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ORIGINAL ARTICLE

Cardiac Surgery in Patients with Trisomy 18

Yukihiro Kaneko · Jotaro Kobayashi · Ikuya Achiwa · Hitoshi Yoda · Keiji Tsuchiya · Yayohi Nakajima · Daiichi Endo · Hajime Sato · Tadashi Kawakami

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Abstract Cardiac surgery is infrequently but increasingly being used to repair congenital heart defects associated with trisomy 18. The clinical details of trisomy 18 patients undergoing cardiac surgery have rarely been reported. Seventeen patients with trisomy 18 and serious cardiac symptoms underwent cardiac surgery in our institution. Age at surgery ranged from 7 to 258 days (median, 66 days). One patient had an atrioventricular septal defect and coarctation of the aorta. The remaining patients had ventricular septal defects, including four patients with coarctation of the aorta. Fourteen patients had associated patent ductus arteriosus. Fourteen patients underwent palliative surgery without cardiopulmonary bypass, and four of these underwent a second-stage intracardiac repair. The other three patients underwent primary intracardiac repair. Postoperatively, 14 patients (82%) were discharged home with improved symptoms. Survival from birth ranged from 12 to 1384 days (median, 324 days). Eight patients survived longer than 1 year. Median postoperative survival was 179 days. Postoperative survival was significantly better after palliative surgery (0 to 1239 days; median, 257 days) than after primary intracardiac repair (1 to 179 days; median, 48 days). Only one patient died of heart failure, suggesting that cardiac surgery was effective in preventing heart failure-related death.

Keywords Trisomy 18 · Congenital heart defects · Cardiac surgery

Y. Kaneko · J. Kobayashi · I. Achiwa
Department of Cardiovascular Surgery, Japanese Red Cross Medical Center, Tokyo, Japan

Y. Kaneko (✉)
Division of Cardiovascular Surgery, National Center for Child Health and Development, 2-10-1, Okura, Setagaya-ku, Tokyo 157-8535, Japan
e-mail: yukihirokaneko@hotmail.com

H. Yoda · Y. Nakajima · D. Endo · T. Kawakami
Department of Neonatology, Japanese Red Cross Medical Center, Tokyo, Japan

K. Tsuchiya
Department of Pediatrics, Japanese Red Cross Medical Center, Tokyo, Japan

H. Sato
Department of Public Health, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

Trisomy 18 is a chromosomal disorder characterized by multiple congenital anomalies and an extremely short lifespan. In population-based studies, the median survival time of patients with trisomy 18 ranged from 3 to 14 days, and <10% of trisomy 18 patients survived for 1 year [5, 16, 17]. Overall, 80%–100% of patients with trisomy 18 have congenital heart defects. The most common cardiac lesions are atrial septal defect, ventricular septal defect, patent ductus arteriosus, and polyvalvular disease [14, 22].

Offering cardiac surgery to patients with trisomy 18 is controversial. Rasmussen et al. analyzed data from multiple-cause mortality files and found that trisomy 18 patients with an associated heart defect survived longer than those without an associated heart defect [16]. They suggested that the presence of a heart defect did not negatively affect the survival of trisomy 18 patients. In a population-based study of trisomy 18, Embleton et al. found that cardiac problems were not implicated in the deaths of 31 of 34 live births [5]. Thus, they concluded that cardiac surgery was probably not likely to improve the survival of infants with trisomy 18.

However, some institution-based studies suggested the contrary. In a pathological study, Kinoshita et al. found that the major causes of death among trisomy 18 patients were heart failure and pulmonary hemorrhage resulting from congenital heart defects [9]. An echocardiographic study by Musewe et al. and an autopsy study by Van Praagh et al. suggested that early and excessive development of pulmonary hypertension induced by congenital heart defects might play a significant role in the premature death of some neonates with trisomy 18 [14, 22]. We previously reported that intensive cardiac management, consisting of pharmacological intervention for ductal patency and cardiac surgery, improved the survival of patients with trisomy 13 or trisomy 18 [8].

