Effectiveness and safety of early combined utilization of budesonide and surfactant by airway for Bronchopulmonary dysplasia prevention in premature infants with RDS: A meta-analysis

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Abstract

Objective: To address the effectiveness and safety of early airway utilization of budesonide and surfactant for BPD prevention in premature infants with RDS. Methods: PubMed, Web of Science, EMBASE, Cochrane Library, Wanfang, CQ VIP and China National Knowledge Infrastructure databases were searched from the inception to May 2021. Stata 16.0 software was used for statistical analysis. Results: This meta-analysis suggested that early combined utilization of budesonide and surfactant by airway tended to have a superiority on BPD incidence (RR=0.63;95%CI:0.54 0.73, P<0.001), mortality (RR=0.63;95%CI:0.43 0.94, P=0.022) and the composite outcome of BPD or mortality (RR=0.59;95%CI:0.49 0.70, P<0.001), the reuse incidence of surfactant (RR=0.54; 95%CI:0.45 0.65, P<0.001), the duration of assisted ventilation (SMD=-1.14;95%CI: -1.58 -0.70, P<0.001), invasive ventilation (SMD=-1.33;95%CI: -1.76 -0.90, P<0.001), and hospital stays (SMD=-1.20;95%CI: -1.88 -0.51, P=0.001) in preterm infants with RDS. And these benefits were not associated with increased adverse outcomes. Furthermore, a decreased incidence of PDA (RR=0.80; 95%CI:0.64 0.99, P=0.041) was found in test group. Subgroup analysis based on budesonide delivery methods (inhalation or intratracheal instillation) indicated that the decrease of mortality (RR=0.62;95%CI:0.41 0.95, P=0.026), duration of assisted ventilation (SMD=-0.95;95%CI: -1.30 -0.61, P<0.001) and hospital stays (SMD=-1.38;95%CI: -2.33 -0.43, P=0.004) were mainly in budesonide intratracheal instillation subgroup. Conclusions: This meta-analysis suggested that early combined utilization of budesonide and surfactant by airway might be an effective and safe clinical practice for BPD prevention in premature infants with RDS, especially when budesonide was delivered by intratracheal instillation.

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Abstract

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Methods: Literature retrieval was carried out in the PubMed, Web of Science, EMBASE, Cochrane Library, Wanfang, CQ VIP and China National Knowledge Infrastructure databases, searching from the inception to May 2021. Stata 16.0 software was used for statistical analysis.

Results: This meta-analysis suggested that early combined utilization of budesonide and surfactant by airway tended to have a superiority on BPD incidence (RR=0.63;95%CI:0.54 0.73,P <0.001), mortality (RR=0.63;95%CI:0.43 0.94,P =0.022) and the composite outcome of BPD or mortality (RR=0.59;95%CI:0.49 0.70, P <0.001), the reuse incidence of surfactant (RR=0.54; 95%CI:0.45 0.65,P <0.001), the duration of assisted ventilation (SMD=-1.14;95%CI: -1.58 -0.70, P <0.001), invasive ventilation (SMD=-1.33;95%CI: -1.76 -0.90, P< 0.001), and hospital stays (SMD=-1.20;95%CI: -1.88 -0.51, P =0.001) in preterm infants with RDS. And these benefits were not associated with increased adverse outcomes. Furthermore, a decreased incidence of PDA (RR=0.80; 95%CI:0.64 0.99, P =0.041) was found in premature infants treated with budesonide and surfactant. Subgroup analysis based on budesonide delivery methods (inhalation or intratracheal instillation) indicated that the decrease of mortality (RR=0.62;95%CI:0.41 0.95, P =0.026), duration of assisted ventilation (SMD=-0.95;95%CI: -1.30 -0.61, P <0.001) and hospital stays (SMD=-1.38;95%CI: -2.33 -0.43, P =0.004) were mainly in budesonide intratracheal instillation subgroup, rather than in budesonide inhalation subgroup.

Conclusions: This meta-analysis suggested that early combined utilization of budesonide and surfactant by airway might be an effective and safe clinical practice for BPD prevention in premature infants with RDS, especially when budesonide was delivered by intratracheal instillation. More well-designed RCTs with larger sample sizes and longer follow-up ought to be conducted in the future.

Keywords: Premature infants, Bronchopulmonary dysplasia, Budesonide, Surfactant, Meta-analysis

Respiratory distress syndrome (RDS) is one of the most common and serious respiratory diseases in premature infants. Bronchopulmonary dysplasia (BPD), which is also called chronic lung disease of infancy, is a major complication in premature infants.[1] The mortality and long-term morbidity in premature infants with BPD is significantly higher than that of ones without BPD.[2] Despite significant advances in neonatal care, such as prenatal utilization of corticosteroids and surfactants, it has been also reported that about 10% to 89% of premature infants were affected by BPD, regardless of definition used and gestational age[3]. And the survivors, who went through only mild respiratory distress in the perinatal period were inclined to late respiratory problems, during childhood and adulthood, including increased incidence of reactive airway disease, exercise intolerance and other adverse sequelae.[4] Management of their condition is both time-consuming and costly, which has affected the resources of the newborns, their family, and ultimately society. Thus, the prevention and treatment of BPD has become a big challenge in NICUs.

The diagnosis of BPD is based on maldevelopment and injury of premature lung. Persistent lung inflammation is thought central to the underlying pathophysiology of BPD and anti-inflammatory medications, for instance, corticosteroids have been recommended to prevent or cure BPD for years.[5-7] Systemic corticosteroids have been demonstrated with promising effects in moderating BPD incidence (defined as death at 28 days of life or at 36 weeks' postmenstrual age in premature infants).[7,8] However, it was also reported to be correlated with serious short-term and/or long-term adverse outcomes.[7] Early administration of corticosteroids by airway was thought to have fewer side effects than systemic treatment.[7] Therefore, delivery of steroids directly to lungs, by inhalation or by intratracheal instillation may be an alternative choice.[9,10]

Airway administration of budesonide was reported to decrease the incidence of BPD in premature infants,[11,12] but it was also shown to increase mortality.[13]Surfactant is now commonly used for premature infants with RDS. When combining budesonide with surfactant, the risk of BPD was demonstrated 43% reduction without increased mortality or adverse physical or neurologic outcomes.[14]

So far, combined utilization of budesonide and surfactant by airway has not yet been promoted during

clinical practice. Several studies had addressed the benefits and risks of this administration mode, but the studies reported conflicting results. Therefore, this study aimed at addressing the effectiveness and safety of early combined utilization of budesonide and surfactant by airway to prevent BPD in premature infants with RDS, and offering reference for clinical practice.

1 MATERIALS AND METHODS

1.1 Search strategy:

The meta-analysis were proceeded using the methodology recommended by the Cochrane Collaboration. [15] The findings were submitted based on the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) statement. [16]Following databases, including PubMed, Web of Science, EMBASE, Cochrane Library, Wanfang, CQ VIP and China National Knowledge Infrastructure (CNKI) were searched by two reviewers independently from the database inception to May 2021. Search terms included: premature infants, preterm infants, infant newborn, chronic lung diseases, bronchopulmonary dysplasia, respiratory distress syndrome, neonatal respiratory distress syndrome, pulmonary surfactant, surfactant, budesonide, inhalation, intratracheal instillation. No language restriction was applied. Furthermore, the primary authors of the included studies were contacted for detailed information when necessary.

