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Review Article

Surgical palliation of univentricular heart disease in children with Down's syndrome: A systematic review

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الملخص

أهداف البحث: لا يتوفر حاليا بروتوكول قياسي لعلاج الأطفال المصابين بمتلازمة داون والبطين الوظيفي الأحادي. يحاول هذا الاستعراض تحديد نتائج المسار الجراحي التلطيفي للبطين الأحادي لدى أطفال متلازمة داون ذوي الخطورة العالية.

طرق البحث: تم البحث في العديد من قواعد البيانات باستخدام شروط شبكة الموضوعات الطبية "مرض القلب الخلقي"، و"عيب الحاجز الأذيني البطيني"، و"عيب الحاجز الأذيني البطيني المتوازن "، و" عيب الحاجز الأذيني البطيني غير المتوازن"، و"متلازمة داون"، و"إصلاح البطين الأحادي"، و"طريقة جلين ثنائية الاتجاه" و" طريقة فونتان". واستخدمت خوارزمية منظمة لاختيار الدراسات لتحليل أعمق.

النتائج: لا يوجد اتفاق عالمي حول النهج الجراحي لمتلازمة داون مع عيب الحاجز الأذيني البطيني غير المتوازن. ولا ينصح معظم جراحي قلب الأطفال بالإجراء الكامل لطريقة فونتان، وبدلا عنها يفضلون تحويلة جلين (الوصل الأعلى للتجويف الرئوي).

الاستنتاجات: التقييم الدقيق لملائمة جراحة فونتان مثل عدم وجود ارتفاع في المقاومة الوعائية الرئوية، ووظيفة وتركيب الشريان الرئوي للبطين المهيمن يعتبر إلزاميا. والإجراء الجراحي على مراحل الذي ينتهي بإصلاح كامل بطريقة فونتان يوفر نتائج مقبولة متوسطة الأجل.

الكلمات المفتاحية: عيب خلقي في القلب؛ عيب الحاجز الأذيني البطيني؛ عيب الحاجز الأذيني البطيني المتوازن؛ عيب الحاجز الأذيني البطيني غير المتوازن؛ متلازمة داون؛ إصلاح البطين الأحادي

Abstract

Objectives: No standard protocol is available for the management of children with Down's syndrome (DS) and a functional single ventricle. This review attempts to determine the outcomes of the single ventricular surgical palliation pathway in high-risk children with DS.

Methods: Several databases were searched using the following MeSH terms: 'Congenital heart disease', 'Atrioventricular septal defect', 'Balanced AVSD', 'Unbalanced AVSD', 'Down's syndrome', 'Univentricular repair', 'bidirectional Glenn procedure', and 'Fontan procedure'. A structured algorithm was used for the selection of studies for an in-depth analysis.

Results: There was no universal agreement on the best surgical approach for unbalanced atrioventricular septal defect in DS. The majority of paediatric cardiac surgeons did not recommend the complete Fontan procedure; conversely, the use of a Glenn shunt (superior cavopulmonary connection) was preferred.

Conclusions: Careful assessment of the suitability for Fontan surgery, including the absence of elevated pulmonary vascular resistance, pulmonary arterial anatomy, and function of the dominant ventricle, is mandatory. A staged surgical procedure ending with complete Fontan repair provides acceptable medium-term results.

Keywords: Atrioventricular septal defect; Balanced AVSD; Congenital heart disease; Down's syndrome; Unbalanced AVSD; Univentricular repair

