Turkish Journal of Thoracic and Cardiovascular Surgery 2023;31(4):440-445

ORIGINAL ARTICLE / ÖZGÜN MAKALE

Effect of cardiac surgery on survival in patients with trisomy 18: A single-center experience

Trizomi 18 hastalarında kalp cerrahisinin sağkalım üzerine etkisi: Tek merkez deneyimi

Mehmet Çelik[1], Mahmut Gökdemir[2], Nimet Cındık[2], Asım Çağrı Günaydın[1]

[1]Department of Cardiovascular Surgery, Başkent University Hospital, Konya, Türkiye
[2]Department of Pediatric Cardiology, Başkent University Hospital, Konya, Türkiye

ABSTRACT

Background: In this study, we aimed to compare the results of operated patients diagnosed with trisomy 18 with those who were followed with medical treatment alone.

Methods: Between May 2014 and January 2022, a total of 18 patients (6 males, 12 females; median age: 39 days; range, 32 to 79 days) diagnosed with trisomy 18 were retrospectively analyzed. Patient data were obtained from the pediatric cardiovascular surgery digital database. The patients were divided into two groups: those who underwent surgery (n=10) and those who were followed with medical treatment (n=8).

Results: Cardiac pathology was detected in all 18 patients included in the study. Three (30%) patients in the surgical group and two (25%) patients in the medical treatment group were discharged and followed with medical treatment. One of the three patients discharged after surgery died during follow-up. The median survival in surgical and medical treatment groups was 150 (range, 75 to 308) days and eight (range, 3 to 51) days, respectively (p=0.009). While patients in the medical treatment group died due to multi-organ failure, those in surgical group died due to sepsis, heart failure, and respiratory failure.

Conclusion: Although cardiac surgery contributed positively to survival in patients with trisomy 18, the mortality rate was still high due to non-cardiac causes. We believe that a multidisciplinary approach would contribute positively to the treatment of this patient group with multi-organ failure and would aid in prolonging their life span.

Keywords: Cardiac surgery, congenital heart disease, trisomy 18.

ÖZ

Amaç: Bu çalışmada trizomi 18 tanısı ile ameliyat edilen hastaların sonuçları, yalnızca tıbbi tedavi ile takip edilen hastalarınki ile karşılaştırıldı.

Çalışma planı: Mayıs 2014 - Ocak 2022 tarihleri arasında trizomi 18 tanılı toplam 18 hasta (6 erkek, 12 kız; medyan yaş: 39 gün; dağılım, 32-79 gün) retrospektif olarak incelendi. Hasta verileri pediatrik kardiyovasküler cerrahi dijital veri tabanından elde edildi. Hastalar iki gruba ayrıldı: ameliyat olanlar (n=10) ve tıbbi tedavi ile izlenenler (n=8).

Bulgular: Çalışmaya alınan 18 hastanın tümünde kardiyak patoloji saptandı. Ameliyat grubunda üç hasta (%30) ve tıbbi tedavi ile izlenen iki hasta (%25) taburcu edildi ve tıbbi tedavi ile takip edildi. Ameliyat sonrası taburcu edilen üç hastanın biri takip sırasında kaybedildi. Cerrahi ve tıbbi tedavi gruplarında medyan sağkalım sırasıyla 150 (dağılım, 75-308) gün ve sekiz (dağılım, 3-51) gün idi (p=0.009). Tıbbi tedavi grubundaki hastalar çoklu organ yetmezliğine bağlı kaybedilirken, ameliyat edilen gruptakiler sepsis, kalp yetmezliği ve solunum yetmezliğine bağlı kaybedildi.

Sonuç: Trizomi 18 hastalarında kalp cerrahisi sağkalıma olumlu katkı sağlasa da, kalp dışı nedenlere bağlı ölüm oranı halen yüksekti. Multidisipliner bir yaklaşımın çoklu organ yetmezliği olan bu hasta grubunun tedavisine olumlu katkısı olacağı ve hastaların yaşam süresini uzatmaya yardımcı olacağı kanısındayız.