Eligibility Criteria

The studies were designed as RCT; 2) the candidates with gestational age less than 33 weeks or birth weight less than 1500g were included, and were diagnosed with RDS; 3) time to start intervention was early in life (< 8 days after birth); 4) intervention: BUD group (airway administration of budesonide and surfactant), control group (surfactant alone was administrated); 5) BPD incidence was an indispensable outcome, and one more of following conditions were reported: mortality, the composite outcome of BPD or mortality, reuse incidence of surfactant, duration of assisted ventilation, duration of invasive ventilation, hospital stays, adverse outcomes: intraventricular hemorrhage (IVH), patent ducts arterious (PDA), retinopathy of prematurity (ROP), infection or septicemia, necrotizing enterocolitis (NEC) and neurological and cognitive outcomes: mental developmental index (MDI) and psychomotor developmental index (PDI). BPD incidence, mortality and the composite outcome of BPD or mortality were defined as the primary outcomes, and the others were secondary outcomes.

1.3 Exclusion criteria

a) Retrospective studies, observational and non-clinical studies; b) insufficient information on baseline or primary or secondary outcome data; c) the candidates with gestational age more than 33weeks and birth weight more than 1500g; and d) use of the other inhaled glucocorticoid.

1.4 Data extraction

For each study, two investigators independently completed data extraction using a self-designed data form. All the discrepancies in the data abstracted were resolved via discussion and consensus. Details of the first author's name, year of publication, the characteristics of patients, sample size (BUD group/control group), and intervention were abstracted.

1.5 Quality assessment

The Cochrane 'Risk of bias' tool was used to evaluate the risk of bias (low, high, or unclear) for all included studies by two investigators independently. Seven domains evaluated following bias, including selection bias, performance bias, detection bias, attrition bias, reporting bias and any other bias.[15]

1.6 Statistical analysis

Standard mean difference (SMD) was selected for continuous variables analysis, and risk ratio (RR) was applied for dichotomous variables analysis. 95% confidence intervals (CIs) were reported for all estimates. A fixed-effects model or random-effects model was used depending on the heterogeneity. Heterogeneity was assessed with I^2 test, by which the differences were considered significant when $I^2 > 50\%$ or P-value <0.1.

Statistical significance indicated a 2-sided p-value < 0.05. Subgroup analysis based on budesonide delivery methods (inhalation or intratracheal instillation) were used. When there was a significant heterogeneity, sensitivity analysis were performed by removing each individual study from the overall analysis.[17] Publication bias was assessed as more than 10 studies included. Statistical analysis was carried out using Stata 16.0 software.[18]

2 RESULTS

2.1 Study selection and characteristics

538 publications were identified in initial screening. Among the publications, only 15 RCTs (16 articles)[19-34] met our inclusion criteria and were included. The detailed process of literature screening is depicted in Fig 1.

Fig 1. Flowchart of selection process for eligible studies.

Among the 15 studies (16 articles),[19-34] 5 (6 articles) [19,20,22,27,32,33] were presented in English, the other 10[21,23-26,28-31,34] were in Chinese. A total of 1607 premature infants with RDS (794 in the BUD group and 813 in the control group) were involved in this meta-analysis. The included studies were carried out in Asian and North America countries, and were published between 2008 and 2021. Sample sizes ranged from 15 to 134. Different dosage of surfactant and different delivery method of budesonide were applied. Table 1 is given for more details.

Table 1. Basic characteristics of included studies.

2.2 Quality of evidence

Cochrane Handbook was employed to estimate the risk of bias of the included studies. The specific assessment results are shown in Fig 2.

Fig 2. Risk bias for included studies. A) Risk of bias graph for included studies. B) Summary of risk bias for included studies.

2.3 Meta-Analysis Results

2.3.1 Changes in the primary outcomes

Compared with control group, meta-analysis found that the incidence of BPD, mortality, and the composite outcome of BPD or mortality (BPD/mortality) tended to be significantly lower in the BUD group, with RR=0.63 (95%CI:0.54 0.73, P <0.001, Fig 3A), RR=0.63 (95%CI:0.43 0.94, P =0.022, Fig 3B), and RR=0.59 (95%CI:0.49 0.70, P <0.001, Fig 3C), respectively.

Subgroup analysis based on the delivery method of budesonide revealed that the incidence of BPD and BPD/mortality were significantly reduced both in intratracheal instillation subgroup (RR=0.66; 95%CI: 0.56 0.77, P<0.001, Fig 3A, and RR=0.60; 95%CI:0.50 0.73,P <0.001, Fig 3C) and in inhalation subgroup (RR=0.50; 95%CI:0.34 0.73, P<0.001, Fig 3A, and RR=0.51; 95%CI:0.34 0.79, P =0.002, Fig 3C). Nevertheless, the mortality was significantly lower only in intratracheal instillation subgroup (RR=0.62; 95%CI:0.41 0.95, P =0.026), rather than in inhalation subgroup (RR=0.71; 95%CI:0.24 2.10, P =0.541) (Fig 3B).

Fig 3. Forest plots of RR estimates on the primary outcomes. A) BPD incidence. B) Mortality. C) The composite outcome of BPD or mortality.

2.3.2 Changes in clinical outcomes

Compared with control group, meta-analysis demonstrated that the reuse incidence of surfactant, duration of assisted ventilation, duration of invasive ventilation and hospital stays all tended to be apparently less in the BUD group, with RR=0.54 (95%CI:0.45 0.65,P <0.001, Fig 4A), SMD=-1.14 (95%CI: -1.58 -0.70,P

<0.001, Fig 4B) , SMD=-1.33 (95%CI: -1.76 -0.90,P< 0.001, Fig 4C), and SMD=-1.20 (95%CI: -1.88 -0.51,P =0.001, Fig 4D), respectively.

Subgroup analysis based on the delivery method of budesonide revealed that the reuse incidence of surfactant and duration of invasive ventilation were significantly less both in intratracheal instillation subgroup (RR=0.56; 95%CI:0.46 0.68, P <0.001, Fig 4A, and SMD=-1.14; 95%CI: -1.64 -0.64, P <0001, Fig 4C) and in inhalation subgroup (RR=0.42; 95%CI:0.22 0.80, P =0.008, Fig 4A, and SMD= -1.73; 95%CI: -2.63 -0.83, P <0.001, Fig 4C). Nevertheless, the duration of assisted ventilation and hospital stays were significantly shorter only in intratracheal instillation subgroup (SMD=-0.95; 95%CI: -1.30 -0.61, P<0.001, Fig 4B, and SMD = -1.38; 95%CI: -2.33 -0.43, P =0.004, Fig 4D), rather than in inhalation subgroup (SMD=-1.98; 95%CI: -4.21 0.24, P=0.081, Fig 4B, and SMD = -0.83; 95%CI: -1.71 0.06, P =0.067, Fig 4D).

Fig 4. Forest plots of RR/SMD estimates on clinical outcomes. A) Reuse incidence of surfactant. B) Duration of assisted ventilation. C) Duration of invasive ventilation. D) Hospital stays.

