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Efficacy of bilevel positive airway pressure ventilation and continuous positive airway pressure ventilation in patients with obesity hypoventilation syndrome: protocol for systematic review and meta-analysis

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Complete List of Authors:	Guan, Lili Wu, Weiliang; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University Huo, Yating; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University Li, Xiaoying; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University Guo, Bingpeng; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University Yang, Yuqiong; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University Xu, Jiawen; State Key Laboratory of Respiratory Disease, First Affiliated Hospital of Guangzhou Medical University Jiang, Fangfang; State Key Laboratory of Respiratory Disease, First Affiliated Hospital of Guangzhou Medical University Zhou, Luqian; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University Chen, Rongchang; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University
Keywords:	Obesity hypoventilation syndrome, Bilevel positive airway pressure ventilation, Continuous positive airway pressure ventilation, Systematic review and Meta-Analysis, Protocol

Efficacy of bilevel positive airway pressure ventilation and continuous positive airway pressure ventilation in patients with obesity hypoventilation syndrome: protocol for systematic review and meta-analysis

Authors' names:

Lili Guan[a*]

Weiliang Wu[a*]

Yating Huo[a*]

Xiaoying Li[b*]

Bingpeng Guo[a]

Yuqiong Yang[a]

Jiawen Xu

Fangfang Jiang

Luqian Zhou[a#]

Rongchang Chen[a#]

Authors' affiliation(s):

[a] State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

[b] The First Affiliated Hospital / School of Clinical Medicine of Guangdong Pharmaceutical University, Guangzhou, China

* These authors contributed equally to this work and should be considered as the co-first authors

[#] These authors contributed equally to this work and should be considered as the joint corresponding authors

Corresponding:

Name: Luqian Zhou;

Address: State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, 151 Yan Jiang Rd. Guangzhou, China;

Post code: 510120

Phone and fax numbers: +862083062882

E-mail: zhlx09@163.com

Name: Rongchang Chen;

Address: State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, 151 Yan Jiang Rd. Guangzhou, China;

Post code: 510120

Phone and fax numbers: +862083062882

E-mail: chenrcstatekeylab@gmail.com

Abbreviations list:

OHS = Obesity hypoventilation syndrome;

$PaCO_2$ = Partial pressure of arterial blood carbon dioxide;

CPAP = Continuous positive airway pressure;

BiPAP = Bilevel positive airway pressure;

RCT = Randomized controlled trial;

Abstract

Introduction Obesity hypoventilation syndrome (OHS) is a major respiratory complication caused by obesity, which will be at high risk of mortality and affecting their daily life if not treated properly. Positive airway pressure therapy is the first line treatment for OHS although the optimal modality of positive airway pressure remains unclear. The goal of this study is to compare the efficacy of the home bilevel positive airway pressure and continuous positive airway pressure ventilation and determine the best strategy for patients with OHS.

Methods and analysis This study will be conducted following the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols 2015 statement. We will search the following databases: PubMed, Web of Science, EMBASE, Cochrane Central Register of Controlled Trials and CINAHL. Ongoing studies will be identified through the ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform Search Portal. Grey literature will be recognized through Google Scholar and other search engines. Only randomized controlled trials meeting the eligibility criteria will be included. The risk of bias of the included studies will be evaluated through the Cochrane Collaboration's tool. RevMan 5.3.5 software will be used for data analysis. The Q statistic and I^2 index will be used for investigating the heterogeneity, and subgroup analysis or sensitivity analysis will be used to explore the source of heterogeneity. In addition, the Grading of Recommendations Assessment, Development and Evaluation system will be used to inspect the quality of evidence.

Ethics and dissemination Ethics approval is not required because this study contains no primary data collected from humans. This systematic review and meta-analysis will be submitted to a peer-reviewed journal for publication.

Trial registration number CRD42017078369

Key words: Obesity hypoventilation syndrome; Bilevel positive airway pressure ventilation; Continuous positive airway pressure ventilation; Systematic review and Meta-Analysis; Protocol;

Strengths and limitations of this study

- The first systematic review and meta-analysis to compare the efficacy of the home bilevel positive airway pressure and continuous positive airway pressure ventilation in patients with obesity hypoventilation syndrome (OHS).
- This study will help to identify the appropriate home positive airway pressure ventilation strategy OHS patients.
- Only randomized controlled trial, representing the high quality of evidence, can be included in this study.
- To determine the most appropriate patients to receive bilevel positive airway pressure ventilation through subgroup analysis.

Word counts ABSTRACT 274 words; TEXT 1993 words,

Introduction

The increasing incidence of obesity has become a worldwide major concern.[1] Obesity hypoventilation syndrome (OHS) is a major respiratory complication caused by obesity that is characterized by the daytime arterial partial pressure of carbon dioxide ($PaCO_2$) > 45 mmHg with BMI > 30 kg/m^2 and excluding other causes of hypoventilation (neuromuscular disorders, chest abnormalities, or COPD, etc.). [2] OHS usually results from the upper airway obstruction, sleep hypoventilation, decreased lung capacity, increased respiratory muscle load, changing respiratory center drive, or leptin resistance. [3,4] Due to the presence of chronic hypercapnia and hypoxemia, patients with OHS will be at high risk of severe respiratory failure, pulmonary hypertension, chronic cor pulmonale and other cardiovascular complications if not treated appropriately. [5,6] Moreover, this will greatly affect the patient's health-related quality of life, exercise performance, survival rate and may become a serious social and economic burden.[7–9]

The treatment therapy is aimed at improving the pathophysiologic abnormalities of patients with OHS which commonly includes positive airway pressure therapy, lifestyle intervention, surgery, and pharmacotherapy. Positive airway pressure therapy is considered to be the first line treatment, which can effectively improve gas exchange, sleep disorders and decrease mortality in OHS patients.[10,11] Positive airway pressure therapy often refers to the continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) ventilation. CPAP provides a constant positive pressure in the airway, which can reduce upper airway resistance and prevent upper airway obstruction events, thereby controlling sleep disorders and improving oxygenation. However, CPAP is not a truly physiologically-based ventilation mode. It just provides a constant pressure at respiratory tract to maintain the upper airway open and increase the lung volume. BiPAP, setting the inspiratory positive airway pressure and expiratory positive airway pressure, is more consistent with the patient's normal breathing pattern which can increase tidal volume, improve alveolar hypoventilation and relieve respiratory fatigue.[12] Therefore, BiPAP should

be more effective in improving oxygenation and reducing arterial carbon dioxide theoretically.

Currently, the optimal mode of home positive airway pressure therapy for patients with OHS has not been determined. Only a few randomized controlled trials (RCTs) [13–15] but no systematic review and meta-analysis, have compared the efficacy of domiciliary BiPAP versus CPAP ventilation in OHS patients. The main objective of this study is to determine whether BiPAP is more effective in treating OHS and to identify the best positive airway pressure setting for patients with OHS as the first line treatment.

Objective

The goal of this systematic literature review and meta-analysis is to compare the curative effect of home BiPAP and CPAP ventilation in patients with OHS. Specifically, what is the efficacy of home BiPAP and CPAP ventilation in patients with OHS as reported in the research published from January 1980 through November 2017?

