META-ANALYSIS

Meta-analysis of dose selection for budesonide in the treatment of Chinese patients with AECOPD

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Abstract

Objective: To systematically observe the curative efficacy and safety of budesonide inhalation in the treatment of acute exacerbation of chronic obstructive pulmonary disease, and to find a suitable dose of aerosolized budesonide for Chinese patients.

Methods: The meta-analysis study was conducted at Wenjiang District People's Hospital, Chengdu City, Sichuan Province, China from May 2019 to August 2019 and comprised randomised controlled trials of glucocorticoids for acute exacerbation of chronic obstructive pulmonary disease on the databases of the China National Knowledge Infrastructure, Wanfang Medical Network, PubMed, Medline, Embase, Cochrane Library and Google Scholar. Data extraction and quality evaluation of the studies was done and meta-analysis was then performed using RevMan 5.3.

Results: There were 25 studies identified that comprised 1959 patients. When the budesonide dose was 6mg/d and the methylprednisolone dose was 40mg/d, no significant difference was found in partial pressure of carbon dioxide and oxygen post-treatment ($p>0.05$). When the nebulized budesonide dose was <6mg/d, methylprednisolone was more effective than budesonide ($p<0.05$), while >6mg/d was not significantly more effective ($p>0.05$). At 4mg/d, the difference in the dyspnoea score post-treatment was significant ($p<0.05$). No significant difference was found in dyspnoea scores after intravenous glucocorticoid treatment when the dose was greater than or equal to 4mg/d. In terms of adverse reactions, the response rate of blood glucose, blood pressure, excitement, insomnia and stomach discomfort in the intravenous group was higher than that in the nebulised group ($p<0.05$). Oropharyngeal discomfort in the nebulized group was higher than that the intravenous group ($p<0.05$).

Conclusion: The optimal dose for the inhalation of budesonide in Chinese patients was between 4mg/d and 6mg/d. The adverse reactions of nebulised budesonide were lower than those of intravenous methylprednisolone.

Keywords: Atomization, Budesonide, AECOPD, Glucocorticoid, Methylprednisolone, Meta-analysis. (JPMA 71: 2018; 2021)

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Introduction

Chronic obstructive pulmonary disease (COPD) is a frequently occurring chronic disease of the respiratory system associated with abnormal inflammatory responses to harmful inhalants in the lungs. COPD is characterised by incomplete, reversible and progressive development of airflow limitation. In patients with acute exacerbation of COPD (AECOPD), the symptoms worsen, and the lung function declines sharply, causing serious impairment to the life quality of these patients. AECOPD is also the main cause of patients' visits, hospitalisation, and death in COPD patients.[1]

Glucocorticoid is a commonly used drug for the treatment of AECOPD because of its remarkable anti-inflammatory effect. However, due to its obvious side effects,[2] the clinical use of glucocorticoids for topical administration or topical medication has been controversial. Additionally, the daily dose and the frequency of glucocorticoid aerosol inhalation treatment of AECOPD are not standardised in China. Budesonide is a commonly used glucocorticoid in the treatment of AECOPD by nebulised inhalation and current study was planned to studying the appropriate therapeutic dose in the population of patients with AECOPD in China is of great importance. The current study was planned to systematically observe the curative efficacy and safety of budesonide inhalation in the treatment of AECOPD, and to find a suitable dose of aerosolized budesonide for Chinese patients.

Methods

The meta-analysis study was conducted at Wenjiang District People's Hospital, Chengdu City, Sichuan Province, China from May 2019 to August 2019 and comprised randomised controlled trials (RCTs) related to use of glucocorticoids in AECOPD cases done from 2008 to 2018. The search was done on the databases of the China National Knowledge Infrastructure (CNKI), Wanfang Medical Network, PubMed, Medline, Embase, Cochrane

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Library and Google Scholar. RCTs included were those related to the treatment of AECOPD Cases with interventions including budesonide aerosol inhalation and glucocorticoid intravenous (IV) injection. Outcome indicators included were dyspnoea score, partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$), seconds of respiratory force volume, and adverse reactions.

The search was based on logical operators, wildcards, range operators, etc., that defined the search formula. The Chinese literature search terms were "雾化," "静脉," "布地奈德," and "慢阻肺急性加重期." The English literature search terms were "nebulisation," "intravenous injection," "budesonide" and "AECOPD." All terms were defined as "clinical trial" or "randomised controlled trial." All subject words were incorporated with random words for the search, and the language was adjusted according to different regional documents.

Two reviewers independently searched, screened and evaluated the articles for data extraction. The third investigator got involved in case of any disagreement between the two reviewers.[3]

Data extracted included the following elements: basic information of the study, including title, author and publication date; basic characteristics of test samples and situations, follow-up, etc., including the inclusion and exclusion criteria of test samples, type of COPD disease, sample baseline, baseline consistency, sample size, etc.; interventions, like medication type, medication course, basic treatment and use of a placebo; methodological information of the test, like randomisation, blinding, allocation concealment, etc.; clinical outcomes and surrogate endpoints, like dyspnoea score on the modified Medical Research Council (mMRC) scale, PaO_2, $PaCO_2$, forced expiratory volume in the first second (FEV1) ,and adverse reactions.

