Effects of Cardiac Surgery and Surgical Procedures on Neurocognitive Function in Patients with Congenital Heart Disease: A Systematic Review and Meta-analysis

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Research

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Abstract

Objective: To determine the neurodevelopmental function in patients with congenital heart disease (CHD) after cardiac surgery and the influence of surgical repair versus transcatheter repair on neurodevelopment.

Methods: We searched PUBMED, EMBASE and Cochrane Controlled Trials (Central) in September 2019 by using Medical Subject Headings. We extracted data using a customized data extraction sheet and employed standard methodological procedures as expected by Cochrane. We used a fixed-effect or random-effect model for meta-analysis.

Results: We included a total of seven articles. The assessed neurodevelopmental outcomes were the full intelligence quotient (full IQ), verbal intelligence quotient (verbal IQ) and performance intelligence quotient (performance IQ). The intelligence quotient was statistically significant after cardiac surgery compared with that of the normal control (full IQ: mean difference = -5.79 [95% CIs -10.14, -1.44], P = 0.009, I²=71%; verbal IQ: mean difference = -4.46 [95% CIs -7.99, -0.93], P = 0.01, I²=56%; performance IQ: mean difference = -7.13 [95% CIs -10.90, -3.35], P =0.0002, I²=64%). The neurodevelopment functions were no different after surgical repair versus transcatheter repair (full IQ: mean difference = 0.19 [95% CIs -4.10, 4.49], P = 0.93, I²=0%; verbal IQ: mean difference = 2.29 [95% CIs -1.60, 6.18], P = 0.25, I²=0%; performance IQ: mean difference = -2.49 [95% CIs -6.49, 1.52], P = 0.22, I²=0%).

Conclusion: We found that patients with CHD undergoing cardiac surgery may exhibit a negative effect on neurodevelopment, and there may be no difference in the effects of the two different surgical methods on neurodevelopment.

Introduction

Approximately 8.224 infants per thousand live births in the world are currently living with congenital heart disease (CHD), and this number continues to grow[1]. Surgery is the main treatment for most of these patients with CHD[2]. It can even be said that surgery is “the gold standard” for the treatment of patients with CHD. With the advancement of surgical techniques, whether simple CHD or complex CHD is present, the mortality rate of patients with CHD is gradually decreasing[3], and their survival rates have significantly improved. Along with social development and daily needs, we not only focus on the postoperative survival rate of patients but also shift the goal from survival rate to quality of life[4]. Moreover, studies on cardiac surgery in patients with CHD have shown that there is a great difference in the quality of life[5]. At present, most studies have revealed that some patients after surgery for CHD experience neurological dysfunction, including (but not limited to) deficits in cognition, movement, and executive function. However, the influence of neurological function in postoperative CHD patients and normal individuals is still unclear.

At present, neurodevelopment in patients with CHD is evaluated by scale and nonscale analyses, such as the Wechsler scale, the Bailey scale, the CNS Vital Signs[6], Leuven glucose control (LGC trial) [7] and so on, which are internationally recognized scales for evaluating neurodevelopment. Using a scale to evaluate neurodevelopment has several advantages. First, it is convenient and simple, which helps evaluators learn and use these tools. Second, the scale evaluation is comprehensive and professional because the score is calculated by software according to the formula. In addition, scales can be comprehensively evaluated, including the assessment of sports, language, communication, and social aspects. Moreover a scale can also focus on special assessments of neurodevelopment in major sports, fine sports, language, communication skills, self-care ability, and oral function. The disadvantage is that younger patients with CHD are less likely to cooperate and may induce errors. Currently, most studies tend to use a scale to assess neurodevelopment[8–11]. This study suggests that there are long-lasting cerebral changes in patients with CHD and that these changes are associated with functional outcome[12], which have adverse effects on executive function, memory, language, social interactions, and quality of life[13]. The possible reason for these effects is that the decrease in white matter microstructure leads to cognitive compromise in patients who have undergone cardiac surgery[14]. Compared with normal controls, the neurodevelopment of children with CHD is relatively delayed[6]. However, it has also been suggested that neurological cognition in patients with congenital heart surgery exhibits no effects compared with that in normal controls[6; 15; 16].

