

The safety and efficacy of aspirin desensitization combined with long-term aspirin therapy in Aspirin-exacerbated respiratory disease

Running head: aspirin desensitization for AERD

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Abstract

Objectives: To assess the safety and efficacy of aspirin desensitization combined with long-term aspirin therapy in subjects with aspirin-exacerbated respiratory disease (AERD).

Methods: We searched the PUBMED, Ovid and Cochrane Library from inception to October 2018, and we imposed a restriction of English on language of publication. Only randomized controlled trials, parallel or cross-over, were included in which adult subjects with AERD were randomly assigned to receive aspirin desensitization and long-term aspirin therapy or placebo.

Results: A total of 869 citations were retrieved and 6 studies met the criteria for analysis. All studies indicated that either nasal symptoms, or asthma symptoms, or both improved significantly after aspirin desensitization treatment. And most studies indicated a decline of corticosteroid dosage, oral or inhaled. The four studies which documented nasal polyps did not demonstrate a change in nasal polyps with aspirin therapy compared to placebo. Dropout rates in all studies reviewed range from 5.8% to 55.7% and the most common adverse events were gastrointestinal symptoms.

Conclusions: Clearly, aspirin desensitization and treatment are beneficial for AERD patients, with a reduction of nasal symptoms, improvements in asthma control and decrease of daily corticosteroid use, without fatal adverse events. However, long-term side effects of aspirin desensitization and optimal dosage of aspirin merit further investigation.

Key words: AERD, Aspirin desensitization, Efficacy, Adverse events.

Resumen

Objetivos: Evaluar la seguridad y la eficacia de la desensibilización a la aspirina junto con la terapia a largo plazo con Aspirina en sujetos con enfermedad respiratoria exacerbada por Aspirina (AERD).

Métodos: Se realizaron búsquedas en PUBMED, Ovid y Cochrane Library desde el inicio hasta octubre de 2018, e impusimos una restricción del inglés en el idioma de publicación. Solo se incluyeron ensayos controlados aleatorios, paralelos o cruzados, en los cuales los sujetos adultos con AERD se asignaron al azar para recibir desensibilización a la Aspirina y terapia con Aspirina a largo plazo o placebo.

Resultados: Se recuperaron un total de 869 citas y 6 estudios cumplieron con los criterios de análisis. Todos los estudios indicaron que los síntomas nasales, los síntomas del asma o ambos mejoraron significativamente después del tratamiento de desensibilización con Aspirina. La mayoría de los estudios mostraron una disminución de la dosis de corticosteroides, orales o inhalados que necesitaron los pacientes. Los cuatro estudios que documentaron pólipos nasales no demostraron un cambio en los pólipos nasales con la terapia con Aspirina en comparación con el placebo. Las tasas de deserción en todos los estudios revisados varían entre el 5,8% y el 55,7% y los efectos adversos más comunes fueron los síntomas gastrointestinales.

Conclusiones: Claramente, la desensibilización y el tratamiento con Aspirina son beneficiosos para los pacientes con AERD, con una reducción de los síntomas nasales, mejoras en el control del asma y una disminución del uso diario de corticosteroides, sin eventos adversos fatales. Sin embargo, los efectos secundarios a largo plazo de la desensibilización a la Aspirina y la dosis óptima de la Aspirina merecen más investigación.

Palabras clave: Enfermedad respiratoria exacerbada por Aspirina; Asma; Aspirina.

Introduction

Aspirin-exacerbated respiratory disease (AERD) is an inflammatory disorder, which was also named “Samter’s Triad”, that is, nasal polyps, asthma, and sensitivity to aspirin.[1] Now AERD is a preferred term in the United States while other countries, such as some European areas and the Middle East, prefer NSAID-exacerbated respiratory disease (NERD). Either aspirin-exacerbated respiratory disease or NSAID-exacerbated respiratory disease suggests that COX inhibitor plays a critical role in the pathogenesis of this disease.

Till now, there are two mainstream opinions on the pathogenesis of AERD, and leukotriene plays a critical role. One is the disorder of arachidonic acid metabolism. Aspirin is a potent cyclooxygenase-1 (COX-1) inhibitor, like other non-selective nonsteroidal antiinflammatory drugs (NSAIDs), blocking one route for the metabolism of arachidonic acid, which reduces the synthesis of prostaglandins, including the production of prostaglandin E2 (PGE2). Another alternative pathway of 5-lipoxygenase (5-LO) still works and leukotriene levels are increased, and leukotriene E4 (LTE4) is one of these leukotrienes which is elevated to the same extent as others and is measured the most because of its stability. The other one is type 2 inflammatory responses.

