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Transcatheter closure, mini-invasive closure, and open-heart surgical repair for treatment of perimembranous ventricular septal defects in children: a protocol of network meta-analysis

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Authors' contributions: Conception and design of research (YT, YK, DZH, HXD, TJH); tested the feasibility of the study (YT, YK, LXG, WXK); wrote the manuscript (YT), approved the final manuscript (YT, GL, TJH).

Data sharing statement: No additional unpublished data are available.

Keywords: transcatheter closure; mini-invasive closure; open-heart surgical repair; perimembranous ventricular septal defects; children; protocol; network meta-analysis

ABSTRACT

Introduction: Both transcatheter device closure and surgical repair are effective treatments, with excellent midterm outcomes, for perimembranous ventricular septal defects (pmVSDs) in children. Mini-invasive periventricular device occlusion (MIPDO) technique became a popular in research and application. The evidence is limited for the differences of transcatheter closure, mini-invasive closure, and open-heart surgical repair. This study are to comprehensively compare the efficacy, safety, and costs of transcatheter closure, mini-invasive closure, and open-heart surgical repair for treatment of pmVSDs in children using Bayesian network meta-analysis.

Methods and analysis: A systematic search will be performed using Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), PubMed, EMBASE.com, and the Cochrane Central Register of Controlled Trials, to include random controlled trials, prospective or retrospective cohort studies comparing the efficacy, safety, and costs of transcatheter closure, mini-invasive closure, and open-heart surgical repair. The risk of bias in included studies will be evaluated according to the risk of bias in non-randomized studies of interventions (ROBINS-I). Bayesian network meta-analysis will be conducted using R-3.3.2 software.

Ethics and dissemination: Ethical approval and patient consent are not required since this study is a network meta-analysis based on published trials. The results of this network meta-analysis will be submitted to a peer-reviewed journal for publication.

Protocol registration number: CRD42016053352

Strengths and limitations of this study

- To the best of our knowledge, this is the first network meta-analysis comparing the efficacy, safety, and costs of transcatheter closure, mini-invasive closure, and open-heart surgical repair for treatment of pmVSDs in children.
- The results of this systematic review will help clinicians and patients to select appropriate repair methods.
- Our results will be limited by both the quantity and quality of the trials available for review.

INTRODUCTION

Ventricular septal defects (VSDs) are the most common type of congenital heart disease, in which 80% are perimembranous ventricular septal defects (pmVSDs) [1]. Treatment of pmVSDs has been improved dramatically over the last 50 years [2-4]. Traditionally, open-heart surgical repair with midline sternotomy and cardiopulmonary bypass (CPB) has been the mainstay of therapy for many years, although it is associated with morbidity, postoperative discomfort, and a large thoracotomy scar [5]. Catheter-based intervention was initially introduced for the closure of muscular VSDs (mVSD), and has been approved by the Food and Drug Administration (FDA) in 2007 [6]. Transcatheter device closure of pmVSDs is a promising alternative [7-9], which has been widely used in developing countries such as China and India, although it is not currently approved in the United States [10,11]. However, it remains a challenge when used on children with low body weight [10,12]. Previous pairwise meta-analysis suggested that there was no significant difference between transcatheter and surgical closure of pmVSDs in terms of early (up to 30 days) efficacy and safety in well-selected patients [13]. During the same period, mini-invasive periventricular device occlusion (MIPDO) technique, which combines the respective advantages of cardiac surgery, interventional cardiology, and medical image techniques guided by transesophageal echocardiography (TEE), became a popular in research and application [14-17]. There were only few researches conducted in the past comparing the efficacy between MIPDO and transcatheter and open-heart surgical closure for pmVSDs.

Network meta-analysis has become increasingly popular to evaluate healthcare interventions, since it allows to estimate the relative effectiveness among all interventions and rank ordering of the interventions [18]. In the absence of head-to-head comparisons of all interventions of interest, indirect treatment comparison analyses using NMAs of various RCTs can provide useful evidence to inform health-care decision making. Even when the results of the direct comparisons are conclusive, combining them with indirect estimates in a mixed treatment comparison may yield more refined estimates [19,20].

OBJECTIVE

The objectives of this study are to comprehensively compare the efficacy, safety, and costs of transcatheter closure, mini-invasive closure, and open-heart surgical repair for treatment of pmVSDs in children using Bayesian network meta-analysis.

METHODS AND ANALYSIS

Design

Bayesian network meta-analysis will be conducted in this study.

