Intensive cardiac management in patients with trisomy 13 or trisomy 18†

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KEYWORDS

trisomy 13 • trisomy 18 • neonate • congenital heart defects • neonatal intensive care • cardiac surgery

ABSTRACT

Intensive cardiac management such as pharmacological intervention for ductal patency (indomethacin and/or mefenamic acid for closure and prostaglandin E1 for maintenance) and palliative or corrective surgery is a standard treatment for congenital heart defects. However, whether it would be a treatment option for children with trisomy 13 or trisomy 18 syndrome is controversial because the efficacy on survival in patients with these trisomies has not been evaluated. We retrospectively reviewed 31 consecutive neonates with trisomy 13 or trisomy 18 admitted to our neonatal ward within 6 hr of birth between 2000 and 2005. The institutional management policies differed during three distinct periods. In the first period, both pharmacological ductal intervention and cardiac surgery were withheld. In the second, pharmacological ductal intervention was offered as an option, but cardiac surgery was withheld. Both strategies were available during the third period. The median survival times of 13, 9, and 9 neonates from the first, second, and third periods were 7, 24, and 243 days, respectively. Univariate and multivariate analyses confirmed that the patients in the third period survived significantly longer than the others. Intensive cardiac management consisting of pharmacological intervention for ductal patency and cardiac surgery was demonstrated to improve survival in patients with trisomy 13 or trisomy 18 in this series. Therefore, we suggest that this approach is a treatment option for cardiac lesions associated with these trisomies. These data are helpful for clinicians and families to consider in the optimal treatment of patients with these trisomies. © 2008 Wiley-Liss, Inc.

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INTRODUCTION

Trisomy 13 and trisomy 18 are common chromosomal disorder characterized by multiple congenital anomalies and an extremely short lifespan. Population-based studies showed that the median survival time of patients with either anomaly ranged from 3 to 14 days and that <10% of patients with trisomy 13 or trisomy 18 survived for 1 year [Root and Carey, [1994]; Wyllie et al., [1994]; Embleton et al., [1996]; Rasmussen et al., [2003]]. Features of trisomy 13 include orofacial clefts, microphthalmia/anophthalmia, and postaxial polydactyly. Features of trisomy 18 include prenatal growth deficiency, typical craniofacial appearance, overriding fingers, nail hypoplasia, short hallux, and short sternum [Carey, [2005]]. Congenital heart defects occur in 80-100% of patients with trisomy 13 or trisomy 18. The most common cardiac lesions associated with trisomy 13 and trisomy 18 are atrial septal defect (ASD), ventricular

septal defect (VSD), patent ductus arteriosus (PDA), and polyvalvular disease [Van Praagh et al., [1989]; Musewe et al., [1990]].

Pharmacological intervention for patency of arterial duct (closure or maintenance) and cardiac surgery (corrective or palliative) are established treatment options for altering the structure of the cardiovascular system in patients with congenital heart defects. Isolated PDA or PDA associated with non-duct dependent heart defects such as ASD, VSD induces excessive pulmonary circulation and insufficient systemic circulation. Closure of PDA to reduce pulmonary blood flow is beneficial in such cases, and thereby pharmacological closure of PDA using indomethacin or mefenamic acid is warranted. On the other hand, spontaneous constriction of PDA causes worsening cyanosis in patients with duct-dependent pulmonary circulation, such as pulmonary atresia and tetralogy of Fallot with severe pulmonary stenosis, and systemic organ ischemia in patients with duct-dependent systemic circulation such as aortic coarctation and hypoplastic left heart. Pharmacological maintenance of PDA using prostaglandin E1 (PGE1) is warranted in these patients. Cardiac surgery is indicated in patients with some heart defects to relieve symptoms and to improve life expectancy. Corrective surgery is the technique of choice in the majority of patients. In patients with serious extracardiac complications or with the heart lesion that is too complex to be repaired in early infancy, palliative surgery is preferred. However, whether pharmacological intervention for ductal patency and cardiac surgery improves the lifespan of patients with trisomy 13 or trisomy 18 remains unknown.

Rasmussen et al. [2003] analyzed data from Multiple-Cause Mortality Files and found that patients with trisomy 13 or trisomy 18 survived longer with, than without, an accompanying heart defect. These authors suggested that having a heart defect did not negatively affect the survival of the patients with trisomy 13 or trisomy 18. Embleton et al. [1996] determined from a population-based study of trisomy 18 that cardiac defects had not been implicated in the deaths of 31 of 34 live births. This group concluded that cardiac surgery would probably not improve the survival of infants with trisomy 18, and was therefore not justified. Wyllie et al. [1994] noted from a population-based study of trisomy 13 that none of the cardiac lesions found in 16 live births would cause early death. Therefore, they concluded that cardiac surgery in infants with trisomy 13 could not be justified.