The document quality evaluation was done using the tool provided by the Collaboration Network to evaluate the random method of the trials, the implementation of blinding, and the implementation of allocation concealment, sample shedding, and selective reporting.

Meta-analysis was done using RevMan 5.3 software. Enumeration data was expressed as odds ratio (OR), and efficacy effects were expressed as 95% confidence intervals (CIs). The difference between the baseline characteristics of the samples was reviewed by t test and chi-square test. $P<0.05$ was deemed to be statistically significant. The heterogeneity of the combined data was analysed by Q test. $P<0.10$ indicated statistical heterogeneity using a random effects model. Subgroup analysis was determined to be appropriate.

Results

Of the 215 studies shortlisted, 25(11.6%) were included in the final analysis.[4-28] Of them, 1(4.0%) was in English, and 24(96.0%) were in the Chinese language (Figure1).

All the studies together had 1959 patients; 982(50.1%) in the budesonide group and 977(49.9%) in the IV group in which the glucocorticoid used was mainly methylprednisolone.

With respect to clinical efficacy 192 patients were included in 3 studies concerning mMRC score for dyspnoea. There were 111(57.8%) cases in the budesonide group B and 81(42.1%) cases in the methylprednisolone group M. The dyspnoea index was graded 0-4 according to the mMRC scale developed by the British Medical Association Research Council and was scored by the patient (Figure 2).[29] When budesonide dose was 3mg/d and the methylprednisolone dose was 40mg/d, the difference was significant ($p<0.05$). After treatment, the dyspnoea score of group B was higher than that of group M. No significant difference was found in the other subgroups of aerosolised budesonide and IV glucocorticoids ($p>0.05$).

A total of 18 studies having 1468 patients investigated PaO_2. There were 736(50.1%) cases in group B and 732(49.8%) cases in group M. Subgroup analyses were performed according to the daily dose (Figure 3). When the

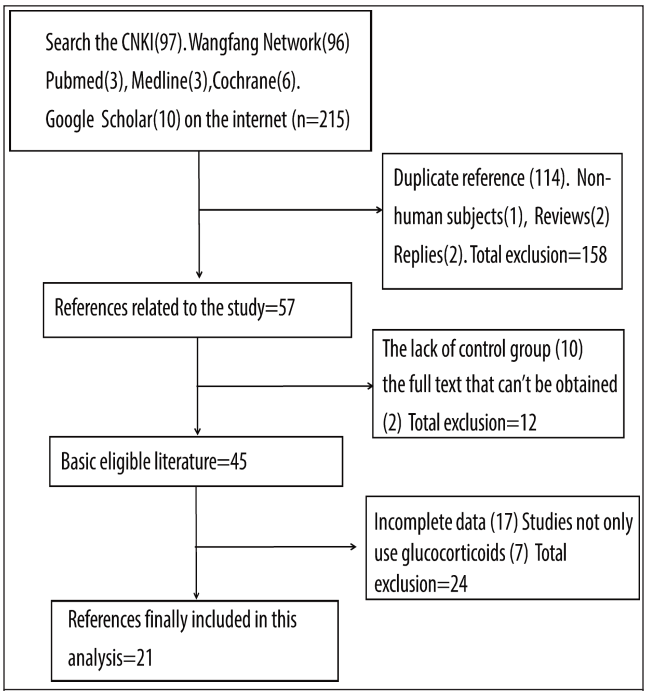

Figure-1: Study flowchart.

dose of methylprednisolone was 40mg.d-1 or 80mg.d-1, and the dose of nebulised budesonide was <6mg.d-1, the difference was significant (p<0.05). PaO_2 value after IV injection in group M was higher than that of the B group (p<0,05). When the dose of methylprednisolone was 40mg.d-1 and the dose of aerosolised budesonide was 6-8mg. d-1, the difference was not significant (p>0.05).

A total of 16 studies having 1213 patients explored $PaCO_2$. There were 607(50.0%) cases in group B and 606(50.0%) cases in group M (Figure 4). When the dose of methylprednisolone was 80mg.d-1 and the dose of budesonide was 2~6mg. d-1, the difference was significant (p<0.05). The value of $PaCO_2$ was higher after intravenously injecting methylprednisolone than in group B. When the dose of methylprednisolone was 40mg.d-1 and the dose of budesonide was <6mg.d-1, the difference was significant (p<0.05), and the $PaCO_2$ value of group M was higher than group B (p<0.05). When the dose of methylprednisolone was 40mg. d-1 and the dose of budesonide was 6-8mg.d-1, the difference was not significant (p>0.05).

A total of 10 studies with 691 patients investigated FEV1. In these studies, 345(49.9%) subjects were in group B and 346(50.0%) were in group M. Subgroup analyses showed that FEV1 values were not significant (p>0.05) (Figure 5).

