Early postnatal cardiac manifestations were associated with perinatal brain injury of preterm infants with twin to twin transfusion syndrome

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INTRODUCTION

Altered hemodynamics associated with twin to twin transfusion syndrome (TTTS) could be manifested in the fetal heart. This study was conducted to evaluate the association of cardiac manifestation immediate after birth with brain injury in preterm infants of twin to twin transfusion syndrome.

METHODS

Medical records of preterm infants who were born at < 35 weeks of gestation with TTTS and admitted to the neonatal intensive care unit at Seoul National University Children's Hospital between January 2011 and January 2018 were reviewed. TTTS was prenatally diagnosed and staged according to the **criteria of Quintero**. **Echocardiographic evaluation** conducted immediate after birth and postnatal imaging studies of brain by ultrasound or MRI were analyzed. **Acute kidney injury** was defined that serum creatinine level of > 1.5mg/dL during more than 48hours or the presence of oliguria (urine output < 1mL/kg/h). **Brain injury** were categorized in the neonatal period as hypoxic ischemic encephalopathy (HIE), severe intraventricular hemorrhage (IVH grade 3 and 4), ventricular dilatation, ischemic or hemorrhagic stroke, periventricular leukomalacia (PVL)

RESULTS (I)

53 infants were enrolled in the study. 6 (11.3%) infants were stage I, 2 (3.8%) stage II, 20 (39.6%) stage III, 16 (30.2%) stage IV and 8 (15.1%) stage V. 32 infants (60.3%) were treated by fetoscopic laser coagulation in the study population. Birth weight was lower in the donor group. Small for gestational age (SGA) and acute kidney injury (AKI) were more prevalent in the recipient group (Table 1). Cardiac manifestations were more prevalent in the recipient group (Table 2). There was no difference in the incidence of brain injury between donors and recipients.

Table 1. Demographics of donors and recipients in TTTS

	Donor (n=23)	Recipient (n=30)	p value
GA (week)	30 (27.9-31.1)	30.4 (27.9-31.4)	0.733
Birth weight (g)	950 (770-1250)	1580 (1160-2010)	< 0.001
Weight discrepancy (%)	-	22 (34.4-27.2)	-
SGA	13 (56.5)	4 (13.8)	0.002
Male	10 (43.5)	13 (43.3)	1.000
C/Sec	18 (78.3)	20 (66.7)	0.539
Initial Hb (mg/dl)	15.2 (14.2-18.6)	14.9 (12.9-18.2)	0.733
Hypotension < PND 7 days	6 (27.3)	10 (33.3)	0.765
Maximum Cr (mg/dl)	1.08 (0.89-1.84)	1.01 (0.89-1.4)	0.270
AKI < PND 7 days	7 (30.4)	2 (6.7)	0.031
Mortality	4 (17.4)	4 (13.3)	0.715

Table 2. Cardiac manifestations and brain injury of donors and recipients in TTTS

	Donor (n=23)	Recipient (n=30)	p value
Cardiac manifestation	11 (47.8)	26 (86.7)	0.006
Pulmonary hypertension	8 (34.8)	15 (50.0)	0.402
Ventricular dysfunction	1 (4.4)	13 (44.8)	0.001
Ventricular hypertrophy	5 (21.7)	14 (48.3)	0.081
IV septal deviation	4 (17.4)	7 (24.1)	0.735
RL shunt	3 (13.0)	4 (13.8)	1.000
TR >3m/s	1 (4.4)	9 (32.1)	0.015
MR	0 (0)	7 (24.1)	0.013
LVOT stenosis	0 (0)	1 (3.5)	1.000
RVOT stenosis	0 (0)	4 (13.8)	0.120
Brain injury	4 (17.4)	11 (36.7)	0.140
Hypoxic injury	1 (4.4)	3 (10.0)	0.624
IVH ≥ 3	0 (0)	1 (3.3)	1.000
Infarction	1 (4.4)	7 (23.3)	0.118
PVL	2 (8.7)	9 (30.0)	0.089
Brain Atrophy	0 (0)	1 (3.3)	1.000

RESULTS (II)

Brain injury was developed in 15 infants (28.3%). In the univariate logistic regression analysis, postnatal hypotension, cardiac manifestations such as ventricular dysfunction and significant tricuspid regurgitation (>3m/s) were associated with brain injury. In the multivariate analysis, acute kidney injury (OR 18.7 95% CI 1.9-205.1), ventricular dysfunction (OR 18.1, 95% CI 2.2-148.1) and significant tricuspid regurgitation (OR 9.7, 95% CI 1.2-79.3) were statistically associated with brain injury in the study population.

