Treatment for hypoplastic left heart syndrome: A literature review

https://doi.org/10.56238/sevened2024.005-018

Augusto Hipólito Chagas Freato[1], Pedro Guilherme Coutinho Ribeiro[2], Calin dos Santos Kishishit Castro[3], Filipe Bochensky Siqueira[4], Josimar Cunha Rodrigues Junior[5], Beatriz Furtado Ferro[6], Camila Coelho Chaves Gaspar[7] and José Kleber de Figueiredo[8]

ABSTRACT

Introduction: Hypoplasia of the left ventricle is identified as extremely reduced dimensions of the cardiac structures of the left side, including the left atrium, mitral valve, left ventricle, aortic annulus and ascending aorta. It is a fatal and difficult to treat disease and its surgical correction is not yet possible, however, palliative surgical interventions are currently proposed that should be performed in the first days of life. Objective: To analyze treatments for hypoplastic left heart syndrome. Method: This is an integrative review, in the sense that this study adopted the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A search was conducted in the following databases: Medical Literature Analysis and Retrieval System Online (Medline/Pubmed) and Latin American and Caribbean Health Sciences Literature (LILACS). Result and Discussion: Based on the aspect of eligibility for the review, 8 articles were selected. According to them, hypoplasia of the left heart continues to be the main serious congenital cardiac anomaly, even with the reduction in mortality. Regarding postnatal treatment, there has been an evolution in the immediate management at birth in the preservation of the clinical condition, with the use of prostaglandin E1 and vasoactive drugs. In this context, the initial Norwood-Sano technique started to have a lower risk, and consequently a higher survival rate in this phase. Conclusion: It is verified that surgical procedures are still considered gold standards for the care of this patient, however, prenatal cardiac interventions are promising treatment options and, as well as stem cell therapy, provide important clues for the application of new approaches.

Keywords: Treatment, Congenital heart disease, Hypoplastic left heart syndrome.

[1] Medical Student at Ceuma University, São Luís-MA
[2] Medical Student at Ceuma University, São Luís-MA
[3] Medical Student at Ceuma University, São Luís-MA
[4] Medical Student at Ceuma University, São Luís-MA
[5] Medical Student at Ceuma University, São Luís-MA
[6] Medical Student at Ceuma University, São Luís-MA
[7] Medical Student at Ceuma University, São Luís-MA
[8] Full Physician of the Brazilian Society of Cardiology

INTRODUCTION

Left ventricular hypoplasia is identified as extremely reduced dimensions of left-sided cardiac structures, including the left atrium, mitral valve, left ventricle, aortic annulus, and ascending aorta. The diagnosis of left ventricular hypoplasia syndrome can be made during pregnancy by means of fetal echocardiography (during prenatal care) or soon after birth, with echocardiography (when suspicion arises during the pediatric physical examination) that should be performed during the maternity ward. A chest X-ray and an electrocardiogram (ECG) are performed for a differential diagnosis, and cardiac catheterization is required (ATIK, 2021).

The uncommon congenital heart anomaly, left ventricular hypoplasia, has an incidence of 266 per 1 million live births. In addition, the annual incidence of hypoplastic left heart syndrome in North America is approximately 2,000 cases (SHENOY, 2014). Between January 1990 and December 2008, during the Fetal Cardiology Consultation, 311 congenital heart diseases were diagnosed, and 67 of these cases (21.5%) corresponded to Hypoplastic Left Heart Syndrome (DIONÍSIO, 2011).

As for the clinical manifestations of left ventricular hypoplasia syndrome, these arise with the closure of the ductus arteriosus during the first 2 days of life. Soon after, signs of heart failure and shock quickly appear, including tachypnea, dyspnea, weak pulse, pale or bluish skin, hypothermia, lethargy, and a reduction in the number of wet diapers (DIONÍSIO, 2011).

When there is a decrease in the blood flow received by the body, the vital organs cease to receive sufficient blood flow. If there is no return of adequate blood flow, the baby dies (ATIK, 2021).