In terms of adverse reactions, 6 studies with 419 patients investigated blood sugar. Among them, 211(50.4%) were in group B and 208(49.6%) were in group M. There was a significant difference in blood glucose elevation between the groups (OR: 0.09, 95% CI: 0.03, 0.28; p<0.0001). The response rate of blood glucose in group B was lower than that of group M (Figure 6).

A total of six studies with 358 patients reported excitement and insomnia. There were 165(46.1%) cases in group B and 193(53.9%) in group M. A significant difference was found in the excitability and insomnia between the groups (OR: 0.19; 95% CI: 0.05, 0.66; p=0.009)). The insomnia response rate of group B was less than that of group M (Figure 7).

A total of 11 studies with 772 patients investigated oropharyngeal and throat discomfort. There were 404(52.3%) cases in group B and 368(47.7%) cases in group M. A significant difference was found in the number of patients with oropharyngeal discomfort after treatment with budesonide compared to group M (OR: 5.08; 95% CI: 2.01, 12.79; p=0.0006). The rate of oropharyngeal and pharynx discomfort in group B was higher than in group M (Figure 8).

A total of 9 studies with 581 patients reported stomach discomfort. Among them, 292(50.3%) were in group B and 289(49.7%) were in group M. A significant difference was found in the number of patients with gastric discomfort

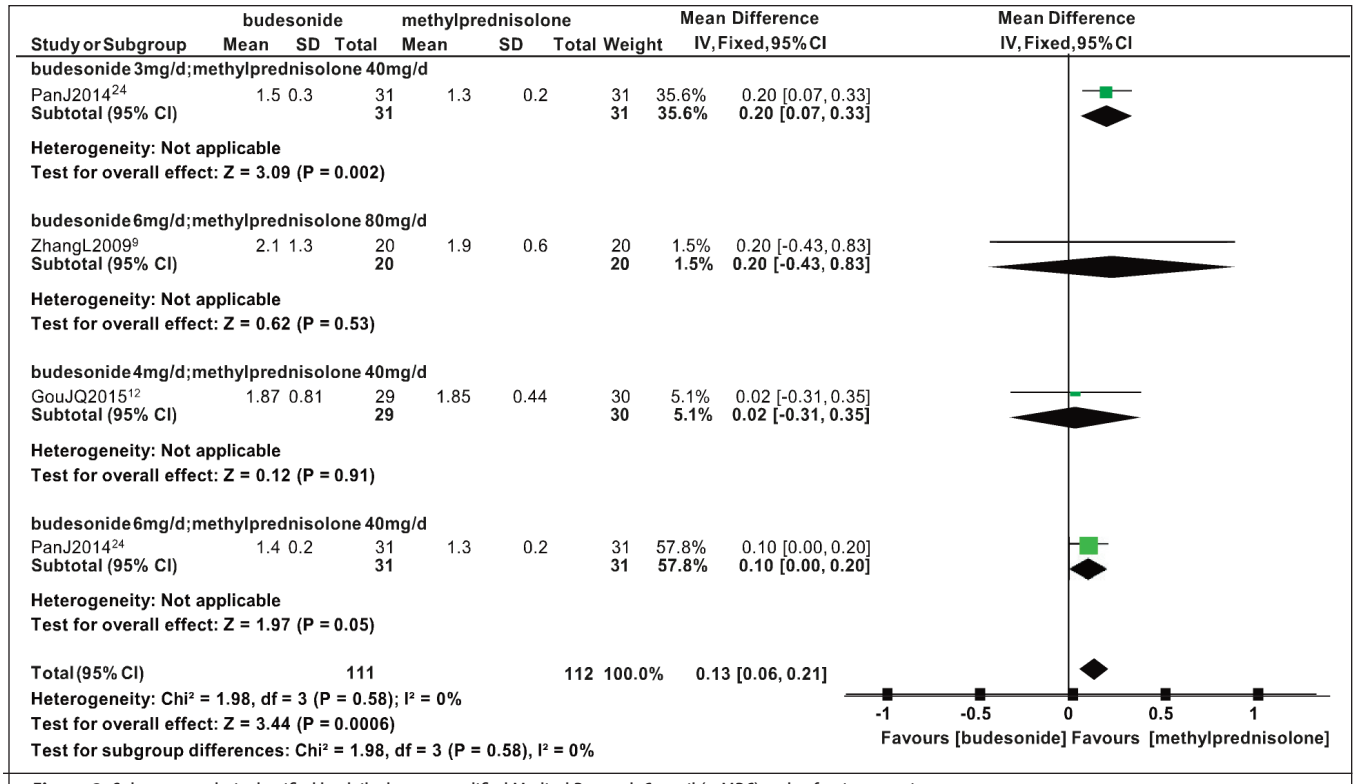

Figure-2: Subgroup analysis classified by daily dose on modified Medical Research Council (mMRC) scale after intervention.