Anahtar sözcükler: Kalp cerrahisi, doğumsal kalp hastalığı, trizomi 18.

Trisomy 18 is the most common form of aneuploidy after trisomy 21.[1,2] Its incidence is 3.19/10,000 pregnancies in the United States.[3] Approximately 70% of trisomy 18 cases diagnosed in the first trimester result in fetal death.[4,5] In live births, the median life expectancy ranges between 6 and 15 days, and the one-year survival rate is 13.4%.[6-8] The primary causes of death in these individuals are cardiac and respiratory diseases.[3] Congenital heart disease is present in approximately 90% of all patients.[3,9]

Corresponding author: Mehmet Çelik.
E-mail: mehmert1981@gmail.com

Doi: 10.5606/tgkdc.dergisi.2023.24741

Received: February 07, 2023
Accepted: July 07, 2023
Published online: October 19, 2023

Cite this article as: Çelik M, Gökdemir M, Cındık N, Günaydın AÇ. Effect of cardiac surgery on survival in patients with trisomy 18: A single-center experience. Turk Gogus Kalp Dama 2023;31(4):440-445. doi: 10.5606/tgkdc.dergisi.2023.24741.

There are different opinions in the literature about the approach to the patient with this anomaly where organ and system involvements are not homogeneous. Approaches vary between the idea of not interfering with the natural course of the disease and the pursuit of correction via cardiac surgery. These decisions are increasingly being made in consultation with the healthcare team and active involvement of the family, after detailed family interviews about genetic anomalies and disorders in other organ systems.

Surgical treatment options are controversial due to the high mortality rate in early period. Few studies have reported that cardiac surgery improves patient survival. In the present study, we aimed to compare the results of patients who underwent surgery with those who were followed with medical treatment.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Başkent University Hospital, Konya, Department of Cardiovascular Surgery between May 2014 and January 2022. A total of 18 patients (6 males, 12 females; median age: 39 days; range, 32 to 79 days) diagnosed with trisomy 18 were included. The type of surgery was decided upon considering the general condition of the patient and the characteristics of their cardiac pathology. Palliative solutions were considered in patients with low body weight in whom cardiopulmonary bypass (CPB) posed a high risk. Corrective surgery was performed in patients with suitable body weight and cardiac pathology.

Patient data were retrospectively obtained from the pediatric cardiovascular surgery digital database. Data such as sex, premature status, birth weight, cardiac pathologies, non-cardiac pathologies, mechanical ventilation needs, feeding tube requirement, age and weight at the time of surgery, type of surgery, complications developed during follow-up, cause of mortality, tracheostomy requirement, and length of stay were retrieved from the database. All parents were informed in detail about the natural course of the disease and cardiac pathology. Patients who did not undergo surgery were treated medically (i.e., medical group, n=8). The follow-up of the surviving patients continued in the pediatric cardiology outpatient clinic, and information about their latest status was obtained.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Continuous data were expressed in median and

Table 1. The data of the operated patients

Patients	Cardiac diagnosis	Surgery	Age at surgery (day)	Weight at surgery (kg)	Prematurity	Preoperative mechanical ventilation	Tracheostomy	Results	Duratio (day)
1	VSD	VSD closure	135	3.6	Yes	Yes	Yes	Discharge	245
2	VSD	VSD closure	134	3.6	No	Yes	Yes	Exitus	158
3	VSD	PAB	35	1.9	Yes	Yes	No	Exitus	2
4	VSD	PAB	23	1.2	No	Yes	No	Exitus	498
5	VSD	PAB	22	2.1	Yes	Yes	No	Discharge	80
6	PDA	PDA ligation	36	2.1	Yes	Yes	No	Exitus	21
7	DORV Hypoplasia of aortic arch	- PDA ligation - Arcus aorta reconstruction - PAB	35	1.4	Yes	Yes	No	Exitus	116
8	VSD PDA	PAB	70	2.2	Yes	Yes	Yes	Exitus	105
9	PDA	PAB	42	2	Yes	Yes	No	Exitus	93
10	VSD	PAB	50	1.4	Yes	Yes	No	Discharge	150