Methods

This manuscript follows the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 statement.[16]

Eligibility criteria:

Study designs

Only RCTs will be included. We will include RCTs analyzing the efficiency of domiciliary BiPAP and CPAP ventilation in patients with OHS.

Participants

Included patients were all diagnosed as OHS (BMI >30 kg/m^2 and daytime $PaCO_2$ >45 mm Hg) and excluded other condition that might lead to hypoventilation including neuromuscular disorders, chest abnormalities, or COPD.[2]

Interventions

BiPAP ventilation equipped with the inspiratory positive airway pressure and expiratory positive airway pressure, is more consistent with the patient's normal breathing pattern which can increase tidal volume, improve alveolar hypoventilation and relieve respiratory fatigue; CPAP ventilation provides a constant positive pressure in the airway, which can reduce upper airway resistance and prevent upper airway obstruction events. [12]

Outcomes

- **Primary outcome:** Daytime $PaCO_2$
- **Secondary outcomes:**
    - Health-related quality of life (The Medical Outcome Study 36-item short-form health survey [17], Epworth Sleepiness Scale [18], Severe Respiratory Insufficiency Questionnaire [19]);
    - Mortality;
    - The incidence of hospital readmissions.
    - Lung function [20];
    - Physical activity (6-minute walk test [21])

Information sources and search strategy

Electronic searches

We will search the following databases: PubMed, Web of Science, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, and CINAHL. The searching period will be from January 1980 to November 2017. Literature retrieved will be limited to human subjects and language or publication status will not be limited. The searches will be reworked before the final analyses, and further studies will also be reviewed for the inclusion. The detailed search strategy of PubMed is presented in Supplement 1.

Searching other resources

Ongoing studies will be identified through the ClinicalTrials.gov (November 2017) and World Health Organization International Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch/). We will contact the authors to get further information on ongoing or unpublished studies, if necessary. In order to ensure that the search is comprehensive, we will look through the bibliography of the included studies or reviews to identify the relevant reports. Grey literature (including reports and conference presentations) will be searched through Google Scholar and other relevant websites.

Study records

Data management

All previously searched literature will be imported into EndNote Version X8 software (Clarivate Analytics, Philadelphia, PA, USA), and duplicates will be removed. The titles and abstracts obtained from the previous searches will be inspected independently by two investigators (WL and XL). If the article meets the eligibility criteria, or if there is any uncertainty about including a particular study, the report will be downloaded.

Selection process

The imported articles will be screened by two independent investigators (WL and XL) to determine whether they meet the criteria for inclusion. We will ask the authors for additional information when necessary. Reasons for excluding the literatures will be recorded. The two investigators will resolve any disagreements through discussion, and the third investigator (LQ) will offer advice when agreement cannot be reached.

Data collection process

Two investigators (BP and YT) will independently extract data using a standardized data collection form. The extracted data will include: 1) study characteristics such as first author, journal, year, and study design; 2) patients' characteristics including the number of patients in each group, age, sex, BMI, and severity of OHS; 3) intervention characteristics (inspiratory positive airway pressure, expiratory positive airway pressure, and back-up rate), mean daily use of ventilation, and treatment duration; and 4) primary and secondary outcomes as described above. For cross-over trials, we will only extract the data from the first phase, primarily because of the carry-over effect. When the extraction process is complete, we will merge the two collections into one for further analysis. Should there be any disagreements at this stage, the two investigators will reach an agreement through discussion. If agreement cannot be reached, the third investigator (LQ) will participate in the discussion to reach a final conclusion.

Risk of bias in individual studies

Two investigators (YQ and JW) will use the Cochrane Collaboration's tool to assess the risk of bias of the included studies.[22,23] Six domains will be assessed: selection bias, performance bias, detection bias, attrition bias, reporting bias, and "other" bias. Each domain will be judged as "low risk," "unclear risk," or "high risk." The support for

these judgments will be clarified in a risk of bias table. Divergences will be discussed first by the two investigators, and if an agreement cannot be reached, the third investigator (LQ) will provide a suggestion.

Data synthesis

Analyses will be done using RevMan 5.3.5 software (Cochrane, London, UK).

Measures of treatment effect

For continuous outcomes such as P_aCO_2, 6-minute walk distance, etc., the weighted mean difference or standardized mean difference with 95% confidence intervals will be used. Dichotomous outcomes such as patient mortality and the incidence of hospital readmission will be described using the risk ratio with 95% confidence intervals.

Dealing with missing data

When data are missing or inapplicable, we will contact the original authors by email or use a formula to convert them into available data.[22,24,25] If the missing data cannot be obtained, we will follow the recommendations of the Cochrane Handbook for Systematic Reviews of Intervention[22]: 1) make precise the hypothesis of any methods used to handle the missing data; 2) sensitivity analyses will be used to assess how sensitive results are to reasonable changes in the assumptions that are made; 3) consider the potential effect of the missing data as limitations in our study.

Assessment of heterogeneity

We will investigate statistical heterogeneity among the included studies using the Q statistic and I^2 index. A *p* value of ≤ 0.10 for the Q statistic will be considered to be statistically significant heterogeneity. I^2 values < 25%, 25%–50%, or > 50% represent low, moderate, or high heterogeneity, respectively. I^2 values greater than 50% will be regarded as substantial heterogeneity. We will apply a fixed-effect model if no heterogeneity exists. When substantial heterogeneity (I^2 > 50% or $P \leq 0.1$) is detected, we will try to interpret the source of heterogeneity by subgroup analysis, sensitivity analysis, or using a random-effects model. If substantial heterogeneity cannot be well explained, we will not proceed with the meta-analysis and a descriptive, qualitative summary will be made.[22]

Additional analyses

Possible sources of heterogeneity will be determined through carrying out subgroup analysis based on the gender, BMI, the severity of the OHS (moderate or severe), whether combined with obstructive sleep apnea; the mean daily home use of the ventilator and the duration of the follow-up periods (short-term (< 12 months) or long-term (>= 12 months)). Sensitivity analysis will also be performed to detect the source of heterogeneity. When substantial heterogeneity exists, we will exclude the study and compare its impact on the pooled estimate. If we find the source of heterogeneity, we will review the literature again to evaluate its quality and bias and decide whether the particular study is to be retained or excluded. If the study is excluded, the reasons for its removal will be explained in the discussion. If the quantitative synthesis is not appropriate, a narrative method will be used. This approach will present the information in a text or table in order to interpret and summarize the features and outcomes among the included studies.

Meta-biases

Publication bias will be assessed through the funnel plot if the number of the included studies is ≥ 10. In addition, in order to assess the reporting bias, we will search the database of the registered protocols mentioned above to confirm that whether the study's prespecified outcomes have not been reported.

Confidence in cumulative estimate

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system will be used for rating the quality of evidence for all outcomes of the included studies. The quality of evidence will be classified into four levels of quality (high, moderate, low, and very low). Because RCTs are considered to be high quality, the quality of the evidence may be downgraded when study limitations, the inconsistency of results, indirectness of evidence, imprecision, or reporting bias occur.[26,27]

Ethics and dissemination

Ethics approval is not required because this is a protocol for a systematic review and meta-analysis in which no primary human data will be collected. Our findings will be submitted to a peer-reviewed journal for publication.