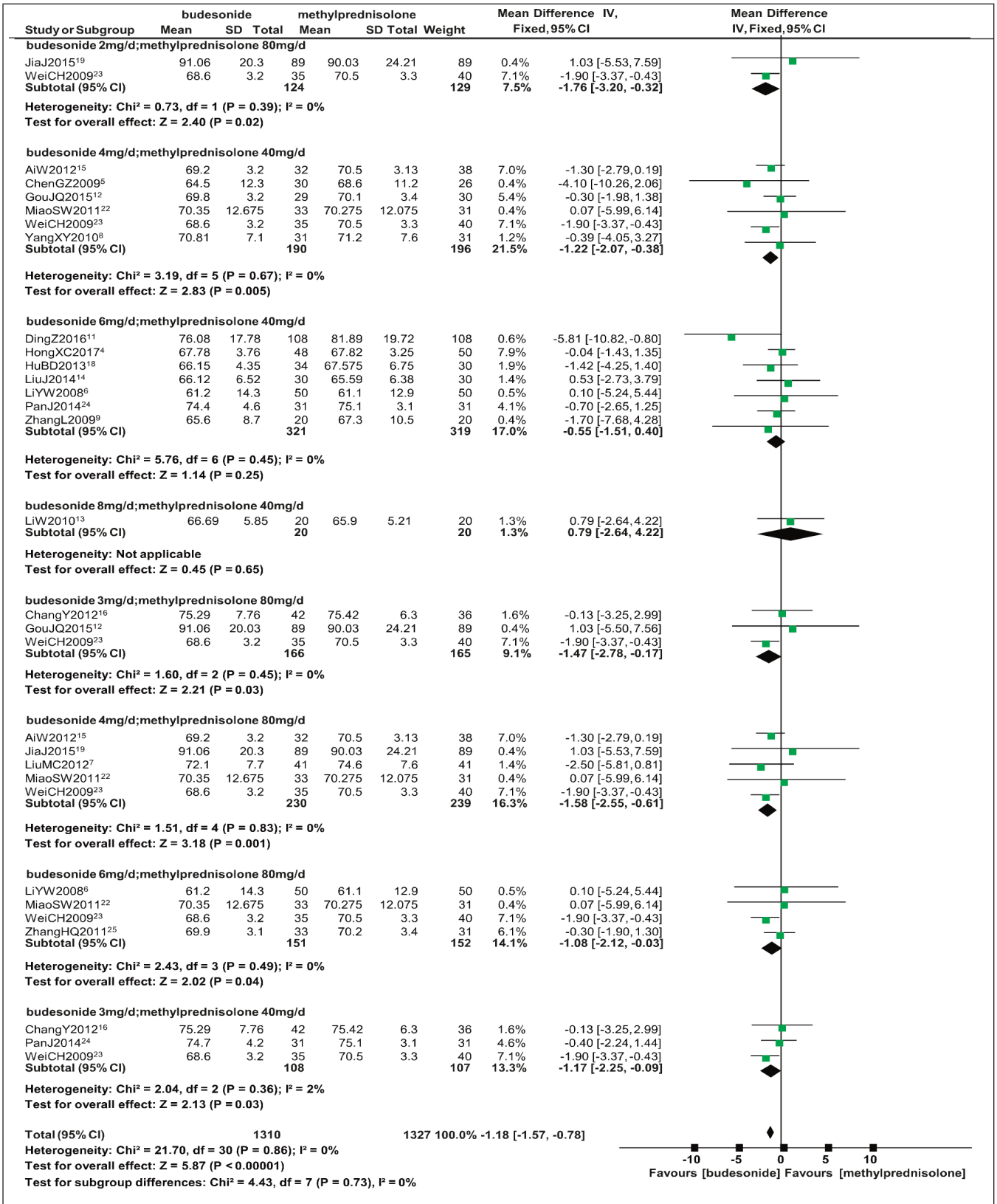

Figure-3: Subgroup analysis classified by daily dose and partial pressure of oxygen (PaO_2) after intervention.