At present, cardiac surgery involves traditional thoracotomy and minimally invasive surgery, both of which have their own advantages and disadvantages. Traditional thoracotomy is suitable for all patients, the operation is safe and reliable, and the technology is mature. However, the amount of trauma is extensive. However, minimally invasive surgery has the advantages of low trauma, mild pain, a short recovery time, and less bleeding, which makes up for the shortcomings of traditional thoracotomy. However, minimally invasive surgery also has its own limitations. For example, the price is high, and the technical requirements for the surgeon are very high. It is difficult to estimate the operation time before surgery. In special cases, it is necessary to convert to intraoperative surgery, and the risk of surgery increases under special circumstances. On the basis of the abovementioned facts, we considered whether traditional surgery versus minimally invasive surgery has an impact on neurodevelopment. At the same time, we have also found that different congenital surgery procedures (surgical repair and transcatheter repair) may cause neurodevelopmental abnormalities[16–18]. However, these previous results are controversial.
Due to the previous two different conclusions, it is necessary to expand the sample size by meta-analysis to explore whether different surgical procedures (surgical repair and transcatheter repair) and postoperative procedures have a potential effect on neurodevelopment in patients with CHD. However, thus far, there has been no meta-analysis by scale to assess the neurodevelopment of patients with congenital surgery. These data are very important for determining whether these patients need early intervention after cardiac surgery. Therefore, we performed a systematic review and meta-analysis. Our aim was to investigate the neurocognitive function of postoperative patients with CHD. Furthermore, we also explored whether different surgical methods (surgical repair and transcatheter repair) have an effect on neurodevelopment.

Method

Literature search

The PubMed, EMBASE, and Cochrane Controlled Trials (Central) databases were searched using MeSH terms ("Heart Defects, Congenital") and ("Surgical Procedures, Operative") and ("Neuropsychological Tests"), respectively. The search strategy was in accord with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[19]. There were no restrictions on the year of publication or the status of publication. The keyword terms are listed in Supplemental Table 1.

Selection of studies

EndNote X9 was used to manage the literature search records. To ensure high reliability between the authors, a pilot literature selection called prescreening was conducted. It was carried out by two independent investigators (X.Q.S. and C.X.), and any discrepancy was resolved by consensus with another reviewer (S.Y.M.). The title and abstract of each identified study were screened. If the abstract was incomplete, the full text was reviewed.

Data extraction and risk of bias assessment

Two investigators (X.Q.S. and C.X.) independently extracted data. In addition to the data on the evaluation indicators, which were mainly obtained from the Wechsler Intelligence Scale-IQ, we also extracted the following data: first author, publication year, country, sample, mean surgery age, surgical procedure, cardiopulmonary bypass time (CPB), aortic cross-clamp time, time of neurodevelopmental assessment, etc. Data are expressed as the mean ± standard deviation (SD) at the end of the study. If there was no mean ± SD, the data were converted according to the Cochrane Handbook version 5.1.0 (http://www.cochrane-handbook.org)[20].

We used "risk of bias" tables to list possible concerns over the potential for bias of each individual study, evaluating sequence generation; allocation sequence concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other potential sources of bias, according to “The Cochrane Collaboration's tool for assessing risk of bias”.

Statistical analysis

We used Review Manager software version 5.3 and Stata version 12.0 for this study. Probability values of \( p < 0.05 \) were considered to be significant.

We used \( I^2 \) statistics to assess the study with respect to heterogeneous effective measures. Values of \( I^2 \) equal to 25%, 50%, and 75% represent low heterogeneity, moderate heterogeneity, and high heterogeneity, respectively. A fixed-effect model was used when no heterogeneity or low heterogeneity was observed, and a random-effect model was used when moderate or high heterogeneity was detected. Subgroup analysis was based on basic severity to explore potential sources of heterogeneity. The hypothesis of publication bias was assessed using funnel plots. We performed Egger's test to assess the risk of publication bias for each outcome. The risk of bias of every included study was assessed according to the recommendation by the Cochrane Collaboration[21]. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to evaluate the quality of the evidence for each outcome.

