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Incidence of Acute Neurologic Complications after Heart Surgery in Children with Congenital Heart Disease: A Systematic Review and Meta Analysis

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Abstract

Background

The aim of this systematic review and meta-analysis was to evaluate the Incidence of Acute Neurologic Complications after Heart Surgery in Children with Congenital Heart Disease. The searches were conducted by two independent researchers (MS, ZM) to find the relevant studies published from 1/1/2009 to the end of 30/12/2018. We searched for published literature in the English language in MEDLINE *via* PubMed, EMBASETM *via* Ovid, The Cochrane Library, and Trip database. For literature published in other languages, we searched national databases, KoreaMed and LILACS, and we searched OpenGrey and the World Health Organization Clinical Trials Registry for unpublished literature and ongoing studies. The keywords used in the search strategy were: Neurologic Manifestations, Thoracic Surgery, complications, children, Heart Defects, Congenital - heart disease and children, which were combined using the AND, OR, and NOT operators. Finally, a meta-analysis was conducted in STATA14 statistical software. A total of 5773 patients with congenital heart disease who had undergone the heart surgery were studied. The age of the participants varied between 15 days to 18 years. Based on the random effect model the total prevalence of neurologic complications in 5773 patients with congenital heart disease who had undergone the heart surgery was 3% (95% confidence interval [CI]:2.6,3.4, I2 = 94%) with seizure being the most prevalent neurologic complication with a prevalence of 1.4% (95% confidence interval [CI]:1.1%,1.8%, I2 = 73.5%). It was showed that overall rate of neurological complication was higher in studies with higher female to male ratio. The frequency of neurologic complications after congenital open-heart surgery was 77.1% (95%CI 75%, 79.1%) of all kind of cardiac surgeries moreover, the frequency of neurologic complications after congenital close heart surgery was 19.2% (95%,16.8%, 21.5%) of all kind of cardiac surgeries.

Keywords: Neurologic Manifestations; Thoracic Surgery; complications; Heart Defects; Congenital; congenital heart disease

Introduction

Accounting for one third of all forms of congenital defects, Congenital Heart Defect (CHD) is one of the most common defects the majority of these defects require surgery in early childhood. Nearly half of 30,000 babies born with congenital heart defects in the United States undergo surgical intervention in their first year of life. Despite considerable survival rate, the majority of babies experiencing such surgeries are diagnosed with neurodegenerative disorders in later stages of their life. The rate of Cardio Pulmonary Bypass (CPB) has increased recently and there are neural strategies in therapeutic and vital care to reduce neurological complications. Advances in cardiac surgery over the past 25 years, including discontinuation of deep hypothermic circulation and early surgical operations, have significantly increased the survival rate of children with congenital heart disease; additionally, brain damage caused by chronic hypoxia and cyanosis (skin bruising) has decreased significantly. However, surgical procedures are supposed to generate specific neurological complications, including seizure, choreoathetosis, ischemic lesions and encephalopathy. Postoperative neural damages are supposed to be caused by several factors, including micro-embolization, hypoxia, hypophysis, hyperfusiogen, and biochemical abnormalities. In the last ten years, it has been estimated that neurological dysfunction complicates open heart surgery in children in 25% of cases, and seizure is the most common postoperative complication. Other neurological symptoms include abnormal bone change, abnormal muscle tone, hemiplegia (mild half-paralysis), organic mental syndromes, dyskinesia, gaze palsies, and personality changes. There is still little information on immediate neurological outcomes following surgical procedures in many developing countries; additionally, rapid diagnosis is not possible in the absence of advanced technology, such as continuous EEG and near-infrared spectroscopy [1].

According to the results of formerly conducted studies, two-third of post-operative seizures in infants occur due to unknown causes; these septic seizures were previously considered to be benign; but, they turned out to be associated with significant long-term cognitive consequences. As a result, the main focus has shifted toward studying neurological complications in children's heart surgery over the past decade. In recent years, neurological complications have been supposed to occur mainly due to chronic hypoxia and polycythemia in cyan tropic children,

uncorrected right-left shunts, and the effects of palliative cardiac surgery. Progress in surgical technique and intensive care management have led to anatomical correction of many heart lesions in the early stages and a significant reduction in congenital heart disease and mortality. The majority of infants born with congenital heart disease and severe hemodialysis disorders manage to survive. Interestingly, the same surgical support techniques to promote survival are associated with the occurrence of neurological complications, which is approximately 25% in some centers. As a result, the mechanism of brain damage in heart surgery has focused on precise studies over the past two decades. Understanding these surgical mechanisms is realized through experimentation on animal models and several large clinical trials, as well as brain monitoring during surgery and Magnetic Resonance Imaging (MRI) [2]. Given the development of recent advances in neuro-protective strategies and critical care management, the present systematic review and meta-analysis was conducted to review global prevalence of acute neuromuscular complications in children with congenital heart disease.