Allergens, viral infections and various environmental factors are all capable of initiating epithelial injury. Injured epithelia release thymic stromal lymphopoietin (TSLP), interleukin-25 (IL-25) and interleukin-33 (IL-33), which have multiple effects on the early stage of type 2 inflammatory responses. [2] type 2 innate lymphoid cells (ILC 2), mast cells and eosinophilia involved produce masses of leukotrienes and in turn leukotrienes enhance these pathways. Of which LTE4 seems to play a dominant role.[3] A study reported that subjects with AERD had elevated basal LTE4 level compared to aspirin-tolerant asthma.[4] Platelets are also involved in the production of leukotrienes in patients with AERD. [5, 6]

AERD is acquired, appearing at any time and the common age of onset is about 30 years old. The incidence of AERD was higher in female.[7, 8]In addition, literature to date have reported no accurate data about the prevalence of this disease in the general population. Although prior statement indicates there are limited prevalence data, AERD is prevalent in some countries, while in China it occurs rarely. [9]

The clinical presentations of AERD vary markedly from absence of symptoms or minimal wheezing to severe respiratory compromise. Some patients report no respiratory symptoms for years, such as nasal congestion, postnasal drip, coughing and wheezing. The only history might be provided is a previous history of intolerance of aspirin or other NSAIDs drugs. Some other patients experience either rhinitis or asthma, or both, and the conditions are chronic and difficult-to-control with routine treatments whose effect is not lasting, which impairs the life quality of patients with AERD seriously.

Routine treatment options of AERD include corticosteroids, desensitization and surgical treatments. Compared with corticosteroids and surgery, desensitization provides long-lasting efficacy. Although numerous studies have highlighted the long-term clinical benefits about subjects with AERD undergoing aspirin desensitization, most have been criticized for the study type of non-experimental study, or lack of control groups of subjects without aspirin therapy. We therefore conducted a systemic review of randomized controlled trials (RCTs) focusing on the long-term efficacy and related adverse effects of aspirin desensitization in AERD.

Methods

Literature search

We conducted a computerized literature search using PUBMED, Ovid, Cochrane Library and Google Scholar. The search included articles published from inception to October 2018. The search criteria included MeSH terms, keywords and a combination of the two. MeSH terms included “Asthma, Aspirin-Induced”, keywords included “Aspirin-exacerbated respiratory disease”, “Aspirin desensitization”. Two authors performed the literature search independently and compared results. Our inclusion criteria were: (1) study subjects were entirely comprised of AERD patients or included a substantial percentage of AERD patients. (2) aspirin desensitization as the primary intervention. (3) RCTs. (4) studies conducted on human. (5) studies with restriction on English language. Exclusion criteria were: (1) studies reporting only biochemical markers. (2) unpublished studies. The reference lists were screened to identify additional eligible studies. The search flow diagram was showed in **figure 1**.

Quality assessment and data extraction

Two authors provided quality assessment and data extraction of these included articles respectively. The Cochrane collaboration’s tool for assessing risk of bias was used for its ability to reliably evaluate randomized controlled trials. The tool consisted of six items and we scored every item for one point when it was assessed as “low risk of bias”, zero point for “high risk” and “unclear risk” of bias, so six was the top points which meant the lowest risk of bias and the highest quality. The quality of studies was showed in **table 1**. Then, the following data were extracted from these studies: the name of the first author and the year of publication, number of participants in each group, participants’ gender and age, interventions, length of follow-up, outcomes. The general characteristics of the 6 studies included in this review were showed in **table 2**. If there were any disagreements in assessing the articles, we performed a discussion between reviewers to reach consensus.

Results

Our initial search obtained 306 articles (PUBMED=149, Ovid=153, Cochrane Library=4). After removing 14 duplicates, 292 articles were left and 285 were screened out by reviewing the titles and abstracts of the 292 papers. So, seven articles were reviewed for full-text and one article was excluded because it was a part of another trial and it reported biomarkers only. Ultimately, 6 articles left for the qualitative assessment.[10-15] The 6 articles comprised 5 randomized placebo-controlled trials[10-13, 15] and 1 randomized double-blind crossover study[14]. The year of publication of these included studies ranged from 1984 to 2017. There were two studies conducted in Scripps Clinic and The Scripps Research Institute,[12, 14] two studies were conducted in Iran, [10, 13] one in Poland[15] and one in Germany[11]. The length of follow-up ranged from 6 months to 36 months.