Recently, neonatologists' attitudes toward neonates with trisomy 18 have been shifting from the position of nonintervention to the position of respecting parental autonomy in treatment decision-making [13]. This shift has led to more of these patients having invasive interventions, including cardiac surgery. This article describes our institution's experience with cardiac surgery in patients with trisomy 18.

Materials and Methods

The hospital records of patients with trisomy 18 undergoing cardiac surgery at the Japanese Red Cross Medical Center were reviewed. Patients' data were collected on August 21, 2008. In patients with trisomy 18 and serious symptoms attributable to associated cardiac defects, cardiac surgery was considered a reasonable option if the attending neonatologist, pediatric cardiologist, and surgeon believed that the procedure would result in a reasonable probability of relieving serious cardiac symptoms, increasing survival, and allowing the patient to be discharged home without mechanical ventilation. Attending neonatologists discussed the option of cardiac surgery with the parents, but they did not recommend it. They informed the parents about the uncertain outcome and the unpredictable risks associated with cardiac surgery in an unbiased and noncoercive manner. They also told the parents that, due to the patients' poor prognosis, cardiac surgery has been withheld from patients with trisomy 18 in the majority of institutions. The physician and parents spoke several times, after which the parents could decide whether to request or forgo surgical intervention.

Survival was defined as the time from birth to death. For patients who were alive at the time of data collection, survival was defined as the time from birth to data collection, assuming that the patient may have died immediately thereafter. Postoperative survival was defined as the time from initial surgery to death. For patients who were alive at the time of data collection, postoperative survival was defined as the time from initial surgery to data collection. Univariate and multivariate techniques were used to analyze the relationships between postoperative survival and related variables. The related risk variables included gender, gestational age, ratio of birth weight to the normative value for gestational age, Apgar score at 1 min, Apgar score at 5 min, type of initial procedure (palliative or intracardiac repair), age at initial surgery, and body weight at initial surgery. The normative birth weight for gestational age was derived from survey results collected by the Ministry of Health and Welfare of Japan in 1994. The log-rank test and Cox proportional hazards model were used for the univariate analysis. A p value of <0.05 was considered statistically significant. To determine which set of variables could best predict postoperative survival, a multivariate Cox regression model was built through stepwise selection of explanatory variables. The significance level for explanatory variables and for the model was set to 0.10; both forward and backward selection of variables was used.

Results

Seventeen patients with trisomy 18 underwent cardiac surgery between November 2003 and May 2008. The patients' profiles, surgical treatments, survival, and causes of death are reported in Table 1.

All of the patients with trisomy 18 had severe heart failure and pulmonary overcirculation before surgery. Though elective surgery was planned for every patient, patients 1 and 6 required surgery earlier than scheduled due to progressive heart failure. Age at surgery ranged from 7 to 258 days (median, 66 days). All patients undergoing palliative surgery ($n = 14$) had pulmonary artery banding. Concomitant procedures included patent ductus arteriosus closure ($n = 11$) and repair of coarctation of the aorta ($n = 4$). Four patients underwent subsequent second-stage intracardiac repair electively at about 1 year of age. Primary intracardiac repair consisted of ventricular septal defect closure and patent ductus arteriosus closure ($n = 3$). In patient 10, a ventricular septal defect was closed with a flap-valved patch because of high pulmonary vascular resistance [15]. Concomitant procedures included rerouting of anomalously connected bilateral upper pulmonary veins in patient 4 and repair of coarctation of the aorta in patient 5.

Survival

Survival of the patient cohort ranged from 12 to 1384 days (median, 324 days). Six patients were alive at the time of data collection. All of the live patients underwent initial palliative surgery.