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Introduction

The incidence of trisomy 21 or Down's syndrome (DS) is 1 in 660 live births. Approximately 40% of patients with DS have congenital heart disease (CHD).[1–5] Atrioventricular septal defect (AVSD) is the most common CHD in these patients. Balanced AVSD is much more common than unbalanced AVSD; the latter occurs in 10–25% of patients with AVSD.[6,7] The clinical manifestations in these patients depend on the type of defect. Most of them present with left-to-right shunt lesions with increased pulmonary blood flow and frequent chest infections. They rarely present with cyanosis in patients with cyanotic lesions. Unbalanced AVSD requires high-risk single ventricular palliation with superior cavopulmonary shunts, i.e., bidirectional Glenn (BDG) and Fontan procedures (complete cavopulmonary connection). The complete Fontan procedure is considered to provide the best palliation in children whose one ventricle is functionally or anatomically unable to support its area of circulation and thus has to be 'excluded' on the pulmonic side.[8,9] A pumping chamber to the lungs does not support Fontan circulation. It is largely dependent on postoperative passive circulation, and to achieve successful outcomes, normal preoperative pulmonary arterial pressure (PAP) and resistance is required.[10] Children with DS usually have small and abnormal airways, making them more prone to developing persistent pulmonary hypertension (PHT), which in turn adversely affects the outcome of univentricular repair (Fontan procedure).[11–13] The impact of such risk factors has convinced some cardiologists to discourage complete Fontan procedure in children with DS, considering the inevitable long-term complications of Fontan surgery. Further, the systemic circulation depends on the dominant ventricle. If the dominant ventricle is the left ventricle, which is the normal systemic ventricle, better outcomes are expected than if the dominant ventricle were the right ventricle (RV).

There are limited data in literature that can provide a standard surgical management protocol for high-risk children with DS and univentricular CHD. Moreover, there is a gap in knowledge regarding optimal management strategies, which makes it difficult to provide a structured framework for managing patients with DS and univentricular CHD. This systematic review elaborates the surgical management of children with DS and univentricular CHD, with a view to provide a unified approach for such patients.

Materials and Methods

Search design

In January 2018, this systematic review was conducted to explore the outcomes for children with DS and risk factors in the single ventricular palliation pathway using the OVID, ISI Knowledge of Science, and Medline (PubMed) databases. The Preferred Reporting Items for Systematic Review and Meta-analysis protocol was applied in selecting articles that have used empirical pre-post design criteria in exploring the impact of complete Fontan, stepwise Fontan, and Glenn procedures.[14] Full-text English-language articles published from 1997 to 2018 were searched using the following MeSH key words: 'Congenital heart disease and Down's syndrome' AND 'Atrioventricular septal defect' AND 'Balanced AVSD' OR 'Unbalanced AVSD' AND 'Univentricular repair' AND 'Atrioventricular septal defect' OR 'Bidirectional Glenn procedure' OR 'Fontan procedure'. This search initially retrieved 6854 citations as shown in Figure 1. Only original studies that compared the long-term results of complete Fontan procedure, BDG repair, and univentricular repair in DS with unbalanced AVSD were included. Reviews, editorial articles, commentaries, personal opinions, and conference proceedings were excluded from this review.

Data extraction

During data synthesis, 3901 studies were found to be ineligible for this systematic review as they were either duplicate publications or had been published prior to 1997. Subsequently, an additional 2904 abstracts and titles were excluded as they were not original articles. We finally selected 49 studies that were relevant and matched the MeSH key words. However, after the full-text analyses of these 49 articles, 39 were excluded owing to inappropriate data. For this systematic review, we finally selected 10 relevant original articles that precisely met the inclusion criteria of this study as follows:

1. Total cavopulmonary anastomosis (Fontan) in children with Down's syndrome (Campbell et al., 1998).[12]
2. Single ventricle repair in children with Down's syndrome (Wada et al., 2008).[8]
3. Mortality after total cavopulmonary connection in children with the Down syndrome (Gupta-Malhotra et al., 2010).[9]
4. Staged left ventricular recruitment after single-ventricle palliation in patients with borderline left heart hypoplasia (Emani et al., 2012).[15]
5. Outcome of univentricular repair in patients with Down's syndrome (Furukawa et al., 2013).[16]
6. Surgical palliation in patients with a single ventricle and dextrocardia (Poh et al., 2014).[17]
7. High-risk single ventricle palliation in children with Down's syndrome: single institution experience (Ooi et al., 2015).[18]
8. Survival in children with Down's syndrome undergoing single-ventricle palliation (Colquitt et al., 2016).[10]
9. Palliation outcomes of neonates born with single-ventricle anomalies associated with aortic arch obstruction (Alsoufi et al., 2017).[19]
10. Long-term outcomes of single-ventricle palliation for unbalanced atrioventricular septal defects: Fontan survivors do better than previously thought (Buratto et al., 2017).[20]

