The literature was searched in the Cochrane Library, PubMed, EMbase, lCNKI, VIP, and Wanfang from their inception to July 2014. Ongoing registered clinical trials were searched in the website of Chinese clinical trial registry (http://www.chictr.org/) and international clinical trial registry by US National Institutes of Health (http://clinicaltrials.gov/). The relevant conference and unpublished literature from colleagues and from the author's organization was also manually searched. The following search terms were used individually or combined: "chronic persistent cough", "subacute cough", postinfectious cough, "post-cold cough", "cough post influenza", "whooping cough", "montelukast", "randomized controlled trial". The search terms used were modified to adapt to different databases with a highly sensitive search strategy for the retrieval of trials developed by The Cochrane Collaboration.

Inclusion criteria: All relevant randomized controlled trials (RCTs) or quasi-randomized controlled trials evaluating montelukast for PIC published before July 31, 2013, were eligible for this review, irrespective of blinding without language limitation. Postinfectious cough was defined as persistent cough lasting more than > three weeks but no more than > eight weeks after experiencing the acute symptoms of URTI with normal chest radiograph findings, without any consideration of the causative agents they were infected with before persistent coughing, regardless of age, gender, ethnicity and pro-

fession. Studies involving a comparison between montelukast alone or in combination with other Western medications and placebo, no treatment, Chinese medicine or the same Western medications as controls were included.

Primary outcomes measures: (a) cough symptom score, which consists of day-time score and night-time score, ranging from 0–3, ranking as 4 levels for cough severity (16); (b) visual analogue scale which uses linear scoring method, ranging from 0–10, ranking as 11 levels for cough severity.

Secondary outcome measures: (a) cough relief time (onset time of drug), which was defined as both the day-time cough score and the night-time cough score ≤ 1 or decreasing one level, and lasted for 48 hours; (b) cough disappearance time, which was delimited as both of day-time cough score and night-time cough score = 0, and lasted for 48 hours; (c) global effectiveness rate (defined as a three-class measurement including 'cure', 'effective' and 'ineffective' according to the degree of overall symptom improvement); (d) adverse events.

Selection of studies: The literature was searched, selected by two review authors (SJ Dong, WT Lu) independently by scanning the titles, abstract sections, and keywords of each study retrieved and the full-text articles if necessary. Multiple publications reported by the same groups of participants were excluded. Disagreement was resolved by discussion and consensus reached through B Mao. Agreement between review authors for inclusion of studies was recorded.

Data extraction and management: To avoid selection bias in the data extraction process, the review authors (B Mao and SJ Dong) independently extracted data using a predefined data extraction form and compared the results. The extracted data cross-checking for accuracy included authors and title of study, year of publication, study design, sample size, methodological information, location of hospital, source of patients, gender, duration, interventions, outcomes, adverse effects, similarity at baseline and intention to treat for each study. Any missing information was supplemented by correspondence with the original authors whenever possible. All review authors participated in resolving discrepancies until a consensus was reached with the third arbitrator (B Mao).

Quality assessment: The quality of included trials were assessed by using the 'risk of bias' assessment tool according to the 'Cochrane Handbook of Systematic Reviews of Interventions' (Chapter 8.5) to address the following six criteria: sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting and other bias. The quality of all the included trials was categorized as low/unclear/high risk of bias. We also used the GRADE approach, being recommended by the Cochrane Collaboration, to assess the quality of the evidence for each included study. According to the GRADE Working Group grades of evidence, we graded the quality of evidence in this review as very low, low, moderate, or high. Risk of bias was independently assessed by two review authors (SJ Dong, YQ Zhong). Disagreements were also resolved by consensus.

Data analysis: Data were summarized with relative risk (RR) with 95% confidence intervals (CI) for binary outcomes or mean difference (MD) with 95% CI for continuous outcomes. Revman 5.0 software was used for data analyses. If we had identified a sufficient number of randomized trials, we had planned to perform sensitivity analyses to explore the influence of trial quality on effect estimates. The quality components of methodology included adequacy of generation of allocation sequence, concealment of allocation, double blinding, and the use of intention-to-treat (yes or no).