2.3.3 Changes in adverse outcomes

Meta-analysis indicated that BUD group had a lower incidence of PDA than that of control group (RR=0.80; 95%CI:0.64 0.99, P =0.041). Subgroup analysis revealed that the incidence of PDA only showed a decreasing trend, rather than statistical difference in budesonide intratracheal instillation subgroup (RR=0.81;95%CI:0.65 1.01,P =0.066). And in budesonide inhalation subgroup, the incidence of PDA showed no significant difference either, with RR=0.73 (95%CI:0.37 1.46, P =0.377). (Fig 5A).

There were no statistic differences in the incidence of IVH, ROP, infection or septicemia and NEC, with corresponding RR=1.08(95%CI:0.90 1.29, P =0.395), RR=0.87(95%CI:0.71 1.08,P =0.203), RR=0.81(95%CI:0.58 1.15, P =0.245) and RR=1.11(95%CI:0.72 1.70, P =0.632), respectively (Fig 5B and Fig 5C).

Fig 5. Forest plots of RR estimates for adverse outcomes. (A) PDA. (B) IVH. (C) ROP, infection or septicemia and NEC.

Two studies[20,22] reported 2-3 years of follow-up data about neurological and cognitive outcomes after budesonide administration. Meta-analysis indicated that BUD group and control group had no statistic difference in MDI and PDI scores, with SMD = 0.17(95%CI:-0.08 0.43,P =0.178) and SMD = 0.09(95%CI:-0.16 0.35, P =0.472), respectively (Fig6A). Meanwhile, there was also no statistic difference in the proportion of low MDI (<=69) or low PDI(<=69) scores between the two groups, with RR=0.89(95%CI:0.57 1.38, P =0.592) and RR=0.86 (95%CI:0.59 1.26, P =0.444) , respectively (Fig 6B).

Fig 6. Forest plots of SMD/RR estimates for neurological and cognitive outcomes. (A) MDI and PDI scores. (B) proportion of low MDI (<=69) or low PDI (<=69) scores.

2.4 Sensitivity analysis

Meta-analysis indicated that there was obvious heterogeneity in duration of assisted ventilation, duration of invasive ventilation and hospital stays. Sensitivity analysis indicated that no individual study has remarkably altered any of the above results (Fig 7).

Fig 7. Sensitivity analysis. (A) Duration of assisted ventilation. (B) Duration of invasive ventilation. (C) Hospital stays.

2.5 Publication bias

Harbord's modified test on small-studies showed that P =0.004, which indicated there existed possible biases, including publication bias, language bias, lack of publication on small trials with opposite results, and flawed methodological designs exaggerated estimates in smaller studies (Fig 8).

Fig 8. Harbord funnel for BPD (Relative risks specified as effect estimate of interest).

Discussion

This meta-analysis suggested that early **combined utilization** of budesonide and surfactant by airway was related to a reduction of BPD, mortality and the composite outcome of BPD or mortality, the reuse incidence of surfactant, the duration of assisted ventilation, invasive ventilation, and hospital stays in premature infants with RDS. And these benefits were not associated with increased adverse outcomes: IVH, ROP, infection or septicemia, NEC and neurological and cognitive outcomes. Furthermore, a decreased incidence of PDA was indicated in premature infants treated with budesonide and surfactant. Heterogeneity was suggested among the included studies. Subgroup analysis on budesonide delivery methods (inhalation or intratracheal instillation) indicated that the decrease of mortality, duration of assisted ventilation and hospital stays were mainly in budesonide intratracheal instillation subgroup, rather than in budesonide inhalation subgroup, which was consistent with the results of Yi-jiang Chen,[35]who demonstrated that budesonide intratracheal instillation was better than inhalation by meta-analysis.

In premature infants, BPD is one of the essential cause of the morbidity and mortality, and is associated with respiratory problems and neurodevelopmental impairment later in life.[36,37]The pathophysiology of BPD is highly complex. Immature lung surfactant scarcity, volutrauma, barotrauma and lung inflammation due to exposure to invasive mechanical ventilation are thought pivotal factors in the pathogenic mechanism of BPD. In recent years, strategies have focused on mitigating lung injury and inflammation for preventing BPD in the postpartum period.[38,39]

Corticosteroids are powerful anti-inflammatory agents, and early systemic corticosteroid administration in premature infants can reduce risk of BPD and facilitated extubation. However, it is correlated with many short-term and/or long-term side effects, including gastrointestinal bleeding, gastrointestinal perforation, hypertension, hyperglycaemia, growth restriction, abnormal findings on neurological examination, cerebral palsy and so on.[7] Thus, intravenous administration of corticosteroid is not recommended nowadays. A plausible alternative to systemic corticosteroid is inhalation glucocorticoid.[40] Budesonide is one of the most commonly used inhaled glucocorticoid, with a potent anti-inflammatory activity, and it has been used in asthma and other airway diseases to decrease lung inflammation for decades without obvious long term adverse outcomes reported.[41,42] It shows an extremely high affinity for glucocorticoid receptors and a high topical-to-systemic activity ratio, so the systemic potency of its metabolites is very low.[43]

Surfactant is the first-line treatment for premature infants with RDS. Studies in rats and rabbits found that intra-tracheal combined utilization of budesonide and exogenous surfactant, which distributed evenly throughout the lungs, could improve pulmonary gas exchange and decrease lung inflammation with the surfactant properties unchanged.[44,45]Recent years, similar results of decreased lung and systemic inflammation have been found in preterm sheep treated with surfactant and budesonide.[46,47] Clinical studies also showed that combination of budesonide and surfactant could dramatically decrease the incidence of BPD by improving pulmonary status and reducing the duration of mechanic ventilation.[19,22]

Using surfactant as a vehicle may improve the solubility and enhance the absorption of budesonide.[48] In lung cells, a reversible conjunction is formed between budesonide and fatty acids, which enables free budesonide release gradually in the surrounding media. The reversible conjugation of budesonide and fatty acids may be beneficial to improving airway selectivity and prolonging the local anti-inflammatory function in airways, [20,22,49]which partly explains the underlying causes for budesonide and surfactant has stronger effect on preventing BPD than surfactant only.

This meta-analysis showed that budesonide and surfactant could significantly decrease the incidence of PDA in premature infants. The underlying mechanism may be that, during the recovery period of RDS, the pulmonary vascular resistance decreases, which links to a propensity of PDA. In addition, the combined utilization of budesonide and surfactant early in life by airway increases the partial pressure of oxygen and decreases the concentration of local vascular prostaglandins, which induces the contraction of the arterial duct smooth muscle and the ductus arteriosus functionally close. Thereby, the incidence of PDA reduces.

Long-term neurological and cognitive adverse effects are the major concern of glucocorticoid therapy. While two studies[19,22] reported 2-3 years of follow-up data were included. Meta-analysis indicated that there

were no long-term adverse effects on neurological and cognitive outcomes after budesonide administration. The potential cause may be that budesonide is absorbed rather than metabolized in lung cells. The half-life of budesonide in the fetal lung is about 4 h, and its*metabolism*in the liver or other tissue is fairly rapidly.[49,50]Thus, its metabolites have minimal systemic side effects. But due to death after discharge, could not be located, unwilling to participate or uncooperative, an attrition bias may have been introduced.