On the other hand, based on detailed observations, some institution-based studies suggested that congenital heart defects with heart failure and pulmonary hypertension would be the primary pathology leading to early deaths in patients with trsiomy 13 or trisomy 18. Kinoshita et al. [1989] found from a pathological study that the major causes of death among patients with trisomy 18 were heart failure and pulmonary hemorrhage resulting from congenital heart defects. An echocardiographic study by Musewe et al. [1990] and an autopsy study by Van Praagh et al. [1989] 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 13 or trisomy 18. Recently, Kosho et al. [2006] reported improved survival (the median survival time 152.5 days; the survival rate at age 1 year 25%) in patients with trisomy 18 under intensive neonatal management including cesarean, resuscitation by intubation, appropriate respiratory support, establishment of enteral nutrition (corrective or palliative surgery for gastrointestinal malformation, if necessary), and pharmacological treatment for congenital heart defects. The patients frequently died of sudden cardiac or cardiopulmonary arrest and possible pulmonary hypertension-related events, on the basis of congenital heart defects with heart failure and pulmonary hypertension.

The Japanese Red Cross Medical Center (JRCMC) is a general hospital with 800 beds including a 12-bed neonatal intensive care unit and a 40-bed neonatal/preterm ward. The JRCMC is approved as one of the 62 General Maternal and Perinatal Medical Care Centers in Japan. Pregnant women and neonates who require intensive care are transferred to the JRCMC mainly from the south-eastern area of the Tokyo metropolis. About 550 neonates have been treated annually in the neonatal intensive care unit and in the neonatal/preterm ward.

Different management policies were adopted at the JRCMC regarding heart defects in patients with trisomy 13 or trisomy 18 during three distinct periods. In the first period, both pharmacological intervention for PDA and cardiac surgery were withheld. In the second, pharmacological intervention for PDA was an option but not cardiac surgery. In the third, both were available choices.

The present study analyzed the survival of patients with trisomy 13 or trisomy 18 admitted to the JRCMC between 2000 and 2005, and investigated whether pharmacological intervention for PDA and/or cardiac surgery improved their lifespan.

METHODS

Institutional Patient Management Policy

G-banded karyotyping was performed in all neonates with suspicion of trisomy 13 or trisomy 18. The karyotype was confirmed between age 4 and 8 days. Until the karyotype was confirmed, the patients received full treatment and diagnostic procedures.

Before August 2002, the institutional management policy regarding heart defects in patients with trisomy 13 or trisomy 18 was to apply general supportive therapies for severely sick neonates. Digoxin, diuretics and catecholamines were administered when symptoms of heart failure developed. Oxygen was applied when patients exhibited cyanosis. The patients received blood transfusions when indicated. Although intubation was not discouraged, it was not actually performed after the karyotype was confirmed. Pharmacological PDA closure or maintenance, as well as palliative or corrective cardiac surgery was withheld.

From August 2002, pharmacological PDA interventions became an option for patients with trisomy 13 or trisomy 18 in the hope of improving survival. Pharmacological PDA closure by administration of mefenamic acid and/or indomethacin was indicated when heart failure attributable to PDA was evident or anticipated, as in patients with a normal karyotype. Ductal patency in patients with duct-dependent pulmonary or systemic circulation was closely monitored by frequent echocardiography. The arterial duct often remained widely patent without intervention in patients with trisomy 13 or trisomy 18. When signs of ductal constriction were detected, PGE1 was administered. However, cardiac surgery was not performed during this period.

The institutional policy changed in November 2003 so that cardiac surgery was no longer precluded even for patients with trisomy 13 or trisomy 18. Thus, such patients with symptoms attributable to cardiac defects became eligible for cardiac surgery if the attending neonatologist, pediatric cardiologist and surgeon believed that the procedure would bring about a reasonable probability of relieving serious cardiac symptoms and increased survival, or of being discharged home without mechanical ventilation. Attending neonatologists informed the parents about the uncertain outcome and unpredictable risks associated with cardiac surgery. The parents could then decide whether or not to approve surgical intervention.

Concerning extracardiac disorders, pharmacological treatments were performed similar to those performed in patients with normal karyotype. Life-saving surgery and surgery to prevent serious consequences were offered, and performed when parental informed consent was obtained. Surgeries that were offered included tracheostomy, nephrostomy, palliation of tracheoesophageal fistula, relief of enteric obstruction, closure of meningocele, and shunt for hydrocephalus. Surgeries for cosmetic indications including polydactyly and cleft lip were withheld. The institutional management policy regarding extracardiac disorders officially remained the same throughout the study period.

Patient Cohort

The inclusion criteria for this study were (1) cytogenetic confirmation of trisomy 13 or trisomy 18, and (2) admission into the JRCMC within 6 hr of birth between January 2000 and December 2005. Mosaicism was an exclusion criterion. Nine neonates with trisomy 13 and 22 with trisomy 18 who met the criteria comprised the patient cohort, and were assigned to treatment groups based on admission dates. Treatment groups A, B, and C comprised patients admitted between January 2000 and July 2002, between August 2002 and October 2003, and between November 2003 and December 2005, respectively. For patients in group A, both pharmacological intervention for PDA and cardiac surgery were withheld. For patients in group B, pharmacological intervention for PDA was an option but not cardiac surgery. For patients in group C, both were available choices.

Between 2004 and 2005, 3 patients with trisomy 18 were transferred to the JRCMC for cardiac surgery at ages 69, 185, and 250 days. They were not included in this study. No other patients with trisomy 13 or trisomy 18 were admitted to JRCMC during the study period.

Data Collection and Statistical Analysis

We collected data about the patients from hospital records on May 31, 2006. Perinatal conditions, congenital heart defects, extracardiac anomalies, pharmacological intervention for PDA, cardiac surgery, treatment course, survival, and cause of death were reviewed.