RESULTS

Description of studies: A flow chart depicted the search process, study selection and exclusion reasons (Fig. 1). After

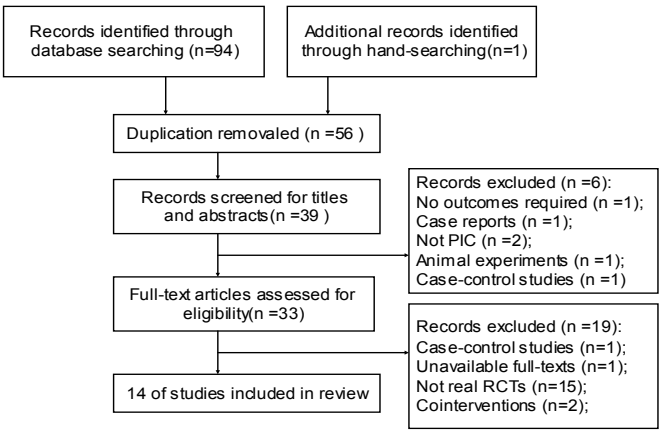

Fig. 1: Flow diagram showing the stages of the identification of studies for review.

primary searches from the seven databases, 95 articles were searched. After reading the titles and abstracts, a majority of them were excluded. Full text of 33 papers were retrieved, and finally a total of only 14 RCTs involving 1372 subjects met all the eligibility criteria. The main characteristics of the included trials are listed in Tables 1 and 2. All the RCTs were conducted in China and published in Chinese (19–32). A total of 1372 participants with PIC were involved, with the average number of 98 per trial, ranging from 47 to 236. All patients were confirmed diagnosed as PIC according to the diagnosis and treatment of coughing guidelines (33) or (ACCP) evidence-based clinical practice guidelines (1). Seven trials included in this review enrolled children (19, 23, 24, 27, 29, 30, 32) and the remaining studies were conducted exclusively in adults (20–22, 25, 26, 28, 31). Nine trials included in this review provided the detailed information on interventions (19, 21, 22–25, 29, 31, 32). Eight trials compared montelukast combined with other conventional Western medications *versus* conventional Western medications alone (19, 22, 23, 26, 27, 29, 30, 32). Two trials compared montelukast combined with other conventional Western medications *versus* combinations of conventional Western medication (20, 25). Two trials compared montelukast alone with the other conventional Western medications alone (21, 31). Two trials compared montelukast plus ketotifen with antibiotics (24, 28).