VSD: Ventricular septal defect; PAB: Pulmonary artery banding; PDA: Patent ductus arteriosus; DORV: Double outlet right ventricle.

interquartile range (IQR; 25th-75th), while categorical data were expressed in number and frequency. The Mann-Whitney U test was used to compare variables between independent groups. The chi-square or Fisher exact tests were used to compare categorical variables. The effect of the type of treatment on survival of trisomy 18 patients was investigated using the log-rank test. A p value of <0.05 was considered statistically significant.

RESULTS

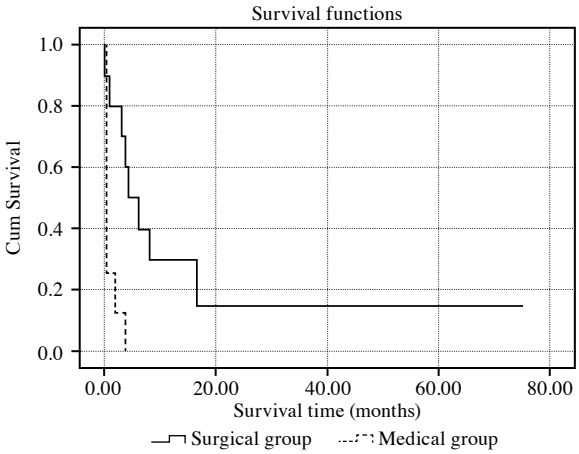
Of a total of 18 patients included in the study, 10 (56%) were operated and eight (44%) underwent medical treatment. Twelve (67%) patients were prematurely born, while four (22%) patients had intrauterine growth restriction (IUGR). The median birth weight of the study population was 1.68 (range, 1.38 to 1.92) kg. Congenital heart disease was detected in all patients.

The median age of the patients at the time of surgery was 39 (range, 32 to 79) days. All patients had biventricular physiology. Three (30%) patients underwent corrective surgery, while seven (70%) patients underwent palliative surgery. The median body weight of the patients who underwent surgery was 2.05 (range, 1.40 to 2.4) kg. Prematurity was detected in eight (80%) patients in the surgical group, and colostomy was performed in one patient before cardiac surgery due to anal atresia. All the patients required preoperative mechanical respiratory support. Infection parameters were negative in the operated patients. The STS/European Association for Cardiothoracic Surgery Congenital Heart Surgery Mortality (STAT) scores of the operated patients were STAT 4 in seven patients, STAT 2 in two patients, and STAT 1 in one patient. Early mortality (during the first 30 days after surgery) occurred in two (20%) patients, one (10%) due to sepsis and one (10%) due to cardiopulmonary failure. Five (50%) patients died from chronic lung failure during the long-term intensive care follow-up. Extracorporeal membrane oxygenation was not performed, as the lung disease was chronic in these patients. Three (30%) patients underwent postoperative tracheostomy. Three (30%) patients were discharged, one with tracheostomy. One patient continued to be followed on nasal oxygen support, and the other was on ventilator support with tracheostomy. The third patient, who was discharged after 80 days of hospitalization, died 165 days after discharge due to lower respiratory tract infection. The median survival of the patients in the surgical group was 150 (range, 75 to 308) days. The data of the operated patients are summarized in Table 1.

The median birth weight of the eight patients (three males) who were followed with medical treatment was 1.7 (range, 1.57 to 1.96) kg. Six (75%) patients had a biventricular physiology. Six (75%) patients died in the first 14 days due to poor general condition and multi-organ failure, while two (25%) patients were discharged. Two patients who were discharged died 63 and 112 days after discharge, respectively. The median survival of the patients in the medical treatment group was eight (range, 3 to 51) days. Patient data are summarized in Table 2.