Of all studies, the diagnosis of AERD was based on the aspirin challenge test, four studies[11, 12, 14,

15] used oral challenge test and two studies [10, 13] used intranasal KETOROLAC and oral aspirin challenge test. Desensitization was carried out with maintenance aspirin dosages spanning from 100 mg daily to 625 mg four times daily.

(1) asthma control and rhinitis/nasal symptoms

All 6 RCTs reported significant clinical improvements in asthma control and rhinitis/nasal symptoms after at least 6-month follow-up when compared with placebo group. These improvements were expressed as decreases of score in questionnaires or self-reported symptoms, improvements of objective measurements and reductions of the dosage of corticosteroids for nasal insufflations, bronchial inhalation or systemic corticosteroids. 6 studies all reported decreases of symptoms of either upper airway alone, lower airway alone, or both. The first randomized double-blind cross-over trial of 25 subjects conducted by *Stevenson et al.* demonstrated significant improvement in upper airway symptoms, such as running nose, nasal congestion, postnasal discharge, sinus pain and sense of smell, rather than in lower airway symptoms, such as chest tightness, wheezing, coughing and shortness of breath. The authors found that 16 subjects experienced less severe asthma or rhinitis symptoms. Of which, 10 subjects experienced fewer asthma symptoms during the aspirin desensitization. In addition, significant differences between ASA group and placebo group were noted in the mean daily nasal symptom score ($p < 0.05$). [14]

The large study of 137 subjects by *Lee* found that the group of subjects who take a dosage of 325 mg bid experienced significant decrease in nasal/sinus symptoms ($p < 0.0001$) and asthma symptoms ($p < 0.001$), as well as improvement in sense of smell ($p < 0.0001$). Another group of subjects taking a dosage of 650 mg bid experienced similar improvements in nasal and asthma symptoms and sense of smell. [12]

The study with the longest follow-up period of 36 months, mainly focusing on upper airway symptoms, reported an obvious reduction in nasal airway obstruction, postnasal drip, coughing and sneezing in the aspirin group compared with the placebo group with a low-dose desensitization of 100 mg daily ($p < 0.0001$). [11]

Another three studies found that subjects in the aspirin group had better sino-nasal-related quality of life assessed by Sino-Nasal Outcome Test questionnaire, SNOT-20 or SNOT-22, and symptoms score assessing nasal symptoms, eye symptoms and bronchial symptoms like cough, difficulty in breath and wheezing compared to the placebo group. [10, 13, 15]

3 studies reported forced expiratory volume in one second (FEV1) as an outcome assessing asthma control, [10, 13, 15] 1 of which reported peak expiratory flow (PEF) and peak nasal inspiratory flow (PNIF) [15]. *Monika et al* found no statistical differences in FEV1 and PEF values throughout the 6-month aspirin desensitization, while PNIF values increased significantly in subjects with aspirin-induced asthma compared with baseline values ($p = 0.001$). [15] *Esmailzadeh et al* found that after 6 month of follow-up, participants in the aspirin group showed significantly higher FEV1 compared to the baseline (87.1 ± 1.7 vs. 79.1 ± 1.9 , $p = 0.001$) and to the placebo group (87.1 ± 1.7 vs. 80.1 ± 1.8 , $p = 0.015$). [10] In addition, the latest study conducted in Iran reported a similar result ($p = 0.032$). [13]

Among all 6 studies, only one study [11] reported inhaled corticosteroids (ICS) dosage or systemic corticosteroid dosage. *Stevenson et al* reported that 20 of 25 subjects received prednisone therapy, of which 14 subjects took the same or less dosage of prednisone after aspirin desensitization,

suggesting decreased severity of the disease.[14] *Lee et al* showed that daily systemic corticosteroid dosage decreased by 3-fold from 3.9 mg/d to 1.3 mg/d ($p < 0.0001$), and intranasal corticosteroid dosage decreased significantly as well ($p < 0.0005$), while inhaled corticosteroid dosage did not change statistically ($p < 0.37$) in subjects taking 325mg bid of aspirin after 1-year follow-up. The group of subjects taking 650 mg bid experienced similar decrease in systemic corticosteroid dosage from 4.0 mg/d to 1.1 mg/d ($p < 0.0001$).[12] A 2014 study showed a reduction of ICS with ASA therapy compared to placebo ($p = 0.03$).[15] In contrast, a 2015 study showed no difference in medication with ASA therapy.[10] In addition, *Negar Mortazavi et al* demonstrated a statistical difference ($p = 0.017$)[13] in medication score between the two groups, using the same way that *Esmailzadeh* had done.