Table 1: Patient characteristics of the included studies

		Methods of random process	Interventions T/C	Duration (days)	Outcomes measures	Dropout T/C	Adverse events T/C
Zhang 2012 (19)	RCT	Random number table	T: Montelukast plus azithromycin C: Azithromycin	14	Cough symptom score	NS	No
Zhu, 2011 (20)	RCT	Computer random number	T: Montelukast plus erythromycin C: Ketotifen plus erythromycin	5	Cough symptom score	No	No
Zhang, 2012 (21)	RCT	Random number table	T: Montelukast C: Clarithromycin	5	Global effectiveness rate	No	
Deng, 2013 (22)	RCT	NS	T: Montelukast plus theophylline sustained-release capsules C: Pentoxyverine plus theophylline sustained-release capsules	7	Cough symptom score	1 patient was lost to follow-up, 5 cases did not complete regimen	
Li, 2013 (23)	RCT	Random number table	T: Montelukast plus antitussive and expectorant agent and antihistamine C:antitussive and expectorant agent and antihistamine	14	Global effectiveness rate	NS	NS
Li, 2012 (24)	RCT	NS	T: Montelukast plus ketotifen C: Antibiotics	5	Cough symptom score Global effectiveness rate	NS	T: dry mouth (4 cases), abdominal pain (1 cases), headache / dizzy (2 cases), nausea (1 cases), drowsiness (3 cases) and loss of appetite (2 cases) C: dry mouth (3 cases), abdominal pain (4 cases), headache / dizzy (2 cases), nausea (3 cases), drowsiness (1 case) and loss of appetite (4 cases)
Du, 2012 (25)	RCT	NS	T: Montelukast plus budesonide-solution inhaled therapy C: Ketotifen plus Budesonide-solution inhaled therapy	7	Cough symptom score Global effectiveness rate	No	
Han, 2011 (26)	RCT	NS	T: Montelukast plus dextromethorphan C: Dextromethorphan	10	Cough symptom score	No	T: headache (2 cases), abdominal pain (1 cases), and influenza like symptoms (1case) C: NS
Huang, 2012 (27)	RCT	NS	T: Montelukast plus antibechic fluid I: Montelukast, azithromycin/ cefaclor plus antibechic fluid C: azithromycin/cefaclor plus antibechic fluid	14*	Cough symptom score	NS	T: headache (2 cases), dry mouth (1 case) and constipation (1 case) C: headache (1 cases), nausea(2 cases) No
Wu, 2012 (28)	RCT	NS	T: Montelukast plus ketotifen I: Montelukast plus ketotifen, antibiotics C: Antibiotics	7	Cough symptom score	NS	NS
Luo, 2012 (29)	quasi-RCT	Registration serial number	T: Montelukast plus erythromycin and antitussive and expectorant agent C: Erythromycin and antitussive and expectorant agent	14	Global effectiveness rate	NS	NS
Liu, 2013 (30)	RCT	NS	T: Montelukast plus dextromethorphan and loratadine C: Dextromethorphan and Loratadine	14	VAS score	NS	NS
Wu, 2011 (31)	RCT	NS	T: Montelukast C: Compound codeine phosphate oral solution	7	Global effectiveness rate	NS	T: headache (1 case), drowsiness (1 case) C: dry mouth (1 case), drowsiness (1 case)
Huang, 2012 (32)	RCT	NS	T: Montelukast plus antibiotics C1: Antibiotics C2: Yupingfeng granule plus Antibiotics I: Montelukast,yupingfeng granule plus antibiotics	90	1.Global effectiveness rate; 2.cough relief time cough; 3.disappearance time; 4.level of IgA, IgE, IgG, CD4, CD8	NS	NS

T: trial group; C: control group; I: Integrated group; NS: not specified, RCT: random controlled trial; VAS: visual analogue

Table 2: Other detailed characteristics of the included studies

	Location of hospital	Source of patients	Sample size T/C	Gender M / F	Age (Mean ± SD or range, years)	Similarity at baseline	Intention to treat	GRADE
Zhang, 2012 (19)	Shandong China	Inpatients		T: 20/23 C: 21/22	T: 4.35 ± 1.25 C: 4.75 ± 1.20	Similar	No	
Zhu, 2011 (20)	Guangdong China	Outpatients		T&C: 32/57	T&C: 1.37 ± 12.59	Similar	No	Low
Zhang, 2012 (21)	Zhejiang China	Outpatients		T: 30/15 C: 25/19	T&C: 24–67	Similar	No	Low
Deng, 2013 (22)	Fujian China	Outpatients		T: 50/65 C: 52/63	T&C: > 18	Similar	No	Low
Li, 2013 (23)	Sichuan China	Outpatients		T: 30/26 C: 29/27	T&C: 1–5	Similar	No	Moderate
Li, 2012 (24)	Guangdong China	Outpatients		T: 30/33 C: 30/32	T: 7.02 ± 2.94 C: 7.15 ± 2.50	Similar	No	Low
Du, 2012 (25)	Yunnan China	Inpatients Outpatients		T&C: 23/37	T&C: 41.46 ± 10.52	Similar	No	Low
Han, 2011 (26)	Guangdong China	Outpatients		T: 16/14 C: 15/15	T: 37 ± 11 C: 35 ± 10	Similar	No	Low
Huang, 2012 (27)	Hunan China	Inpatients		T, I & C: 52/38	T, I & C: 2-12	Similar	No	Low
Wu, 2012 (28)	Zhejiang China	Outpatients	T: 38 I: 42 C: 30	T: 20/18 I: 22/20 C: 15/15	T: 29 ± 10 I: 28 ± 11 C: 29 ± 10	Similar	No	Low
Luo, 2012 (29)	Jiangxi China	Outpatients	T: 25 C: 25	T: 15/10 C: 14/11	T: 7.1 ± 1.9 C: 6.8 ± 2.3	Similar	No	Low
Liu, 2013 (30)	Sahngdong China	Outpatients	T: 50 C: 50	T: 24/26 C: 28/22	T&C: 8–14	Similar	No	Low
Wu, 2011 (31)	Shanghai China	Outpatients	T: 25 C: 22 T: 31	T: 10/15 C: 9/13	T: 15–65 C: 16–67	Similar	No	Low
Huang, 2012 (32)	Zhejiang China	Outpatients	C1: 30 C2: 28 I: 35	T, I & C: 65/59	T, I & C: 4.29 ± 1.48	Similar	No	Low