Table 2. The data of non-operated patients

Patients	Diagnosis	Birth weight (kg)	Prematurity	Results	Duration (day)
1	Hypertrophic cardiomyopathy	2.2	Yes	Exitus	1
2	Tetralogy of Fallot	1.6	Yes	Exitus	6
3	Pulmonary stenosis	2	No	Discharge	63
4	Ventricular septal defect	0.8	Yes	Exitus	5
5	Ventricular septal defect Bicuspid aortic valve Mitral stenosis Hypoplasia of right pulmonary artery	1.7	Yes	Exitus	9
6	Ventricular septal defect Unicuspid aortic valve Isthmus hypoplasia	1.7	No	Discharge	112
7	Ventricular septal defect Subaortic stenosis	1.5	No	Exitus	2
8	Truncus arteriosus type 1 Complete atrioventricular septal defect	1.8	No	Exitus	14



No at risk					
Surgical group	10	3	2	2	2
Medical group	8	0	0	0	0

Figure 1. The effect of the type of treatment on survival.

No significant difference was observed between the two groups in terms of birth weight (p=0.563). Median life expectancy in the surgical group was longer than that in the medical treatment group (p=0.009) (Figure 1). There was no significant difference between the two groups in terms of in-hospital mortality (p=1).

DISCUSSION

Trisomy 18 is a genetic anomaly with fatal multisystem involvement, mostly resulting in fetal death. Approximately 90% of live-born cases die within the first year of life.[4-8] Congenital heart disease accompanies approximately 90% of all patients, and heart failure is the most common cause of mortality in these individuals.[3,9,10] In addition, gastrointestinal, respiratory, genitourinary, and central nervous system anomalies, along with neuromuscular disorders are also frequently observed in these patients.[3] Although there is no consensus in the literature on performing surgery in these patients, different approaches regarding the type and timing of surgery to be performed have been described. Studies have reported that surgical intervention increases the life expectancy and quality of life of these patients.[3] In the present study, cardiac surgery did not alter the discharge rate in patients with trisomy 18, but prolonged their survival. Although cardiac-related mortality was prevented in the early period, patients died in the later period mainly due to non-cardiac causes, particularly lung failure and sepsis.

Carvajal et al.[3] reported that the mortality rate was high in trisomy 18 patients younger than one month of age. They also reported that the risk of mortality was higher for patients who required mechanical ventilation for more than two preoperative days and those who weighed less than 2.5 kg. Additionally, they also found that corrective surgery had a positive effect on extubation and survival rates. In our study, eight patients in the surgical group had a body weight of less than 2.5 kg, nine required preoperative mechanical respiratory support, and two underwent surgery before one month of age. Davisson et al.[11] reported that patients with trisomy 18 who underwent cardiac surgery had a lower mortality rate than those who were followed with medical treatment. However, they reported a high need for tracheostomy and feeding tubes after surgery. In our study, two of the three discharged patients in the surgical group required tracheostomy. Our results support the finding that a significant proportion of patients with trisomy 18 have respiratory and gastrointestinal system failures. Although Kaneko et al.[12] reported 82% discharge rates in their study, only one of their patient survived for more than one year. The authors also reported that survival was longer in patients who underwent palliative surgery. In our study, three of 10 patients underwent corrective surgery and seven underwent palliative surgery. Therefore, the effect of the type of surgery on survival could not be elucidated in our study. Muneuchiet al.[13] compared patients who underwent surgery and those who were followed medically. They reported that cardiac surgery prolonged survival, but did not affect the discharge rate. Similarly, our results showed that surgery prolonged survival, but had no effect on patient discharge.

A study by Costello et al.[14] included 13 patients diagnosed with trisomy 18. Surgery was performed in seven patients, while six were followed with medical treatment. Although they recommended corrective surgery, no significant difference was found in terms of in-hospital mortality. While several centers recommending cardiac surgery to patients with trisomy 18 suggest corrective surgery options, Nakai et al.[15] performed palliative surgery in all their patients with trisomy 18 who underwent surgery. They reported that genetic anomalies, young age, and blood transfusion increased the mortality rate, and palliative surgery could protect the patients from these negative effects, since the systemic inflammatory response to CPB was critically important in these patients. Of our 10 patients who underwent surgery, six were alive and three had a follow-up period of more than one year, whereas

none of the patients who received medical treatment lived longer than one year. Based on these results, they concluded that palliative surgery could prolong the survival in these patients. The fact that the patient had trisomy 18 did not affect the decision of type of surgery in our study, and it was considered in a similar manner as for patients without trisomy 18.