Registration information

This study protocol was registered on the international prospective register of systematic review (PROSPERO). The protocol of network meta-analysis is planed according to the preferred reporting items for systematic review and meta-analysis

protocol (PRISMA-P) recommendation, and the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions [21,22].

Information source

Information search will be performed using Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), PubMed, EMBASE.com, and the Cochrane Central Register of Controlled Trials (CENTRAL). The references of included articles and relevant systematic reviews will be tracked to identify other relevant studies.

Search strategy

The search terms will be the following: ventricular septal defect*, perimembranous, peri-membranous, VSD, occlusion, transcatheter, percutaneous, mini-invasive, sternotomy, and child. Full details of the search strategy regarding PubMed as follows:

((((("Heart Septal Defects, Ventricular"[Mesh]) OR (("ventricular septal defect*"[Title/Abstract] OR VSD[Title/Abstract]))))) AND ((thorascopic[Title/Abstract] OR sternotomy[Title/Abstract] OR "minimally invasive"[Title/Abstract] OR mini-invasive[Title/Abstract] OR "surgical closure"[Title/Abstract] OR transcatheter[Title/Abstract] OR "percutaneous occlusion"[Title/Abstract]))) AND ((infant[MeSH] OR child[MeSH] OR adolescent[MeSH]))))) AND (((perimembranous OR peri-membranous)))

Eligibility criteria

Type of patients: children younger than 18 years of age with pmVSDs, who was confirmed by clinical and transthoracic echocardiographic (TTE), and scheduled for transcatheter closure, mini-invasive closure, or open-heart surgical repair.

Type of designs: random controlled trials, prospective or retrospective cohort studies; systematic reviews or meta-analyses will be also included to track their references.

Type of interventions: transcatheter closure, mini-invasive closure, and open-heart surgical repair.

Type of outcomes: procedural success rate, operative time (min), ICU stay (h), hospital stay (d), total cost (Yuan), significant residual shunt, major complications, minor complications.

Other criteria: we will include trials reported in the English and Chinese languages. There will be no limitations on year of publication, publication status.

Study selections

Literature search records will be imported into ENDNOTE X6 software. Two independent reviewers will examine the title and abstract of studies found in the search to identify related studies according to eligibility criteria. Thus, full-text versions of all potentially relevant studies will be obtained. Excluded trials and the reasons for their exclusion will be listed and examined by a third reviewer.

Data items

A standard data abstraction form will be created using Microsoft Excel 2013 (Microsoft Corp, Redmond, WA, www.microsoft.com) to collect data of interest. Two independent reviewers will extract following data and conflict will be resolved by discussion, including first author, location, study design, study period, study arms, sample, mean age, mean body weight, gender, VSD size, type of surgery, method of surgical closure, device used, mean device size, cardiopulmonary bypass time, median follow-up, and outcomes. We will consider the following factors as effect modifiers: mean age, type of design, mean body weight, VSD size, device used, and sample size.

Risk of bias individual studies

The risk of bias of included all trials will be evaluated according to the tool for assessing risk of bias in non-randomized studies of interventions (ROBINS-I) [23], including bias due to confounding (pre-intervention), bias in selection of participants into the study (pre-intervention), bias in classification of interventions (at intervention), bias due to deviations from intended interventions (post-intervention), bias due to missing data (post-intervention), bias in measurement of outcomes (post-intervention), bias in selection of the reported result (post-intervention), and overall risk of bias. We will evaluate methodological quality as low, moderate, serious, critical risk of bias, and no information. The risk of bias assessment will be completed by two independent reviewers, and conflicts will be resolved by a third reviewer.

Geometry of the network

A network plot will be drawn to describe and present the geometry of transcatheter closure, mini-invasive closure, and open-heart surgical repair using R-3.3.2 software (R Foundation for Statistical Computing, Vienna, Austria). Nodes will be used to represent different interventions and edges to represent the head-to-head comparisons between interventions. The size of nodes and thickness of edges are associated with sample sizes of intervention and numbers of included trials, respectively.

Statistical analysis

A Bayesian network meta-analysis will be performed using package *'gemtc' version 0.8.1* of R-3.3.2 software [24]. The function *mtc.run* will be used to generate samples from using the Markov Chains Monte Carlo sampler. Four Markov Chains will be run simultaneously. We will set 5000 simulations for each chain as the 'burn-in' period. Then posterior summaries will be based on 50 000 subsequent simulations. The model convergence will be assessed using Brooks-Gelman-Rubin plots method [25].