T: trial group; C: control group; I: Integrated group; NS: not specified

The total treatment duration ranged from three to 14 days except one trial (31). The reported outcome measures included cough symptom score, visual analogue scale, cough relief time, cough disappearance time, global effectiveness rate and adverse events. One trial reported withdrawals and dropouts explained by the following reasons: one patient was lost to follow-up and five patients could not complete the regimen (22). All of the 14 studies reported baseline homogeneity of demographic characteristics and showed detailed descriptive statistical data.

Methodological quality: All the included studies claimed "randomization", but only four studies clearly described the method of randomization [a random number table or computer random number] (19, 20, 22, 24). One study implemented a quasi-random method by allocating patients according to registration serial number, by which assignments could possibly be known and caused high selection bias (29). The remaining studies just mentioned "randomization", but did not disclose any information about sequence generation. Thus, the information of sequence generation of four studies was adequate at low risk of bias (19, 20, 22, 24), and nine studies were inadequate with uncertain risk of bias (21, 23, 25–28, 30–32). Only one study described allocation concealment by third-party controlled telephone allocation (22). The remaining studies reported no information of allocation concealment, and the domain was judged as "unclear" risk of selection bias in the studies due to lack of adequate information of allocation concealment for judgment. No trial described blinding procedures (the blinding of either participants or investigators after assignment to interventions), and the domain was judged as "unclear" risk of bias in all studies. Only one trial reported the information of withdrawals and dropouts and explained the reasons, supporting the balance between groups (22). Four studies indicated no missing data and expressed the consistency between the initial number of participants randomly allocated and the final number of participants included in results analysis (20, 21, 25, 26). The remaining studies did not mention dropout information, and the domain was judged as "unclear" risk of bias in the studies due to lack of adequate information for judgment. No trial described intention-to-treat analyses or the method of assessing compliance. No studies mentioned a previously published protocol. Thus, selective

outcome reporting was also at uncertain risk of bias in all studies. None of the studies described any pre-calculated sample size, and information was insufficient. Overall, the domain was also classified as "unclear" in all studies. Considering the lack of negative reports and the limited countries included in which studies were conducted, potential publication bias might not be excluded. Detailed information is shown in Table 3 and Fig 2.

Table 3: Assessment of risk of bias in the included studies

Study ID	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Free of Selective outcome reporting	Free of other sources of bias
Zhang , 2012 (19)	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Zhu, 2011 (20)	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Zhang, 2012 (21)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Deng, 2013 (22)	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Li, 2013 (23)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Li, 2012 (24)	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Du, 2012 (25)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Han, 2011(26)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Huang, 2012 (27)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Wu, 2012 (28)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Luo, 2012 (29)	High risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Liu, 2013 (30)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Wu, 2011 (31)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Huang, 2012 (32)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk

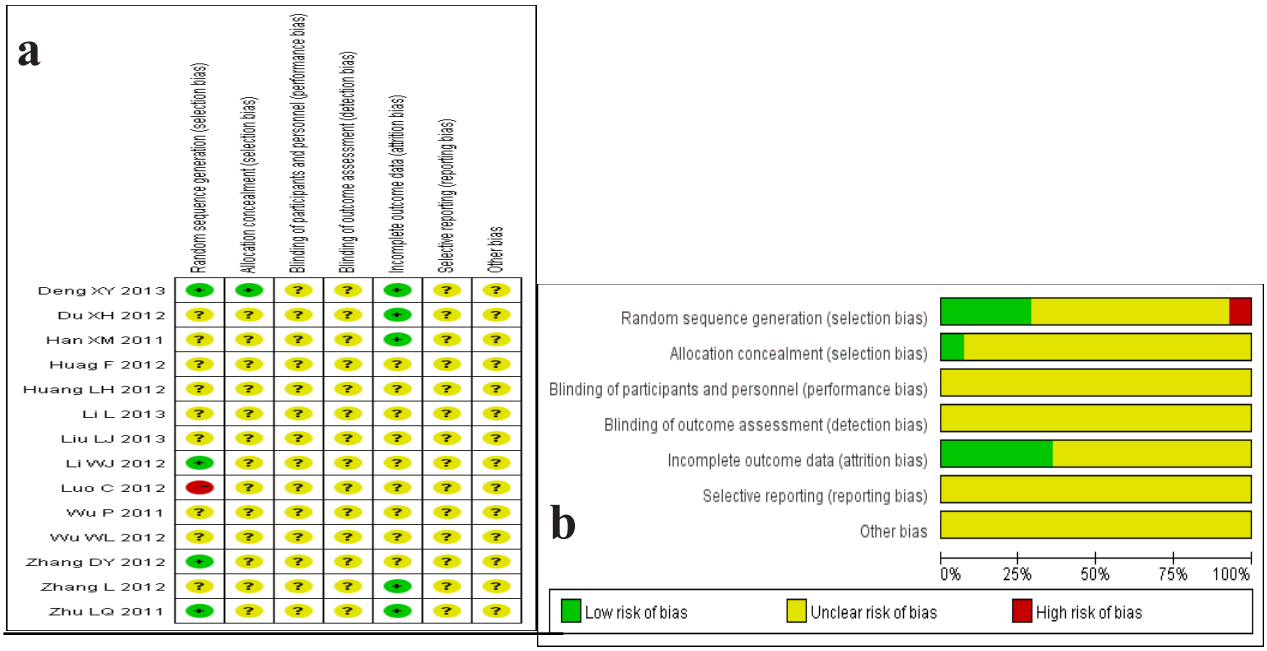

Fig 2: (a) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies (− : high risk of bias, +: low risk of bias, ?: unclear risk of bias); (b) Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Quality of evidence: The quality of evidence of each included study was evaluated by the "GRADEprofiler" of the Cochrane Collaboration Network, being recommended by the Cochrane Collaboration. According to the GRADE Working Group grades of evidence, we graded the quality of evidence in this review as very low, low, moderate, or high. In our review, the quality of evidence was graded as low to moderate. One study was classified as "moderate" and the remaining studies as "low". Detailed information is shown in Table 3.

Cough Symptom Score: For children, cough symptom score was reported in three studies (19, 24, 27). All of them showed better effect in favour of montelukast. Zhang and yao (19) found that montelukast combined with azithromycin therapy could improve the cough sign score compared with azithromycin alone. Li *et al* (24) showed that montelukast combined with ketotifen led to a greater reduction of night-time cough symptom scores compared with antibiotics. Huang *et al* (27), demonstrated that montelukast had a better effect, compared

to montelukast combined with antibiotics. As for adults, cough symptom score was reported in five studies (20, 22, 25, 26, 28). All of them showed better effect in favour of montelukast improving the cough sign score. Zhu *et al* (20) and Du *et al* (25) showed that montelukast gave a greater reduction on cough symptom scores compared with ketotifen. Li *et al* (24) showed that montelukast combined with ketotifen improved cough symptom scores compared with antibiotics. Deng *et al* (22) applied montelukast compared with pentoxyverine, and showed a similar result. Han (26) compared montelukast with dextromethorphan and concluded a better effect in montelukast group.

Visual analogue scoree: was reported in one study (29). Luo (29) compared montelukast plus erythromycin and an antitussive expectorant agent with erythromycin and an antitussive and expectorant agent, and found statistical significant difference favouring montelukast.