Survival curves for the three treatment groups were determined using the Kaplan-Meier method and compared using a log-rank test. Relationships between survival and related variables were examined using univariate and multivariate analyses. The related variables included treatment group, gender, affected chromosome, gestational age, ratio of birth weight to the normative value for gestational age, and Apgar score at 5 min. The normative birth weight for gestational age was derived from Japanese survey results collected by the Ministry of Health and Welfare in 1994. The Cox proportional hazards model was used for the univariate analysis. A *P* value below 0.05 was considered statistically significant. The Cox proportional hazards model with a forward stepwise procedure was used for the multivariate analysis with the regression coefficient threshold set at 0.05. Associations between the treatment group and other related variables were explored using Fisher's exact test. All statistical analyses were performed using SAS Version 8.2 software (SAS Institute, Inc., Cary, NC).

RESULTS

Table I summarizes the prenatal and perinatal findings of the patients, and Table II lists associated cardiac defects and non-cardiac anomalies. Table III shows the types of intervention, prognosis and causes of death. Congenital heart defects were diagnosed in 30 patients. Echocardiography could not be performed in Patient 1 as he required continual resuscitation during his brief lifetime of 3 hr. The parents denied an autopsy, so the presence of a congenital heart defect could not be proven.

Table I. Prenatal and Perinatal Findings

Patient	Karyotype	Prenatal diagnosis	Gestational age (weeks/days)	Cesarean	Resuscitation by intubation	Neonatal transfer	Birth weight (g)	Apgar score (1 min/5 min)
Group A								

1	47, XY, +18		24/2		+		410	1/2
2	47, XX, +18		39/5			+	2,246	5/6
3	47, XY, +18	Amniocentesis	38/3		+		1,510	2/5
4	47, XY, +18	Ultrasound	33/0	+			1,278	2/4
5	47, XY, +13	Ultrasound	33/3	+	+		2,400	4/8
6	47, XY, +18	Amniocentesis	31/6				1,239	1/4
7	47, XX, +18	Ultrasound	42/0				2,518	6/7
8	47, XY, +13		27/4		+		936	2/6
9	47, XX, +18	Ultrasound	36/3		+	+	1,568	2/8
10	47, XX, +18	Ultrasound	40/0			+	1,882	6/6
11	47, XX, +18	Ultrasound	37/1	+			1,436	6/8
12	47, XX, +18	Ultrasound	37/6				1,880	6/7
13	47, XX, +13		36/6		+		1,498	1/5
Group B								
14	47, XY, +18	Ultrasound	26/2		+		604	4/4
15	47, XX, +18	Ultrasound	31/0	+	+		896	1/1
16	46, XX, +13, der (13;13)(q10;q10)	Ultrasound	39/1	+			2,120	5/7
17	47, XY, +18	Ultrasound	42/0		+		1,968	3/5
18	47, XX, +13	Ultrasound	37/1		+		1,882	4/4
19	47, XY, +13		40/0			+	2,906	5/8
20	47, XY, +13		38/6	+		+	3,098	6/8
21	47, XY, +18	Ultrasound	34/2		+		1,124	3/7
22	47, XY, +18	Ultrasound	32/0	+	+		1,214	5/8
Group C								
23	47, XX, +18	Ultrasound	32/3	+	+		746	6/8
24	48, XXY, +18	Ultrasound	38/5				1,402	6/8
25	47, XX, +18	Amniocentesis	40/3				1,744	6/9
26	47, XY, +18	Ultrasound	36/2				1,874	2/7
27	47, XY, +18	Ultrasound	38/6	+			2,126	7/8
28	47, XX, +18	Ultrasound	38/3				1,686	7/8
29	47, XX, +18	Ultrasound	37/1	+			1,460	6/8
30	47, XY, +13	Ultrasound	35/4				2,067	5/8
31	47, XX, +13		38/2	+			2,894	8/9

Table II. Structural Defects

Patient	Congenital heart defects	PDA closure desirable	Arterial duct dependent circulation	Central nervous system anomalies	Thoracic organ anomalies	Abdominal organ anomalies
Group A						
1						
2	VSD, PDA			CH		
3	VSD, MS			CH, holoprosencephaly		
4	VSD, PDA				TEF	

5	VSD, PDA, AS				LH	HN
6	VSD, PDA	+		CH	TEF	OC
7	DORV, CoA, PDA		+	CH		
8	ToF, PDA					OC
9	DORV, MA, hypo LV, IAA, PDA, AS		+		DE	
10	VSD, MS, PDA					
11	DORV, MA, CoA,			CH		
12	VSD, PDA, CoA		+		TEF	
13	VSD, PDA	+				
Group B						
14	MS, VSD, IAA, Hypo LV		+		TEF	AA, HN
15	TA, VSD			CH	TS, LH	
16	VSD, PDA	+			DE	HN
17	VSD, PDA	+				OC
18	ToF		+			
19	VSD, PDA, CoA					
20	ToF, PA		+			
21	VSD, PDA	+			TEF	AA
22	VSD, PDA	+		CH		
Group C						
23	VSD, PDA, CoA		+	CH	TEF	
24	VSD, PDA, CoA		+	CH	TEF	
25	VSD					
26	ToF			CH		HN
27	VSD, PDA	+		CH		
28	VSD, PDA, CoA		+	Meningocele		HN
29	VSD, PDA	+		CH		
30	VSD, ASD, PDA	+		CH		OC, HN
31	VSD, PDA	+			TS	OC, HN