Limitation: In our meta-analysis, there were several limitations, which might affect the interpretation of findings. First, this meta-analysis included premature infants with GA < 33 weeks, and GA-based subgroup analysis could not be performed for lack of individual patient data. Nevertheless, the premature infants with GA < 28 weeks were massive associated with BPD. Second, the dosage, duration, and inhalation or instillation of budesonide also were inconsistent across studies. Third, there were only two studies[19,22] reported 2-3 years of follow up data about long-term neurological and cognitive adverse effects, more large-scale and long-term follow-up studies are urgently needed. Furthermore, Harbord's modified test on small-studies*indicate*d that a potential publication bias existed. Last but not least, a majority of the included studies were from Asian populations, so there were ethnic limitations.

Conclusions

This meta-analysis suggested that early combined utilization of budesonide and surfactant by airway might be an effective and safe clinical practice for BPD prevention in premature infants with RDS, especially when budesonide was delivered by intratracheal instillation. However, the quality of the evidence may be decreased due to the obvious heterogeneity among included studies. In further research work, more well-designed RCTs with larger sample sizes ought to be conducted to assess the appropriate dosage and duration of budesonide. Before the treatment is widely recommended, more well-designed RCTs with larger sample sizes and longer follow-up ought to be conducted to assess the appropriate dosage and duration of budesonide, as well as long-term safety of airway delivery of budesonide.

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References

1. Hilgendorff A, Reiss I, Ehrhardt H, Eickelberg O, Alvira CM. Chronic lung disease in the preterm infant. Lessons learned from animal models.*American journal of respiratory cell and molecular biology.*2014;50(2):233-245.

2. Thébaud B, Goss KN, Laughon M, et al. Bronchopulmonary dysplasia.*Nature reviews Disease primers.* 2019;5(1):1-23.

3. Siffel C, Kistler KD, Lewis JF, Sarda SP. Global incidence of bronchopulmonary dysplasia among extremely preterm infants: a systematic literature review. *The Journal of Maternal-Fetal & Neonatal Medicine.* 2021;34(11):1721-1731.

4. Gough A, Spence D, Linden M, Halliday HL, McGarvey LP. General and respiratory health outcomes in adult survivors of bronchopulmonary dysplasia: a systematic review. *Chest.* 2012;141(6):1554-1567.

5. Cummings JJ, D'Eugenio DB, Gross SJ. A controlled trial of dexamethasone in preterm infants at high risk for bronchopulmonary dysplasia. *New England Journal of Medicine.*1989;320(23):1505-1510.

6. Baud O, Maury L, Lebail F, et al. Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): a double-blind, placebo-controlled, multicentre, randomised trial. *The Lancet.*2016;387(10030):1827-1836.

7. Doyle LW, Cheong JL, Ehrenkranz RA, Halliday HL. Early (< 8 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. *Cochrane Database of Systematic Reviews.* 2017(10): CD001146.

8. Zeng L, Tian J, Song F, et al. Corticosteroids for the prevention of bronchopulmonary dysplasia in preterm infants: a network meta-analysis.*Archives of Disease in Childhood-Fetal and Neonatal Edition.*2018;103(6):F506-F511.

9. Shah SS, Ohlsson A, Halliday HL, Shah VS. Inhaled versus systemic corticosteroids for preventing chronic lung disease in ventilated very low birth weight preterm neonates. *Cochrane Database of Systematic Reviews.* 2012(5): CD002058.

10. O'Callaghan C, Hardy J, Stammers J, Stephenson T, Hull D. Evaluation of techniques for delivery of steroids to lungs of neonates using a rabbit model. *Archives of disease in childhood.* 1992;67(1 Spec No):20-24.

11. Bassler D, Plavka R, Shinwell ES, et al. Early inhaled budesonide for the prevention of bronchopulmonary dysplasia. *New England Journal of Medicine.* 2015;373(16):1497-1506.

12. Shinwell ES, Portnov I, Meerpohl JJ, Karen T, Bassler D. Inhaled corticosteroids for bronchopulmonary dysplasia: a meta-analysis.*Pediatrics.* 2016;138(6): e20162511.

13. Bassler D, Shinwell ES, Hallman M, et al. Long-term effects of inhaled budesonide for bronchopulmonary dysplasia. *New England Journal of Medicine.* 2018;378(2):148-157.

14. Venkataraman R, Kamaluddeen M, Hasan SU, Robertson HL, Lodha A. Intratracheal administration of budesonide-surfactant in prevention of bronchopulmonary dysplasia in very low birth weight infants: a systematic review and meta-analysis. *Pediatric pulmonology.*2017;52(7):968-975.

15. Shuster JJ. Cochrane handbook for systematic reviews for interventions, Version 5.1. 0, published 3/2011. Julian PT Higgins and Sally Green, Editors. In: Wiley Online Library; 2011.

16. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine.* 2009;6(7):e1000097.

17. Mander A, Clayton D. Assessing the influence of a single study in meta-analysis. *Stata Tech Bull Reprints.* 1999;8:108-110.

18. Stata C. Stata statistical software: Release 12. *College Station, US: StataCorp LP.* 2007.

19. Yeh TF, Lin HC, Chang CH, et al. Early intratracheal instillation of budesonide using surfactant as a vehicle to prevent chronic lung disease in preterm infants: a pilot study. *Pediatrics.*2008;121(5):e1310-e1318.

20. Kuo HT, Lin HC, Tsai CH, Chouc I, Yeh TF. A follow-up study of preterm infants given budesonide using surfactant as a vehicle to prevent chronic lung disease in preterm infants. *The Journal of pediatrics.* 2010;156(4):537-541.

21. Ke H, Li Z-K, Yu X-P, Guo J-Z. Efficacy of different preparations of budesonide combined with pulmonary surfactant in the treatment of neonatal respiratory distress syndrome: a comparative analysis.*Chinese journal of contemporary pediatrics.* 2016;18(5):400-404.

22. Yeh TF, Chen CM, Wu SY, et al. Intratracheal administration of budesonide/surfactant to prevent bronchopulmonary dysplasia.*American journal of respiratory and critical care medicine.*2016;193(1):86-95.

23. Deng L-J, Peng H-B, Gong X-Q. Effect of budesonide combined with pulmonary surfactant on severe respiratory distress syndrome in bronchopulmonary dysplasia. *Chinese Journal of Neonatology.*2017;32(5):361-364.

24. Pan J, Chen M-W, Ni W-Q, et al. Clinical efficacy of pulmonary surfactant combined with budesonide for preventing bronchopulmonary dysplasia in very low birth weight infants. *Chinese Journal of Contemporary Pediatrics.* 2017;19(2):137-141.

25. Cao Y-Y, Yao G, Wang Y, Shi B-H, Liu J-L, Li G-F. Aerosol inhalation of budesonide and pulmonary surfactant to prevent bronchopulmonary dysplasia. *Journal of Pediatric Pharmacy.* 2018;24(3):25-29.