Acknowledgement

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Contributions

LL, RC, and LQ contributed to the conception and design of the study, drafting the submitted article and revising the draft critically for important intellectual content. LL and YT contributed to the search strategy. Data management and selection process were proceeded by WL and XY. BP and YT were responsible for the data collection. YQ, FF and JW contributed to the risk of bias assessment. All authors contributed to data analysis, amending the paper, being responsible for all aspects of the work and approving the final version of the manuscript.

DISCLOSURE STATEMENT

Conflicts of interest: none

Data sharing statement

Extra data is available by emailing the corresponding author.

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PubMed:

#1 "Obesity Hypoventilation Syndrome"[Mesh]

#2 OHS [Title/Abstract] OR "Hypoventilation Syndrome, Obesity" [Title/Abstract] OR " Syndrome, Obesity Hypoventilation" [Title/Abstract] OR "Pickwickian Syndrome" [Title/Abstract] OR "Syndrome, Pickwickian" [Title/Abstract] OR "Obesity-Hypoventilation Syndrome" [Title/Abstract]

#3 "Continuous Positive Airway Pressure"[Mesh]

#4 "CPAP Ventilation" [Title/Abstract] OR "Ventilation, CPAP" [Title/Abstract] OR "Biphasic Continuous Positive Airway Pressure" [Title/Abstract] OR "Nasal Continuous Positive Airway Pressure" [Title/Abstract] OR "nCPAP Ventilation" [Title/Abstract] OR "Ventilation, nCPAP" [Title/Abstract] OR "Airway Pressure Release Ventilation" [Title/Abstract] OR "APRV Ventilation Mode" [Title/Abstract] OR "APRV Ventilation Modes" [Title/Abstract] OR "Ventilation Mode, APRV" [Title/Abstract] OR "Ventilation Modes, APRV" [Title/Abstract]

#5 "Noninvasive Ventilation"[Mesh]

#6 "Noninvasive Ventilations" [Title/Abstract] OR "Ventilation, Noninvasive" [Title/Abstract] OR "Ventilations, Noninvasive" [Title/Abstract] OR "Non-Invasive Ventilation" [Title/Abstract] OR "Non-Invasive Ventilations" [Title/Abstract] OR "Ventilation, Non-Invasive" [Title/Abstract] OR "Ventilations, Non-Invasive" [Title/Abstract] OR "Non Invasive Ventilation" [Title/Abstract] OR "Non Invasive Ventilations" [Title/Abstract] OR "Ventilation, Non Invasive" [Title/Abstract] OR "Ventilations, Non Invasive" [Title/Abstract]

#7 BiPAP [Title/Abstract] OR "bilevel" [Title/Abstract] OR "bi-level" [Title/Abstract]

#8 "randomized controlled trial" [Publication Type] OR "clinical trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Controlled Clinical Trials as Topic"[Mesh] OR "Clinical Trials as Topic"[Mesh] OR randomized [Title/Abstract] OR randomly [Title/Abstract] OR trial [Title/Abstract]

#9 ("1980/01/01"[PDAT]: "2017/11/01"[PDAT]) AND "humans"[Mesh Terms]

#10 (#1 OR #2)

#11 (#3 OR #4)

#12 (#5 OR #6 OR #7)

#13 (#8 AND #9 AND #10 AND #11 AND #12)

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Complete List of Authors:	Guan, Lili; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Respiratory Medicine Wu, Weiliang; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Respiratory Medicine Huo, Yating; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Respiratory Medicine Li, Xiaoying; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Respiratory Medicine Guo, Bingpeng; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Respiratory Medicine Yang, Yuqiong; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Respiratory Medicine Xu, Jiawen; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Respiratory medicine Jiang, Fangfang; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Respiratory medicine Zhou, Luqian; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Respiratory medicine Chen, Rongchang; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Respiratory medicine
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Authors' names:

Lili Guan[a*]

Weiliang Wu[a*]

Yating Huo[a*]

Xiaoying Li[b*]

Bingpeng Guo[a]

Yuqiong Yang[a]

Jiawen Xu

Fangfang Jiang

Luqian Zhou[a#]

Rongchang Chen[a#]

Authors' affiliation(s):

[a] Department of respiratory medicine, State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

[b] Department of respiratory medicine, The First Affiliated Hospital / School of Clinical Medicine of Guangdong Pharmaceutical University, Guangzhou, China

* These authors contributed equally to this work and should be considered as the co-first authors

# These authors contributed equally to this work and should be considered as the joint corresponding authors

Corresponding:

Name: Luqian Zhou;

Address: State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, 151 Yan Jiang Rd. Guangzhou, China;

Post code: 510120

Phone and fax numbers: +862083062882

E-mail: zhlx09@163.com

Name: Rongchang Chen;

Address: State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, 151 Yan Jiang Rd. Guangzhou, China;

Post code: 510120

Phone and fax numbers: +862083062882

E-mail: chenrcstatekeylab@gmail.com

Abbreviations list:

OHS = Obesity hypoventilation syndrome;

$PaCO_2$ = Partial pressure of arterial blood carbon dioxide;

PAP = Positive airway pressure;

CPAP = Continuous positive airway pressure;

RCT = Randomized controlled trial;

S/T = Spontaneous/timed

VAPS = Volume-assured pressure support

Abstract

Introduction Obesity hypoventilation syndrome (OHS) is a major respiratory complication caused by severe obesity, being associated with significant morbidity, negative impacts on quality of life and reduced survival if not treated appropriately. Positive airway pressure therapy is the first line treatment for OHS although the optimal modality of positive airway pressure remains unclear. The goal of this study is to identify the efficacy of home bilevel positive airway pressure therapy by comparison to continuous positive airway pressure therapy and determine the best strategy for patients with OHS.

Methods and analysis This study will be conducted following the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols 2015 statement. We will search the following databases: PubMed, Web of Science, EMBASE, Cochrane Central Register of Controlled Trials and CINAHL. Ongoing studies will be identified through the ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform Search Portal. Grey literature will be recognized through Google Scholar and other search engines. Only randomized controlled trials meeting the eligibility criteria will be included. The risk of bias of the included studies will be evaluated through the Cochrane Collaboration's tool. RevMan 5.3.5 software will be used for data analysis. The Q statistic and I^2 index will be used for investigating heterogeneity, and subgroup analysis or sensitivity analysis will be used to explore the source of heterogeneity. In addition, the Grading of Recommendations Assessment, Development and Evaluation system will be used to inspect the quality of evidence.

Ethics and dissemination Ethics approval is not required because this study contains no primary data collected from humans. This systematic review and meta-analysis will be submitted to a peer-reviewed journal for publication.

Trial registration number CRD42017078369

Key words: Obesity hypoventilation syndrome; Bilevel positive airway pressure therapy; Continuous positive airway pressure therapy; Systematic review and Meta-Analysis; Protocol;

Strengths and limitations of this study

- The first systematic review and meta-analysis to compare the efficacy of home bilevel positive airway pressure and continuous positive airway pressure therapy in patients with obesity hypoventilation syndrome (OHS).
- This study will help to identify the most appropriate home positive airway pressure therapy strategy for OHS patients.
- Only randomized controlled trials, representing the high quality of evidence, will be included in this study.
- To determine the most appropriate patients to receive bilevel positive airway pressure therapy through subgroup analysis.