Results

Search results

We initially identified 592 studies. After reviewing the titles and abstracts, 30 studies were selected for further review. Next, 13 studies were excluded, including six cases of unreported data, four cases not satisfying the inclusion criteria, 1 case not showing the desired results, and 3 cases in non-English. We ultimately included seven studies[16; 17; 22-26]. Screening of the reference lists of included studies and referring articles did not yield additional articles. Figure 1 shows a flowchart for the selection of studies.
Characteristics of the included studies

A total of seven articles were included in our study (Table 1). The publication year ranged from 2004 to 2018, which was a relatively large time span. The evaluation indicators were all found on the Wechsler scale. 6 studies included the analysis of surgical intervention groups versus healthy control groups, 3 of which studies reported the evaluation of surgical groups versus catheter groups. One study examined thoracotomy groups and nonthoracic catheter groups. Among the 7 articles, two were about transposition of the great arteries (TGA), and one reported on left ventricular dysplasia. The remaining four articles were on ventricular septal defects, atrial septal defects, and unclassified congenital conditions. Three articles[22; 23; 25] reported the age of surgery in the neonatal period, the average age of the recruited participants ranging from 1 to 31 day, and the other four articles addressed childhood or adolescence, the average age of the recruited participants ranging from 3.91 to 16 years. The time span of neurodevelopment assessment in the articles was relatively large, ranging from 7 days to 6.9 years. A number of 6 studies presented the cardiopulmonary bypass time and reported the aortic cross-clamp time, and one study[22] did not mention these measurements.
Table 1
Characteristics of the Included Studies

| Author, year | Location | CHD subtype | Sample size | Age at operation | Operation Procedures | CPB (min) | Cross-Clamp Time (min) | Age at evaluation | Outcome assessment |
|--------------|----------|-------------|-------------|------------------|----------------------|----------|------------------------|-------------------|-------------------|
| Karl, 2004[22] | America | TGA | 74 | NP | ASO | NP | NP | 109.7±34.3 months | WPPSI-R, WISC |
| William, 2004[16] | America | ASD | 41 | between 5 and 20 years of age | Surgery and Transcatheter | 46.5±37.6 | 30±27.4 | 7–18 days after surgery | WASI |
| Rijken, 2007a[17] | Netherlands | CHD | 43 | between 6 and 16 years | Surgery | 201.7±120.4 | 109.4±69.9 | 1 year after intervention | WISC |
| Rijken, 2007b[17] | Netherlands | CHD | 19 | between 6 and 16 years | Catheterization | 201±120.4 | 109.4±69.9 | 1 year after intervention | WISC |
| Sarajuuri, 2012a[23] | Finland | HLHS | 23 | 7 (3–18) day | Norwood | 177±85.2 | 44±37.8 | At the age of 5 years | WPPSI-R |
| Sarajuuri, 2012b[23] | Finland | Other UVHs | 13 | 2 (1–31) day | Norwood | 175±48.1 | 44±40 | At the age of 5 years | WPPSI-R |
| Guan, 2014a[24] | China | VSD | 29 | 3.91±0.84 years | Surgery | 73.6±26.1 | 36.4±11.5 | 6-13 years | WISC |
| Guan, 2014b[24] | China | VSD | 35 | 4.22±1.57 years | Transcatheter | NP | NP | 6-13 years | WISC |
| Heinrichs, 2013[25] | Germany | TGA | 56 | 7.1±5.1 years | ASO | 61.7 ± 14.1 | 65.4±7.4 | 16.9 years | HAWIE-R |
| Jin, 2018a[26] | China | VSD | 29 | 3.91±0.84 years | Surgery | 73.6±26.1 | 36.4±11.5 | 6-13 years | WISC |
| Jin, 2018b[26] | China | VSD | 35 | 4.22±1.57 years | Transcatheter | NP | NP | 6-13 years | WISC |

CPB, cardiopulmonary bypass;
Age at operation, Age at evaluation, CPB (min), Cross-Clamp Time(min), mean±SD
VSD, ventricular septal defect;
ASD, Atrial septal defect;
TGA, transposition of the great arteries;
HLHS: hypoplastic left heart syndrome;
UVHs: univentricular heart defects;
ASO, arterial switch operation;
WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence-Revised;
WISC, Wechsler Intelligence Scale for Children;
WASI, Wechsler Abbreviated Scale of Intelligence;
HAWIE-R, Hamburg-Wechsler intelligence test revised;
NP, not report.