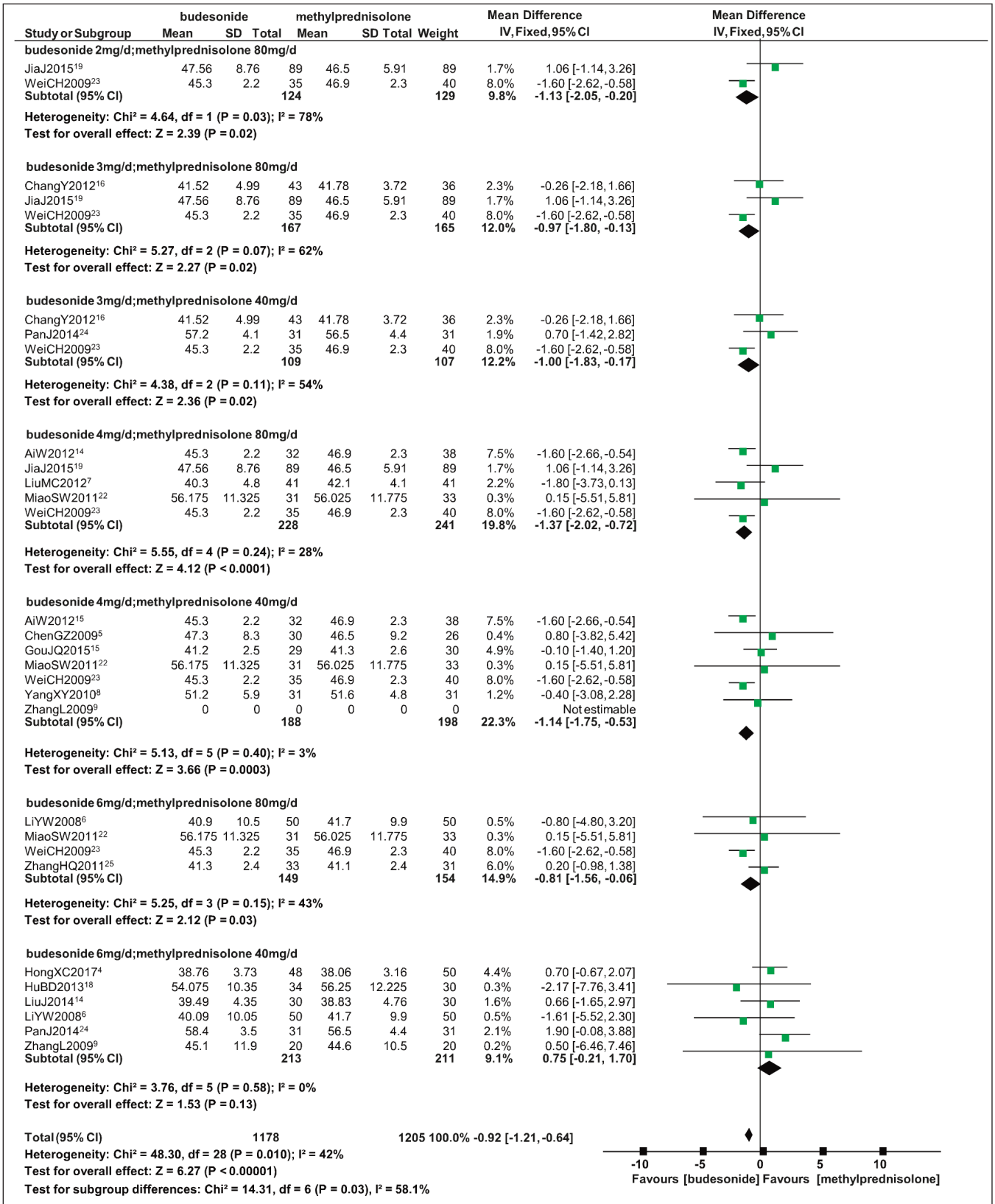

Figure-4: Subgroup analysis classified by daily dose and partial pressure of carbon dioxide ($PaCO_2$) after intervention.