Word counts ABSTRACT 277 words; TEXT 2187 words,

Introduction

The increasing incidence of obesity has become a major concern worldwide.[1] Obesity hypoventilation syndrome (OHS) is a major respiratory complication caused by obesity and is characterized by a daytime arterial partial pressure of carbon dioxide ($PaCO_2$) > 45 mmHg with BMI > 30 kg/m^2 and excluding other causes of hypoventilation (such as neuromuscular disorders, chest wall abnormalities or significant lung diseases.). [2] OHS usually appears to be the end consequence of a complex interplay between upper airway obstruction, sleep hypoventilation, decreased lung capacity, increased respiratory muscle load, changing respiratory center drive, or leptin resistance. [3,4] Due to the presence of chronic hypercapnia and hypoxemia, patients with OHS are at high risk of severe respiratory failure, pulmonary hypertension, chronic cor pulmonale and other cardiovascular complications if not treated appropriately. [5,6] Moreover, this will greatly affect the patient's health-related quality of life, exercise performance, survival rate and may become a serious social and economic burden.[7–9]

Treatment of this disorder is aimed at improving the pathophysiologic abnormalities of patients with OHS which commonly includes positive airway pressure therapy, lifestyle intervention, surgery, and pharmacotherapy. Positive airway pressure (PAP) therapy is considered to be the first line treatment, which can effectively improve gas exchange, sleep disorders and decrease mortality in OHS patients.[10,11] Additionally, Castro-Añón O al. indicated that even with PAP therapy, OHS patients' mortality remained higher than eucapnic OSA patients who received PAP therapy.[8] PAP therapy may be delivered as either the continuous positive airway pressure (CPAP) or bilevel therapy (including spontaneous, timed, spontaneous/timed (S/T) or volume-assured pressure support (VAPS) modes). CPAP provides a constant positive pressure in the airway, which can reduce upper airway resistance and prevent upper airway obstructive events, thereby controlling sleep disorders and improving oxygenation. However, CPAP is not a truly physiologically-based ventilation mode. It simply provides a constant pressure to the airway to maintain the

upper airway open and increase lung volumes. In contrast, bilevel therapy, more consistent with the patient's normal breathing pattern, provides a differential pressure between inspiration and expiration (pressure support level) which acts to increase tidal volume, improve alveolar hypoventilation and relieve respiratory fatigue.[12] Therefore, theoretically bilevel therapy should be more effective in improving oxygenation and reducing arterial carbon dioxide levels.

Currently, the optimal mode of home PAP therapy for patients with OHS has not been determined. Only a few randomized controlled trials (RCTs) [13–15] but no systematic review and meta-analysis, have compared the efficacy of domiciliary bilevel versus CPAP therapy in OHS patients. The main objective of this study is to determine whether bilevel therapy is more effective than CPAP therapy in treating OHS and to identify the best PAP setting for patients with OHS as the first line treatment.

Objective

The goal of this systematic literature review and meta-analysis is to determine the curative effect of the home bilevel therapy by comparison to CPAP therapy in patients with OHS. Specifically, what is the difference of treatment effect between home bilevel and CPAP therapy in patients with OHS as reported in the research published from January 1980 through November 2017?

Methods

This manuscript follows the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 statement.[16]

Eligibility criteria:

Study design

Only RCTs will be included. We will include RCTs comparing the efficiency of domiciliary bilevel and CPAP therapy in patients with OHS.

Participants

Only subjects diagnosed with OHS (i.e. BMI >30 kg/m^2 and daytime $PaCO_2$ >45 mm Hg) with exclusion of other conditions that might lead to hypoventilation including neuromuscular disorders, chest abnormalities, or COPD will be included in this analysis. [2]

Interventions

Bilevel therapy, providing a differential pressure between inspiration and expiration, is more consistent with the patient's normal breathing pattern which can increase tidal volume, improve alveolar hypoventilation and relieve respiratory fatigue; CPAP therapy provides a constant positive pressure in the airway, which can reduce upper airway resistance and prevent upper airway obstruction events. [12]

Outcomes

- **Primary outcome:** Daytime $PaCO_2$
- **Secondary outcomes:**
    - Adherence (Whether average PAP therapy use of ≥ 2 hours per night)[15]
    - Health-related quality of life (The Medical Outcome Study 36-item short-form health survey [17], Epworth Sleepiness Scale [18], Severe Respiratory Insufficiency Questionnaire [19]);
    - Mortality;

- The incidence of hospital readmissions.
- Lung function [20];
- Physical activity (6-minute walk test [21])

Information sources and search strategy

Electronic searches

We will search the following databases: PubMed, Web of Science, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, and CINAHL. The searching period will be from January 1980 to November 2017. Literature retrieved will be limited to human subjects and language or publication status will not be limited. The searches will be reworked before the final analyses, and further studies will also be reviewed for the inclusion. The detailed search strategy of PubMed is presented in Supplement 1.

Searching other resources

Ongoing studies will be identified through the ClinicalTrials.gov (November 2017) and World Health Organization International Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch/). We will contact the authors to get further information on ongoing or unpublished studies, if necessary. In order to ensure that the search is comprehensive, we will look through the bibliography of the included studies or reviews to identify the relevant reports. Grey literature (including reports and conference presentations) will be searched through Google Scholar and other relevant websites.

Study records

Data management

All previously searched literature will be imported into EndNote Version X8 software (Clarivate Analytics, Philadelphia, PA, USA), and duplicates will be removed. The titles and abstracts obtained from the previous searches will be inspected independently by two investigators (WL and XL). If the article meets the eligibility criteria, or if there is any uncertainty about including a particular study, the report will be downloaded.

Selection process

The imported articles will be screened by two independent investigators (WL and XL) to determine whether they meet the criteria for inclusion. We will ask the authors for additional information when necessary. Reasons for excluding studies will be recorded. The two investigators will resolve any disagreements through discussion, and the third investigator (LQ) will offer advice when agreement cannot be reached.

Data collection process

Two investigators (BP and YT) will independently extract data using a standardized data collection form. The extracted data will include: 1) study characteristics such as first author, journal, year, and study design; 2) patients' characteristics including the number of patients in each group, age, sex, BMI, and severity of OHS; 3) intervention characteristics (type of PAP therapy, mode of bilevel therapy, inspiratory positive airway pressure, expiratory positive airway pressure, and back-up rate), mean daily use of ventilation, and treatment duration; and 4) primary and secondary outcomes as described above. For cross-over trials, we will only extract the data from the first phase, primarily because of the carry-over effect. When the extraction process is complete, we will merge the two collections into one for further analysis. Should there be any disagreements at this stage, the two investigators will reach an agreement through discussion. If agreement cannot be reached, the third investigator (LQ) will participate in the discussion to reach a final conclusion.

Risk of bias in individual studies

Two investigators (YQ and JW) will use the Cochrane Collaboration's tool to assess the risk of bias of the included studies.[22,23] Six domains will be assessed: selection bias, performance bias, detection bias, attrition bias, reporting bias, and "other" bias. Each domain will be judged as "low risk," "unclear risk," or "high risk." The support for these judgments will be clarified in a risk of bias table. Divergences will be discussed first by the two investigators, and if an agreement cannot be reached, the third investigator (LQ) will provide a suggestion.

