Blood pressure evaluation in children treated with laser surgery for twin-twin transfusion syndrome at 2-year follow-up

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OBJECTIVE: Twin survivors of twin-twin transfusion syndrome (TTTS) may be at risk for early onset of cardiovascular disease. The aim of this study was to determine prevalence and risk factors for elevated blood pressure (BP) among children treated with selective laser photocoagulation of communicating vessels.

STUDY DESIGN: Data were prospectively collected from surviving children treated for TTTS with laser surgery from 2008 through 2010. Systolic BP (SBP) and diastolic BP (DBP) were obtained from 91 child survivors at age 24 months (±6 weeks) and evaluated based on age, sex, and height percentile. BP percentiles were calculated for each patient and categorized as normal (<95%) or abnormal (>95%). Clinical variables were evaluated using multilevel regression models to evaluate risk factors for elevated BP.

RESULTS: BP was categorized as normal in 38% and abnormal in 62% of twin survivors based on percentile for sex, age, and height; a comparable distribution was found for DBP elevation. There were no differences between donor and recipient twins for absolute SBP and DBP or BP classification. In a multivariate analysis, significant risk factors for higher SBP included prematurity (β −0.54; 95% confidence interval [CI], −0.99 to −0.09; $P = .02$), higher weight percentile (β 0.24; 95% CI, 0.05–0.42; $P = .01$), and presence of cardiac disease (β 0.50; 95% CI, 0.10–0.89; $P = .01$). Prematurity was also a significant risk for abnormal DBP (odds ratio, 0.89; 95% CI, 0.80–1.00; $P = .05$).

CONCLUSION: Child survivors of TTTS had elevated SBP and DBP measurements at 2 years of age, with no differences seen between former donor and recipient twins. Prematurity may be a risk factor for elevated BP measurements in this population. Future studies are warranted to ascertain whether these cardiovascular findings persist over time.

Key words: cardiovascular disease, elevated blood pressure, fetal interventions, fetal physiology, twin-twin transfusion syndrome

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Twin-twin transfusion syndrome (TTTS) is a severe complication that occurs in approximately 10% of monochorionic-diamniotic (MC-DA) twin pregnancies.[1] It carries a high risk of fetal death if left untreated (80-100%) and a high perinatal morbidity and mortality, including increased risks of cardiovascular (CV) changes and structural heart disease.[1-3] In TTTS, twins are exposed to different hemodynamic conditions and environmental factors caused by an unbalanced exchange of blood through vascular communications in the monochorionic placenta with preferential shunting of blood from one twin (donor) to the other twin (recipient). Recipient twins can develop progressive volume and pressure overload, congestive heart failure, and hydrops with striking echocardiographic findings such as cardiomegaly, valve regurgitation, and ventricular hypertrophy and dysfunction.[2,4] Donor twins have less dramatic cardiac findings, but can develop hypovolemia with hyperdynamic left ventricular function and right ventricular diastolic impairment due to increased placental resistance.[5]

The preferred treatment for TTTS is selective laser coagulation of communicating vessels (SLPCV), which effectively separates the twin placental circulations, normalizing the blood volume in both twins.[2,6-8] Fetal laser surgery has resulted in greatly improved perinatal survival as well as improved neurologic outcomes.[9-11] As survival rates for TTTS treated with fetal laser surgery have continued to improve, the focus is

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shifting towards evaluation of long-term risks in this population.[12,13]

Previous reports provide evidence that prenatal disease states with abnormal flow patterns, volume loading, and afterloading conditions can lead to permanent CV changes that persist after birth. One such example is adult survivors of neonatal coarctation repair who develop early onset of systolic hypertension due to presumed abnormalities in vascular reactivity, arterial distensibility, and baroreceptors reflex function.[14-17] In another example, adults with a single umbilical artery were found to have structural and functional differences between their upper and lower extremity arteries, suggesting permanent changes in arterial structure from altered prenatal flow patterns.[18]

In TTTS, the cardiomyopathy seen in recipient twins is due to a combination of increased afterload, hypervolemia, and exposure to increased levels of circulating vasoconstrictive substances.[1,6,19] The immediate impact of SLPCV in the recipient twin has been improved ventricular function, normalization of peripheral Doppler, decreased valve regurgitation, and improved flow across the pulmonary valve.[20-22] However, it is possible that altered fetal hemodynamics in the recipient twin prior to SLPCV may cause lasting CV changes that predispose to early childhood hypertension. The donor twin can have a transient hydrops phenomenon after SLPCV, possibly secondary to acute increases in volume and afterload resulting in transient cardiac dysfunction.[23,24] Former donor twins have been shown to have CV changes that persist even after SLPCV, such as increased cardiothoracic ratio.[25] Thus, donor twins have a different set of hemodynamic stressors that may put them at risk for permanent CV changes.