Table 3. Characteristics in TTTS twins in the brain injury group and the no brain injury group

	No brain injury (n=38)	Brain injury (n=15)	p value
GA (week)	30.1 (27.9-31.9)	30.6 (27.9-31.1)	0.859
Birth weight (g)	1195 (900-1490)	1500 (880-1930)	0.260
Recipient	19 (50)	11 (73.3)	0.140
Weight discrepancy (%)	33.3 (27.2-42.2)	35.6 (30.1-43.3)	0.537
Male	17 (44.7)	6 (40)	1.000
SGA	14 (36.8)	3 (21.4)	0.127
C/Sec	27 (71.1)	11 (73.3)	1.000
Initial Hb (mg/dl)	15.2 (13.1-17.1)	14.7 (13.3-20.4)	0.636
Maximum Cr (mg/dl)	0.95 (0.79-1.29)	1.5 (1.3-1.9)	<0.001
AKI	4 (10.5)	5 (33.3)	0.097
Hypotension < PND 7 days	8 (21.6)	8 (53.3)	0.044
Quintero stage			0.913
Stage ≤ 2	6 (15.8)	2 (13.3)	
Stage > 2	32 (84.2)	13 (86.7)	
TTTS Treatment			0.475
No treatment	5 (13.2)	3 (20)	
Amnioreduction	11 (29)	2 (13.3)	
Fetoscopic laser coagulation	22 (57.9)	10 (66.7)	
GA at TTTS Treatment (week)	23.1 (21.1-25.4)	22.4 (21-24.4)	0.793
Treatment failure	23 (67.7)	8 (66.7)	1.000
Cardiac manifestation	23 (60.5)	14 (93.3)	0.022
Pulmonary hypertension	13 (34.2)	10 (66.7)	0.063
Ventricular dysfunction	5 (13.5)	9 (60)	0.001
Ventricular hypertrophy	13 (35.1)	6 (40)	0.760
TR >3m/s	4 (10.8)	6 (42.9)	0.018
MR	5 (13.5)	2 (13.3)	1.000
LVOT stenosis	0 (0)	1 (6.7)	0.288
RVOT stenosis	2 (5.4)	2 (13.3)	0.569

Table 4. Logistic regression analysis of risk factors for brain injury in TTTS

	OR	95% CI	adjOR ^a	95% CI	adjOR ^b	95% CI
GA (week)	0.98 [0.79 , 1.21]		1.10 [0.82 , 1.45]		1.18 [0.84 , 1.65]	
Quintero stage > 2	1.22 [0.22 , 6.84]		1.86 [0.13 , 26.25]		0.83 [0.07 , 9.58]	
AKI	4.25 [0.96 , 18.89]		15.07 [1.17 , 194.76]		18.74 [1.71 , 205.13]	
Hypotension	4.14 [1.15 , 14.92]		4.90 [0.80 , 29.93]		5.97 [0.74 , 48.28]	
Cardiac manifestation	3.85 [1.58 , 9.39]		31.84 [1.31 , 772.23]			
Ventricular dysfunction	3.85 [1.08 , 13.63]				18.11 [2.22 , 148.08]	
TR >3m/s	9.60 [2.37 , 38.87]				9.65 [1.17 , 79.28]	

a: adjusted for GA, Quintero>2, AKI, Hypotension, Cardiac manifestation

b: adjusted for GA, Quintero>2, AKI, Hypotension, Ventricular dysfunction, TR>3m/s

CONCLUSION

Immediate postnatal cardiac manifestations such as ventricular dysfunction and tricuspid regurgitation could be surrogate marker for perinatal hemodynamic disturbance, which were associated with neonatal brain injury in preterm infants with TTTS.