Data synthesis

Analyses will be done using RevMan 5.3.5 software (Cochrane, London, UK).

Measures of treatment effect

For continuous outcomes such as P_aCO_2, 6-minute walk distance, etc., the weighted mean difference or standardized mean difference with 95% confidence intervals will be used. Dichotomous outcomes such as patient mortality and the incidence of hospital readmission will be described using the risk ratio with 95% confidence intervals.

Dealing with missing data

When data are missing or inapplicable, we will contact the original authors by email or use a formula to convert them into available data.[22,24,25] If the missing data cannot be obtained, we will follow the recommendations of the Cochrane Handbook for Systematic Reviews of Intervention[22]: 1) make precise the hypothesis of any methods used to handle the missing data; 2) sensitivity analyses will be used to

assess how sensitive results are to reasonable changes in the assumptions that are made; 3) consider the potential effect of the missing data as limitations in our study.

Assessment of heterogeneity

We will investigate statistical heterogeneity among the included studies using the Q statistic and I^2 index. A *p* value of ≤ 0.10 for the Q statistic will be considered to be statistically significant heterogeneity. I^2 values < 25%, 25%–50%, or > 50% represent low, moderate, or high heterogeneity, respectively. We will apply a fixed-effect model if no heterogeneity exists. When substantial heterogeneity (I^2 > 50% or $P \leq 0.1$) is detected, we will try to identify the source of heterogeneity by subgroup analysis, sensitivity analysis, or using a random-effects model. If substantial heterogeneity cannot be well explained, we will not proceed with the meta-analysis and a descriptive, qualitative summary will be made.[22]

Additional analyses

Possible sources of heterogeneity will be determined through carrying out subgroup analysis based on gender, BMI, the condition of patients (acute decompensation or stable period), the severity of the OHS (mild ($PaCO_2$ 46–60 mmHg), moderate ($PaCO_2$ 60–80 mmHg) or severe ($PaCO_2$ ≥80 mmHg)),[26] whether combined with obstructive sleep apnea; the mode of bilevel therapy; the mean daily home use of the ventilator and the duration of the follow-up periods (short-term (< 3 months) or long-term (≥ 3 months)). Sensitivity analysis will also be performed to detect the source of heterogeneity. When substantial heterogeneity exists, we will exclude the study and compare its impact on the pooled estimate. If we find the source of heterogeneity, we will review the literature again to evaluate its quality and bias and decide whether the particular study is to be retained or excluded. If the study is excluded, the reasons for its removal will be explained in the discussion. If the quantitative synthesis is not appropriate, a narrative method will be used. This

approach will present the information in a text or table in order to interpret and summarize the features and outcomes among the included studies.

Meta-biases

Publication bias will be assessed through the funnel plot if the number of the included studies is ≥ 10. In addition, in order to assess the reporting bias, we will search the database of the registered protocols mentioned above to confirm whether the study's prespecified outcomes have not been reported.

Confidence in cumulative estimate

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system will be used for rating the quality of evidence for all outcomes of the included studies. The quality of evidence will be classified into four levels of quality (high, moderate, low, and very low). Because RCTs are considered to be high quality, the quality of the evidence may be downgraded when study limitations, the inconsistency of results, indirectness of evidence, imprecision, or reporting bias occur.[27,28]

Discussion

As we all know, PAP therapy is considered as the first line treatment for OHS patients. However, for now the most optimal type of PAP therapy is still unclear. To our best knowledge, this is the first systematic review and meta-analysis to make a comparison between domiciliary bilevel and CPAP therapy for patients with OHS. Therefore, it is vital importance to conduct this study to confirm the most appropriate home PAP therapy for OHS patients

It's worth noting that bilevel therapy can be triggered by S, T, S/T or VAPS modes.[29] In S mode, ventilator will only be triggered when it detects a pressure or flow change by the inspiratory effort of patient. When using this mode, patient may fail to trigger the ventilator with excessive leakage or central sleep apnea, leading to poor nocturnal gas exchange and sleep quality.[30,31] Ventilator is triggered at a preset rate during T mode which will result in patient/ventilator asynchrony and patient discomfort. S/T mode allows patient triggers the ventilator and if patient's spontaneous respiratory rate is lower than the back-up rate of the ventilator, then the ventilator will deliver a breath automatically. When using this mode, it can reduce the rate of patient/ventilator asynchrony, relieve inspiratory effort of patient and better control gas exchange by setting a high back-up rate. [29]Notably, VAPS mode, a mixed mode of bilevel therapy, adjusts the inspiratory pressure level (within the preset range) automatically in order to maintain a target tidal volume of the patient. With the VAPS mode, it can well reduce patient's intolerance, improve the alveolar ventilation and adapt the lung changes when using ventilator.[32,33] Hence subgroup analysis will be performed to find out which modes of bilevel therapy are better for OHS patients. In future studies, more RCTs or systematic review and meta-analysis for different modes of bilevel therapy are needed to proceed.

Ethics and dissemination

Ethics approval is not required because this is a protocol for a systematic review and meta-analysis in which no primary human data will be collected. Our findings will be submitted to a peer-reviewed journal for publication.

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Contributions

LL, RC, and LQ contributed to the conception and design of the study, drafting the submitted article and revising the draft critically for important intellectual content. LL and YT contributed to the search strategy. Data management and selection process were proceeded by WL and XY. BP and YT were responsible for the data collection. YQ, FF and JW contributed to the risk of bias assessment. All authors contributed to data analysis, amending the paper, being responsible for all aspects of the work and approving the final version of the manuscript.

DISCLOSURE STATEMENT

Conflicts of interest: none

Data sharing statement

Extra data is available by emailing the corresponding author.

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PubMed:

#1 "Obesity Hypoventilation Syndrome"[Mesh]

#2 OHS [Title/Abstract] OR "Hypoventilation Syndrome, Obesity" [Title/Abstract] OR " Syndrome, Obesity Hypoventilation" [Title/Abstract] OR "Pickwickian Syndrome" [Title/Abstract] OR "Syndrome, Pickwickian" [Title/Abstract] OR "Obesity-Hypoventilation Syndrome" [Title/Abstract]

#3 "Continuous Positive Airway Pressure"[Mesh]

#4 "CPAP Ventilation" [Title/Abstract] OR "Ventilation, CPAP" [Title/Abstract] OR "Biphasic Continuous Positive Airway Pressure" [Title/Abstract] OR "Nasal Continuous Positive Airway Pressure" [Title/Abstract] OR "nCPAP Ventilation" [Title/Abstract] OR "Ventilation, nCPAP" [Title/Abstract] OR "Airway Pressure Release Ventilation" [Title/Abstract] OR "APRV Ventilation Mode" [Title/Abstract] OR "APRV Ventilation Modes" [Title/Abstract] OR "Ventilation Mode, APRV" [Title/Abstract] OR "Ventilation Modes, APRV" [Title/Abstract]

#5 "Noninvasive Ventilation"[Mesh]