Recent long-term TTTS follow-up studies have been more encouraging, showing normalization of cardiac function in the majority of child survivors 10 years after successful fetal laser surgery for TTTS despite severe prenatal cardiac findings.[26-29] However, there are also many characteristics of TTTS survivors, including low birthweight, small for gestational age (SGA), and prematurity that are associated with increased risk for CV changes in neonates.[30,31] We suspect these additional risk factors combined with the prenatal hemodynamic stressors of TTTS may increase the risk for CV changes such as hypertension.

The goal of our study was to assess the prevalence and risk factors for elevated blood pressure (BP) among children treated with SLPCV for TTTS who survived to age 2 years old. We hypothesized that surviving twins would be at increased risk for elevated BP based on their in-utero exposure to the hemodynamic changes seen in TTTS. Furthermore, we compared former donor and recipient twins directly to look for differences suggesting one population may be more at risk for CV changes.

Materials and Methods

Study population

As part of a neurodevelopmental outcome study, all consecutive patients treated for TTTS from December 2007 through May 2010 were considered eligible and contacted for this study. TTTS was diagnosed at initial assessment at Los Angeles Fetal Therapy (University of Southern California) if the MC-DA gestation had a maximum vertical pocket of fluid $\geq$8 cm in the recipient's sac and $\leq$2 cm in the donor's sac. Each case was classified prospectively according to the Quintero staging system.[19] All patients were given the options of expectant treatment, pregnancy termination, amnioreduction, laser surgery (SLPCV), or selective reduction (at another center). Patients were not offered SLPCV if preoperative ultrasound scans revealed gross abnormalities of intracranial anatomy. Cases were treated exclusively by SLPCV with or without sequential technique, as described in detail previously.[12,13]

A study nurse, who was blinded to the predictors, contacted all consecutive laser-treated TTTS patients during the study period before the time their child was to reach 2 years old and invited them to participate. There were no exclusion criteria. All subjects were evaluated in the Southern California Clinical Translational Science Institute's Clinical Trials Unit at Children's Hospital Los Angeles. Families were given an incentive per child of $25 for their participation. There was no travel budget. This study was approved by the institutional review boards of the Health Sciences Campus of the University of Southern California and Children's Hospital Los Angeles.

Measures

A single research study nurse measured weight and height for each patient and then used an automated BP machine that employs the oscillometric method for determining noninvasive BP with a reported mean error of $\leq$5 mm Hg and SD of $\leq$8 mm Hg (Dinamap Procare; GE Healthcare, Milwaukee, WI). Measurements were made using a child cuff appropriate to the size of the child (Critikon Soft-Cuf; GE Healthcare). A single measurement for systolic BP (SBP) and diastolic BP (DBP) was recorded for each patient on a random arm and multiple attempts were made if the machine was unable to register. The children were sitting while BP measurements were taken, and had sedentary play prior to BP measurements. The subjects also underwent developmental testing as a separate part of the study.[32] Height, weight, and body mass index (BMI) percentiles and Z-scores for age and sex were calculated for each subject using published normative values.[33] The chronologic age of the child was used to generate normative parameters, as children in the study sample had reached age 2 years at which time catch-up growth is to be expected and correction for prematurity is no longer the standard. The raw measurements were used along with uncorrected age and height percentile to calculate SBP and DBP percentile for each child using published normative values.[33] Subjects were classified as having either abnormally elevated BP ($\geq$95%) or normal BP ($<$95%) based on their calculated BP percentile.

Additionally, we evaluated and recorded prenatal, neonatal, and current childhood risk factors potentially associated with elevated BP classification including: (1) prenatal risk factors: donor/recipient status (donor = 1, recipient = 0), Quintero stage (1-4), gestational age (GA) at surgery (weeks),