26. Luo L-Y, Chen K-H, Cao B-B. Observation on the efficacy of budesonide combined with pulmonary surfactant to prevent bronchopulmonary dysplasia in premature infants.*Zhejiang Clinical Medical Journal.* 2018;5(20): 796-798.

27. Sadeghnia A, Beheshti BK, Mohammadizadeh M. The effect of inhaled budesonide on the prevention of chronic lung disease in premature neonates with respiratory distress syndrome. *International journal of preventive medicine.* 2018;9:15.

28. Kou C, Han D, Li Z-N, et al. Effect of intratracheal administration of pulmonary surfactant plus budesonide on bronchopulmonary dysplasia in premature infant. *China Medicine.* 2019;1(14):53-57.

29. Ping L-L, Zhang S-Y, Zhai S-F. Influence of combined drug therapy by intratracheal infusion on clinical prognosis of premature infants with severe RDS. *Chinese Journal of Postgraduates of Medicine.*2019;2(42):154-157.

30. Wang Y-S, Yang M, Han P, Dai Q-M, Cui C-Y. Effect of budesonide suspension oxygenation atomization inhalation on prevention and treatment of bronchopulmonary dysplasia in premature infants.*Journal of Clinical and Experimental Medicine.* 2019;19:2121-2124.

31. Zhou X-P, Zhou J,Hu B, Wang X-H. Effects of budesonide combined with pulmonary surfactant on short-term efficacy,blood oxygenation index and risk of bronchopulmonary dysplasia in premature infants with severe respiratory distress syndrome. *Journal of Pediatric Pharmacy* . 2019;11(25):27-30.

32. Du F, Dong W, Zhang C, et al. Budesonide and Poractant Alfa prevent bronchopulmonary dysplasia via triggering SIRT1 signaling pathway.*European review for medical and pharmacological sciences.*2019;23(24):11032-11042.

33. Heo M, Jeon GW. Intratracheal administration of budesonide with surfactant in very low birth weight infants to prevent bronchopulmonary dysplasia. *Turkish Journal of Pediatrics.* 2020;62(4): 551-559.

34. Yang B, Lei H-L, Ren Y, et al. Pulmonary surfactant in combination with intratracheal budesonide instillation for treatment of respiratory distress syndrome in preterm infants: a randomized controlled trial.*Chinese Journal of Neonatology.* 2021;2(36):33-37.

35. Yi-jiang C, Shui-tang Z, Run-na Y. Intratracheal administration of budesonide within seven days after birth for preventing bronchopulmonary dysplasia in preterm infants: a systematic review and meta-analysis.*Chinese Journal of Evidence-Based Pediatrics.* 2016;4(11):259-264.

36. Doyle LW, Anderson P, Callanan C, et al. Respiratory function at age 8–9 years in extremely low birthweight/very preterm children born in Victoria in 1991–1992. *Pediatric pulmonology.*2006;41(6):570-576.

37. Vom Hove M, Prenzel F, Uhlig HH, Robel-Tillig E. Pulmonary outcome in former preterm, very low birth weight children with bronchopulmonary dysplasia: a case-control follow-up at school age. *The Journal of pediatrics.* 2014;164(1):40-45. e44.

38. Dumpa V, Bhandari V. Surfactant, steroids and non-invasive ventilation in the prevention of BPD. *Seminars in perinatology.*2018;42(7):444-452.

39. Morrow LA, Wagner BD, Ingram DA, et al. Antenatal determinants of bronchopulmonary dysplasia and late respiratory disease in preterm infants. *American journal of respiratory and critical care medicine.* 2017;196(3):364-374.

40. Cole CH. Postnatal glucocorticoid therapy for prevention of bronchopulmonary dysplasia: routes of administration compared.*Seminars in Neonatology.* 2001;6:343-350.

41. Esmailpour N, Hogger P, Rohdewald P. Binding kinetics of budesonide to the human glucocorticoid receptor. *European journal of pharmaceutical sciences.* 1998;6(3):219-223.

42. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *New England Journal of Medicine.* 2000;343(15):1064-1069.

43. Szefler SJ. Pharmacodynamics and pharmacokinetics of budesonide: a new nebulized corticosteroid. *Journal of allergy and clinical immunology.* 1999;104(4):S175-S183.

44. Huang L-T, Yeh T-F, Kuo Y-L, Chen P-C, Chen C-M. Effect of surfactant and budesonide on the pulmonary distribution of fluorescent dye in mice. *Pediatrics & Neonatology.* 2015;56(1):19-24.

45. Li L, Yang C, Feng X, Du Y, Zhang Z, Zhang Y. Effects of intratracheal budesonide during early postnatal life on lung maturity of premature fetal rabbits. *Pediatric pulmonology.* 2018;53(1):28-35.

46. Kothe TB, Kemp MW, Schmidt A, et al. Surfactant plus budesonide decreases lung and systemic inflammation in mechanically ventilated preterm sheep. *American Journal of Physiology-Lung Cellular and Molecular Physiology.* 2019;316(5):L888-L893.

47. Hillman NH, Kothe TB, Schmidt AF, et al. Surfactant plus budesonide decreases lung and systemic responses to injurious ventilation in preterm sheep. *American Journal of Physiology-Lung Cellular and Molecular Physiology.* 2020;318(1):L41-L48.

48. Wiedmann T, Bhatia R, Wattenberg L. Drug solubilization in lung surfactant. *Journal of controlled release.* 2000;65(1-2):43-47.

49. Barrette AM, Roberts JK, Chapin C, et al. Antiinflammatory effects of budesonide in human fetal lung. *American journal of respiratory cell and molecular biology.* 2016;55(5):623-632.

50. Moore CD, Roberts JK, Orton CR, et al. Metabolic pathways of inhaled glucocorticoids by the CYP3A enzymes. *Drug Metabolism and Disposition.* 2013;41(2):379-389.

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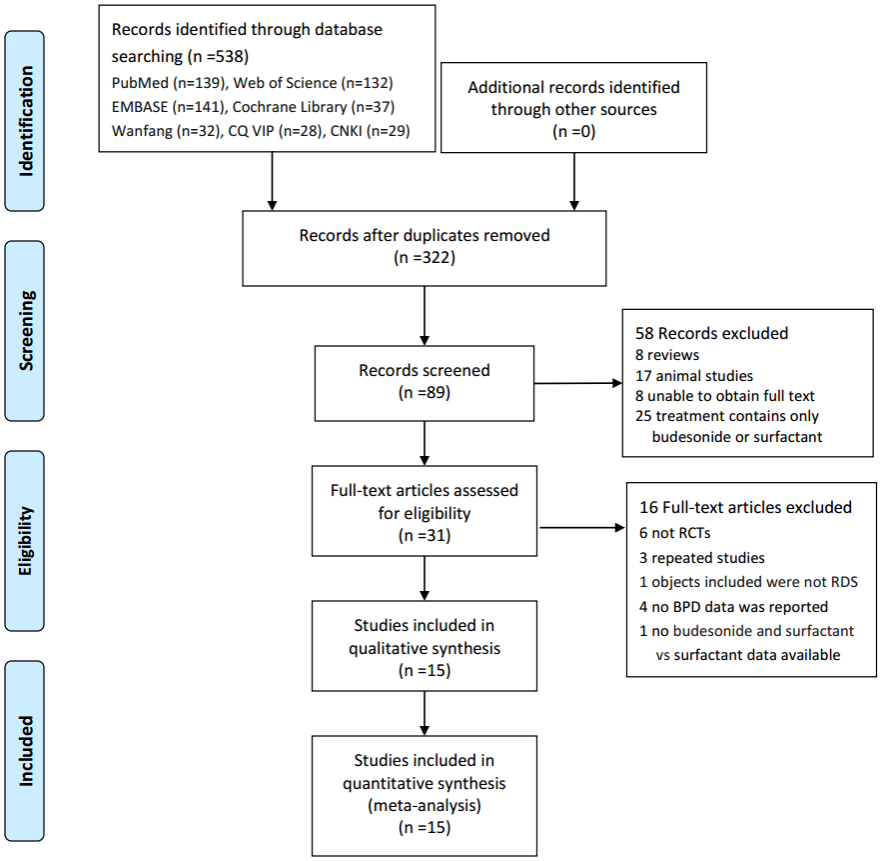