Summary measures

Posterior medians of odds ratio (OR) with 95% credible intervals (CrIs) will be used for procedural success rate, significant residual shunt, major complications, and minor complications. Median mean differences (MDs) with 95% CI for operative time, ICU stay, hospital stay, and total cost. Rank probabilities indicate the probability for each

treatment to be best, second best, etc. Clinical decisions about the choice of treatments can be recommended based on the probability results of ranking when the differences in effect size of different treatments are small [26]. The '*gemtc'* package provides a matrix of the treatment rank probabilities, as well as a plot of the rank probabilities.

Analysis of heterogeneity

We will assess clinical and methodological heterogeneity by carefully examining the characteristics and design of included trials. For pairwise meta-analysis, heterogeneity of treatment effects across head-to-head trials will be assessed by I^2 statistics. If the I^2 is ≦50%, it suggests that there is no statistical heterogeneity and the fixed effects model will be used for meta-analysis. If the I^2 is >50%, we will explore sources of heterogeneity by subgroup analysis and meta-regression using effect modifiers. If there is no clinical heterogeneity, the random effects model will be used to perform meta-analysis. In addition, we will also assess the global heterogeneity on the bias of the magnitude of heterogeneity variance parameter (I^2 or τ^2) estimated from the network meta-analysis models using *mtc.anohe* command of '*gemtc'* package.

Assessment of inconsistency

If a loop connecting three arms exists, inconsistency between direct and indirect comparisons will be evaluated by node splitting method [27].

Funnel plot analysis

Publication bias will be examined with the Begg's [28] and Egge's [29] funnel plot method. The comparison-adjusted funnel plot will be used to identify whether there is small sample effect between intervention networks.

DISCUSSION

Surgical repair through median sternotomy on CPB has been regarded as the gold method for treatment of pmVSDs. Hijazi et al. [30] firstly closed pmVSDs using an Amplatzer membranous VSD occlude in 2002. Over the past decade, some studies has found that the Amplatzer pmVSD occluder was associated with a relatively high risk of complete atrioventricular block [31]. Interest is growing as to whether some new techniques can replace traditional open-heart surgery as the "gold standard" for treatment of pmVSD [31]. Recent RCTs demonstrated that both transcatheter device closure and surgical repair are effective treatments, with excellent midterm outcomes, for pmVSDs in children [31]. MIPDO technique combines the respective advantages of cardiac surgery, interventional cardiology, and medical image techniques, has become a popular in research and application [14-17]. To the best of our knowledge, there are no relevant RCTs to compare the differences of transcatheter closure, mini-invasive closure, and open-heart surgical repair. Present study will firstly compare the efficacy, safety, and costs of transcatheter closure, mini-invasive closure, and open-heart surgical repair for treatment of pmVSDs in children using Bayesian network meta-analysis. However, some limitations are predictable. For example, meta-analysis findings partly rely on the quality of original studies. In addition, the number of

eligible RCTs are predictably small.

ETHICS AND DISSEMINATION

Ethical issues

Ethical approval and patient consent are not required since this is a meta-analysis based on published studies.

Publication plan

This protocol has been registered on the international prospective register of systematic review (PROSPERO) [32]. The procedures of network meta-analysis will be conducted according to the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions. The results of this network meta-analysis will be submitted to a peer-reviewed journal for publication.

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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	Response
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	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1
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	7
Support:			
Sources	5a	Indicate sources of financial or other support for the review	1
Sponsor	5b	Provide name for the review funder and/or sponsor	1
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	1
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
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	4
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	4
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	4
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
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)	4
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	5
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	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
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	5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	5
	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)	5
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	5
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	5
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	n/a

*** 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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Transcatheter closure, mini-invasive closure, and open-heart surgical repair for treatment of perimembranous ventricular septal defects in children: a protocol of network meta-analysis

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Authors' contributions: Conception and design of research (YT, YK, DZH, HXD, TJH); tested the feasibility of the study (YT, YK, LXG, WXK); wrote the manuscript (YT), approved the final manuscript (YT, GL, TJH).

Data sharing statement: No additional unpublished data are available.