Evaluation of postoperative neurocognitive function in patients with CHD.
A total of six studies (surgical group: n = 296, control group: n = 362) focused on intellectual outcomes, i.e., full IQ\verbal IQ\performance IQ. There was a strongly significant difference in intelligence between CHD patients after surgery intervention and healthy controls in our study results (Figure 2, full IQ: mean difference = -5.79 [95% CIs -10.14, -1.44], $P = 0.009$, $I^2=71\%$; verbal IQ: mean difference = -4.46 [95% CIs -7.99, -0.93], $P = 0.01$, $I^2=56\%$; performance IQ: mean difference = -7.13 [95% CIs -10.90, -3.35], $P = 0.0002$, $I^2=64\%$).

**Effect of surgical methods on neurocognitive function**

Four studies reported the effects of surgical repair and transcatheter repair on the intelligence of patients after congenital surgery, and there was no statistically significant difference in the postoperative intelligence with the two types of surgical procedures. (Figure 3, full IQ: mean difference = 0.19 [95% CIs -4.10, 4.49], $P = 0.93$, $I^2=0\%$; verbal IQ: mean difference = 2.29 [95% CIs -1.60, 6.18], $P = 0.25$, $I^2=0\%$; performance IQ: mean difference = -2.49 [95% CIs -6.49, 1.52], $P = 0.22$, $I^2=0\%$).

**Subgroup analysis**

The studies were divided into subgroups according to severity of disease. Articles on TGA and left ventricular dysplasia were considered severe groups, and the remaining publications comprised mild groups. We performed a subgroup analysis. The severe groups and the mild groups showed statistically significant findings compared with those of the respective control groups (Supplementary Figure 1).

**Sensitivity analysis**

After inclusion and exclusion of each study, a meta-analysis of the changes in the full IQ and performance IQ levels (the two heterogeneous outcomes) after heart surgery was conducted, and neither of the results was changed after performing the sensitivity analysis (Supplementary Figure 2). At the same time, about comparison of two surgical procedures on neurocognitive function in patients with CHD, the results did not change after inclusion and exclusion of each study (Supplementary Figure 3).

**Publication bias**

We performed Egger's test and graphed funnel plots (Supplementary Figure 4 and Supplementary Figure 5). The plots were symmetrical, suggesting no evidence of publication bias. In other words, no evidence of publication bias for the Webster Intelligence Scale was observed in the present study.

**Risk of bias**

Most trials were considered to have a low risk of bias. In cases where the published article was incomplete, we sought to study other information about the author, which resulted in a lower risk of bias in the overall assessment (Supplementary Figure 6).

**Quality of evidence assessment**

According to the GRADE guidelines\[27-35\], the quality of evidence for each outcome is listed in Supplementary Table 2 and Supplementary Table 3. Overall, the quality of evidence of mental development in patients with CHD was assessed as low and moderate.

**Discussions**

This is the first systematic review and meta-analysis of neurological development after congenital heart surgery and the effects of different surgical procedures (surgical repair and transcatheter repair) on neurodevelopment in patients with CHD. Our results show that the mental development of patients after congenital heart surgery is slow, although the other outcome measures are negative. Moreover, there was no significant difference in postoperative neurodevelopment (full IQ, verbal IQ and performance IQ) between the surgical methods.