Left Ventricular Hypoplasia Syndrome is, therefore, a fatal disease that is difficult to treat (NERY, 2021). Surgical correction is not yet possible, however, palliative surgical interventions are currently proposed that should be performed in the first days of life, so the treatment of this syndrome can be done through neonatal heart transplantation or staged palliative surgery described by Norwood (FANTINI *et al.*, 2004).

However, preoperative prophylactic clinical treatment should be established soon after birth in those patients who do not require urgent surgery through the use of prostaglandins (0.05 to 0.1 mcg/kg/min) in order to preserve the systemic flow through the ductus arteriosus until the surgical approach, in addition to vasodilators such as dobutamine and adrenaline. they play an important role as they are able to maintain lung pressure and cardiac output at adequate levels (ATIK, 2021).

The surgical procedure is performed in a few steps. During the first week of life, the first step is made with the Norwood procedure (SIFFEL et al., 2015), which aims to place the right ventricle in a systemic position by sectioning the pulmonary trunk and connecting the ascending aorta with the ventricle (NERY, 2021).

The second stage is performed at 3 to 6 months of age through the bidirectional Gleen or hemi-Fortan procedure, the superior vena cava is connected to the right pulmonary artery so that part of the systemic venous return bypasses from the right atrium to the lungs, aiming at oxygenation in the third stage is performed between 18 and 36 months of age and consists of a modified Fontan procedure, in which the flow from the superior vena cava to the superior vena cava and pulmonary artery is modified. (SIFFEL et al., 2015). The aim of this study was to analyze treatments for hypoplastic left heart syndrome .

METHOD

This is an integrative review, in the sense that this study adopted the criteria of the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA). A search was conducted in the following databases: Medical Literature Analysis and Retrieval System Online (Medline/Pubmed) and Latin American and Caribbean Health Sciences Literature (LILACS). Data was collected from April and May 2023. The descriptors for the search were defined after consultation in the DeCS (Descriptors in Health Sciences), namely: treatment, congenital heart *defects, congenital heart defects* and *hypoplastic left heart syndrome*

The descriptors were associated with each other according to the language and other combinations by the Boolean operator "AND". Articles in Portuguese/English languages published in the last 10 years were considered for eligibility evaluation. To delimit the eligibility of the studies, the titles and abstracts of all research results were selected in two stages by a reviewer (study authors), using the defined inclusion and exclusion criteria, namely: inclusion criteria: scientific articles with full text available free of charge, case reports, quantitative, qualitative, cross-sectional, randomized, Portuguese language and English studies; and exclusion criteria: duplicates, revisions, protocols, letters, editorials, monographs and theses. The search strategy is detailed in Chart 1.