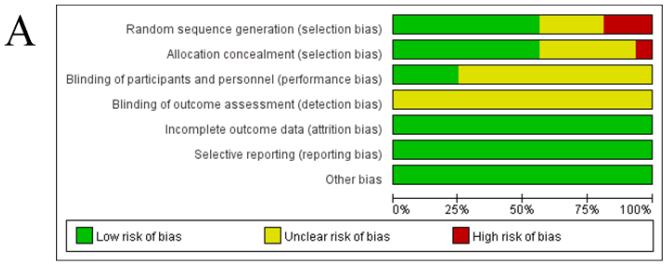

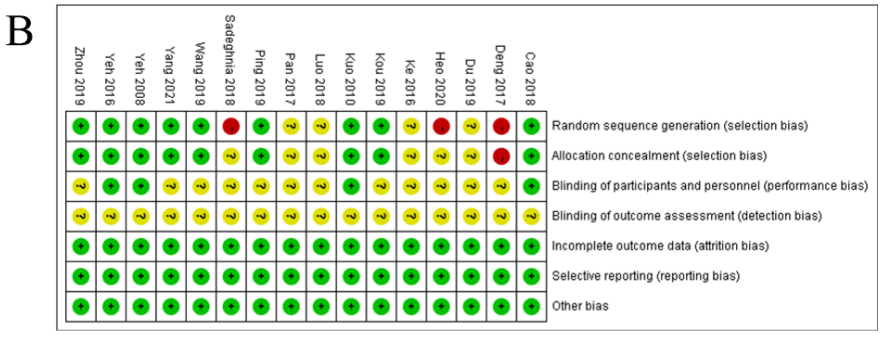

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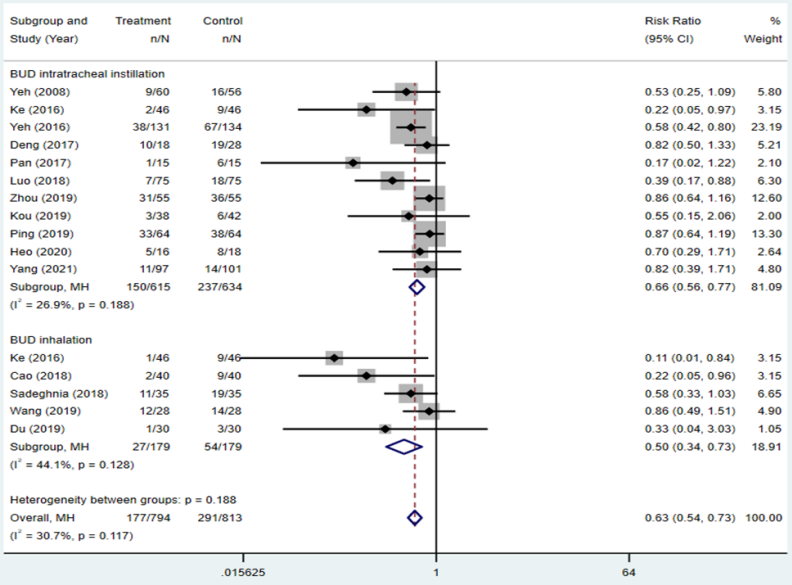

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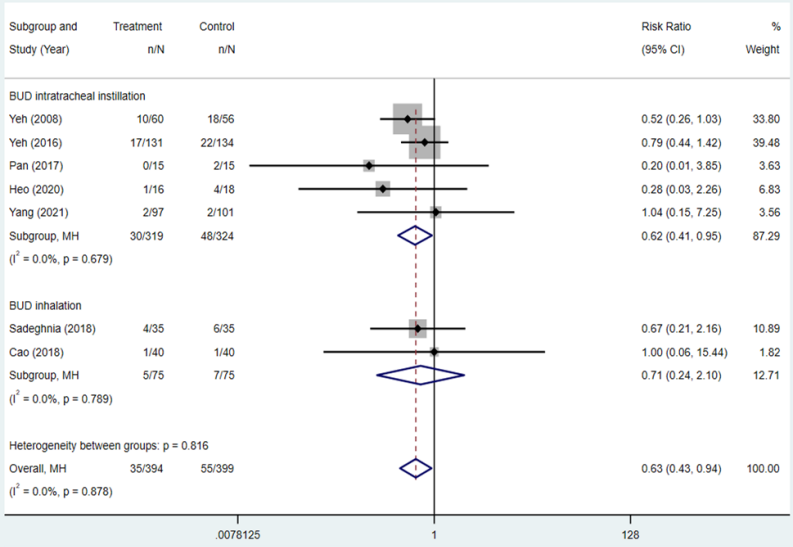

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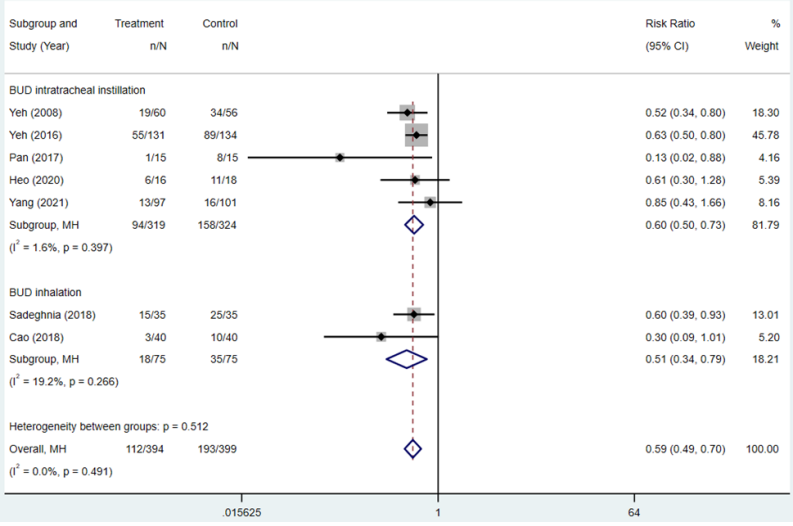