VSD, ventricular septal defect; PDA, patent ductus arteriosus; AS, aortic stenosis; CoA, aortic coarctation; DORV, double outlet right ventricle; MA, mitral atresia; hypo LV, hypoplastic left ventricle; IAA, interrupted aortic arch; ToF, tetralogy of Fallot; MS, mitral stenosis; PA, pulmonary atresia; TA, tricuspid atresia, ASD, atrial septal defect; CH, cerebellar hypoplasia; TEF, tracheoesophageal fistula; LH, lung hypoplaia; DH, diaphragmatic

eventration; TS, tracheal stenosis; OC, omphalocele, HN, hydronephrosis; AA, anal atresia.

Table III. Interventions, Prognoses, and Causes of Death

Patient	Pharmacological ductal intervention	Cardiac surgery	Non-cardiac surgery (age at surgery; days)	Age at discharge (days)	Survival (days)	Underlying factors associated with death	Principal cause of death
Group A							
1					0	HF, asphyxia, pneumothorax, RF	RF
2					0	CHD, HF, PH, asphyxia, apnea	HF
3					0	CHD, PH, DE, RF	RF
4					0	CHD, HF, PH, TEF, asphyxia, RF	RF
5			Nephrostomy (0)		3	CHD, HF, PH, RF, KF	RF
6					6	CHD, HF, PH, TEF	HF
7					7	CHD, HF, PH, RF	HF
8			OC repair (0)		7	CHD, HF, anemia, RF	HF
9					8	CHD, HF, PH, DE, RF	HF
10					19	CHD, HF, PH	HF
11					44	CHD, HF, PH, Apnea	HF
12					60	CHD, HF, PH	HF
13					96	CHD, HF, PH, KF, tracheal stenosis	HF
Group B							
14					0	CHD, PH, KF, TEF, AA	Peritoneal bleeding
15			Tracheostomy (0)		0	CHD, PH, tracheal stenosis, asphyxia, RF	RF
16	Indo (days 3-5)				10	CHD, HF, PH, DE, KF, PHE	HF
17					23	CHD, HF, PH, PHE	HF
18	PGE1 (day 1-death)				24	CHD, anemia	Pneumonia

19				26	55	CHD, HF, PH, hypoglycemia, apnea	Sudden death
20	PGE1 (day 1-death)				61	CHD, HF, Apnea	HF
21	Indo (days 3-9)				91	CHD, HF, PH, TEF, RF, KF	Malnutrition
22	MA + Indo (days 5-12)				367	CHD, HF, PH, RF	HF
Group C							
23					3	CHD, HF, PH, TEF, RF	Gastric rupture
24					7	CHD, HF, PH, TEF, RF, PHE	HF
25		+		117	207	Apnea	Sudden death
26				105	238	CHD	Pneumonia
27	MA (day 4)				243	CHD, PH, anemia	Pneumonia
28		+	MC repair (0), VP shunt (81)	253	601	Alive	
29	MA + Indo (days 2-6)	+		108	740	Alive	
30	Indo (day 10)	+	OC repair (0), Ileus lysis (175)		782	Alive	
31	Indo (days 3-9)		OC repair (0)	83	834	Alive	

Indo, indomethacin; MA, mefenamic acid; CHD, congenital heart defect; HF, heart failure; PH, pulmonary hypertension; RF, respiratory failure; KF, kidney failure; PHE, pulmonary hemorrhage; MC, meningocele; OC, omphalocele; VP, ventriculoperitoneal. See text for details of ductal intervention and cardiac surgery.

Pharmacological Intervention for Arterial Duct Patency

Among 10 patients for whom pharmacological ductal intervention was offered, the parents of 9 patients consented (the parents of Patient 17 elected not to proceed with this therapy). Mefenamic acid and/or indomethacin were administered to seven patients to induce ductal closure (Table III). Indomethacin was administered, but discontinued despite persistent ductal patency in Patient 16 because of worsening renal dysfunction. Mefenamic acid and indomethacin were ineffective in Patient 29 who subsequently underwent emergent cardiac surgery. Pharmacological intervention for PDA closure was effective in improving heart failure in the remaining five patients. Reopening of PDA was not observed.

Pharmacological ductal maintenance was attempted in Patients 18 and 20 who showed decreasing pulmonary blood flow due to closing PDA. Persistent ductal patency was confirmed in both patients by echocardiography. No adverse events related to PGE1were noted. Repeated echocardiography revealed persistent ductal patency without the use of PGE1 in all patients with duct-dependent systemic circulation (Patients 7, 9, 12, 23 and 24, and Patient 28 who had duct-dependent systemic circulation until cardiac surgery).

Cardiac Surgery

Cardiac surgery was offered as an option to four patients in group C after the karyotype was confirmed. The parents of these patients agreed to the surgery.