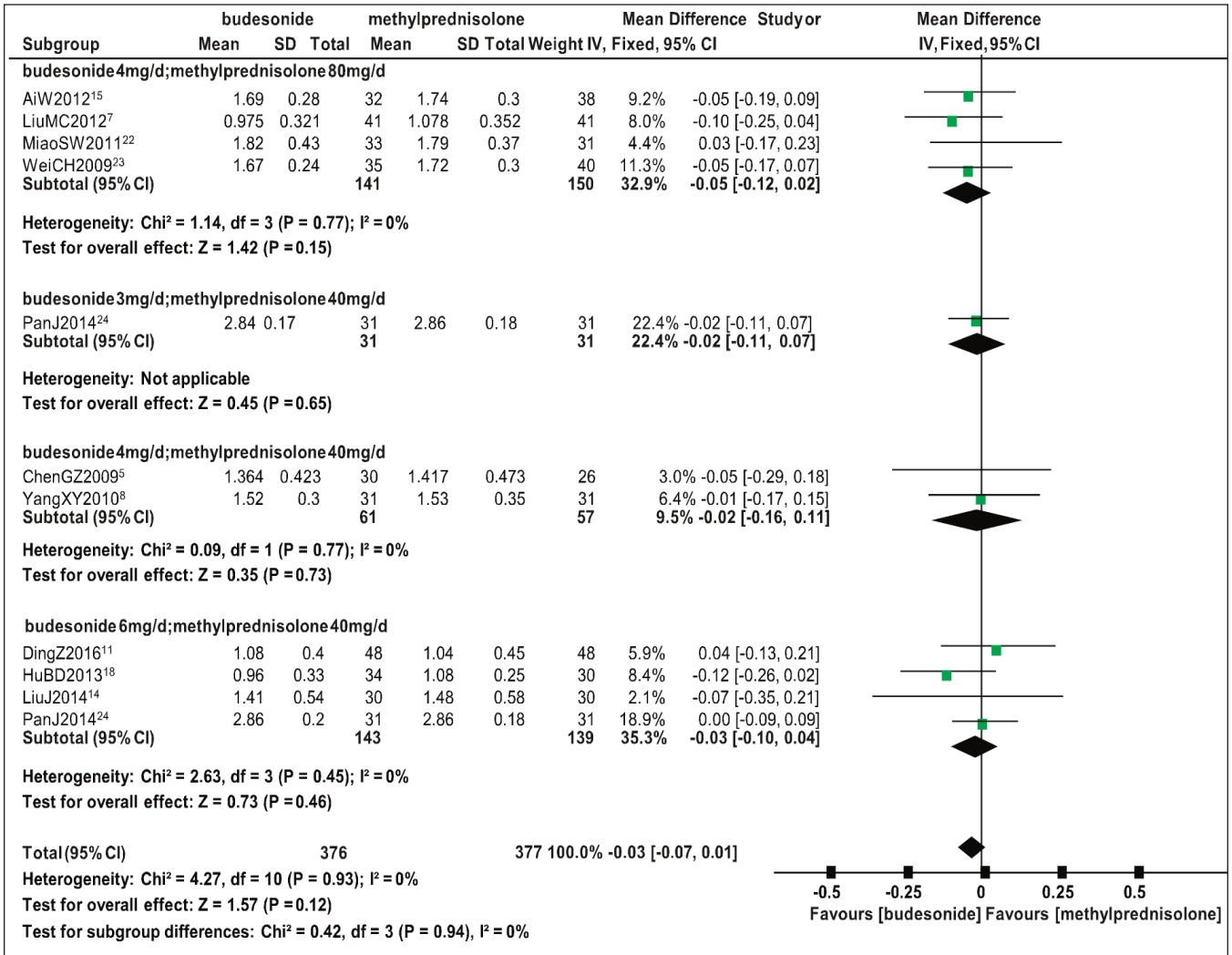

Figure-5: Subgroup analysis classified by daily dose and forced expiratory volume in the first second (FEV1) after intervention.

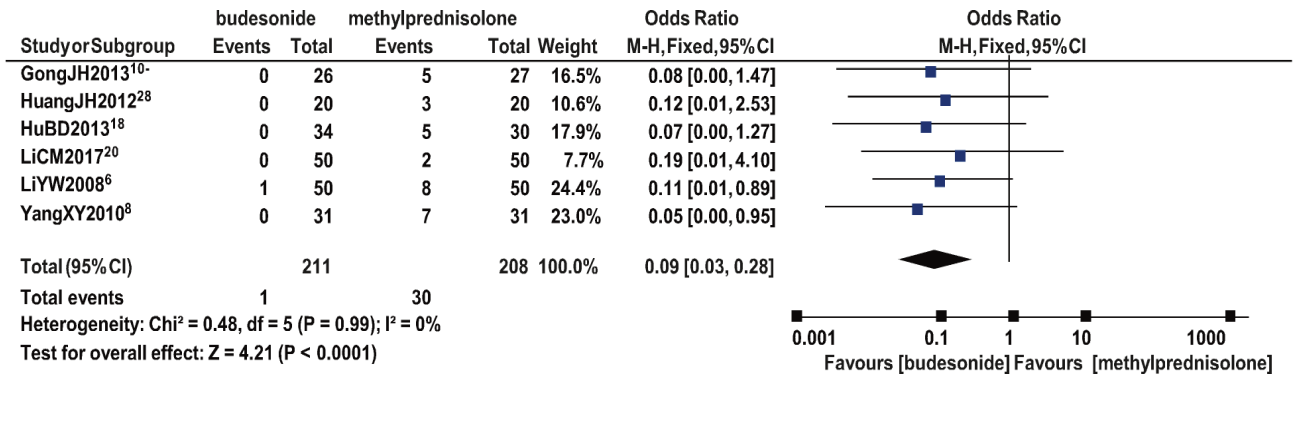

Figure-6: Elevated blood sugar.

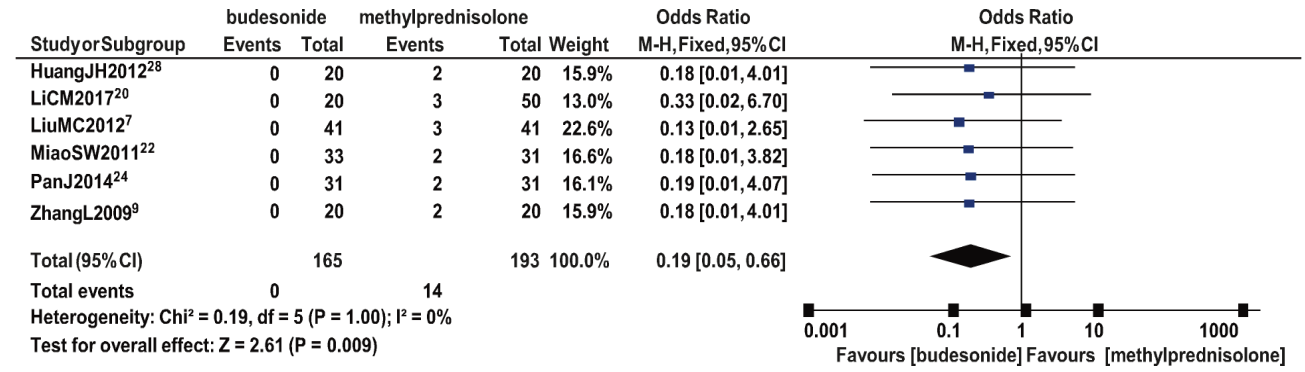

Figure-7: Excitement and insomnia.