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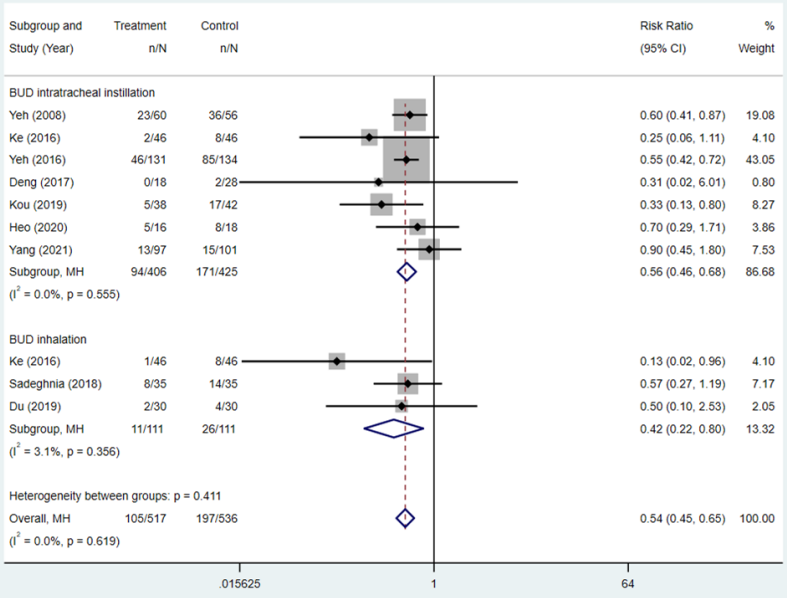

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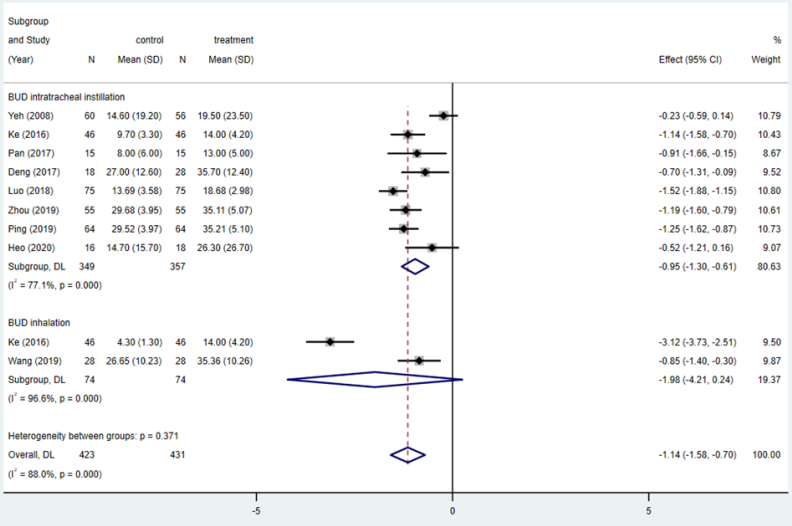

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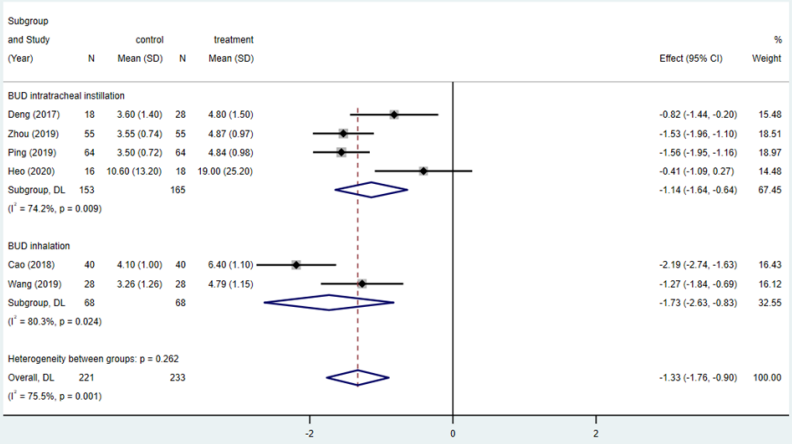

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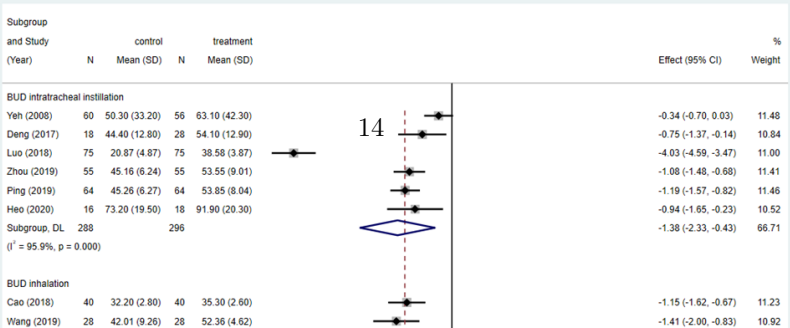

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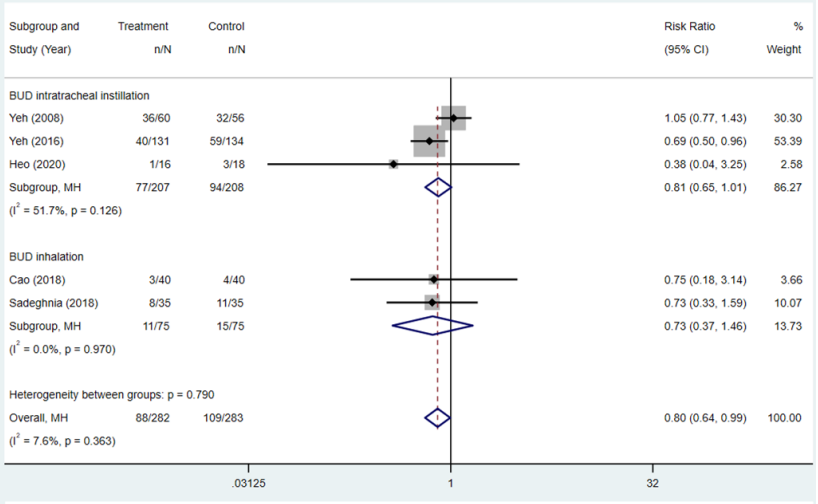

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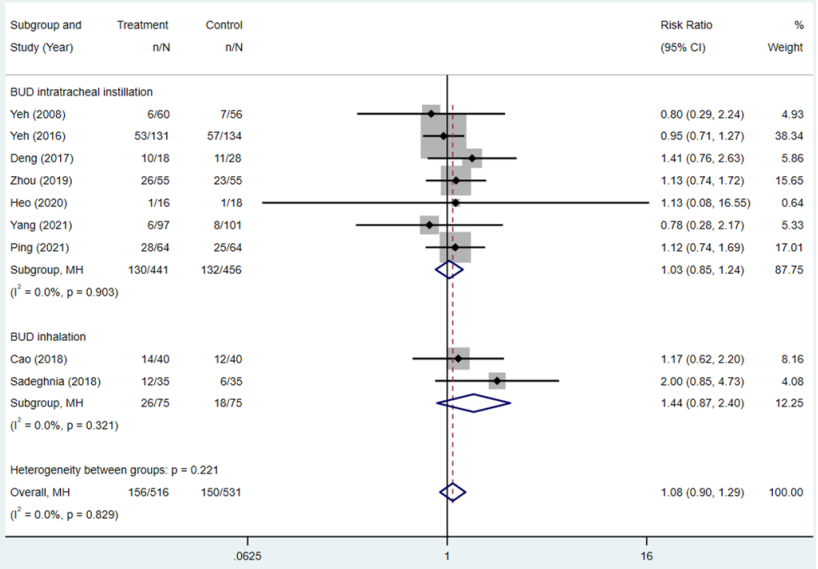