Methodology

Search strategy

The searches were conducted by two independent researchers (MS, ZM) to find the relevant studies published from 1/1/2009 until the end of 30/12/2018. We searched for published literature in English language in MEDLINE *via* PubMed, EMBASETM *via* Ovid, The Cochrane Library, and Trip database. For literature published in other languages, we searched national databases and, KoreaMed and LILACS, and we searched OpenGrey and the World Health Organization Clinical Trials Registry for unpublished literature and ongoing studies. To ensure the literature saturation, the list of the included research references or the relevant reviews found by searching was studied (FP). The special search strategies were created using the Health Sciences Librarian website with specialization in systematic review searches using the MESH phrases and open phrases in accordance with the PRESS standards. After finalizing the MEDLINE strategy, the results were compared to search the other databases. Similarly, PROSPERO was searched to find the recent or ongoing systematic reviews. The keywords used in the search strategy were “Neurologic Manifestations, Thoracic Surgery, complications, children, Heart Defects, Congenital - heart disease and children, which were combined using the AND, OR, and NOT operators [4].

Study selection and data extraction

Two researchers independently analyzed the titles and abstracts of the articles with regard to the research eligibility criteria (ZM, MS). After omitting the redundant studies, the full texts of the studies were assessed against the eligibility criteria and the information of the authors was collected when required. General information (the corresponding author, province, and year of publication), the study information (the sampling technique, information collection method, research conditions, sample size, and risk of bias), and the output scales (prevalence of neurologic complication) were collected [5].

Quality assessment

The scale developed by was used to assess the quality of the methodology and the risk of bias for each observational study. This 10-item scale is used to assess the quality of the studies with respect to their external validity (items 1 to 4 assess the target population, sampling framework, and minimum participation bias) and internal validity (items 5 to 9 assess the data collection method, problem statement, research scale, and data collection instruments while item 10 assesses the data analysis bias). The risk of bias was measured independently by two researchers (FP, MS), and the differences were solved by reaching a consensus [6].

Data aggregation

All of the eligible studies were included in the data aggregation following a systematic review and the data was integrated using a forest plot. The random effects model was assessed based on the overall prevalence of neurological complications. The heterogeneity of the preliminary studies was tested using the I2 test. Besides, the subgroups were analyzed to determine the heterogeneity based on the prevalence of seizure and year of publication of the respondents. Finally, a meta-analysis was conducted in STATA14 statistical software [7].

Results

Research specifications

A total of 5773 patients with congenital heart disease who had undergone the heart surgery were studied. The age of the participants varied between 15 days to 18 years. Of the 10 studies, 5 presented retrospective data, 4 study were cross sectional, one study was a prospective cohort survey. A total of 10 studies from 6 countries meeting the inclusion criteria were reviewed. Of these 10 studies, two studies were from Iran, two were from USA, Spain, UK, Australia, Germany, Tennessee and Pakistan each had one study included. The common sampling techniques was convenience sampling (n=10). 80% of the studies had low risk of bias. The most prevalent data collection methods were the Medical records, self-report and interview methods. The most common study locations were hospitals and out patient’s clinic (n=10) [9] (**Table 1**).

Author	year	Country	Sampling method	Study design	Setting	Study population	Mode of data collection	Participants	Age mean ± SD or range	Risk of bias
Esteghamat	2015	Iran	Convenience	Cross-secti	Hospital	Children with	Interview	364	15 >	Low

				onal		congenital heart disease surgery				
Tritten wein	2003	Australia		Cross-sectional				534	-	Low
Avila-Alvarez	2012	Spain	Convenience	Cross-sectional	Hospital + patient clinic	Children undergoing cardiac surgery	Medical record / Self report	900	-	Low
Mirzaei	2016	Iran	Convenience	Cross-sectional	Hospital + patient clinic	Children undergoing cardiac surgery	Medical record / Self report	203	3.65± 4.-47 years	Low
Bryan	1994	USA	Convenience	Retrospective	Hospital	Survivors of pediatric heart transplantation	Medical record	14	-	moderate
Carollin	2002	USA	Convenience	Retrospective	Hospital	Children with Open-heart Operation	Self report	706	-	Low
Jafri	2017	Pakistan	Convenience	Retrospective	Hospital + pat	Children under	Medical record	2000	-	Low
					ient clinic	going cardiac surgery				
Fallon	1995	UK	Convenience	Retrospective	Hospital	Children undergoing cardiac surgery	Medical record	523	-	Moderate
Lori	2015	Germany	Convenience	Prospective cohort	Hospital	Children with congenital heart disease surgery	Medical record	204	16<	Low
Hemant	2014	Tennessee	Convenience	Retrospective	Hospital	Pediatric undergoing cardiac surgery	Medical record	325	18>	low

Table 1: Demographic characteristics for the included studies.