The presence of cardiac pathology in majority of the patients and the fact that heart failure is the primary cause of death seem to support the idea that mortality can be reduced, if the cardiac defect is corrected.[3,11,12,15] There is no consensus on the type and timing of surgery.[16,17] In addition to studies advocating that corrective surgery has a positive effect on survival and extubation rates, some authors have suggested that palliative surgery can protect the patient from the negative effects of CPB, independent of cardiac pathology. There are opinions that evaluate the need for preoperative mechanical respiratory support as a relative contraindication to surgery in the patient group.[18] Recently, successful results of surgical treatment in patients with trisomy 18 have been reported.[19] In our study, the patients' genetic syndrome did not affect the surgical approach in terms of surgical indication, type, and timing of surgery. Specific guidelines for patients with trisomy 18 may have a positive impact on the results.

Nonetheless, there are some limitations to this study. First, it is a single-center, retrospective study with a limited number of patients. Second, due to the nature of the pathology, the patient group was heterogeneous. In the literature, trisomy 18 and 13 are usually investigated. Since there were no patients diagnosed with trisomy 13 during the study, we could not include them.

Furthermore, the mortality rate seems to be high in our study. We believe that the reason for this is that most of our patient group was premature or experienced IUGR and, therefore, pathologies in other organ systems played an important role in mortality, even if cardiac-related deaths were prevented.

In conclusion, our study results showed that surgical treatment prolonged survival, but did not affect patient discharge. Although survival was prolonged with surgical treatment, mortality occurred due to immune deficiency and respiratory system failure. Even if mortality due to heart failure was prevented by cardiac surgery in the early period, patients died due to pathologies of other organ systems. In addition to primary respiratory system and immunodeficiency status, prolonged hospitalization and mechanical ventilation periods highlight non-cardiac deaths due to respiratory failure and hospital infection. We believe that a multidisciplinary approach, including interventions by immunology, pulmonary diseases, and infectious diseases departments would contribute positively to the treatment of this disease group with multi-organ failure, and would aid in prolonging their life span.

Ethics Committee Approval: The study protocol was approved by the Başkent University Medical and Health Sciences Research Board Ethics Committee (date: 31.08.2022, no: KA22/372). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: The need for informed consent was waived due to the retrospective nature of the study.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: All authors contributed equally to the article.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: This study was approved by supported by Başkent University Research Fund.

REFERENCES

1. Mai CT, Isenburg J, Langlois PH, Alverson CJ, Gilboa SM, Rickard R, et al. Population-based birth defects data in the United States, 2008 to 2012: Presentation of state-specific data and descriptive brief on variability of prevalence. Birth Defects Res A Clin Mol Teratol 2015;103:972-93. doi: 10.1002/bdra.23461.
2. Kosiv KA, Gossett JM, Bai S, Collins RT 2nd. Congenital heart surgery on in-hospital mortality in trisomy 13 and 18. Pediatrics 2017;140:e20170772. doi: 10.1542/peds.2017-0772.
3. Carvajal HG, Callahan CP, Miller JR, Rensink BL, Eghtesady P. Cardiac surgery in trisomy 13 and 18: A guide to clinical decision-making. Pediatr Cardiol 2020;41:1319-33. doi: 10.1007/s00246-020-02444-6.
4. Cavadino A, Morris JK. Revised estimates of the risk of fetal loss following a prenatal diagnosis of trisomy 13 or trisomy 18. Am J Med Genet A 2017;173:953-8. doi: 10.1002/ajmg.a.38123.
5. Morris JK, Savva GM. The risk of fetal loss following a prenatal diagnosis of trisomy 13 or trisomy 18. Am J Med Genet A 2008;146A:827-32. doi: 10.1002/ajmg.a.32220.
6. Rasmussen SA, Wong LY, Yang Q, May KM, Friedman JM. Population-based analyses of mortality in trisomy 13 and trisomy 18. Pediatrics 2003;111:777-84. doi: 10.1542/peds.111.4.777.
7. Meyer RE, Liu G, Gilboa SM, Ethen MK, Aylsworth AS, Powell CM, et al. Survival of children with trisomy 13 and trisomy 18: A multi-state population-based study. Am J Med Genet A 2016;170A:825-37. doi: 10.1002/ajmg.a.37495.