(2) *polyp recurrence and the Lund–Mackay score*

Nasal endoscopic assessment was performed in 4 studies.[10, 11, 13, 15] *K. Fruth et al* classified the endoscopic outcomes of polyposis using a 0-3 polyp score and polyp recurrence was regarded as a score of one and more. After a 36-month follow-up, the results demonstrated no statistical difference between two groups—8 in 13 subjects (62%) showed nasal polyp relapse in the placebo group and 5 in 18 (28%) in the aspirin group. However, these data may provide a trend that aspirin desensitization might be helpful to reduce nasal polyp recurrence because the nasal polyposis score of aspirin group was lower ($p = 0.0702$).[11] To assess nasal polyp more objectively, another three studies used the Lund–Mackay score of the sinus CT scan and no significant change was noted among the subjects between the aspirin group and placebo group.

(3) *asthma attacks, adverse events and dropout*

Clinical efficacy is a critical component and should be taken into account when determining the optimal dosage of aspirin for desensitization therapy. But aspirin-related side effects are non-negligible. All but one studies[11] included in our review reported aspirin-related adverse effects. (see **table 3**) *Stevenson* was the first to conduct a RCT on 38 subjects with AERD, only 25 completed the trial and 13 dropped out because of adverse effects. Of these 13 dropouts, 8 were in the ASA group and 5 in the placebo group. There were 3 subjects taking ASA who experienced growing asthma symptoms and another 3 subjects experienced gastrointestinal pain and then stopped the therapy. [14]

Lee investigated the effect of aspirin desensitization with different maintenance dosages on 137 subjects. In the study 70 subjects were randomized to take 325mg bid and 67 subjects 650mg bid. The results showed that dyspepsia occurred in 9 subjects in the 325mg bid group and 3 in the other group (9/70 vs. 3/67, respectively). And 1 and 3 subjects in the two groups discontinued therapy because of asthma attacks, respectively.[12] Another RCT enrolled 70 subjects and was conducted with low-dose aspirin of 100mg daily. Only 31 subjects completed all the study and 39 subjects discontinued taking aspirin over the 3-year follow up. The dropout rate was up to 55.7% for various reasons, but no one dropped out for aspirin-related adverse effects.[11] Recently, another 3 RCTs have been published in which 4 of 20 (20%)[15], 1 of 34 (3%)[10] and 1 of 22 (5%)[13] subjects respectively dropped out because of adverse gastrointestinal effects like gastrointestinal bleeding and dyspepsia. And *Negar Mortazavi* reported that 14 out of 38 subjects experienced at least one episode of asthma attack. Of the 14 subjects, 9 were in the placebo group and 5 in the ASA group.

No statistical difference was observed in the rate of asthma attack between the two groups.[13] *Esmailzadeh* reported similar results throughout the study (RR=2; 95%CI, 0.79-5.06; p=0.137). [10].

Discussion

Summary of main results

This review identified 6 RCTs[10-15] assessing the effects of aspirin desensitization for AERD. These studies reported changes in upper and lower respiratory tract symptoms, daily ICS dosage, lung function, nasal polyp relapse and adverse effects after placebo and aspirin therapy. All studies indicated that either nasal symptoms, or asthma symptoms, or both improved significantly after aspirin desensitization treatment. One study indicated that PNIF values increased from baseline, another two studies indicated improvement of FEV1 compared to patients without intervention. Of the five studies reported steroid dose, four studies indicated a decline of corticosteroid dosage. Of the four studies assessing nasal polyp, no significant changes was noted between placebo and aspirin group. Of all studies, dropout rates range from 5.8% to 55.7%; the most common adverse events were gastrointestinal symptoms, such as abnormal pain, gastrointestinal bleeding and dyspepsia. Rare complications included aspirin-related bleeding, skin rash, ecchymosis, tinnitus and myalgias. In addition, only patients in the ASA group experienced adverse gastrointestinal effects and patients in the placebo group did not.