Global effectiveness rate: Global effectiveness rate was commonly used to evaluate efficacy in China. It was reported in 11 studies (20–29, 32). All of them showed statistical significant difference favouring montelukast, increasing total effective rate.

Cough relief time: Cough relief time was reported in one study (19). Zhang and Yao (19) found that montelukast sodium combined with azithromycin therapy could shorten improvement time, as compared to the control group ($p < 0.05$), indicating that montelukast could act as a rapid cough relief.

Cough disappearance time: Cough disappearance time was investigated in one study (32). Huang and Zhou (32) found better effect in the montelukast group on shortening cough disappearance time compared with the antibiotics group.

Adverse events were discussed in nine studies (19–22, 24–27, 31). Three studies claimed no adverse event was observed (19, 20, 27). Six studies reported that adverse events were mild (21, 22, 24–26, 31). The remaining studies did not provide any information on adverse events. But all of these adverse events gradually disappeared after proper medical treatment and had no effects on results estimation.

DISCUSSION

In this review, montelukast demonstrated a potential positive effect for PIC on cough symptom score, global effectiveness rate, cough relief time and cough disappearance time, compared with other symptomatic therapeutic medications. However, due to the lack of high quality trials and repeated tests, we could not make a definitive conclusion on the therapeutic effect of Montelukast for PIC. In addition, in the "Guideline: diagnosis and management of cough (version 2009)" issued by the Asthma Study Group, Committee of Respiratory Disease, Chinese Medical Association, it was revealed that there was a lack of evidence for clinical use and guidelines for montelukast in China.

The following reasons might contribute to the inconclusive results of montelukast for PIC. Firstly, most of the included trials were of poor methodology quality, which were in accordance with previous studies. Only 14 RCTs stated randomization procedure, however, four of them provided insufficient information to judge whether randomization was conducted properly (19, 20, 22, 24) and one study implemented a quasi-random method by allocating patients according to registration serial number causing high selection bias (29). Therefore, we could not exclude the possibility that some of these claimed RCTs are not real RCTs. Unfortunately, all RCTs did not mention blinding, but only one article claimed blinding to the outcome assessors and data analyser by the third-party, but the sample size was small (22). Therefore, we are not sure if they could provide enough power to detect the difference between groups. It is well known that methodologically poorly designed trials show larger differences between experimental and control groups than those conducted rigorously and as such the small improvements in outcomes should be regarded with caution. Secondly, as a result of the definition of PIC which appeared recently, differences in definition of the disease may bias our search results. Although a comprehensive search strategy was adopted, we still cannot guarantee that all eligible trials have been identified. Thirdly, there is a lack of information about quality control for studies, which is a quite common problem in Chinese clinical trials. Future trials should provide information about quality control, detailed regimen, and pre-calculated sample size. Fourthly, there is no placebo-controlled trial on evaluating the efficacy and safety of montelukast for PIC. Finally, there is a publication bias in this review. All of the included studies showed better effect favouring montelukast. We were also unable to use formal methods to determine if there was any publication bias as too few studies were available. The possibility that there are unpublished studies or other published studies that were not indexed in the electronic databases we searched cannot be excluded, because negative or no significant findings are less likely to be published.

Moreover, the mechanism of montelukast in the treatment of PIC is complex and little is known so far. However, in this review, it seems that compared with antitussive expectorant agents and antihistamine drugs, montelukast might have better potential effects on cough symptom score, which suggested that montelukast might not only act as a symptomatic therapeutic medication. More reseach about the mechanism of montelukast for PIC should be done in the future.

CONCLUSION

Montelukast may have positive effect for PIC, improving cough symptom score, increasing global effectiveness rate, shortening cough relief time and cough disappearance time with mild adverse reactions being identified. Since various limitations involving many aspects still existed, a confirmative conclusion was not taken. We hope more and newer evidence of high quality will arise to provide clinical evidence of montelukast for PIC to ensure evidence-based clinical practice.

AUTHORS' NOTE

All authors declare that they have no conflict of interests.

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