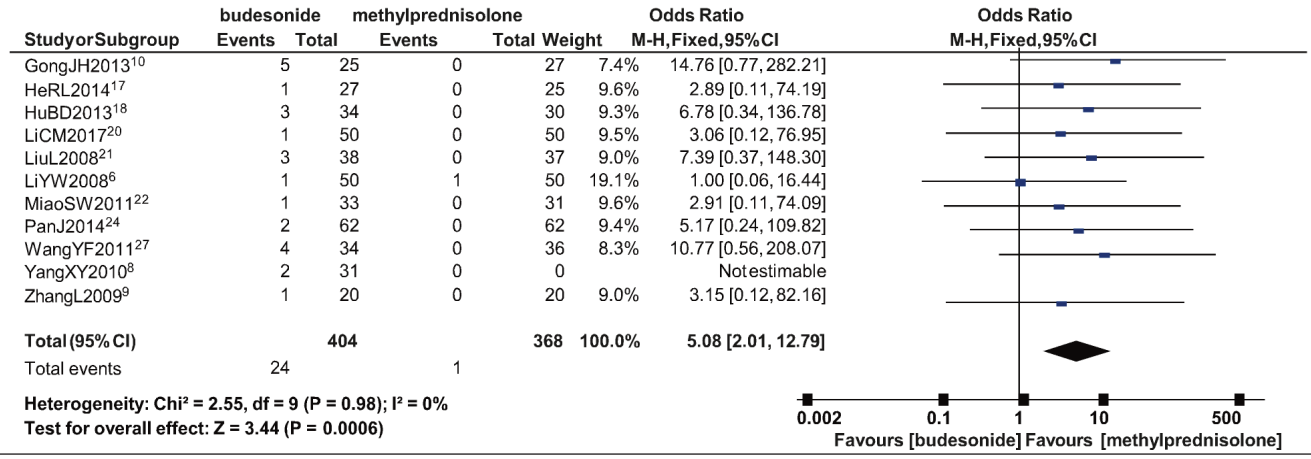

Figure-8: Oropharyngeal and throat discomfort.

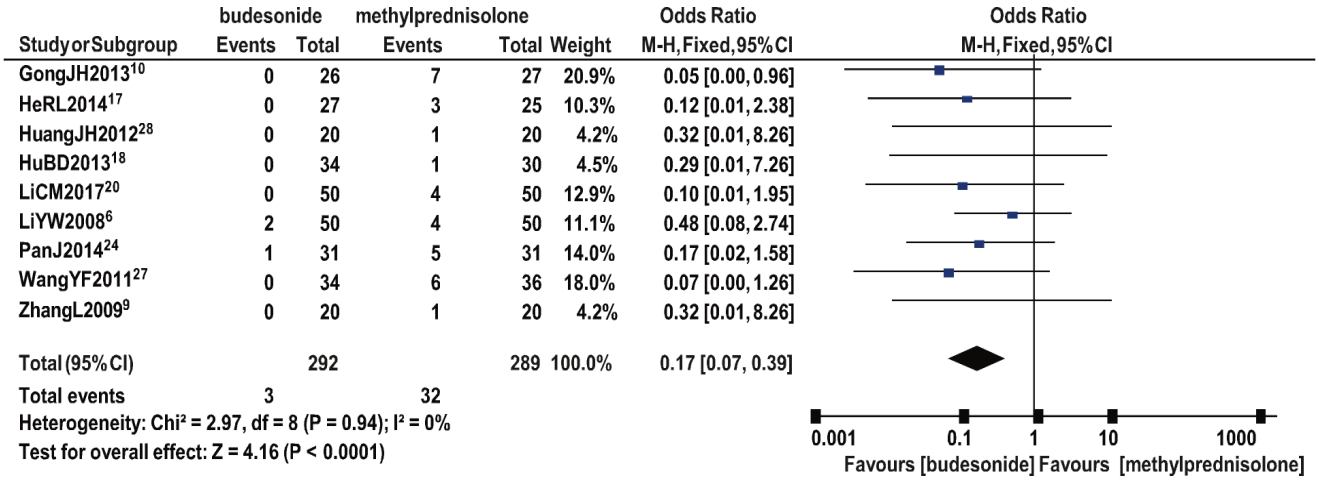

Figure-9: Stomach discomfort.