Agreements and disagreements with other studies

We searched as many medical databases as possible, after careful assessment, only six RCTs[10-15] were identified. However, we found several open studies which offer some more information on this topic. In 1990, an observational cohort study enrolled 66 subjects with aspirin therapy and 40 subjects without aspirin. During the average follow up of 3.8 years, subjects with aspirin desensitization had improved sense of smell and asthma control, and decreased steroid use. In the aspirin group, 30 subjects dropped out because of gastrointestinal intolerance.[16] In 2003, the same group visited 173 subjects by telephone survey and compared outcomes between the first year of aspirin desensitization and the prior year of aspirin treatment. 14% of subjects discontinued therapy because side effects, of which the most common was gastrointestinal tract symptoms.[17]

In 2013, *Comert* and colleagues conducted a trial to investigate the efficacy of 300 mg daily of aspirin in the treatment of subjects with AERD. 40 subjects were enrolled and were treated with aspirin 300 mg/day with median (IQR) duration of 31.5(10.5-48.5) months. It reported that annual rates of use of systemic corticosteroid and episodes of sinusitis was significantly lower at 1-year and 3-year follow-up. And symptoms of nasal congestion, postnasal drainage and sense of smell improved significantly. [18]

In 2016, another study in Poland enrolled 14 AERD subjects who were followed up for 3 months with aspirin 650mg/day and analyzed the changes in clinical symptoms and some blood and urine measurements. It reported that eight subjects completed the treatment and nasal symptoms decreased by 50%-60%, PNIF values had a significant increase of mean 48%, while only slight improvement in the asthma control was noted with unchanged FEV1. The levels of urinary cysteinyl LTs and LTE4 and prostaglandin D2 metabolite did not change after aspirin desensitization.[19]

In addition to these studies mentioned above, several other trials indicated that aspirin desensitization could significantly improve the prognosis of AERD, including sinus and bronchial symptoms, nasal polyp relapse lung function, and daily corticosteroids use.[20-22] [23, 24] It seems that these non-RCT trials had better results. A possible reason might be the difficulty of doing RCTs in AERD. Clearly, aspirin desensitization and treatment have benefited many AERD patients worldwide. Patients read about and their referring physicians know by experience the benefits of this treatment, following desensitization patients experience immediate relief. This would end the blinding if patients were then sent out on placebo, and they would not need to go far to find the “study drug”, that is aspirin. This also supports the effectiveness of aspirin therapy from another side.

Several questions need answers

Aspirin desensitization is an alternative treatment for AERD, which starts at a low dosage of aspirin and gradually increase the dosage of aspirin over a period of time, often in 3 days. And a 1-day desensitization procedure is also justified safely and effectively, which is common in the U.S.[25] [26] During desensitization therapy, the drug-induced symptoms become milder and shorter gradually and finally disappear. Then the final dosage is usually recommended to be a maintenance aspirin dosage given at home. But, the actual maintenance dosage of aspirin varies depending on the individual physician. As mentioned above, the maintenance dosage ranges from 100mg daily to 650mg twice daily. Whether a dose-response relationship of aspirin desensitization exists is unclear. Some evidence suggested that the daily aspirin dose correlated with clinical improvement but that was not confirmed in our analysis. [14] In 2007, the authors found that in terms of clinical improvement with 325 mg bid of aspirin or 650 mg bid, a fairly equivalent effect was found.[12] But, the populations of the two studies were small and the dropout rates were high, making it difficult to generalize the results and ensure the stability of these results. So, clinical trials with larger sample size are needed to discern whether a dose-response relationship existed in subjects with AERD taking aspirin desensitization treatment. Individualized desensitization treatment strategies are needed in the future.

In 2013, *Fruth* and colleagues conducted a study with a maintenance dose less than 300mg daily and it is the only study in our review that reported no aspirin-related adverse effects.[11] It is logical to speculate that 100mg aspirin daily may be an optimal dosage for desensitization with less adverse effects and equivalent benefits than higher dosage of aspirin. But the high dropout rate might be an obstacle in the pursuit of efficacy and safety profile of lower dosage of aspirin in desensitization. Actually, retrospective analysis on side effects like increased asthma symptoms and nasal congestion, it cannot be ruled out whether the subjects had a viral upper respiratory tract infection coincidentally at the beginning of the trial and they dropped out because of so-called “adverse effects”. What’s more, aspirin desensitization is a long-time therapy for years and subjects require relatively higher dosage of aspirin than other aspirin therapy, such as a primary prevention strategy of cardiovascular events[27], how safe is long-term use of aspirin for 5 years, 10 years or longer? What are the indicators to cease treatment with aspirin because of severe side events? All of those questions need to be resolved.