Patient 25 exhibited worsening heart failure and was intubated on Day 69 because of ventricular tachycardia requiring cardiopulmonary resuscitation. She underwent urgent pulmonary artery banding (PAB) on Day 72, which increased systemic arterial pressure from 68/50 to 86/52 mmHg, and decreased pulmonary arterial pressure from 56/50 to 38/30 mmHg. Left ventricular diastolic diameter/systolic diameter (LVDd/Ds) on ultrasound decreased from preoperative 18.0/11.4 mm to postoperative 15.4/10.0 mm. The endotracheal tube was removed 7 hr after surgery. She was discharged on Day 117, but suddenly died at home on Day 207, most likely because of central apnea.

Patient 28 was intubated and underwent closure of a meningocele on Day 1. She underwent elective aortic coarctation repair and PAB on Day 10. Pulmonary arterial pressure decreased from 58/22 to 33/18 mmHg, while systemic arterial pressure remained unchanged at 60/34 mmHg. She was extubated on Day 16, and discharged on Day 253. She showed progressive heart failure, although intubation and mechanical ventilation were not needed Cardiac catheterization on Day 303 showed systemic arterial pressure of 108/72 mmHg, pulmonary arterial pressure of 36/12 mmHg, pulmonary-to-systemic blood flow ratio of 1.67, and pulmonary arterial resistance of 4.0 U m^2. She underwent VSD closure and pulmonary artery debanding on Day 340 when she weighed 3,950 g. She could not be weaned from mechanical ventilation, because of respiratory depression related to hydrocephalus, resulting from meningocele and triggered by intraoperative cardiopulmonary bypass [Trittenwein et al., [2003]]. At 601 days of age, she remains hospitalized, intubated, and mechanically ventilated with stable cardiopulmonary status.

Patient 29 had a large PDA, despite administration of mefenamic acid and indomethacin from Days 2 to 6. She showed progressive heart failure, although intubation and mechanical ventilation were not needed. Surgical PDA closure and pulmonary artery banding on Day 7 increased systemic arterial pressure from 43/33 to 50/38 mmHg, and decreased pulmonary arterial pressure from 38/18 to 24/8 mmHg. Preoperative LVDd/Ds on ultrasound of 12.3/8.0 mm decreased to 10.7/5.9 mm after surgery. She was extubated 24 hr after surgery and discharged home on Day 106 in a stable condition. Cardiac catheterization on Day 301 disclosed systemic arterial pressure of 120/55 mmHg, pulmonary arterial pressure of 19/9 mmHg, pulmonary-to-systemic blood flow ratio of 0.8, and pulmonary arterial resistance of 2.8 U/m^2. Electrocardiography showed intermittent third-degree artioventricular block. She underwent VSD closure, pulmonary artery debanding and permanent pacemaker implantation on Day 349 when she weighed 3,814 g. She was extubated 17 hr after surgery, and discharged home 16 days later. At 740 days of age, her cardiopulmonary status is stable. She rolls over, smiles, and cries. She does not crawl or babble.

Patient 30 received indomethacin on Day 10, followed by PDA closure. However, high pulmonary blood flow through a VSD resulted in worsening heart failure. Episodic apnea was frequent. He was intubated on Day 78. Pulmonary artery banding on the following day increased systemic arterial pressure from 50/26 to 75/36 mmHg, and decreased pulmonary arterial pressure from 40/19 to 34/18 mmHg. Preoperative LVDd/Ds on echocardiography of 18.5/13.5 mm decreased to 15.6/9.6 mm postoperatively. Heart failure ameliorated after surgery, and the frequency of apnea significantly decreased. He was extubated on the third postoperative day. He remains alive without heart failure on Day 782, but does not crawl or babble.

Survival

All of the patients in group A died during initial hospitalization within 96 days (median 7 days) and all of those in Group B died within 367 days (median 23 days). Only Patient 22 survived 1 year, but was never discharged. Only Patient 19 could be discharged, but died on Day 55.

Five of the nine patients in group C died; four remained alive at the time of data acquisition. If we assume that the live patients died immediately after data acquisition, patient survival ranged from 3 to 834 days (median 243 days). Five patients were discharged without home mechanical ventilation or oxygen, and four patients survived for more than 1 year.

Figure 1 shows the Kaplan-Meier survival curves of the three groups. Survival significantly differed between groups A and C ($P = 0.003$), and between groups B and C ($P = 0.01$), but not between groups A and B ($P = 0.13$).

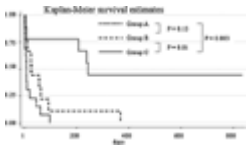

Figure 1. The Kaplan-Meier survival estimates of the three treatment groups.
[Normal View 24K | Magnified View 33K]

Univariate analysis showed that being in group C ($P = 0.001$) and having a higher Apgar score at 5 min ($P = 0.001$) were significantly related to a longer survival. Univariate analysis showed that survival was not significantly related to gender ($P = 0.48$; female gender was slightly better), affected chromosome ($P = 0.38$; trisomy 13 was slightly better), gestational age ($P = 0.051$; older was slightly better) or ratio of birth weight to normative value for gestational age ($P = 0.35$; higher was slightly better). Significant relationships were not demonstrated between treatment groups and any of these variables.

Since univariate analysis showed that survival did not significantly differ between groups A and B, they were combined into group A + B for multivariate analysis. Multivariate analysis showed that treatment group (group A + B vs. C) and Apgar score at 5 min satisfied the regression coefficient threshold.