Keywords: transcatheter closure; mini-invasive closure; open-heart surgical repair;

perimembranous ventricular septal defects; children; protocol; network meta-analysis

ABSTRACT

Introduction: Both transcatheter device closure and surgical repair are effective treatments with excellent midterm outcomes for perimembranous ventricular septal defects (pmVSDs) in children. The mini-invasive periventricular device occlusion (MIPDO) technique has become prevalent in research and application, but evidence is limited for the assessment of transcatheter closure, mini-invasive closure, and open-heart surgical repair. This study comprehensively compares the efficacy, safety, and costs of transcatheter closure, mini-invasive closure, and open-heart surgical repair for treatment of pmVSDs in children using Bayesian network meta-analysis.

Methods and analysis: A systematic search will be performed using Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), PubMed, EMBASE.com, and the Cochrane Central Register of Controlled Trials, to include random controlled trials, prospective or retrospective cohort studies comparing the efficacy, safety, and costs of transcatheter closure, mini-invasive closure, and open-heart surgical repair. The risk of bias for the included prospective or retrospective cohort studies will be evaluated according to the risk of bias in non-randomized studies of interventions (ROBINS-I). For random controlled trials, we will use risk of bias tool from Cochrane Handbook version 5.1.0. A Bayesian network meta-analysis will be conducted using R-3.3.2 software.

Ethics and dissemination: Ethical approval and patient consent are not required since this study is a network meta-analysis based on published trials. The results of this network meta-analysis will be submitted to a peer-reviewed journal for publication.

Protocol registration number: CRD42016053352

Strengths and limitations of this study

- To the best of our knowledge, this is the first network meta-analysis comparing the efficacy, safety, and costs of transcatheter closure, mini-invasive closure, and open-heart surgical repair for treatment of pmVSDs in children.

- The results of this systematic review will help clinicians and patients to select appropriate repair methods.
- Our results will be limited by both the quantity and quality of the trials available for review.

INTRODUCTION

Ventricular septal defects (VSDs) are the most common type of congenital heart disease, in which 80% are perimembranous ventricular septal defects (pmVSDs) [1]. Treatment of pmVSDs has been improved dramatically over the last 50 years [2-4]. Traditionally, open-heart surgical repair with midline sternotomy and cardiopulmonary bypass (CPB) has been the mainstay of therapy for many years, however it is associated with morbidity, postoperative discomfort, and a large thoracotomy scar [5]. Catheter-based intervention was initially introduced for the closure of muscular VSDs (mVSD) and has been approved by the Food and Drug Administration (FDA) in 2007 [6]. Transcatheter device closure of pmVSDs is a promising alternative [7-9] that has been widely used in developing countries, such as China and India, but it is not currently approved in the United States [10,11]. Moreover, it remains a challenge for use on children with low body weight [10,12]. Previous pairwise meta-analysis suggests that there is no significant difference between transcatheter and surgical closure of pmVSDs in terms of early (up to 30 days) efficacy and safety in well-selected patients [13]. During the same period, the mini-invasive periventricular device occlusion (MIPDO) technique, which combines the respective advantages of cardiac surgery, interventional cardiology, and medical image techniques guided by transesophageal echocardiography (TEE), became popular in research and application [14-17]. Previously, there have been limited studies conducted that compare the efficacy between MIPDO, transcatheter, and open-heart surgical closure for pmVSDs.

Network meta-analysis has become increasingly popular to evaluate healthcare interventions, since it allows to estimate the relative effectiveness among all interventions and rank ordering of the interventions [18]. In the absence of head-to-head comparisons of all interventions of interest, indirect treatment comparison analyses using NMAs of various RCTs can provide useful evidence to inform health-care decision making. Even when the results of the direct comparisons are conclusive, combining them with indirect estimates in a mixed treatment comparison may yield more refined estimates [19,20].

OBJECTIVE

The objectives of this study are to comprehensively compare the efficacy, safety, and costs of transcatheter closure, mini-invasive closure, and open-heart surgical repair for treatment of pmVSDs in children using Bayesian network meta-analysis.

METHODS AND ANALYSIS

Design

Bayesian network meta-analysis will be carried out in this study.

Registration information

We registered on the international prospective register of systematic review (PROSPERO) to publish our study protocol. The protocol of network meta-analysis is planed according to the preferred reporting items for systematic review and meta-analysis protocol (PRISMA-P) recommendation, and the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions [21,22].

Information source

A systematic search will be performed using Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), PubMed, EMBASE.com, and the Cochrane Central Register of Controlled Trials (CENTRAL). The references of included articles and relevant systematic reviews will be tracked to identify other relevant studies. The preliminary searches were performed on December 19th, 2016.