Conclusions and future directions

Clearly, aspirin desensitization and treatment are beneficial for AERD patients, with a reduction of nasal symptoms, improvements in asthma control and decrease of daily corticosteroid use. But, when applying to clinical practice, safety is considered more than efficacy. Hence, the long-term side effects of aspirin desensitization and indicators to discontinue therapy are necessary to investigate. Optimal dosage of aspirin tailored for individuals with minimal adverse effects and maximal benefits are worth exploring.

Dr. li has nothing to disclose.

Dr. luo has nothing to disclose.

Accepted Article

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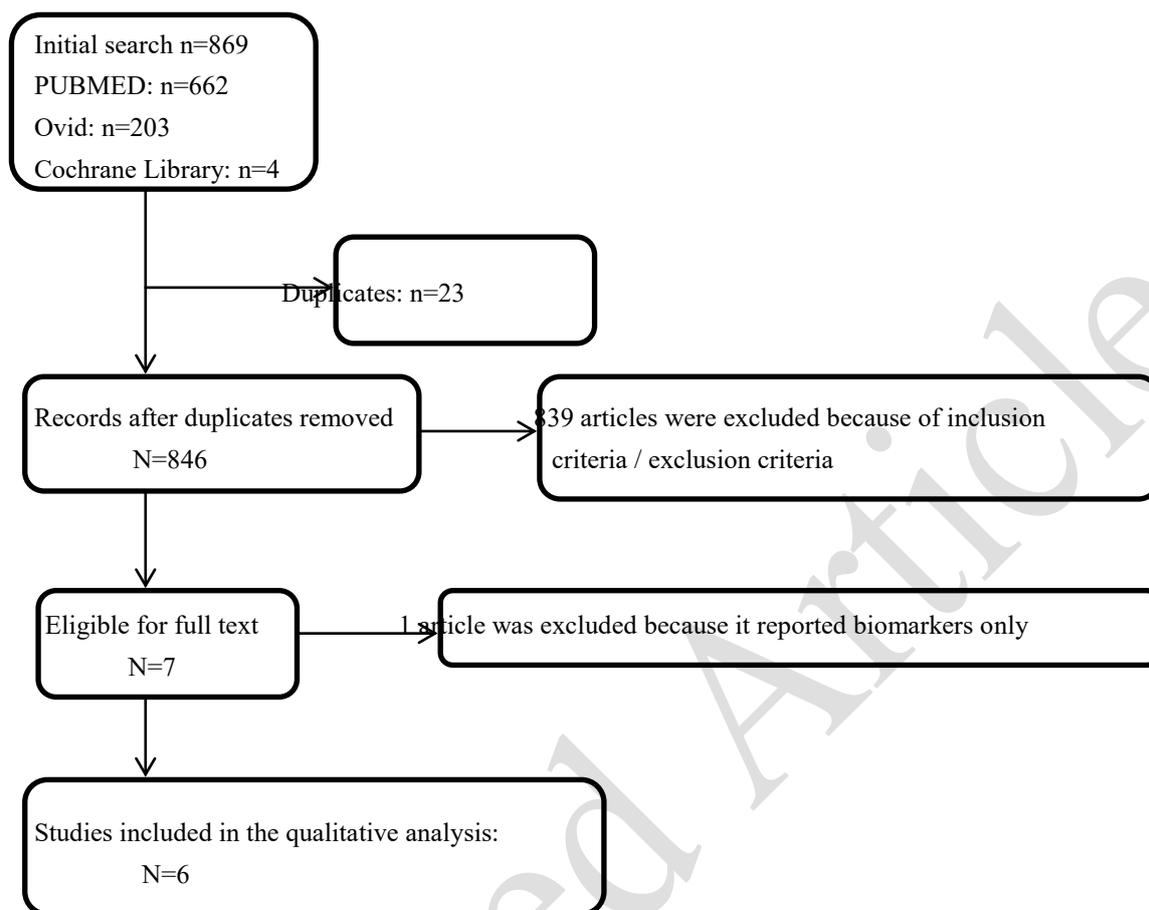


figure 1: the search flow diagram

study	A	B	C	D	E	F	total
1984	1	1	1	1	1	0	5
2007	1	0	1	1	1	0	4
2013	1	1	1	1	1	0	5
2014	1	1	1	1	1	0	5
2015	1	1	1	1	1	1	6
2017	1	1	1	1	1	1	6

Table 1 quality assessment

A: random sequence generation; B: allocation concealment; C: blinding of participants and personnel; D: incomplete outcome data; E: selective reporting; F: other sources of bias.