8. Nelson KE, Rosella LC, Mahant S, Guttmann A. Survival and surgical interventions for children with trisomy 13 and 18. JAMA 2016;316:420-8. doi: 10.1001/jama.2016.9819.
9. Cereda A, Carey JC. The trisomy 18 syndrome. Orphanet J Rare Dis 2012;7:81. doi: 10.1186/1750-1172-7-81.
10. Graham EM, Bradley SM, Shirali GS, Hills CB, Atz AM; Pediatric Cardiac Care Consortium. Effectiveness of cardiac surgery in trisomies 13 and 18 (from the Pediatric Cardiac Care Consortium). Am J Cardiol 2004;93:801-3. doi: 10.1016/j.amjcard.2003.12.012.
11. Davisson NA, Clark JB, Chin TK, Tunks RD. Trisomy 18 and congenital heart disease: Single-center review of outcomes and parental perspectives. World J Pediatr Congenit Heart Surg 2018;9:550-6. doi: 10.1177/2150135118782145.
12. Kaneko Y, Kobayashi J, Achiwa I, Yoda H, Tsuchiya K, Nakajima Y, et al. Cardiac surgery in patients with trisomy 18. Pediatr Cardiol 2009;30:729-34. doi: 10.1007/s00246-009-9427-0.
13. Muneuchi J, Yamamoto J, Takahashi Y, Watanabe M, Yuge T, Ohno T, et al. Outcomes of cardiac surgery in trisomy 18 patients. Cardiol Young 2011;21:209-15. doi: 10.1017/S1047951110001848.
14. Costello JP, Weiderhold A, Louis C, Shaughnessy C, Peer SM, Zurakowski D, et al. A contemporary, single-institutional experience of surgical versus expectant management of congenital heart disease in trisomy 13 and 18 patients. Pediatr Cardiol 2015;36:987-92. doi: 10.1007/s00246-015-1109-5.
15. Nakai Y, Asano M, Nomura N, Matsumae H, Mishima A. Effectiveness of cardiac surgery in patients with trisomy 18: A single-institutional experience. Cardiol Young 2016;26:1391-6. doi: 10.1017/S1047951115002723.
16. Rasmussen SA, Wong LY, Yang Q, May KM, Friedman JM. Population-based analyses of mortality in trisomy 13 and trisomy 18. Pediatrics 2003;111:777-84. doi: 10.1542/peds.111.4.777.
17. Embleton ND, Wyllie JP, Wright MJ, Burn J, Hunter S. Natural history of trisomy 18. Arch Dis Child Fetal Neonatal Ed 1996;75:F38-41. doi: 10.1136/fn.75.1.f38.
18. Cooper DS, Riggs KW, Zafar F, Jacobs JP, Hill KD, Pasquali SK, et al. Cardiac surgery in patients with trisomy 13 and 18: An analysis of the Society of Thoracic Surgeons congenital heart surgery database. J Am Heart Assoc 2019;8:e012349. doi: 10.1161/JAHA.119.012349.
19. Rosenblum JM, Kanter KR, Shashidharan S, Shaw FR, Chai PJ. Cardiac surgery in children with trisomy 13 or trisomy 18: How safe is it? JTCVS Open 2022;12:364-71. doi: 10.1016/j.xjon.2022.09.005.