Postoperative survival ranged from 0 to 1239 days (median, 179 days). Univariate analyses using the log-rank

Table 1 Patients' characteristics and outcomes

Patient no.	Gender	Gestational age (days)	Birth weight (g)	Apgar score (1 min/5 min)	Cardiac diagnosis	Age at admission (days)	Age at surgery (days)	Weight at surgery (g)	Surgery	Postop-erative survival	Survival	Cause of death
1	F	248	1224	4/6	AVSD, CoA, PDA	1	12	1000	P	0	12	Heart failure
2	M	252	1632	7/9	VSD, CoA, PDA	53	57	1960	P	10	67	Sepsis
3	F	270	1662	6/8	VSD, PDA	1	7	1500	P	92	99	*Alive*
4	M	291	2018	8/9	VSD, PDA, PAPVC	36	54	2371	ICR	48	102	Sudden death
5	F	277	1632	6/8	VSD, CoA, PDA	113	126	1900	ICR	1	127	Sepsis
6	F	283	1744	6/9	VSD	1	72	2315	P	135	207	Sudden death
7	F	290	2730	6/9	VSD	65	66	2806	P	163	229	Pneumonia
8	M	288	1997	5/6	VSD	186	190	2100	P	125	315	Sudden death
9	F	281	1826	6/9	VSD, PDA	1	37	1900	P	180	324	*Alive*
10	F	266	1830	N/A	VSD, PDA	250	258	4058	ICR	179	437	Pneumonia
11	F	279	2215	9/9	VSD, PDA	69	72	2070	P	396	468	Respiratory failure
12	F	269	1686	7/8	VSD, CoA, PDA	1	11, 340	1500, 4000	P + SICR	590	601	Sepsis
13	F	260	1710	2/7	VSD, CoA, PDA	1	18, 300	1500, 2371	P + SICR	620	638	*Alive*
14	F	294	2204	9/10	VSD, PDA	1	75	2100	P	663	738	*Alive*
15	F	251	1232	3/7	VSD, PDA	72	73	1680	P	770	843	*Alive*
16	F	260	1460	6/8	VSD, PDA	1	7, 349	1414, 3814	P + SICR	1239	1246	Pneumonia
17	F	272	1902	9/10	VSD, PDA	186	194, 402	3198, 5035	P + SICR	1190	1384	*Alive*

Note: *AVSD* atrioventricular septal defect, *CoA* coarctation of the aorta, *F* female, *ICR* intracardiac repair, *M* male, *P* palliation, *PAPVC* partial anomalous pulmonary venous connection, *PDA* patent ductus arteriosus, *SICR* second-stage intracardiac repair, *VSD* ventricular septal defect

test and the Cox proportional hazards model showed that female gender ($p = 0.01$) and palliative surgery ($p = 0.02$) were significantly associated with longer postoperative survival. Age at surgery, body weight at surgery, and gestational age did not affect postoperative survival. Multivariate analyses, with both backward and forward selection of variables, showed that the type of initial surgical procedure was the best predictor of postoperative survival, and no additional variables improved the prediction.

Hospital Mortality

Hospital mortality was 18%; patients 1, 2, and 5 died before hospital discharge. Patient 1, who had cardiogenic shock, underwent palliation and died of refractory arrhythmia during thoracotomy. Patients 2 and 5 died of sepsis 10 days and 1 day, respectively, after surgery.

Discussion

A literature review identified one article that focused on cardiac surgery in 24 patients with trisomy 18 [7]. The hospital survival rate was 86%, indicating that cardiac surgery was safe for these patients; however, follow-up after hospital discharge was not performed. Other articles reported on three or fewer patients undergoing cardiac surgery [2, 20, 21]. A literature search failed to find any articles reporting long-term clinical results of patients with trisomy 18 undergoing cardiac surgery.

Ethical Considerations

Ethical issues are a concern in the management of patients with trisomy 18. Until recently, the medical community that cared for infants with trisomy 18 seemed to agree that it did not serve these infants' best interest to undergo invasive procedures such as cardiac surgery [13]. It was believed that invasive treatment was futile because trisomy 18 was a lethal condition. Dame Elizabeth at the British High Court ruled that a 9-month-old male with trisomy 18 should not be mechanically ventilated [3]. In her decision, Dame Elizabeth wrote that mechanical ventilation would be against the child's interest, because it was highly likely that he would become ventilator-dependent, depriving him of his mother's cuddle for the rest of his life. Another British decision, by Mr. Justice Hedley, authorized doctors not to ventilate an 18-month-old female with trisomy 18. The judge was convinced by the majority medical opinion that the infant was unlikely to survive even with ventilation, and that it would not be in her best interest to die in the course of futile aggressive treatment [4].