Causes of Death

Causes of death were classified into underlying factors associated with death and principal causes of death, as described by Kosho et al. [2006]. The most frequent principal cause of death was heart failure. The prevalence was nine of 13 patients (69%) in group A, 4 of 9 (44%) in group B, and one of five (20%) in group C. The prevalence decreased as cardiac management intensified. The second most frequent principal cause of death was respiratory failure: four patients in group A and one in group B.

Heart-related factors were the most frequent underlying factors associated with death. These included congenital heart defect (25 patients, 93%), pulmonary hypertension (21 patients, 78%), heart failure (20 patients, 74%), and pulmonary hemorrhage (3 patients, 11%). Bronchopulmonary disorders were the second most frequent underlying factors associated with death. These included respiratory failure (12 patients, 44%), tracheoesophageal fistula (6 patients, 22%), pulmonary hemorrhage (3 patients, 11%), diaphragmatic eventration (3 patients, 11%), tracheal stenosis (2 patients, 7 %), and pneumothorax (1 patient, 4%). Other factors included kidney failure (5 patients, 19%), apnea (5 patient, 19%), birth asphyxia (4 patients, 15%), and anemia requiring blood transfusion (3 patients, 11%).

DISCUSSION

We have presented detailed clinical courses of 31 patients with trisomy 13 or trisomy 18, managed under three distinct policies focusing cardiac lesions. The results showed significant improvement in survival through both pharmacological intervention for ductal patency and cardiac surgery, compared with general supportive therapy or only pharmacological intervention for ductal patency. To our knowledge, this is the first study to investigate the effect of intensive management including optional cardiac surgery on the survival of patients with trisomy 13 or trisomy 18.

Study Limitations

This study has several limitations. Firstly, both patients with trisomy 13 and those with trisomy 18 were included. The disorders, with a distinct karyotypic difference, share various clinical characteristics including cardiac lesions (variation of defects and early development of pulmonary hypertension) and courses to death (apnea as the most commonly known cause of death and short lifespan) [Taylor, [1968]]. Secondly, the use of an open-labeled chronology-based comparison might have decreased analytical reliability. However, we believe that this had a minimal influence because several studies have shown that the survival of patients with trisomy 13 or trisomy 18 has not improved with time [Root and Carey, [1994]; Rasmussen et al., [2003]]. Thirdly, and importantly the sample size might be too small for meaningful generalization.

Pharmacological Intervention for Arterial Duct Patency

The success rate of pharmacological PDA closure in the present study was 71%, and reopening after successful pharmacological PDA closure did not occur. The success rate of pharmacological PDA closure using indomethacin or mefenamic acid and the reopening rate in this series were not suggested to be worse than those reported in preterm infants (the success rate 70-90%; reopening rate 20-30%) [Gersony et al., [1983]; Sakhalkar and Merchant, [1992]; Weiss et al., [1995]; Yoda et al., [1999]]. On the other hand, indomethacin had to be discontinued in a patient in this series because of worsening renal dysfunction. Urinary tract abnormalities, that might precipitate renal failure, have been frequently reported in patients with trisomy 13 and patients with trisomy 18 [Barakat and Butler, [1987]]. Pharmacological PDA closure using indomethacin or mefenamic acid is suggested to be an appropriate treatment option in patients with trisomy 13 or trisomy 18, although renal function might have to be cautiously monitored in using them.

Two patients with duct-dependent pulmonary circulation showed closing arterial duct detected by ultrasonography and received PGE1 with sufficient effectiveness and without any adverse effect including central apnea, whereas six patients with duct-dependent systemic circulation did not show closing arterial duct. In a series by Kosho et al. [2006], PGE1 was administered in 4 patients, and was discontinued in 2 of them after long-term use (88 and 33 days). Central apnea is a serious adverse effects of PGE1 administered in early infants, and also a frequent complication of trisomy 13 and trisomy 18, possibly resulting in sudden death. Although PGE1 could be a treatment option for duct-dependent circulation associated with the trisomies, it would be mandatory to decide carefully to start PGE1 by detection of closing arterial duct, and to monitor respiratory status and ductal patency closely during the treatment.

Cardiac Surgery

Sporadic reports have documented the effectiveness of cardiac surgery in patients with trisomy 13 or trisomy 18 [Van Dyke and Allen, [1990]; Baty et al., [1994]; Teraguchi et al., [1997]; Stromme et al., [2000]; Derbent et al., [2001]]. Graham et al. [2004] reported cardiac surgeries among 35 patients with trisomy 13 or trisomy 18. Complete repair was performed in 21 patients, palliative surgery with subsequent complete repair was performed in 4, and 10 underwent only palliative surgery. The hospital survival rate was 91%, indicating that cardiac surgery was safe for these patients. However, the Graham et al. study was not designed to determine whether

the lifespan of the patients was increased by surgical intervention.