Meta-analysis of Frequency of Acute Neurologic Complications after Heart Surgery in Children with Congenital Heart Disease:

Based on the random effect model the total prevalence of neurologic complications in 5773 patients with congenital heart disease who had undergone the heart surgery was 3% (95% confidence interval [CI]:2.6,3.4, I2=94%) [10] (**Figure 2**)

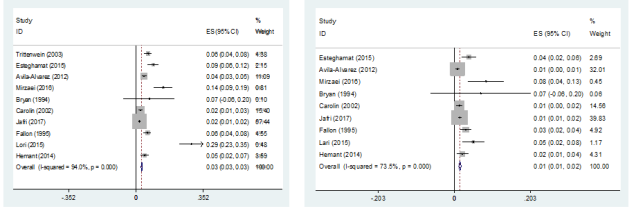

Figure 2: Frequency of Heart Surgery in Children with Congenital Heart Disease.

Heart Surgery in Children with Congenital Heart Disease

Frequency of Acute Neurologic Complications after Heart Surgery in Children with Congenital Heart Disease and its 95% interval for the studied cases according to the year and the country where the study was conducted based on the model of the random effects model. The midpoint of each section of the line estimates the% value and the length of the lines showing the 95% confidence interval in each study. The oval sign shows Frequency of Acute Neurologic Complications after Heart Surgery in Children with Congenital Heart Disease [11].

Frequency of Seizure after Heart Surgery in Children with Congenital Heart Disease and its 95% interval for the studied cases according to the year and the country where the study was conducted based on the model of the random effects model. The midpoint of each section of the line estimates the% value and the length of the lines showing the 95% confidence interval in each study. The oval sign shows Frequency of Acute Seizure after Heart Surgery in Children with Congenital Heart Disease [12].

Sub-group analysis

Meta-analysis of Frequency of Seizure after Heart Surgery in Children with Congenital Heart Disease:

Based on the random effect model the total prevalence of seizure in 5409 patients with congenital heart disease who had undergone the heart surgery was 1.4% (95% confidence interval [CI]:1.1%,1.8%, I2=73.5%).

Meta-analysis of Frequency of Acute Neurologic Complications after Heart Surgery in Children with Congenital Heart Disease based on the country:

The frequency of neurologic complications after congenital cardiac surgery was the most in Iran 10.5% (95% CI 8%-13%) based on two conducted studies (37,39), followed by Australia 6.4% (95% CI 4.3%-8.4%) based on one study (38), UK 6% (95% CI 4%-8%) based on one study (43), Spain 4.2% (95% CI 2.9%-5.5%) based on one study (33) and USA 2.3% (95% CI 1.2%-3.4%) based on two studies conducted (40,41), respectively [13] (**Figure 3**).

Figure 3: Meta-regression Frequency Congenital Heart Disease

Meta-analysis of Frequency of Acute Neurologic Complications after Heart Surgery in Children with Congenital Heart Disease based on the type of surgery:

The frequency of neurologic complications after congenital open-heart surgery was 77.1% (95%CI 75%,79.1%) of all kind of surgeries and the frequency of neurologic complications after congenital close heart surgery was 19.2% (95%CI 16.8%, 21.5%) of all kind of surgeries (**Figure4)** [14]**.**

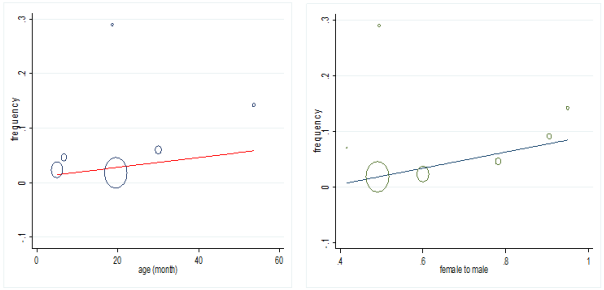

Figure 4: Meta-Regression female to male ratio of Prevalence of Neurological complication after congenital heart surgery

Meta-Regression Results

Meta-regression between year of the publication and Prevalence of Neurological complication after congenital heart surgery:

The studies' meta-regression was according to the association between prevalence of neurological complications and the publication year of the studies and the overall rate of neurological complication. There was no statistically significant linear trend in univariate meta-regression to explain effect size variation by publication year of study with coefficient = -1.35 (95% CI –14.89, 12.18), P = 0.826 (**Figure 5**) [15].