Search strategy

Search terms will be: ventricular septal defect*, perimembranous, peri-membranous, VSD, occlusion, transcatheter, percutaneous, mini-invasive, sternotomy, and child. Full details of the search strategy regarding PubMed are:

((((("Heart Septal Defects, Ventricular"[Mesh]) OR (("ventricular septal defect*"[Title/Abstract] OR VSD[Title/Abstract])))) AND ((thorascopic[Title/Abstract] OR sternotomy[Title/Abstract] OR "minimally invasive"[Title/Abstract] OR mini-invasive[Title/Abstract] OR "surgical closure"[Title/Abstract] OR transcatheter[Title/Abstract] OR "percutaneous occlusion"[Title/Abstract]))) AND ((infant[MeSH] OR child[MeSH] OR

adolescent[MeSH]))))) AND (((perimembranous OR peri-membranous)))

Eligibility criteria

Type of patients: children younger than 18 years of age with pmVSDs confirmed by clinical and transthoracic echocardiographic (TTE) and scheduled for transcatheter closure, mini-invasive closure, or open-heart surgical repair.

Type of designs: random controlled trials, prospective or retrospective cohort studies; systematic reviews or meta-analyses will be also included to track their references.

Type of interventions: transcatheter closure, mini-invasive closure, and open-heart surgical repair.

Type of outcomes: procedural success rate, operative time (min), ICU stay (h), hospital stay (d), total cost, any residual shunt after procedure (residual shunt was classified as small if the width was $\leqslant$ 2 mm and as significant if $\geqslant$ 3 mm [23]), major complications (such as thromboembolism, endocarditis, repeat operation, death due to the procedure, complete atrioventricular block requiring a permanent pacemaker, new-onset valvular regurgitation requiring surgical repair, device embolization requiring surgical removal), minor complications (such as wound complication requiring intervention, groin hematoma, device embolization with transcatheter removal, cardiac arrhythmia, new or increased valvular regurgitation of 2 grades or less, hemolysis requiring only medication, pericardial/ pleural effusion, pneumothorax, pneumopericardium, and pneumoderma requiring chest tube or aspiration) [23].

Other criteria: we will include trials reported in the English and Chinese languages. There will be no limitations on year of publication, publication status.

Study selections

Literature search records will be imported into ENDNOTE X6 software. Two independent reviewers will examine the title and abstract of studies found in the search to identify related studies according to eligibility criteria. Thus, full-text versions of all potentially relevant studies will be obtained. Excluded trials and the reasons for their exclusion will be listed and examined by a third reviewer.

Data items

A standard data abstraction form will be created using Microsoft Excel 2013 (Microsoft Corp, Redmond, WA, www.microsoft.com) to collect data of interest. Two independent reviewers will extract following data and conflict will be resolved by discussion, including first author, year of publication, location, study design, study period, study arms, sample, mean age, mean body weight, gender, VSD size, type of surgery, method of surgical closure, device used, mean device size, cardiopulmonary bypass time, median follow-up, and outcomes. We will consider the following factors as effect modifiers: mean age, type of study design, mean body weight, VSD size, device used, year of publication, length of follow-up, and sample size.

Risk of bias individual studies

The risk of bias of included prospective or retrospective cohort studies will be evaluated according to the tool for assessing risk of bias in non-randomized studies of interventions (ROBINS-I) [24], including bias due to confounding (pre-intervention), bias in selection of participants into the study (pre-intervention), bias in classification of interventions (at intervention), bias due to deviations from intended interventions (post-intervention), bias due to missing data (post-intervention), bias in measurement of outcomes (post-intervention), bias in selection of the reported result (post-intervention), and overall risk of bias. We will evaluate risk of bias as low, moderate, serious, critical risk of bias, and no information.

The risk of bias tool from Cochrane Handbook version 5.1.0 will be also used if random controlled trials are included, which including method of random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (detection bias), selective reporting (detection bias), and other bias [25]. We will evaluate risk of bias as low, high, or unclear risk of bias.

The risk of bias assessment will be completed by two independent reviewers, and conflicts will be resolved by a third reviewer.

Geometry of the network

A network plot will be drawn to describe and present the geometry of transcatheter closure, mini-invasive closure, and open-heart surgical repair using R-3.3.2 software (R Foundation for Statistical Computing, Vienna, Austria). Nodes will be used to represent different interventions and edges to represent the head-to-head comparisons between interventions. The size of nodes and thickness of edges are associated with sample sizes of intervention and numbers of included trials, respectively.