We selected palliative surgery for all of the surgical cases in this series, although cardiac lesions were amenable to corrective surgery. We would have preferred primary corrective surgery in patients with similar heart defects, similar body weight, and a normal karyotype. It has not been addressed in the medical literature whether use of initial palliative surgery should be recommended in patients with trisomy 13 or trisomy 18. Our predilection for palliative surgery in this series was based on the following speculative reasons. Firstly, the survival benefit conferred by complete repair in these patients would not be so large as that in patients with a normal karyotype. Most patients with trisomy 13 or trisomy 18 have several life-threatening extracardiac disorders. Difference between incremental survival by corrective surgery and that by palliative surgery would not be very large. Secondly, the risk of corrective surgery to these patients might be higher than that of palliative surgery. The detrimental effect of a whole-body inflammatory response induced by cardiopulmonary bypass might be critical in neonates and young infants with trisomy 13 or trisomy 18 [Kouchoukos et al., [2003]]. It has been indicated that genetic syndrome, young age, and perioperative blood transfusion are risk factors of postoperative infection and death [Numa et al., [1992]; Ryan et al., [1997]; Van de Watering et al., [1998]; Allpress et al., [2004]; Kagen et al., [2007]]. Corrective surgery usually takes longer than palliative surgery, requires more blood transfusion, and thereby might entail a higher risk of perioperative infection and death in neonates and young infants with trisomy 13 or trisomy 18 [Mangram et al., [1999]]. Thirdly, as for PAB, these patients might not outgrow the prosthetic pulmonary band for several years because of slower somatic growth, and might not require corrective surgery for life.

Our surgical series did not include complex cardiac lesions requiring intricate, multi-staged operations. The appropriate management of complex cardiac lesions associated with trisomy 13 or trisomy 18 has not been elucidated.

During the study period, pharmacological intervention for arterial duct patency was offered to eight patients, cardiac surgery to two, and both to other two patients. Parental informed consent was obtained for all but one patient, indicating that the policy of intensive cardiac management for these severely ill infants was accepted by the parents. A Taiwanese study found that fewer parents of neonates with trisomy 18 signed a do-not-resuscitate consent form after a National Health Insurance program was implemented [Lin et al., [2006]]. The high ratio of parental consent to intensive cardiac treatment in this study might be associated with the Japanese health care system in which the Neonatal Medical Cost Subsidy Program bears all of the medical costs for neonates and infants with severe medical conditions including trisomy 13 and trisomy 18.

Implications on Management Policy

The survival differed significantly between Group A and C, and between Group B and C, but not between Group A and B. The median survival time of patients in Group A and Group B was 14.5 days and the survival rate at age 1 year 4.5%, which were within the range of previous population-based studies. The median survival time of patients in Group C was 243 days and the survival rate at age 1 year 44%, which represents the longest among all population-based and institution-based studies reported to date. Thus, we suggest that intensive cardiac management, consisting both of pharmacological intervention for ductal patency and cardiac surgery, improves the survival of patients with trisomy 13 or trisomy 18.

Significant improvement in survival of patients with trisomy 13 or trisomy 18 under intensive cardiac management might also be attributable to unintentional intensification of general management and care. Before intensive cardiac management was applied to patients with trisomy 13 or trisomy 18, we had an impression that they would finally die of progressive heart failure associated with congenital heart defects, as observed by Kosho et al. [2006]. Anticipation of their imminent and inevitable death could have made us hesitate to treat their extracardiac

problems intensively. However, introduction of intensive cardiac management allowed us to have hope for improvement of heart failure and a better prognosis, probably leading to intensive extracardiac treatment and positive general care.

In conclusion, intensive cardiac management consisting of pharmacological intervention for ductal patency and cardiac surgery, possibly coupled with unintentional intensification of treatment of extracardiac problems and general care, improved survival in patients with trisomy 13 or trisomy 18 (the median survival time as 243 days; the survival rate at age 1 year as 44%); and therefore is suggested to be a treatment option for cardiac lesions associated with these syndromes. These data are helpful for clinicians and families to consider the best treatment to patients with trisomy 13 or trisomy 18.

REFERENCES

Allpress AL, Rosenthal GL, Goodrich KM, Lupinetti FM, Zerr DM. 2004. Risk factors for surgical site infections after pediatric cardiovascular surgery. *Pediatr Infect Dis J* **23**: 231-234. Links

Barakat AY, Butler MG. 1987. Renal and urinary tract abnormalities associated with chromosomal aberrations. *Int J Pediatr Nephrol* **8**: 215-226. Links

Baty BJ, Blackburn BL, Carey JC. 1994. Natural history of trisomy 18 and trisomy 13: I. Growth, Physical assessment, medical histories, survival, and recurrence risk. *Am J Med Genet* **49**: 175-188. Links

Carey JC. 2005. Trisomy 18 and trisomy 13 syndromes. In: Cassidy SB , Allanson JE , editors. *Management of genetic syndromes*. 2nd edition. New York: Wiley-Liss. p 555-568.

Derbent M, Saygili A, Tokel K, Baltaci V. 2001. Pulmonary artery sling in a case of trisomy 18. *Am J Med Genet* **101**: 184-185. Links

Embleton ND, Wyllie JP, Wright MJ, Burn J, Hunter S. 1996. Natural history of trisomy 18. *Arch Dis Child Fetal Neonatal Ed* **75**: F38-F41. Links

Gersony WM, Peckham GJ, Ellison RC, Miettinen OS, Nadas AS. 1983. Effects of indomethacin in premature infants with patent ductus arteriosus: Results of a national collaborative study. *J Pediatr* **102**: 895-906. Links

Graham EM, Bradley SM, Shirali GS, Hills CB, Atz AM, Pediatric Cardiac Care Consortium. 2004. Effectiveness of cardiac surgery in trisomies 13 and 18 (from the Pediatric Cardiac Care Consortium). *Am J Cardiol* **93**: 801-803. Links