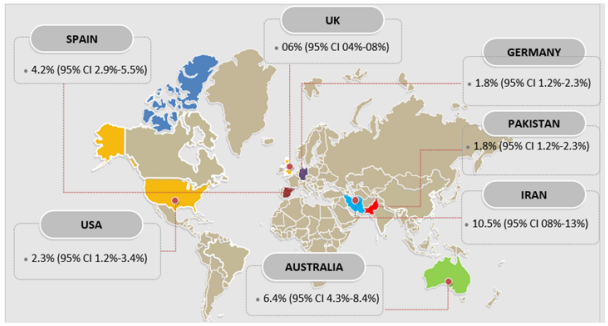

Figure 5: Prevalence of neurological complications in children undergoing congenital heart surgery based on the country

Meta-regression finding between year of the publication and frequency of seizure after Heart Surgery in patients with Congenital Heart Disease:

The studies' meta-regression was according to the association between prevalence of seizure and the publication year of the studies and the overall rate of seizure.

There was no statistically signi icant linear trend in univariate meta-regression to explain effect size variation by publication year of study with coefficient = -0.481 (95% CI –4.85, 3.89), P = 0.802 **(Figure 6)** [16]**.**

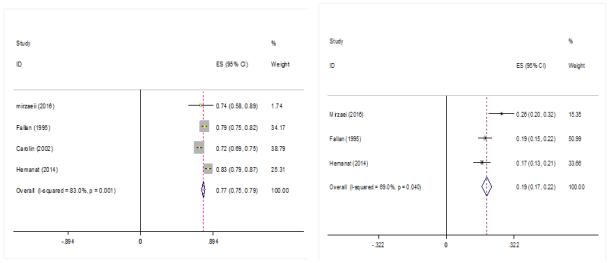

Figure 6. Meta-analysis of Frequency of Acute Neurologic Complications after open-heart Surgery and close Heart Surgery in Children with Congenital Heart Disease.

Meta-regression between age of the participants and Prevalence of Neurological complication after congenital heart surgery:

The studies' meta-regression was according to the association between prevalence of neurological complications and the age of the participants and the overall rate of neurological complication. It showed the overall rate of neurological complication was lower in younger age than the older ones. But there was no statistically significant linear trend in univariate meta-regression to explain effect size variation by age of the participants with coefficient = 5.54 (95% CI –15.4, 26.50), P = 0.50 [17].

Meta-regression between female to male ratio of the participants and Prevalence of Neurological complication after congenital heart surgery:

The studies' meta-regression was according to the association between prevalence of neurological complications and the female to male ratio of the participants and the overall rate of neurological complication. It showed the overall rate of neurological complication was higher in studies with higher female to male ratio. But there was no statistically significant linear trend in univariate meta-regression to explain effect size variation by age of the participants with coefficient = 9.9 (95% CI –26.02, 45.9), P = 0.50 (**Figure 7**) [18].

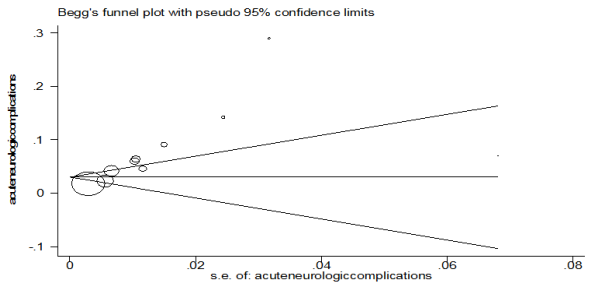

Figure 7: Funnel plot of publication bias. It is shown in Funnel plot symmetrically. Circles' size shows the weight of studies

Publication bias

Funnel plot shows no indication of publication bias. It is shows in funnel plot symmetrically. Circles' size shows the weight of studies (bigger circles shows more sample and smaller circles shows fewer sample).