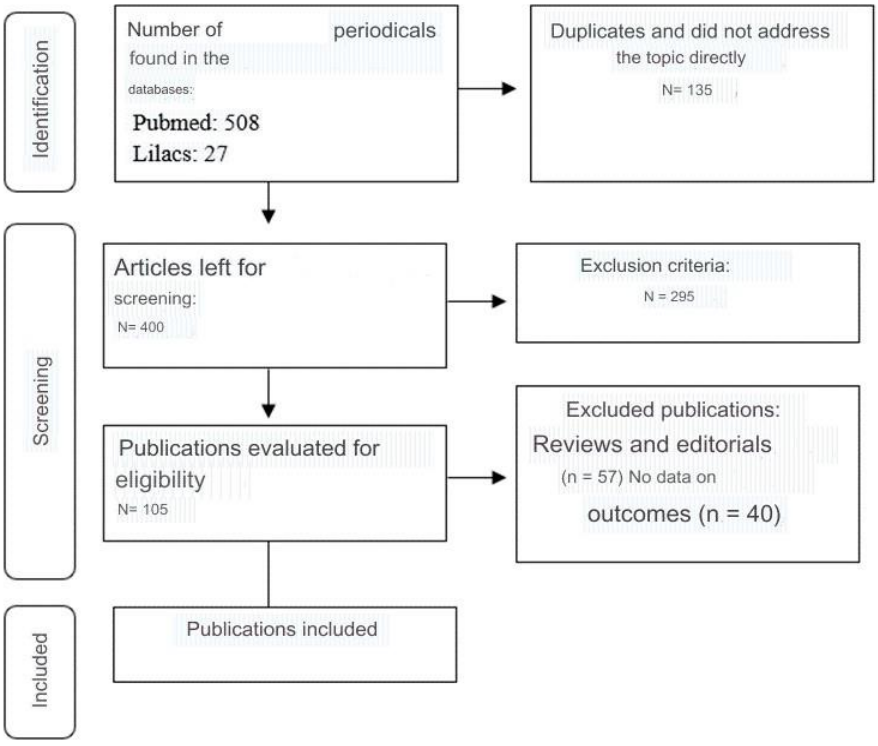
Medline/Pubmed			
Searchs	**Filters**	**Keywords**	**Results**
1	Free Full Text/ 10 years	*treatment AND heart defects, congenital AND hypoplastic left heart syndrome*	436
2	Free Full Text/ 10 years	*treatment AND hypoplastic left heart syndrome*	33
3	Free Full Text/ 10 years	*hypoplastic left heart syndrome*	39
Lilacs			
1	Free Full Text/ 10 years	tratamento AND cardiopatias congênitas AND síndrome de hipoplasia do coração esquerdo	5
2	Free Full Text/ 10 years	tratamento AND síndrome de hipoplasia do coração esquerdo	9
3	Free Full Text/ 10 years	síndrome de hipoplasia do coração esquerdo	13

After the searches, the articles were selected for the result, in which the titles and abstracts were read and reviewed to verify whether they should be included or excluded. Next, the full text of the journals identified in the previous phase was reviewed to determine their eligibility for data extraction.

RESULTS AND DISCUSSION

The flowchart (Figure 1) shows the process of managing the selection of publications in this review.

Figure 1 – Article eligibility flowchart.



Source: Authors, (2023)

Based on the aspect of eligibility for the review, a total of 8 articles were selected for analysis. In order to present the analyzed articles in a more didactic way and to facilitate a comparative analysis, it was decided to arrange their characteristics in the form of a chart 1.

The probability of survival was 66% during the first week, 27% during the first year of life, and 24% during the first 10 years. For children with information on surgical intervention (

Author (Year)	**Method**	**Sample**	**Treatment**	**Main result**
Atik (2021)	Case report	21-year-old patient has been followed since birth with a diagnosis of left heart hypoplasia	Norwood operation at 4 days of age, bidirectional Glenn technique at 5 months and total cavopulmonary with non-fenestrated external tube at 5 years of age.	The patient showed good long-term evolution.
Bezerra et al. (2022)	Retrospective cohort	80 patients with HLHS	Norwood Operation	The 30-day survival rate was 91.3% and the intermediate survival rate was 81.3%.
Burkhart et al. (2019)	Prospective, non-randomized clinical trial	10 patients	Direct intramyocardial injection of autologous mononuclear cells derived from umbilical cord blood	All patients successfully underwent stage II palliation and intramyocardial injection of cord blood-derived mononuclear cells. Operative mortality was 0%. There was a single adverse event related to cell release: an epicardial bleed at the injection site that required simple superseeding. The cohort demonstrated no significant safety concerns through 6 months. Furthermore, the treatment group did not demonstrate any reduction in cardiac function in the study setting related to intramyocardial injections of autologous cells.
Kovacevic et al. (2018)	Retrospective multicenter study	67 fetuses	Medline/Pubmed	Searches
Filters	Descriptors	Results	1	Free Full Text/ 10 years
treatment AND	436	two	Free Full Text/ 10 years	treatment AND
33	3	Free Full Text/ 10 years	hypoplastic left heart syndrome	39 The daily goal was to administer ≥ 8 h of oxygen at 8 – 9 L/min of 100% FiO2 until delivery. Maternal arterial partial oxygen pressure (PaO2) was measured after 1 h of 8 L/min O2. If PaO2 was less than 250 mmHg O2, the flow was increased to 9 L/min. Mothers were sent home with an oxygen condenser and mask and encouraged to continue MH therapy for as long as possible each day.
Lilacs	1	Full texts/ 10 years	treatment AND congenital heart diseases AND	5n = 88), overall survival was 52%, and preterm infants had significantly worse survival (31%) compared to full-term newborns (56%). For children who survived to 1 year of age, long-term survival was ~90%.