Kagen J, Lautenbach E, Bilker WB, Matro J, Bell LM, Dominguez TE, Gaynor JW, Shah SS. 2007. Risk factors for mediastinitis following median sternotomy in children. *Pediatr Infect Dis J* **26**: 613-618. Links

Kinoshita M, Nakamura Y, Nakano R, Morimatsu M, Fukuda S, Nishimi Y, Hashimoto T. 1989. Thirty-one autopsy cases of trisomy 18: Clinical features and pathological findings. *Pediatr Pathol* **9**: 445-457. Links

Kosho T, Nakamura T, Kawame H, Baba A, Tamura M, Fukushima Y. 2006. Neonatal management of trisomy 18: Clinical details of 24 patients receiving intensive treatment. *Am J Med Genet Part A* **140A**: 937-944. Links

Kouchoukos NT, Blackstone EH, Doty DB, Hanley FL, Karp RB. 2003. *Kirklin/Barratt-Boyes cardiac surgery: Morphology, diagnostic criteria, natural history, techniques, results, and indication.* 3rd edition. Pholadelphia: Churchill Livingstone. p 66-130.

Lin HY, Lin SP, Chen YJ, Hung HY, Kao HA, Hsu CH, Chen MR, Chang JH, Ho CS, Huang FY, Shyur SD, Lin DS, Lee HC. 2006. Clinical characteristics and survival of trisomy 18 in a medical center in Taipei, 1988-2004. *Am J Med Genet Part A* **140A**: 945-951. Links

Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. 1999. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol* **20**: 250-278. Links

Musewe NN, Alexander DJ, Teshima I, Smallhorn JF, Freedom RM. 1990. Echocardiographic evaluation of the spectrum of cardiac anomalies associated with trisomy 13 and trisomy 18. *J Am Coll Cardiol* **15**: 673-677. Links

Numa A, Butt W, Mee RBB. 1992. Outcome of infants with birthweight 2000 g or less who undergo major cardiac surgery. *J Pediatr Child Health* **28**: 318-320. Links

Rasmussen SA, Wong LY, Yang Q, May KM, Friedman JM. 2003. Population-based analyses of mortality in trisomy 13 and trisomy 18. *Pediatrics* **111** (4 Pt 1): 777-784. Links

Root S, Carey JC. 1994. Survival in trisomy 18. *Am J Med Genet* **49**: 170-174. Links

Ryan T, Mc Carthy JF, Rady MY, Serkey J, Gordon S, Starr NJ, Cosgrove DM. 1997. Early bloodstream infection after cardiopulmonary bypass: Frequency rate, risk factors, and implications. *Crit Care Med* **25**: 2009-2014. Links

Sakhalkar VS, Merchant RH. 1992. Therapy of symptomatic patent ductus arteriosus in preterms using mefenemic acid and indomethacin. *Indian Pediatr* **29**: 313-318. Links

Stromme P, Thaulow E, Geiran O. 2000. Cardiac surgery in a girl with trisomy 13. *Cardiol Young* **10**: 638-640. Links

Taylor AI. 1968. Autosomal trisomy syndromes: A detailed study of 27 cases of Edward's syndrome and 27 cases of Patau's syndrome. *J Med Genet* **5**: 227-251. Links

Teraguchi M, Nogi S, Ikemoto Y, Ogino H, Kohdera U, Sakaida N, Okamura A, Hamada Y, Kobayashi Y. 1997. Multiple hepatoblastomas associated with trisomy 18 in a 3-year-old girl. *Pediatr Hematol Oncol* **14**: 463-467. Links

Trittenwein G, Nardi A, Pansi H, Golej J, Burda G, Hermon M, Boigner H, Wollenek G. 2003. Early postoperative prediction of cerebral damage after pediatric cardiac surgery. *Ann Thorac Surg* **76**: 576-580. Links

Van de Watering LM, Hermans J, Houbiers JG, van den Broek PJ, Bouter H, Boer F, Harvey MS, Huysmans HA, Brand A. 1998. Beneficial effects of leukocyte depletion of transfused blood on postoperative complications in patients undergoing cardiac surgery: A randomized clinical trial. *Circulation* **97**: 562-568. Links

Van Dyke DC, Allen M. 1990. Clinical management considerations in long-term survivors with trisomy 18. *Pediatrics* **85**: 753-759. Links

Van Praagh S, Truman T, Firpo A, Bano-Rodrigo A, Fried R, McManus B, Engle MA, Van Praagh R. 1989. Cardiac malformations in trisomy-18: A study of 41 postmortem cases. *J Am Coll Cardiol* **13**: 1586-1597. Links

Weiss H, Cooper B, Brook M, Schlueter M, Clyman R. 1995. Factors determining reopening of the ductus arteriosus after successful clinical closure with indomethacin. *J Pediatr* **127**: 466-471. Links

Wyllie JP, Wright MJ, Burn J, Hunter S. 1994. Natural history of trisomy 13. *Arch Dis Child* **71**: 343-345. Links

Yoda H, Kawakami T, Shima Y, Nakajima Y, Hirata M, Yamamoto Y. 1999. Pharamacological treatment of patent ductus arteriosus in preterms using mefenamic acid and indimethacin. *Jpn J Pediatr* **52**: 1481-1486. Links