Results

The salient features of the selected studies, characteristics of the study population, and major outcomes are detailed in Table 1. The key findings of the selected studies are that approximately 40% of children with DS have CHD.[1–5] Balanced AVSD was much more common than unbalanced

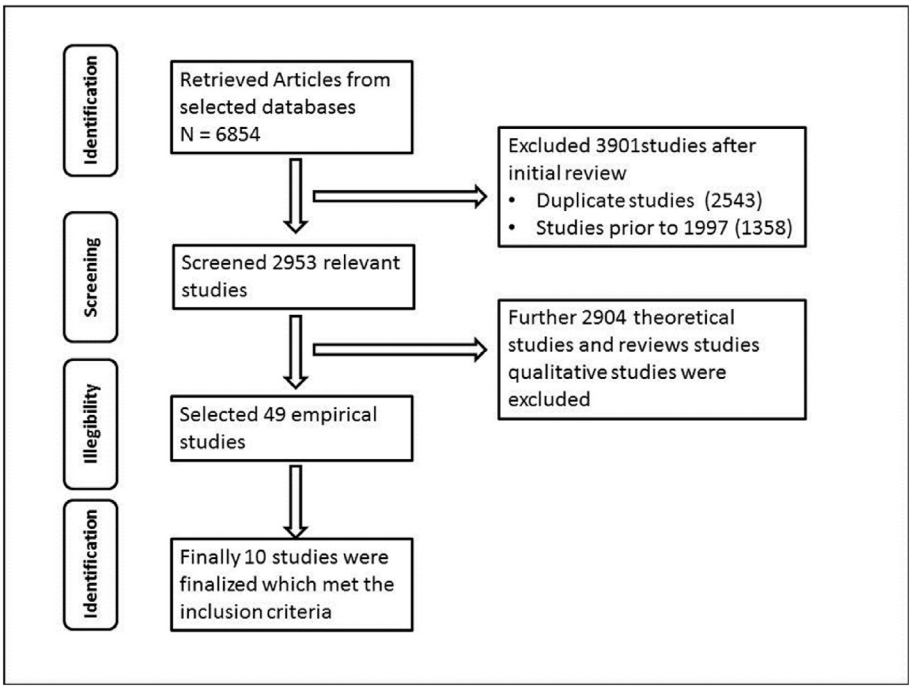

Figure 1: Flow diagram showing the step-wise selection of studies in this systematic review.

AVSD in patients with DS and CHD,[6,7] regardless of the chromosomal abnormality, which can include non-disjunction (94%), mosaicism (3%), or parental translocation (3%).[21] Unbalanced AVSD, as did any single ventricular dominance in CHD, required palliation with BDG followed by Fontan completion. Performing these palliative surgical procedures in patients with DS was considered high risk, since they require near normal preoperative pulmonary pressure and pulmonary vascular resistance (PVR),[10] which are lacking in affected patients who inherently have higher pulmonary pressures and PVR values[11–13] (Table 1).

A reasonable number of studies have indicated non-significant differences in mortality with palliative single ventricular surgical procedures for DS with single-ventricle anatomy as compared to univentricular heart and normal chromosomal complement, while accounting for PVR.[10] However, a majority of cardiologists and cardiac surgeons do not advocate BDG and Fontan surgery in patients with DS and a single ventricle.[8,9,21–24] There was insufficient data on the indications for these palliative surgical procedures and long-term prognosis in this group of patients. One and a half ventricular repair (BDG with some forward RV to pulmonary artery (PA) flow) rather than Fontan completion was attempted by some experts for DS with univentricular heart, which yielded good outcomes.[12,25] A great number of studies have recommended a flexible management plan for DS with unbalanced AVSD. The decision to undertake univentricular surgical palliation should be determined on the basis of the patients' anatomical pathology findings, presence or absence of other risk factors, including other congenital cardiac and non-cardiac malformations, parents' preference, and financial capacity.