Source: Authors,(2023)

According to the selected articles, hypoplasia of the left heart continues to be a congenital cardiac anomaly of concern for the medical field, even with the reduction in mortality.

There are prenatal interventions, such as fetal aortic valvuloplasty and maternal hyperoxygenation. According to Kovacevic et al. (2018), fetal aortic stenosis can progress to hypoplastic left heart syndrome, and fetal aortic valvuloplasty has been proposed to improve left heart hemodynamics and maintain biventricular circulation, however, such a procedure is associated with a 10% loss and increased prematurity, and therefore the risk-benefit ratio remains uncertain.

Maternal hyperoxygenation (MH), on the other hand, consists of providing supplemental oxygen to the mother during pregnancy to improve the cardiovascular hemodynamics of the fetus. The effect of MH is due to increased fetal pulmonary blood flow, which results in increased venous return to the left heart. This effect becomes more apparent with increasing gestational age. However, to date, there are no data on the long-term evolution of fetuses affected with the syndrome undergoing MH therapy, particularly with regard to possible harmful effects (LARA et al., 2016).

Regarding postnatal treatment, there has been an evolution in the immediate management at birth in the preservation of the clinical condition with more adequate systemic output, with the use of prostaglandin E1 and vasoactive drugs. In this context, the initial Norwood-Sano technique started to have a lower risk, and consequently a higher survival rate in this phase (ATIK, 2021; ROGERS et al., 2017).

However, the literature documents that stage 1 surgery is still recognized as technically challenging for pediatric cardiac surgery (ROGERS et al., 2017), since according to Bezerra et al. (2022) state that higher mortality occurs in the period between the Norwood and Glenn procedures, that is, a rate of 25% of deaths can occur. Pajak et al. (2017) also state that severe *preoperative* atrioventricular valve *regurgitation,* arrhythmias, and pneumonia/sepsis are closely correlated with mortality in patients with disease after second-stage palliation. It should be noted that most mortality occurs in the first year of life, with relative stability survival after 1 year of age (SIFFEL et al., 2015).

In addition, it is reported that multiple different factors may contribute to survival rates, including body weight and age at surgery, size and function of heart valves and chambers, native aortic size, and variables intrinsic to the surgical procedure (cardiopulmonary bypass (CPB time), shunt size, and shunt banding to control excessive pulmonary flow rate). Therefore, the verification and identification of these risk factors can contribute to the improvement of general definitions of treatment, surgical technique, and auxiliary therapeutic measures, aiming to improve survival rates (BEZERRA et al., 2022).

Regardless of the approach, traditional surgical-stage palliation or the hybrid procedure, survivals have greatly improved, and many these patients are surviving not only through Fontan in

early childhood, but also into adolescence and young adulthood. As this population grows, it becomes increasingly important to understand the long-term outcomes of these Fontan patients, not only in terms of survival but also in terms of disease burden, neurodevelopmental outcomes, psychosocial development, and quality of life (BEZERRA et al., 2022; ATIK, 2021; PAJAK et al., 2017; ROGERS et al., 2017).

However, there are other procedures currently available, as Burkhart et al. (2019) point out that direct administration of umbilical cord blood-derived mononuclear cells into the right ventricular myocardium at the time of stage II palliation in patients with the disease can be a viable and cost-effective regenerative product for the pediatric public, maximizing the long-term safety profile using a autologous.