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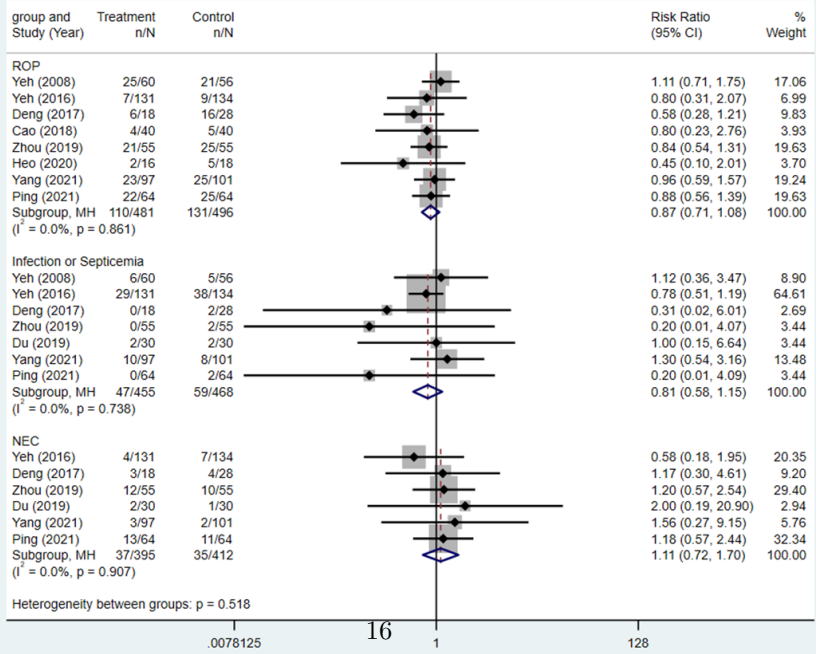

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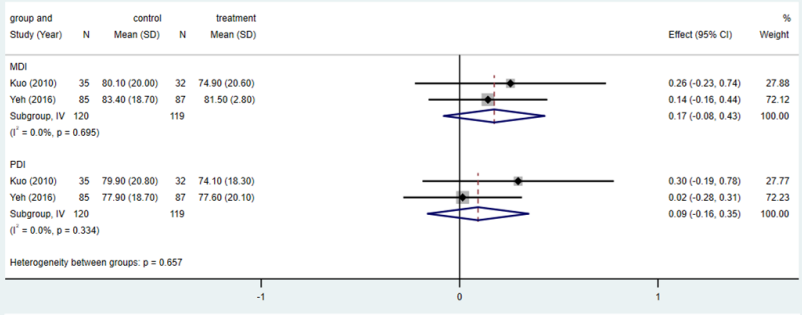

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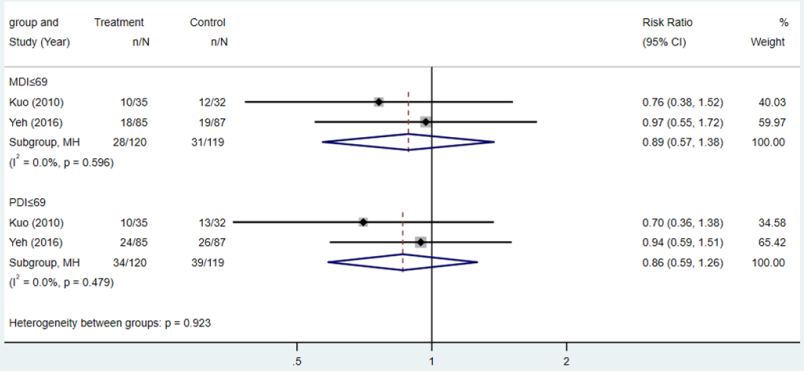

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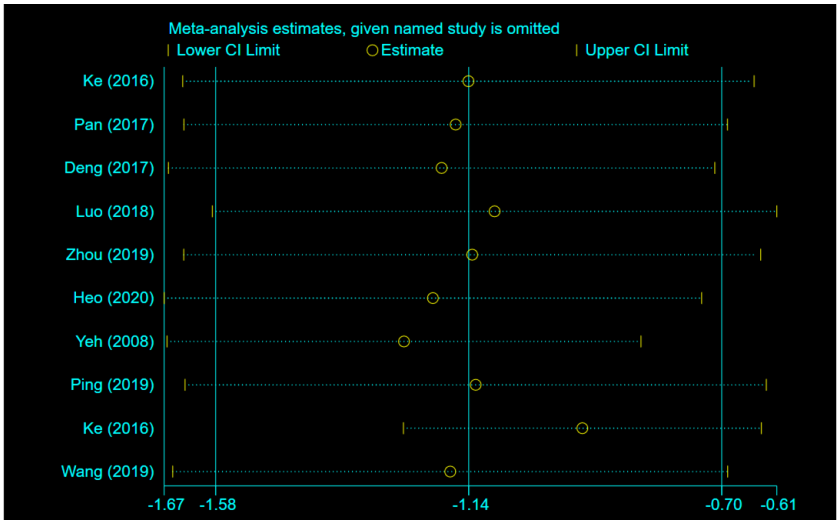

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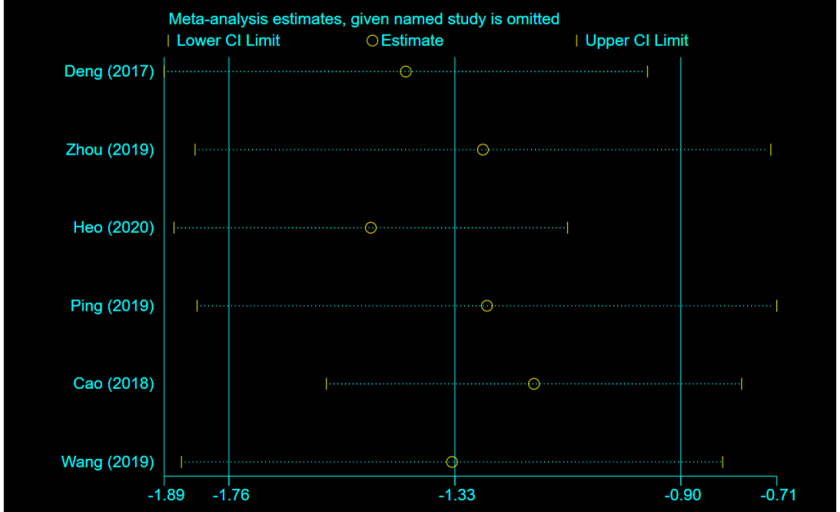

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