Statistical analysis

A Bayesian network meta-analysis will be performed using package '*gemtc' version 0.8.1* of R-3.3.2 software [26]. The function *mtc.run* will be used to generate samples from using the Markov Chains Monte Carlo sampler. Four Markov Chains will be run simultaneously. We will set 5000 simulations for each chain as the 'burn-in' period. Then posterior summaries will be based on 50 000 subsequent simulations. The model convergence will be assessed using Brooks-Gelman-Rubin plots method [27].

Summary measures

Posterior medians of odds ratio (OR) with 95% credible intervals (CrIs) will be used for procedural success rate, significant residual shunt, major complications, and minor complications. Median mean differences (MDs) or standard mean differences (SMDs) with 95% CrI for operative time, ICU stay, hospital stay, and total cost. In addition, rank probabilities will be calculated, which indicate the probability for each treatment to be best, second best, etc. Clinical decisions about the choice of treatments can be recommended based on the results of rank probabilities when the differences in effect size of different treatments are small [28]. The '*gemtc'* package provides a matrix of the treatment rank probabilities, as well as a plot of the rank probabilities.

Analysis of heterogeneity

We will assess clinical and methodological heterogeneity by carefully examining the characteristics and design of included trials. For pairwise meta-analysis, heterogeneity of treatment effects across head-to-head trials will be assessed by I^2 statistics. If the I^2 is $\leqq$50%, it suggests that there is negligible statistical heterogeneity and the fixed effects model will be used for meta-analysis. If the I^2 is >50%, we will explore

sources of heterogeneity by subgroup analysis and meta-regression using effect modifiers. If there is no clinical heterogeneity, the random effects model will be used to perform meta-analysis. In addition, we will also assess the global heterogeneity on the bias of the magnitude of heterogeneity variance parameter (I^2 or τ^2) estimated from the network meta-analysis models using the *mtc.anohe* command of the '*gemtc'* package.

Assessment of inconsistency

If a loop connecting three arms exists, inconsistency between direct and indirect comparisons will be evaluated by a node splitting method [29].

Funnel plot analysis

Publication bias will be examined with the Begg's [30] and Egge's [31] funnel plot method. The comparison-adjusted funnel plot will be used to identify whether there will be a small sample effect between intervention networks.

DISCUSSION

Surgical repair through median sternotomy on CPB has been regarded as the gold method for treatment of pmVSDs. Hijazi et al. [32] firstly closed pmVSDs using an Amplatzer membranous VSD occlude in 2002. Over the past decade, some studies have found that the Amplatzer pmVSD occluder was associated with a relatively high risk of complete atrioventricular block [33]. Interest has grown in the development of new techniques that can replace traditional open-heart surgery as the "gold standard" for treatment of pmVSD [33]. Recent RCTs demonstrated that both transcatheter device closure and surgical repair are effective treatments, with excellent midterm outcomes, for pmVSDs in children [33]. The MIPDO technique combines the respective advantages of cardiac surgery, interventional cardiology, and medical image techniques, and its use has become popular in research and application [14-17]. To the best of our knowledge, there are no relevant RCTs to compare the differences of transcatheter closure, mini-invasive closure, and open-heart surgical repair. The present study will firstly compare the efficacy, safety, and costs of transcatheter closure, mini-invasive closure, and open-heart surgical repair for treatment of

pmVSDs in children using Bayesian network meta-analysis. However, some limitations are predictable. For example, costs aren't reported in most studies, vary over time, different exchange rates, and costs differences in different countries. In the US implants are performed by cardiologists, but in other countries surgeons implant the devices, so surgical costs may be cheaper in some countries compared to device closure. Additionally, meta-analysis findings partially rely on the quality of original studies, and the number of eligible RCTs is predictably small.

ETHICS AND DISSEMINATION

Ethical issues

Ethical approval and patient consent are not required since this is a meta-analysis based on published studies.

Publication plan

This protocol has been registered on the international prospective register of systematic review (PROSPERO)[34]. The procedures of network meta-analysis will be conducted according to the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions. The results of this network meta-analysis will be submitted to a peer-reviewed journal for publication.

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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	Response
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	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1
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	7
Support:			
Sources	5a	Indicate sources of financial or other support for the review	1
Sponsor	5b	Provide name for the review funder and/or sponsor	1
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	1
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
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	4
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	4
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	4
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
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)	4
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	5
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	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
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	5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	5
	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)	5
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	5
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	5
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	n/a

*** 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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