Discussion

In patients with CHD, when one of the ventricles is rudimentary or hypoplastic, staged palliation with bidirectional superior cavopulmonary shunt, also called BDG, followed by Fontan completion (total cavopulmonary connection (TCPC)) is the best surgical palliation. Francis Fontan first conducted this surgical procedure in 1971 to palliate a patient with tricuspid atresia.[26] Since then, several modifications in the surgical techniques have been attempted. Fontan completion provides good palliation, yielding satisfactory quality of life for many years.[27–32]

A major pre-requisite for a well-functioning Fontan circulation is to have near normal preoperative PAP and PVR.[10] Several factors predispose children with DS to develop higher PAP and PVR.[11–13] They have a higher incidence of abnormal segmental branching of the pulmonary arterial tree, abnormalities in the bronchi, tracheomalacia, and laryngomalacia.[33] Obstructive sleep apnoea syndrome occurs in approximately 50% of children with DS, and increases the risk of associated PHT.[34] The other possible factors that contribute to PHT development in patients with DS include frequent aspiration pneumonia and gastroesophageal reflux.[35]

DS and univentricular heart repair

Data on the morbidity and mortality in patients with DS after TCPC are limited because many cardiac centres worldwide still do not prefer complete Fontan palliation in these patients.[8,9,21–24] Conversely, the majority of surgeons do not recommend complete Fontan procedure and will stop at the BDG stage. The Glenn shunt is sometimes

Table 1: Characteristics and key findings of the 10 selected studies in the systematic review.

Study	Country and institute	Study years	Sample and study population	Findings
Campbell et al. (1998)[12]	Canada Toronto Congenital Cardiac Centre for Adults, Toronto General Hospital, University of Toronto	1976–1997	Of 533 patients who underwent Fontan surgery, 4 had trisomy 21.	This report suggested that in appropriately selected patients with trisomy 21 and ventricular hypoplasia who are unsuitable for two or one and a half ventricular repair, the Fontan procedure is not contraindicated and provides short-term and medium-term benefits.
Wada et al. (2008)[8]	Japan Sakakibara Heart Institute, Japan Promotion Society for Cardiovascular Diseases	1991–2004	This study investigated six patients with Down's syndrome (DS) among 263 who had undergone the bidirectional superior cavopulmonary shunt procedure	DS is a risk factor in patients with a functional single ventricle owing to persistent pulmonary hypertension and airway obstruction.
Gupta-Malhotra et al. (2010)[9]	United States of America Children's Memorial Hermann Hospital, University of Texas, Houston, Texas	1982–2010	This study assessed mortality and contributing factors after Fontan surgery in children with DS and mortality data after Fontan surgery from the Paediatric Cardiac Care Consortium Registry. Among all patients who underwent Fontan procedure (n = 2853), those with DS (n = 17) were selected, of whom 13 had available hemodynamic data. Thirteen children without chromosomal aberrations were selected as controls, matched 1 to 1 for sex, age, weight, lesion, and type of Fontan procedure.	DS was found to be an independent parameter associated with a significantly higher risk for mortality in the early postoperative period after Fontan surgery.
Emani et al. (2012)[15]	United States of America Children's Hospital Boston, Boston, Massachusetts	1995–2010	A total of 34 patients with borderline LH disease underwent staged LV recruitment; 34 patients underwent traditional single ventricular palliation (SVP). Attempts at staged LV recruitment were initiated in 2001. The traditional SVP group consisted of 11 patients who underwent stage 1 palliation before 2001 and 23 patients who were contemporary with the staged LV recruitment patients.	Among the patients with borderline LH disease who underwent SVP, the LH dimensions could be increased using an LV recruitment strategy. In a specific group of patients, this strategy allowed the implementation of biventricular circulation.
Furukawa et al. (2013)[16]	Japan Sakakibara Heart Institute, Tokyo	2004–2010	Eight patients with Down's syndrome among 235 patients who had undergone total cavopulmonary connection (TCPC) were studied.	Patients with DS had a prolonged recovery period after TCPC. However, in contrast to published data, the mortality of patients undergoing TCPC was lower, but was not significantly different compared to children without DS.
Poh et al. (2014)[17]	Australia Royal Children's Hospital, Melbourne	1990–2008	The medical data of 41 consecutive patients with single-ventricle physiology and dextrocardia in a single institution were investigated. In this cohort, 19 patients had heterotaxy syndrome. Twenty-five of the 41 patients had atrioventricular valve regurgitation (AVVR) on presentation (mild, 13; moderate, 9; severe, 3).	The surgical outcomes of single ventricular palliation were less optimal in patients with dextrocardia. Aggressive management of congenital AVVR can potentially improve the long-term prognosis.