Of the six articles on mental development in patients with CHD, two studies showed that the mental development and growth of patients after congenital heart surgery was delayed compared with the corresponding measures in healthy controls, and the remaining four studies showed that the mental development of patients after congenital heart surgery had no significance compared with healthy controls. The results of our meta-analysis are statistically significant. That is, the intellectual development of postoperative patients with CHD is slow, which is consistent with the conclusion of Karl 2004, Sarajuuri, 2012\[22; 23\]. However, the heterogeneity of the three outcome indicators (full IQ, verbal IQ and performance IQ) is more than 50\%, so we want to find the source of their heterogeneity. In this regard, we carried out subgroup analysis and
sensitivity analysis. We found that the CHD type in the patients in these three studies[22; 23; 25] was more serious compared to that of the patients enrolled in the other studies. Therefore, we performed a subgroup analysis based on the severity of disease in children with CHD. The analysis results of the severe group showed that the large heterogeneity, and the results of full IQ and verbal IQ were not statistically significant, but the performance IQ result were statistically significant. The analysis results of the mild group showed that there was no heterogeneity, and the results of full IQ and performance IQ were statistically significant. Further, we performed a sensitivity analysis. The results of the sensitivity analysis showed that when we did not include it in Heinrichs 2013[25], the heterogeneity decreased. After carefully reading Heinrichs’ study, we found that the cardiopulmonary bypass time of this study was shorter than the other three studies in severe group. As a result, we boldly speculate that the time of extracorporeal circulation also has a certain impact on brain development and neurocognitive function[36; 37], which may be due to insufficient blood supply to the brain during the long period of surgery. Therefore, we speculated that there was little influence over a short period of time but gradual deterioration after longer durations of circulatory arrest[38].

Four articles on surgical procedures were included in this paper, two of which showed no statistical significance[16; 17], and the other two articles did not perform a statistical analysis[24; 26]. The results of our meta-analysis showed no significant difference between surgical repair and transcatheter repair. We considered whether the condition of the patients with CHD in the included literature was relatively mild, and all cases involved atrial septal defect or ventricular septal defect[39], which may be the reason the results of the two surgical methods were consistent. Therefore, regardless of the type of surgical method (surgical repair or transcatheter repair), there was little effect on mental development. However, we believe that different surgical methods for severe CHD have an impact on mental development[18]. We need more research to clarify the effects of surgical methods on neurodevelopment. Additionally, for the results of the meta-analysis about surgical procedures, we also performed a sensitivity analysis. The results of the analysis did not change after the inclusion and exclusion of each study. In other words, our results are stable and reliable.

In addition, no publication bias was found in our study. With the GRADE approach, there was low-quality or unclear-quality evidence for each of the analyzed outcomes.

Our research has the following advantages. This study is unique in providing information on nerve development after cardiac surgery and differences between different operations (surgical repair and transcatheter repair) based on longitudinal follow-up, which is of great significance for whether early intervention is needed to promote neurodevelopment after such procedures. Our findings show that the mental development of patients with CHD is retarded after surgery, meaning that it is necessary to develop intellectual training programs to solve the problems we are facing.

The present meta-analysis also has potential limitations. First, our results show that neurological development is delayed after surgery and is either caused by the operation or existed before the operation. However, the mechanism is unknown. Second, regarding surgical repair and transcatheter repair, the number of articles included in the literature is small, the sample size is not large, there are no randomized controlled trials, which makes it unclear whether the results are affected. Third, the study only concerns intelligence assessment, and there are many aspects of neurodevelopment, such as motor language execution ability, which is not covered in the present study. Fourth, the time of the postoperative evaluation is different, and the version of the scale is inconsistent, which may have a potential impact. In addition, our study did not reveal whether the time of CPB and the time of carotid artery clipping have a certain influence on postoperative neurocognitive function. Finally, patients with CHD have different disease severities. Although we conducted a subgroup analysis, the sample size of the included studies was relatively small, which may have affected the reliability of the results obtained. Additional studies are needed in the future to evaluate these potential influences.

**Conclusions**

Our meta-analysis suggests that neurodevelopment is delayed for patients with CHD after surgery and is no different for patients with CHD between surgical repair and transcatheter repair. These findings suggest that patients with CHD need effective interventions to improve their neurodevelopment after surgery, which requires further exploration, including larger samples and well-designed prospective studies.

**Declarations**

**Acknowledgments**

None declared.

**Authors’ contributions**

Dr Cheng Xu and Prof Xuming Mo conceptualized and designed the study, and reviewed and revised the manuscript. Miss Xiaqi Su drafted the initial manuscript. Ms Siyu Ma and Miss Yiwei Pu designed the data collection instruments, collected data, carried out the initial analyses, and
reviewed and revised the manuscript. Dr Zhiqi Wang, Zhaocong Yang conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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**Availability of data and materials**

Please contact the author for data requests.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Consent for publication was obtained from the parents of the child.

**Competing interests**

The authors declare that there is no conflict of interest.

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