#6 "Noninvasive Ventilations" [Title/Abstract] OR "Ventilation, Noninvasive" [Title/Abstract] OR "Ventilations, Noninvasive" [Title/Abstract] OR "Non-Invasive Ventilation" [Title/Abstract] OR "Non-Invasive Ventilations" [Title/Abstract] OR "Ventilation, Non-Invasive" [Title/Abstract] OR "Ventilations, Non-Invasive" [Title/Abstract] OR "Non Invasive Ventilation" [Title/Abstract] OR "Non Invasive Ventilations" [Title/Abstract] OR "Ventilation, Non Invasive" [Title/Abstract] OR "Ventilations, Non Invasive" [Title/Abstract]

#7 BiPAP [Title/Abstract] OR "bilevel" [Title/Abstract] OR "bi-level" [Title/Abstract]

#8 "randomized controlled trial" [Publication Type] OR "clinical trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Controlled Clinical Trials as Topic"[Mesh] OR "Clinical Trials as Topic"[Mesh] OR randomized [Title/Abstract] OR randomly [Title/Abstract] OR trial [Title/Abstract]

#9 ("1980/01/01"[PDAT]: "2017/11/01"[PDAT]) AND "humans"[Mesh Terms]

#10 (#1 OR #2)

#11 (#3 OR #4)

#12 (#5 OR #6 OR #7)

#13 (#8 AND #9 AND #10 AND #11 AND #12)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	5
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-3
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	16
Sponsor	5b	Provide name for the review funder and/or sponsor	16
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Not applicable
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	7-8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	9-10
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	10
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	10-11

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	11
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	12
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	12
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10, 12
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	12
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	13
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	13
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	14
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	14-15

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Efficacy of bilevel positive airway pressure and continuous positive airway pressure therapy in patients with obesity hypoventilation syndrome: protocol for systematic review and meta-analysis

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Complete List of Authors:	Guan, Lili; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Respiratory Medicine Wu, Weiliang; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Respiratory Medicine Huo, Yating; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Respiratory Medicine Li, Xiaoying; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Respiratory Medicine Guo, Bingpeng; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Respiratory Medicine Yang, Yuqiong; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Respiratory Medicine Xu, Jiawen; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Respiratory medicine Jiang, Fangfang; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Respiratory medicine Zhou, Luqian; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Respiratory medicine Chen, Rongchang; State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Respiratory medicine
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Respiratory medicine
Keywords:	Obesity hypoventilation syndrome, Bilevel positive airway pressure therapy, Continuous positive airway pressure therapy, Systematic review and Meta-Analysis, Protocol

Efficacy of bilevel positive airway pressure and continuous positive airway pressure therapy in patients with obesity hypoventilation syndrome: protocol for systematic review and meta-analysis

Authors' names:

Lili Guan[a*]

Weiliang Wu[a*]

Yating Huo[a*]

Xiaoying Li[b*]

Bingpeng Guo[a]

Yuqiong Yang[a]

Jiawen Xu

Fangfang Jiang

Luqian Zhou[a#]

Rongchang Chen[a#]

Authors' affiliation(s):

[a] Department of respiratory medicine, State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

[b] Department of respiratory medicine, The First Affiliated Hospital / School of Clinical Medicine of Guangdong Pharmaceutical University, Guangzhou, China

* These authors contributed equally to this work and should be considered as the co-first authors

# These authors contributed equally to this work and should be considered as the joint corresponding authors

Corresponding:

Name: Luqian Zhou;

Address: State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, 151 Yan Jiang Rd. Guangzhou, China;

Post code: 510120

Phone and fax numbers: +862083062882

E-mail: zhlx09@163.com

Name: Rongchang Chen;

Address: State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical University, 151 Yan Jiang Rd. Guangzhou, China;

Post code: 510120

Phone and fax numbers: +862083062882

E-mail: chenrcstatekeylab@gmail.com

Abbreviations list:

OHS = Obesity hypoventilation syndrome;

$PaCO_2$ = Partial pressure of arterial blood carbon dioxide;

PAP = Positive airway pressure;

CPAP = Continuous positive airway pressure;

RCT = Randomized controlled trial;

S/T = Spontaneous/timed

VAPS = Volume-assured pressure support

Abstract

Introduction Obesity hypoventilation syndrome (OHS) is a major respiratory complication caused by severe obesity, being associated with significant morbidity, negative impacts on quality of life and reduced survival if not treated appropriately. Positive airway pressure therapy is the first line treatment for OHS although the optimal modality remains unclear. The goal of this study is to identify the efficacy of home bilevel positive airway pressure therapy by comparison to continuous positive airway pressure therapy and determine the best strategy for patients with OHS.

Methods and analysis This study will be conducted following the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols 2015 statement. We will search the following databases: PubMed, Web of Science, EMBASE, Cochrane Central Register of Controlled Trials and CINAHL. Ongoing studies will be identified through the ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform Search Portal. Grey literature will be recognized through Google Scholar and other search engines. Only randomized controlled trials meeting the eligibility criteria will be included. The risk of bias of the included studies will be evaluated through the Cochrane Collaboration's tool. RevMan 5.3.5 software will be used for data analysis. The Q statistic and I^2 index will be used for investigating heterogeneity, and subgroup analysis or sensitivity analysis will be used to explore the source of heterogeneity. In addition, the Grading of Recommendations Assessment, Development and Evaluation system will be used to inspect the quality of evidence.

Ethics and dissemination Ethics approval is not required because this study contains no primary data collected from humans. This systematic review and meta-analysis will be submitted to a peer-reviewed journal for publication.

Trial registration number CRD42017078369

Key words: Obesity hypoventilation syndrome; Bilevel positive airway pressure therapy; Continuous positive airway pressure therapy; Systematic review and Meta-Analysis; Protocol;

Strengths and limitations of this study

- The first systematic review and meta-analysis to compare the efficacy of home bilevel positive airway pressure and continuous positive airway pressure therapy in patients with obesity hypoventilation syndrome (OHS).
- This study will help to identify the most appropriate home positive airway pressure therapy strategy for OHS patients.
- Only randomized controlled trials, representing a high quality of evidence, will be included in this study.
- To determine the most appropriate patients to receive bilevel positive airway pressure therapy through subgroup analysis.

Word counts ABSTRACT 273 words; TEXT 2207 words,

Introduction

The increasing incidence of obesity has become a major concern worldwide.[1] Obesity hypoventilation syndrome (OHS) is a major respiratory complication caused by obesity and is characterized by a daytime arterial partial pressure of carbon dioxide ($PaCO_2$) > 45 mmHg with BMI > 30 kg/m^2 and excluding other causes of hypoventilation (such as neuromuscular disorders, chest wall abnormalities or significant lung diseases.). [2] OHS usually appears to be the end consequence of a complex interplay between upper airway obstruction, sleep hypoventilation, decreased lung capacity, increased respiratory muscle load, changing respiratory center drive, and leptin resistance. [3,4] Due to the presence of chronic hypercapnia and hypoxemia, patients with OHS are at high risk of severe respiratory failure, pulmonary hypertension, chronic cor pulmonale and other cardiovascular complications if not treated appropriately. [5,6] Moreover, this will greatly affect the patient's health-related quality of life, exercise performance, survival rate and may become a serious social and economic burden.[7–9]

Treatment of this disorder is aimed at improving the pathophysiologic abnormalities of patients with OHS which commonly includes positive airway pressure therapy, lifestyle intervention, surgery, and pharmacotherapy. Positive airway pressure (PAP) therapy is considered to be the first line treatment, which can effectively improve gas exchange, sleep disorders and survival in OHS patients.[10,11] Additionally, Castro-Añón O al. indicated that even with the introduction of PAP therapy, mortality in OHS remains higher than that seen in eucapnic OSA individuals.[8] PAP therapy may be delivered as either continuous positive airway pressure (CPAP) or bilevel therapy (including spontaneous, timed, spontaneous/timed (S/T) or volume-assured pressure support (VAPS) modes). CPAP provides a constant positive pressure in the airway, aiming to reduce upper airway resistance and prevent upper airway obstructive events, thereby controlling sleep disordered breathing and improving oxygenation. However, CPAP is not a truly physiologically-based ventilation mode. It simply provides a constant pressure to the airway to maintain the upper airway open

and increase lung volumes. In contrast, bilevel therapy provides a differential pressure between inspiration and expiration (pressure support level) which acts to increase tidal volume, improve alveolar hypoventilation and relieve respiratory fatigue.[12] Therefore, theoretically bilevel therapy should be more effective in improving oxygenation and reducing arterial carbon dioxide levels than CPAP.