The attitude toward treatment of patients with trisomy 18 is becoming less conservative, driven largely by physicians' desire to honor parents' wishes. The most recent American Heart Association neonatal resuscitation guideline included trisomy 13 but omitted trisomy 18 from the list of examples of conditions for which cardiopulmonary resuscitation is withheld [1]. The guideline thereby indicated that resuscitation in neonates with trisomy 18 is not always futile. Judgment of the ethical acceptability of intensive treatment in patients with congenital syndromes is complicated by financial and resource allocation issues, as well as by personal diversity in quality-of-life evaluation, which is strongly influenced by cultural, religious, and philosophical perspectives [11, 18, 19].

We believe that the cardiac surgery and the related intensive treatment in the present study was ethically acceptable. Although one patient died intraoperatively, no other patients died of heart failure after surgery. The fact that 82% of the patients were discharged home in stable condition indicates that cardiac surgery offered the majority of these patients the opportunity of enjoying their parents' cuddle and alleviation of serious cardiac symptoms. Judging from the above-mentioned British decisions, the management approach used in the present study does not seem to be against patients' best interests.

Before cardiac surgery was used in patients with trisomy 18 at our institution, we had no effective method to alleviate heart failure in these patients when their heart failure was too severe to be controlled pharmacologically. Anticipation of worsening cardiac symptoms and imminent death made medical and nursing staffs hesitant to care for patients with heart failure intensively, because aggressive life-prolonging treatment that did not relieve cardiac symptoms did not seem to meet patients' best interests. We usually offered parents the option of comfort care only. After the introduction of cardiac surgery, patients with trisomy 18 who otherwise would have died after suffering serious cardiac symptoms were discharged home after cardiac surgery in stable condition. Accumulating experience of alleviated heart failure and hospital discharge after cardiac surgery allowed us increasingly to believe that intensive care, including optional cardiac surgery, in selected patients with trisomy 18 is ethically acceptable. Aggressive treatment based on the premise of withholding cardiac surgery in patients with trisomy 18 and serious cardiac symptoms seems to be less ethically acceptable.

Surgical Strategy

In patients with a normal karyotype and a body weight of 2 kg or more, we prefer primary intracardiac repair for the cardiac lesions listed in Table 1. However, we performed palliative surgery in patients with trisomy 18 having these

cardiac lesions unless it was anticipated that palliative surgery would be ineffective. Primary intracardiac repair was performed to repair anomalous connection of bilateral upper pulmonary veins in patient 4, to repair aortic arch hypoplasia that could barely be addressed without cardiopulmonary bypass in patient 5, and to alleviate elevated pulmonary vascular resistance (16.9 Wood units) in patient 10.

Five patients (nos. 1, 3, 12, 13, and 16) with birth weights of <2000 g underwent cardiac surgery before the age of 3 weeks. The primary lesion was widely patent ductus arteriosus causing pulmonary overcirculation and insufficient systemic perfusion in two patients and severe coarctation of the aorta with patent ductus arteriosus causing pulmonary overcirculation and insufficient duct-dependent lower body circulation in the other three patients. In patients with a normal karyotype, similar birth weights, and similar hemodynamics, we usually perform palliative surgery within 2 weeks of age. Therefore, we decided to performed surgery in these five patients with trisomy 18 within the first 3 weeks of life. Unfortunately, one patient died intraoperatively. The other four patients were discharged home with alleviated symptoms. The median survival of these five patients was 590 days. Therefore, we consider the timing of surgery in these patients to be medically appropriate.