Table 1 (*continued*)

Study	Country and institute	Study years	Sample and study population	Findings
Ooi et al. (2015)[18]	United States of America Children's National Health System, The George Washington University School of Medicine, Washington	2005–2011	A total of 310 patients underwent at least one ventricular surgical intervention. Of these, 8 patients had DS, five of whom had associated risk factors: low birth weight, high pulmonary vascular resistance, pulmonary vein stenosis, significant AVVR, and extracardiac anomalies.	Despite many improvements in the care of patients with a single ventricle, the prognosis of those with DS and associated high-risk factors remains poor. The need for more multi-centre longer-term studies to validate and quantify the cumulative effects of negative prognostic factors in this complex group of patients was highlighted.
Colquitt et al. (2016)[10]	United States of America Baylor College of Medicine	1992–2014	This research recruited 28 patients with DS and 30 patients without DS.	Children with DS and single-ventricle anatomy have excellent survival when the PVR is less than 3 Wood units per meter squared in the first year of life, with minimal mortality beyond 2 years of age. When accounting for the PVR, DS alone is not associated with an increased mortality in patients with single-ventricle anatomy.
Alsoufi et al. (2017)[19]	United States of America Children's Healthcare of Atlanta, Emory University	2002–2012	This study included 94 consecutive neonates with a single ventricle and aortic arch obstruction (excluding hypoplastic left heart syndrome) who underwent Norwood procedure (n = 65) or pulmonary artery band (PAB) and coarctation of the aorta (COA) repair (n = 29).	The anatomic and patient characteristics determine the palliation outcomes in neonates born with single ventricular anomalies associated with aortic arch obstruction. Although the Norwood procedure is applicable in most of these patients, the PAB and COA repair strategy is a strong substitute in carefully selected patients.
Buratto et al. (2017)[20]	Australia Royal Children's Hospital, Melbourne	1976–2016	A total of 139 patients underwent SVP for unbalanced atrioventricular septal defect (UAVSD). A neonatal palliative procedure was performed in 83.5% of these patients (116 of 139), and early mortality occurred in 11.2% (13 of 116). Ninety-four patients underwent stage II palliation, with an early mortality of 6.4% (6 of 94). Eighty patients (57.6%) underwent Fontan completion, with an early mortality of 3.8% (3 of 80). The interstage mortality was 11.7% (12 of 103) between stages I and II and 17.0% (15 of 88) between stage II and Fontan.	Children undergoing SVP for UAVSD have a substantial mortality, with <60% survival at 25 years. However, the survival of children who achieve Fontan completion is better than what has been reported previously.

modified to leave the RV to PA forward flow. This maintains higher oxygen saturation levels and theoretically prevents pulmonary arteriovenous malformations. Independently, patients with DS had a high mortality after TCPC palliation. Gupta et al. observed that patients with DS had worsening PHT in the early post-Fontan period compared to patients without chromosomal abnormalities.[9] This was seen despite the fact that the preoperative PAPs and PVR of the selected cohort were normal. In 2015, Ooi et al. reported a poor prognosis when single ventricular palliation was offered to children with DS and univentricular heart.[18]