Currently, the optimal mode of home PAP therapy for patients with OHS has not been determined. Only a few randomized controlled trials (RCTs) [13–15] but no systematic reviews or meta- analyses have compared the efficacy of domiciliary bilevel versus CPAP therapy in OHS patients. The main objective of this study is to determine whether bilevel therapy is more effective than CPAP therapy in treating OHS and to identify the best PAP setting for patients with OHS as the first line treatment.

Objective

The goal of this systematic literature review and meta-analysis is to determine the effect of the home bilevel therapy by comparison to CPAP therapy in patients with OHS. Specifically, what is the difference of treatment effect between home bilevel and CPAP therapy in patients with OHS as reported in the research published from January 1980 through November 2017?

Methods

This manuscript follows the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 statement.[16]

Eligibility criteria:

Study design

Only RCTs will be included. We will include RCTs comparing the efficiency of domiciliary bilevel and CPAP therapy in patients with OHS.

Participants

Only subjects diagnosed with OHS (i.e. BMI >30 kg/m^2 and daytime $PaCO_2$ >45 mm Hg) with exclusion of other conditions that might lead to hypoventilation including neuromuscular disorders, chest abnormalities, or COPD will be included in this analysis. [2]

Interventions

Bilevel therapy, providing a differential pressure between inspiration and expiration, which can increase tidal volume, improve alveolar hypoventilation and relieve respiratory fatigue; CPAP therapy provides a constant positive pressure in the airway, which can reduce upper airway resistance and prevent upper airway obstruction events. [12]

Outcomes

- **Primary outcome:** Daytime $PaCO_2$
- **Secondary outcomes:**
    - Adherence (Whether average PAP therapy use of ≥ 4 hours per night)[17,18]
    - Health-related quality of life (The Medical Outcome Study 36-item short-form health survey [19], Epworth Sleepiness Scale [20], Severe Respiratory Insufficiency Questionnaire [21]);
    - Mortality;
    - The incidence of hospital readmissions.

- Lung function [22];
- Physical activity (6-minute walk test [23])

Information sources and search strategy

Electronic searches

We will search the following databases: PubMed, Web of Science, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, and CINAHL. The searching period will be from January 1980 to November 2017. Literature retrieved will be limited to human subjects and language or publication status will not be limited. The searches will be reworked before the final analyses, and further studies will also be reviewed for the inclusion. The detailed search strategy of PubMed is presented in Supplement 1.

Searching other resources

Ongoing studies will be identified through the ClinicalTrials.gov (November 2017) and World Health Organization International Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch/). We will contact the authors to get further information on ongoing or unpublished studies, if necessary. In order to ensure that the search is comprehensive, we will look through the bibliography of the included studies or reviews to identify the relevant reports. Grey literature (including reports and conference presentations) will be searched through Google Scholar and other relevant websites.

Study records

Data management

All previously searched literature will be imported into EndNote Version X8 software (Clarivate Analytics, Philadelphia, PA, USA), and duplicates will be removed. The titles and abstracts obtained from the previous searches will be inspected independently by two investigators (WL and XL). If the article meets the eligibility criteria, or if there is any uncertainty about including a particular study, the report will be downloaded.

Selection process

The imported articles will be screened by two independent investigators (WL and XL) to determine whether they meet the criteria for inclusion. We will ask the authors for additional information when necessary. Reasons for excluding studies will be recorded. The two investigators will resolve any disagreements through discussion, and the third investigator (LQ) will offer advice when agreement cannot be reached.

Data collection process

Two investigators (BP and YT) will independently extract data using a standardized data collection form. The extracted data will include: 1) study characteristics such as first author, journal, year, and study design; 2) patients' characteristics including the number of patients in each group, age, sex, BMI, and severity of OHS; 3) intervention characteristics (type of PAP therapy, mode of bilevel therapy, inspiratory positive airway pressure, expiratory positive airway pressure, and back-up rate), mean daily use of ventilation, and treatment duration; and 4) primary and secondary outcomes as described above. For cross-over trials, we will only extract the data from the first phase, primarily because of the carry-over effect. When the extraction process is complete, we will merge the two collections into one for further analysis. Should there be any disagreements at this stage, the two investigators will reach an agreement through discussion. If agreement cannot be reached, the third investigator (LQ) will participate in the discussion to reach a final conclusion.

Risk of bias in individual studies

Two investigators (YQ and JW) will use the Cochrane Collaboration's tool to assess the risk of bias of the included studies.[24,25] Six domains will be assessed: selection bias, performance bias, detection bias, attrition bias, reporting bias, and "other" bias. Each domain will be judged as "low risk," "unclear risk," or "high risk." The support for these judgments will be clarified in a risk of bias table. Divergences will be discussed first by the two investigators, and if an agreement cannot be reached, the third investigator (LQ) will provide a suggestion.

Data synthesis

Analyses will be done using RevMan 5.3.5 software (Cochrane, London, UK).

Measures of treatment effect

For continuous outcomes such as P_aCO_2, 6-minute walk distance, etc., the weighted mean difference or standardized mean difference with 95% confidence intervals will be used. Dichotomous outcomes such as patient mortality and the incidence of hospital readmission will be described using the risk ratio with 95% confidence intervals.

Dealing with missing data

When data are missing or inapplicable, we will contact the original authors by email or use a formula to convert them into available data.[24,26,27] If the missing data cannot be obtained, we will follow the recommendations of the Cochrane Handbook for Systematic Reviews of Intervention[24]: 1) make precise the hypothesis of any methods used to handle the missing data; 2) sensitivity analyses will be used to

assess how sensitive results are to reasonable changes in the assumptions that are made; 3) consider the potential effect of the missing data as limitations in our study.