Discussion

In a systematic review and meta-analysis Denise van der Linde et al reported that total CHD birth prevalence increased from 0.6 per 1,000 live births (95% confidence interval [CI]: 0.4 to 0.8) in 1930 to 1934 to 9.1 per 1,000 live births (95% CI: 9.0 to 9.2) after 1995. Significant progress has been made in the survival of new borns with Congenital Heart Disease (CHD) due to progress in surgery and also pre-surgical care and management over the past two decades. Despite the fact that the majority of children with CHD continue to live nowadays, many of them may experience and develop complications developing in their nervous systems. Along with decreasing early mortality rates, a significant proportion of survivors are diagnosed with evolutionary neurodevelopmental disabilities in the future. The significance of neurological complications in congenital cardiac surgeries has been highlighted for many years. Concluded that infants with congenital cyanotic or non-cyanotic heart disease are at high risk for brain damage and brain development impairment on the other hand. showed that lower brain development in MRI was associated with more serious brain damage both before and after surgery. In the present systematic review and meta-analysis, which is the first systematic review and meta-analysis on this title, we investigated the overall frequency of acute neurological complications among the 5773 studied subjects. while studying different reviews on this topic we noted that most of them reported seizure as the most prevalent complication so we decided to evaluate the global prevalence of seizure after congenital heart surgery. the overall frequency of acute neurological complications was 1.75% with seizures being the most prevalent complication with a frequency of 1.4%. postoperative. Seizures continues to be a significant symptom of neurologic complications in newborns. In particular, seizure in newborns undergoing heart surgery is a long-known fact. They reported that these seizures appear in about 19% of the total non-hypoplastic left heart syndrome survivors, they also reported that these seizures are associated with certain types of congenital heart disease. Adverse neurological outcomes after neonatal and infant cardiac surgery are related to both non-modifiable and modifiable mechanisms. non-modifiable factors include many variables specific to each individual patient, including genetic susceptibility, gender, race, socioeconomic status, and in utero central nervous system development. Modifiable factors include not only intraoperative variables (cardiopulmonary bypass, deep hypothermic circulatory arrest, and hemodilution) but also such variables as hypoxemia, hypotension, and low cardiac output due to the small number of the studies conducted on this title and limited data about these factors in conducted studies we were only able to analyze the effect of age, female to male ratio and the type of cardiac surgery on prevalence of neurological complications were about four times higher in open surgeries in comparison with the close ones.(77.1% vs 19.2%). Inflammatory cascades have been implicated in the end-organ injury seen after cardiopulmonary bypass and might play a role in neurological dysfunction this is while Fallon et al in their study indicated that There was no difference in in the prevalence of neurological complications between patients who had undergone open-heart surgery using cardiopulmonary bypass or a closed heart

approach (6-1% and 6-2% respectively) they also reported that Patients with adverse neurological events had a significantly longer mean cardiopulmonary bypass time than normal survivors (113 v 93 minutes; p<005), as did patients who subsequently died (199 v 93 minutes; p<OOO1) and the aortic cross clamp time in patients who subsequently died was significantly longer (48 v 79 minutes) (7).there were some other effective factors mentioned in some of the studies included in this systematic review. Álvarez et al in their study reported that Patients with neurological complications had a longer bypass time (P=.009), longer aortic cross time (P=.012), longer hospitalization in intensive care (P=.001), longer duration of mechanical ventilation (P=.004) and an increased number of days under inotropic support (P=.001).Anesthesiologists can nowadays monitor and control the brain in congenital heart surgery with clinical monitors that are available in many cases and potentially improve neurological outcomes with appropriate therapeutic strategies. All of the above-mentioned materials suggest that neurological observations should always be implemented and followed in congenital heart surgery. If the anesthesiologist interprets what is presented on the monitors, more costs will be saved by preventing a number of neurological complications with conventional monitors and hardware monitoring and disposable sensors.

Limitations

Data presented in the present research has been collected from several sources of data in multiple studies. Some of the studies were clinical trials and others were observational. Research plans and objectives, inclusion and exclusion criteria, and collected data varied greatly. In addition, the characteristics of individuals in combined data sets, such as diagnosis of disease and surgical class, have changed throughout the research period. Also, the number of studies conducted in this topic was really limited.

Strengths

The present research is the first systematic review and meta-analysis published on the prevalence of neurological complications after congenital heart surgery in the world. Additionally, the findings include almost all information about the results of developing neurological complications in children who have had heart surgery due to congenital heart disease.

Conclusion

The incidence of neurological complications after cardiac surgery in children with congenital heart disease turned out to be 3% in the present study. Clinical seizure is the most common complication with a prevalence of 1.4%. Also, this study showed that the prevalence of neurological complications after open-heart surgery was about four times more than the close ones. Care units for patients with congenital heart disease should perform neurological monitoring during and after cardiac surgery specially in children undergoing open cardiac surgery in order to detect and prevent these complications earlier. It is recommended to conduct studies on neuro-protection in neonatal heart surgery to investigate the prevention of neonatal seizures monitored by continuous EEG image. The main objective is to improve the lives of these children suffering from complex heart disease through better diagnosis of neurological events and conducting appropriate treatment.

Acknowledgements

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