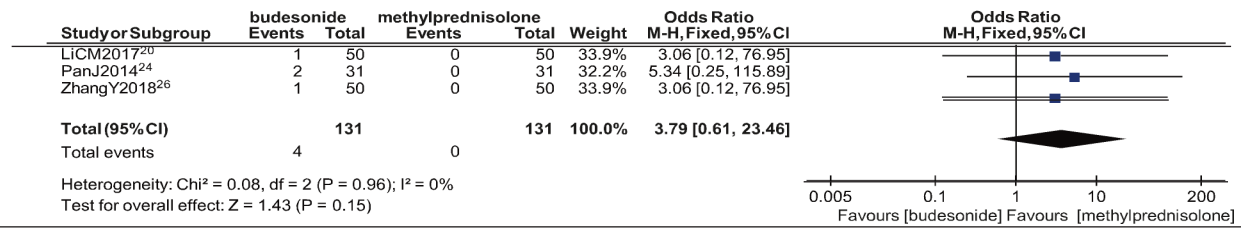

Figure-10: Oral mould infection.

after treatment with budesonide compared to those treated with methylprednisolone (OR: 0.17; 95% CI: 0.07, 0.39; $p<0.0001$). Gastric discomfort in group B was lower than group M (Figure 9).

A total of 3 studies with 262 patients investigated oral mould infection. There were 131(50.0%) cases in group B and 131(50.0%) cases in group M. No significant difference was found in the rate of oral mould infection between the groups (OR: 3.79; 95% CI: 0.61, 23.46; $p=0.15$) (Figure 10).

Discussion

Some efficacy indicators and adverse reaction indicators may have created publication bias in the current study. A total of 25 RCTs and 1959 patients were included in the current systematic review which included a large number of studies, a large sample size, and a certain level of representativeness, but some shortcomings still existed in the written normativeness, test rigour, and data integrity of the included studies. Many studies did not mention their random methods; it was unclear whether they utilised selective report or allocation concealment. Most of the studies' subjects, investigators and outcome evaluators did not implement blinding, and only two studies explicitly mentioned single-blinding. Four studies had patients with shedding and did not report relevant intentional or protocol treatment options. Thus, data may have been incomplete. Regarding these issues, the current team will continue to attend to and add new relevant test reports, as well as implement sequential meta-analysis to improve the accuracy of the evaluation. In addition, the samples of this study were all from China, and further research is needed to reveal whether the data can be applied to different ethnic groups.

No significant difference was found in PaO_2 and $PaCO_2$ values after IV inhalation of budesonide at >6mg compared to IV injection of 40mg of methylprednisolone. When nebulised budesonide was <6mg, the effect of methylprednisolone was better than budesonide. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines believe that inhalation of 8mg of budesonide in one day is equivalent of IV infusion of 40mg of methylprednisolone. AECOPD consensus from Chinese experts, as updated in 2017, follows the GOLD guidelines.[30] However, the results of this study were not consistent with the recommendations of the guidelines. In this study, 6mg of nebulised inhaled budesonide was the equivalent of IV infusion of 40mg of methylprednisolone. If the dosage of budesonide was >6mg, the efficacy was not significantly different between budesonide methylprednisolone. However, this higher dose of budesonide increased the probability of adverse reactions and economic pressure. The ethnic differences between the East and the West may be one of the reasons for the inconsistency of the conclusions. In terms of dyspnoea score, the difference was significant ($p<0.05$) when the budesonide dose was 3mg and the IV infusion of methylprednisolone dose was 40mg per day. The dyspnoea score after treatment in group B was higher than group M. When a nebulised budesonide dose of 4mg or more was given daily, no significant difference in dyspnoea score was found between the groups. This indicated that in the matter of improved dyspnoea, the inhalation of budesonide <4mg was not effective. Therefore, to ensure efficacy, the daily dose of budesonide cannot be <4mg.

No significant difference was found in the value of FEV1 between inhaled budesonide and IV methylprednisolone. This was inconsistent with the analysis of PaO_2 and $PaCO_2$ values after the treatment, which meant that improvement in lung function was not directly related to lung ventilation. The reason may have been that the improvement of lung function requires a period of treatment, and the short-term improvement effect is not obvious. Additionally, the improvement of lung function is also related to the patient's tolerance and physical fitness.

The included studies found that adverse reactions caused by glucocorticoids included blood sugar elevation, blood pressure elevation, excitement and insomnia, oropharyngeal discomfort, stomach discomfort, and oral mould infections. Among them, the response rate of blood glucose, blood pressure, excitement, insomnia and stomach discomfort in the IV group was higher than that in group B. The oropharyngeal discomfort rate of group B was higher than that of group M. In terms of the type and quantity, the adverse reaction rate of IV glucocorticoids was higher than that of group B. In addition, long-term adverse effects of glucocorticoids, such as decreased immunity and

osteoporosis, were not mentioned in the included studies. This may have been because the study duration of the included literature was short.

Conclusion

Based on the findings, the dose of budesonide inhalation in AECOPD Chinese patients was preferably 6mg per day. The optimal dose was between 4mg/d and 6mg/d. The adverse reactions of nebulised budesonide were lower than those of IV methylprednisolone.

Disclaimer: None.

Conflict of Interest: None.

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