Assessment of heterogeneity

We will investigate statistical heterogeneity among the included studies using the Q statistic and I^2 index. A *p* value of ≤ 0.10 for the Q statistic will be considered to be statistically significant heterogeneity. I^2 values < 25%, 25%–50%, or > 50% represent low, moderate, or high heterogeneity, respectively. We will apply a fixed-effect model if no heterogeneity exists. When substantial heterogeneity (I^2 > 50% or $P \leq 0.1$) is detected, we will try to identify the source of heterogeneity by subgroup analysis, sensitivity analysis, or using a random-effects model. If substantial heterogeneity cannot be well explained, we will not proceed with the meta-analysis and a descriptive, qualitative summary will be made.[24]

Additional analyses

Possible sources of heterogeneity will be determined through carrying out subgroup analysis based on gender, BMI, the baseline presentation of the patient (acute decompensation or during clinical stability), the severity of the OHS (mild ($PaCO_2$ 46–60 mmHg), moderate ($PaCO_2$ 60–80 mmHg) or severe ($PaCO_2$ ≥80 mmHg)),[28] whether combined with obstructive sleep apnea; the mode of bilevel therapy; the mean daily home use of the ventilator and the duration of the follow-up periods (short-term (< 3 months) or long-term (≥ 3 months)). Sensitivity analysis will also be performed to detect the source of heterogeneity. When substantial heterogeneity exists, we will exclude the study and compare its impact on the pooled estimate. If we find the source of heterogeneity, we will review the literature again to evaluate its quality and bias and decide whether the particular study is to be retained or excluded. If the study is excluded, the reasons for its removal will be explained in the discussion. If the quantitative synthesis is not appropriate, a narrative method will be used. This

approach will present the information in a text or table in order to interpret and summarize the features and outcomes among the included studies.

Meta-biases

Publication bias will be assessed through the funnel plot if the number of the included studies is ≥ 10. In addition, in order to assess the reporting bias, we will search the database of the registered protocols mentioned above to confirm whether the study's prespecified outcomes have not been reported.

Confidence in cumulative estimate

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system will be used for rating the quality of evidence for all outcomes of the included studies. The quality of evidence will be classified into four levels of quality (high, moderate, low, and very low). Because RCTs are considered to be high quality, the quality of the evidence may be downgraded when study limitations, inconsistency of results, indirectness of evidence, imprecision, or reporting bias occur.[29,30]

Patient and Public Involvement statement

Patients and public were not involved in this manuscript.

Discussion

PAP therapy is considered as the first line treatment for OHS patients. However, the optimal mode of PAP therapy is still not clear. To the best of our knowledge, this is the first systematic review and meta-analysis to undertake a comparison between domiciliary bilevel and CPAP therapy for patients with OHS. Therefore, the findings

will aid clinicians in choosing the most appropriate long-term home therapy for these individuals.

Bilevel therapy can be delivered as spontaneous (S), timed (T), spontaneous/timed S/T) or VAPS mode.[31] In S mode, ventilator will only be triggered when it detects a pressure or flow change by the inspiratory effort of patient. In this mode, inspiratory trigger failure may occur due to excessive leakage or from the emergence of central apnea, leading to poor nocturnal gas exchange and sleep quality.[32,33] With the timed mode, all breaths are triggered by the ventilator only which can produce patient/ventilator asynchrony and patient discomfort. The S/T mode allows the patient to trigger the device to initiate inspiratory support but is the patient's spontaneous respiratory rate drops below the back-up rate set by the clinician, then the ventilator will trigger the breath. This may reduce the rate of patient/ventilator asynchrony, relieve inspiratory effort and provide better gas exchange if the high back-up rate is set high enough. [32] VAPS mode, a mixed mode of bilevel therapy, automatically adjusts the inspiratory pressure level within a preset pressure range in order to maintain a clinician-set target tidal volume. With the VAPS mode, it can adapt to variations in ventilatory need created by changes in body position, sleep stage or lung mechanics.[34,35] Hence subgroup analysis will be performed to find out which modes of bilevel therapy provide better outcomes for OHS patients.

Ethics and dissemination

Ethics approval is not required because this is a protocol for a systematic review and meta-analysis in which no primary human data will be collected. Our findings will be submitted to a peer-reviewed journal for publication.

Acknowledgements

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Contributions

LL, RC, and LQ contributed to the conception and design of the study, drafting the submitted article and revising the draft critically for important intellectual content. LL and YT contributed to the search strategy. Data management and selection process were proceeded by WL and XY. BP and YT were responsible for the data collection. YQ, FF and JW contributed to the risk of bias assessment. All authors contributed to data analysis, amending the paper, being responsible for all aspects of the work and approving the final version of the manuscript.

DISCLOSURE STATEMENT

Conflicts of interest: none

Data sharing statement

Extra data is available by emailing the corresponding author.

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doi:10.2147/COPD.S126970

PubMed:

#1 "Obesity Hypoventilation Syndrome"[Mesh]

#2 OHS [Title/Abstract] OR "Hypoventilation Syndrome, Obesity" [Title/Abstract] OR " Syndrome, Obesity Hypoventilation" [Title/Abstract] OR "Pickwickian Syndrome" [Title/Abstract] OR "Syndrome, Pickwickian" [Title/Abstract] OR "Obesity-Hypoventilation Syndrome" [Title/Abstract]

#3 "Continuous Positive Airway Pressure"[Mesh]

#4 "CPAP Ventilation" [Title/Abstract] OR "Ventilation, CPAP" [Title/Abstract] OR "Biphasic Continuous Positive Airway Pressure" [Title/Abstract] OR "Nasal Continuous Positive Airway Pressure" [Title/Abstract] OR "nCPAP Ventilation" [Title/Abstract] OR "Ventilation, nCPAP" [Title/Abstract] OR "Airway Pressure Release Ventilation" [Title/Abstract] OR "APRV Ventilation Mode" [Title/Abstract] OR "APRV Ventilation Modes" [Title/Abstract] OR "Ventilation Mode, APRV" [Title/Abstract] OR "Ventilation Modes, APRV" [Title/Abstract]

#5 "Noninvasive Ventilation"[Mesh]

#6 "Noninvasive Ventilations" [Title/Abstract] OR "Ventilation, Noninvasive" [Title/Abstract] OR "Ventilations, Noninvasive" [Title/Abstract] OR "Non-Invasive Ventilation" [Title/Abstract] OR "Non-Invasive Ventilations" [Title/Abstract] OR "Ventilation, Non-Invasive" [Title/Abstract] OR "Ventilations, Non-Invasive" [Title/Abstract] OR "Non Invasive Ventilation" [Title/Abstract] OR "Non Invasive Ventilations" [Title/Abstract] OR "Ventilation, Non Invasive" [Title/Abstract] OR "Ventilations, Non Invasive" [Title/Abstract]

#7 BiPAP [Title/Abstract] OR "bilevel" [Title/Abstract] OR "bi-level" [Title/Abstract]

#8 "randomized controlled trial" [Publication Type] OR "clinical trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Controlled Clinical Trials as Topic"[Mesh] OR "Clinical Trials as Topic"[Mesh] OR randomized [Title/Abstract] OR randomly [Title/Abstract] OR trial [Title/Abstract]

#9 ("1980/01/01"[PDAT]: "2017/11/01"[PDAT]) AND "humans"[Mesh Terms]

#10 (#1 OR #2)

#11 (#3 OR #4)

#12 (#5 OR #6 OR #7)

#13 (#8 AND #9 AND #10 AND #11 AND #12)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	5
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-3
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	16
Sponsor	5b	Provide name for the review funder and/or sponsor	16
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Not applicable
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	7-8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	9-10
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	10
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	10-11

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	11
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	12
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	12
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10, 12
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	12
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	13
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	13
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	14
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	14-15

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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