Author year	Intervention group			Placebo group			Follow-up	Outcomes
	n	M/F	age	n	M/F	age		
2017	22	NA	33±2	19	10/9	29±1	6months	① SNOT-22: p=0.001 ② Lund-MacKay score: p=0.229 ③ Symptom score: p=0.005 ④ Medication score: p=0.017 ⑤ FEV1: p=0.032
2015	18	5/13	31±4.3	16	6/10	27±5.5	6 months	① FEV1: p=0.015 ② SNOT-22: p=0.015 ③ Symptom score: p=0.014 ④ Medication score: p=0.138 ⑤ Lund-MacKay score: p=0.102
2014	12	3/9	48.5±18	8	2/6	39.5±27	6 months	① SNOT-20: p=0.04 ② ACQ score: p=0.037 ③ ICS dosage: p=0.03 ④ PNIF: p=0.001
2013	36	19/17	44.9±11.3	34	20/14	45.9±10.4	36months	① Overall nasal and paranasal complaints: p=0.0019 ② Quality of life impairment by nasal and paranasal complaints: p=0.0083 ③ General health condition: p=0.029 ④ Symptom score: p<0.0001

2007(1)	50	NA	NA	baseline			12months	① No. of hospitalizations for asthma/y: p<0.0001 ② Nasal sinus score: p<0.0001 ③ Smell score: p<0.0001 ④ Asthma score: p<0.03 ⑤ Systemic corticosteroid: p<0.0001
2007(2)	55	NA	NA	baseline				① No. of hospitalization for asthma/y: p<0.0001 ② Nasal sinus score: p<0.0001 ③ Smell score: p<0.0001 ④ Asthma score: p<0.001 ⑤ Systemic corticosteroid: p<0.0001
1984	19	NA	45(18-71)	19	NA	45(18-71)	7 months	① Nasal congestion symptom scores: p=0.05 ② Nasal symptom scores for sinus pain: p=0.05 ③ Nasal symptom scores for sense of smell : p=0.057 ④ Combined nasal symptom scores: p=0.05 ⑤ Combined chest symptom scores: p=N.S

Table 2: summary of included studies and clinical outcomes between intervention group and placebo group

n= number; M/F=male/female; NA=not mention; SNOT= Sino-Nasal Outcome Test questionnaire; FEV1= forced expiratory volume in one second; ACQ= Asthma Control Questionnaire; ICS= inhaled corticosteroids; PNIF= peak nasal inspiratory flow; N.S=no significance;

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Author /year	Adverse effects(n)	Dropout rate	Aspirin-related adverse effects	others
1984	13	34.2%	<i>ASA group:</i> Gastrointestinal pain*3 Asthma symptoms↑*3 <i>Placebo group:</i> Nasal congestion↑*1 Uterine bleeding*1	Uncooperative*5
2007	32	16%	<i>325mg bid group:</i> Dyspepsia*9 Asthma*1 Ecchymosis*1 Urticarial*3 Tinnitus*1 <i>650mg bid group:</i> Dyspepsia*3 Asthma*3 Ecchymosis*1 bleeding*2 Angioedema*1	Pt jailed*1 Myalgias*1 Pregnancy*1 Unknown*4
2013	39	55.7%	none	No motivation*9 Moved away*8 Other disease*8 No compliance*4 Pregnancy*3 no subjective benefit*2 revision surgery advised*2 unknown*3
2014	5	25%	<i>ASA group:</i> Dyspepsia*4 <i>Placebo group:</i> none	Lack of improvement*1
2015	2	5.8%	<i>ASA group:</i> Gastrointestinal pain*1 Skin rash*1 <i>Placebo group:</i> none	none
2017	3	13.6%	<i>ASA group:</i> Gastrointestinal bleeding*1 <i>Placebo group:</i> none	Lost*1 Pregnancy*1

Table 3: Dropout rate and side effects

ASA=aspirin; bid=twice a day; ↑=increased symptoms;