Two clinical studies with large cohorts reported that patients with DS had a higher incidence of hospital deaths after TCPC palliation compared to patients without DS.[22,23] In contrast, another large single-centre study on 28 patients has reported that DS with univentricular heart alone was not associated with a higher mortality if the preoperative PVR was taken into account. The investigators found a 100% survival in their study group when the PVR was less than 3 Wood units per meter squared (WUm^2) in the first year of life, with minimal mortality after 2 years of age.[10] Furukawa and colleagues also showed no significant difference in mortality between patients with DS and univentricular heart after TCPC and patients without DS. However, the researchers reported a significant prolongation of the postoperative course and higher occurrence of chylothorax

in DS after Fontan surgery.[16] The Fontan results between patients with DS and children with normal chromosomal templates in other studies were also inconclusive.[8,9,12,16,24]

Nathan et al. and other researchers found that a ventricular volume of greater than 20 mL/m^2 in a hypoplastic ventricle is favourable for biventricular conversion with a relatively lower mortality.[36] Careful determination of the ventricular volume using two-dimensional echocardiography, three-dimensional echocardiography, magnetic resonance imaging, or cardiac catheterisation is mandatory. However, a significant rate of reintervention is expected when a policy of two ventricle repairs is followed aggressively.[36,37] The proponents of this approach argue that aggressive biventricular conversion for a failed single ventricular palliation performed for unbalanced AVSD is much better with a significantly lower mortality than medical treatment or heart transplantation. However, Colquitt et al.[10] reported a 100% survival rate after single ventricular palliation in their study group of DS with univentricular heart when the PVR was less than 3 WUm^2. The authors have proposed that aggressive conversion to biventricular repair should only be offered to patients with a high PVR.[10]

Central PA stenosis, which can lead to unequal blood flow to the lungs, and moderate-to-severe atrioventricular valve regurgitation are reported to be risk factors for poor outcomes following TCPC in patients with DS and functional single ventricle.[38–40] Therefore, significant main pulmonary arterial and atrioventricular valvular lesions, if present, should be repaired during staged palliation at the Glenn stage. The absence of large multi-centre studies mandates revision of the approach for palliating DS with univentricular heart. Based on the findings of this systematic review, the following management framework is suggested and can be used as a benchmark model: 1) early PAP protection using a tight PA band early in life in patients with DS and unbalanced AVSD that can permit single ventricular palliation or future surgery to one and a half ventricle or biventricular conversion, if possible; 2) comprehensive counselling of parents, particularly discussing the higher early postoperative mortality; 3) proper patient preparation by managing any possible factors that can increase postoperative mortality, such as reactive and obstructive airway diseases; 4) close PAP monitoring in the perioperative period to prevent any possible pulmonary hypertensive crises, such as the administration of nitric oxide and medications to decrease the PVR prophylactically in the critical early perioperative period; and 5) after single ventricular palliation, infants with DS need to be monitored closely with pharmacological and ventilation manoeuvres to be started at the earliest signs of deterioration of their pulmonary or systemic circulations. This can only be achieved in highly advanced intensive care units. Further, patients with DS also have multiple disabilities in addition to cardiac issues. These issues cannot be solved unless a multi-disciplinary approach is adopted for their management.

Conclusions

In patients with DS, univentricular heart or unbalanced AVSD is rare. In the rare event of detection of a univentricular heart or unbalanced AVSD in these patients, the management strategy remains debatable, as there is no universal agreement on the best surgical palliation for such children. This systematic review presents convincing evidence that designing a management framework for single ventricular palliation (Glenn or Fontan) in children with DS and a single functional ventricle is not straightforward. Parents and families should be thoroughly counselled. The ventricular volumes and pulmonary arterial anatomy and resistances should be meticulously determined by appropriate imaging studies. Surgical intervention should be undertaken in units appropriately experienced and equipped to deal with high-risk Fontan cases. Additional multi-centre studies with large numbers of patients with DS and single ventricles are required to establish the best management option.

Conflict of interest

The author has no conflict of interest to declare.

Ethical approval

There are no ethical or financial issues, conflicts of interests, or animal experiments related to this research.

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