In the present study, survival was shorter after intracardiac repair than after palliative surgery. We hypothesize that the patients who underwent intracardiac repair had more complicated cardiac lesions and, therefore, died early. Because they were transferred from other hospitals, their age at surgery was older. Consequently, longer preoperative exposure to excessive pulmonary blood flow and heart failure could have had a negative impact on survival. Some of the patients may not have been able to tolerate the surgical stress of intracardiac repair, resulting in a higher early mortality. Most patients with trisomy 18 have several life-threatening extracardiac disorders. Therefore, palliative surgery may be sufficient to prevent heart-related death before death occurs from other causes.

The results of the present study indicate that initial palliative surgery is the preferred procedure for patients with trisomy 18 and simple cardiac lesions. Because age and body weight at surgery did not affect postoperative survival, deferring cardiac surgery once it is indicated is not recommended.

Causes of Death

In the population-based report by Embleton et al., the median survival of patients with trisomy 18 was 3 days, and apnea was the most prevalent cause of death. A heart defect was the cause of death in 3 of 31 patients (10%). Sepsis was the cause of death in 3 of 31 patients (10%) [5]. In the institution-based report by Goc et al., the mean survival of patients with trisomy 18 was 20 days, and the most frequent cause of death was cardiopulmonary or multiorgan failure. Six patients (43%) died of a duct-dependent congenital heart defect, heart failure, or cardiopulmonary failure, with a mean survival time of 23 days. Sepsis was the cause of death in 2 of 14 patients (14%) [6]. Kosho et al. reported the clinical details of 24 patients with trisomy 18 who received intensive medical treatment but from whom cardiac surgery was withheld. Their median survival was 152 days, and the most frequent mode of death was cardiac or cardiopulmonary arrest. A congenital heart defect and heart failure were the most frequent underlying factors related to death in 22 patients (96%), with a median survival of 125 days. Four patients having simple cardiac lesions died of heart defect-related problems before 6 weeks of age. Sepsis was the cause of death or an underlying factor related to death in 5 of 23 patients (22%) [10]. In the present report, infection, including pneumonia and sepsis, was the most frequent cause of death, with a prevalence of 44% (5 of 11 patients). Heart failure was the cause of death in only one patient (9%). Van Dyke and Allen reported on patients with trisomy 18 surviving beyond 1 year. Infection was a major cause of death in three of five patients; congestive heart failure contributed to the death of three patients [21].

The literature review delineates the causes of death prevalent in different age groups of patients with trisomy 18. Neonates aged <1 week frequently die of apnea. Congenital heart defects play little role in the death of these patients. Patients ranging in age from 1 week to 1 month frequently die of cardiopulmonary or multiorgan failure. Patients older than 1 month of age frequently die of congenital heart defect-related problems. Congenital heart defect-related deaths are not uncommon in infants <6 weeks of age. Our experience showed that cardiac surgery was effective in preventing congenital heart defect-related deaths. Infection is a serious hazard to survival in patients with trisomy 18, particularly after infancy. The high prevalence of infection-related deaths in older patients with trisomy 18 is probably due to compromised immunity associated with trisomy 18 [23]. To improve the survival of patients with trisomy 18 after cardiac surgery, prevention of life-threatening infections is important.

Limitations

This was a surgical series of selected patients with trisomy 18. The decision to proceed to cardiac surgery in this series was based on physician judgment and parental autonomy. The indications for cardiac surgery in patients with trisomy 18 were not defined. Because of the skewed patient mix, the survival time of these patients is not comparable to that

in population-based studies. The patients in the present study had only simple cardiac lesions; patients with complex cardiac lesions requiring intricate, multistaged operations were not included. Consequently, the issue of the appropriate management of complex cardiac lesions associated with trisomy 18 was not addressed.

Conclusion

The results of the present study suggest that, with respect to the surgical treatment of simple cardiac lesions in patients with trisomy 18: (1) 82% of the patients undergoing heart surgery were discharged home with alleviated cardiac symptoms; (2) congenital heart defect-related death occurred in only one patient, suggesting that cardiac surgery is effective in preventing congenital heart defect-related death; and (3) initial palliative surgery was associated with longer survival than intracardiac repair.

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