CONCLUSION

It is concluded that surgical procedures are still considered gold standards for the care of this patient, however, prenatal cardiac interventions, such as fetal aortic valvuloplasty and maternal hyperoxygenation, are promising treatment options and, as well as stem cell therapy, provide important clues for the application of new approaches. In view of this, more public policies aimed at assisting patients in treatment are needed, without the use of financial resources, given the scarcity of such treatment in public health in Brazil.

This study has limitations, since this review is largely based on foreign studies and in the Brazilian literature there are few studies focused on the subject, therefore, the development of studies is necessary, since this can be used to optimize parental counseling, as well as the pre and postnatal management of affected children and disseminate knowledge about treatment. to minimize the cases of death due to this pathology.

REFERENCES

1. ATIK, Edmar. (2021). Hipoplasia do Coração Esquerdo em Evolução até 21 Anos, Após Operação Cavopulmonar Total Realizada com 5 Anos de Idade. *Arquivos Brasileiros de Cardiologia, 117*, 142-145.

2. BEZERRA, Rodrigo Freire et al. (2022). Resultados Precoces do Procedimento de Norwood em um Centro de Referência no Brasil. *Arquivos Brasileiros de Cardiologia, 119*, 282-291.

3. BURKHART, Harold M. et al. (2019). Autologous stem cell therapy for hypoplastic left heart syndrome: safety and feasibility of intraoperative intramyocardial injections. *The Journal of thoracic and cardiovascular surgery, 158*(6), 1614-1623.

4. DIONÍSIO, Maria Teresa et al. (2011). Síndrome do Coração Esquerdo Hipoplásico: 19 anos de diagnóstico pré-natal. *Diagnóstico Prenatal, 22*(1), 2-6. [Link](http://dx.doi.org/10.1016/j.diapre.2010.01.003)

5. FANTINI, Fernando A. et al. (2004). A operação de Norwood modificada para tratamento da síndrome de hipoplasia do coração esquerdo. *Revista Brasileira de Cirurgia Cardiovascular, 1*(19), 42-46.

6. KOVACEVIC, Alexander et al. (2018). Fetal hemodynamic response to aortic valvuloplasty and postnatal outcome: a European multicenter study. *Ultrasound in Obstetrics & Gynecology, 52*(2), 221-229.

7. LARA, D. A. et al. (2016). Pilot study of chronic maternal hyperoxygenation and effect on aortic and mitral valve annular dimensions in fetuses with left heart hypoplasia. *Ultrasound in Obstetrics & Gynecology, 48*(3), 365-372.

8. NERY, Ascom Hospital Ana. SÍNDROME DA HIPOPLASIA DO CORAÇÃO ESQUERDO: cardiopatia congênita grave. Disponível em: [Link](https://ver.han.net.br/sindrome-da-hipoplasia-do-coracao-esquerdo-cardiopatia-congenita-grave/). Acesso em: 22 nov. 2021.

9. PAJAK, Jacek et al. (2017). Preoperative single ventricle function determines early outcome after second-stage palliation of single ventricle heart. *Cardiovascular Ultrasound, 15*(1).

10. ROGERS, Libby et al. (2018). Interventional treatments and risk factors in patients born with hypoplastic left heart syndrome in England and Wales from 2000 to 2015. *Heart, 104*(18), 1500-1507.

11. SHENOY, Rajesh U.; PARNESS, Ira A.. (2014). Hypoplastic Left Heart Syndrome. *Journal Of The American College Of Cardiology, 64*(19), 2036-2038. [Link](http://dx.doi.org/10.1016/j.jacc.2014.09.018)

12. SIFFEL, Csaba et al. (2015). Survival of Children With Hypoplastic Left Heart Syndrome. *Pediatrics, 136*(4), 864-870. [Link](http://dx.doi.org/10.1542/peds.2014-1427)

13. SIFFEL, Csaba et al. (2015). Survival of children with hypoplastic left heart syndrome. *Pediatrics, 136*(4), e864-e870.