OBSTETRICS

Neurodevelopmental outcome at 2 years in twin-twin transfusion syndrome survivors randomized for the Solomon trial

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BACKGROUND: The preferred treatment for twin-twin transfusion syndrome is fetoscopic laser coagulation of inter-twin vascular anastomoses on the monochorionic placenta. Severe postoperative complications can occur when inter-twin vascular anastomoses remain patent including twin-anemia polycythemia sequence or recurrent twin-twin transfusion syndrome. To minimize the occurrence of residual anastomoses, a modified laser surgery technique, the Solomon technique, was developed in which the entire vascular equator is coagulated. In the Solomon randomized controlled trial (NTR1245), the Solomon technique was associated with a significant reduction in twin-anemia polycythemia sequence and recurrence of twin-twin transfusion syndrome when compared with the standard laser surgery technique. Although a significant improvement in perinatal outcome was shown after the Solomon technique, the clinical importance should also be ascertained with long-term follow-up evaluation of the surviving children.

OBJECTIVE: The purpose of this study was to compare the long-term neurodevelopmental outcome in surviving children with twin-twin transfusion syndrome who were included in the Solomon randomized trial and treated with either the Solomon technique or standard laser surgery technique.

STUDY DESIGN: Routine standardized follow-up evaluation in survivors, at least 2 years after the estimated date of delivery, was performed at 2 of the 5 centers that participated in the Solomon trial: Buzzi Hospital Milan (Italy) and Leiden University Medical Center (The Netherlands). The primary outcome of this follow-up study was survival without long-term neurodevelopmental impairment at age 2 years. *Neurodevelopmental impairment* was defined as cerebral palsy, cognitive and/or motor development score of <85, bilateral blindness, or deafness. Cognitive and motor development was evaluated with the use of Bayley-III. All analyses per fetus, neonate, or child were conducted with the generalized estimated equation module to account for the effect that observations between co-twins are not independent.

RESULTS: The primary outcome (survival without neurodevelopmental impairment) was detected in 95 of 141 cases (67%) in the Solomon group and in 99 of 146 cases (68%) in the standard group ($P = .92$). Neurodevelopmental impairment in long-term survivors who were included for follow-up evaluation was detected in 12 of 107 cases (11%) in the Solomon and in 10 of 109 cases (9%) in the standard group ($P = .61$). Neurodevelopmental impairment was due to cerebral palsy in 1 case (1%; spastic unilateral) in the Solomon group and in 2 cases (2%; spastic unilateral and spastic bilateral) in the standard group ($P = .58$). Cognitive development <85 cases was detected in 2 of 105 children (2%) in the Solomon group and in 6 of 106 children (6%) in the standard group ($P = .23$). Motor development <85 occurred in 8 of 103 children (8%) in the Solomon group and 3 of 104 children (3%) in the standard group ($P = .23$).

CONCLUSION: We found no difference in survival without neurodevelopmental impairment between the Solomon and standard laser techniques. In view of the reduction of short-term complications and the absence of increased adverse long-term effects, these data support the use of the Solomon technique in the treatment of twin-twin transfusion syndrome.

Key words: laser surgery, neurodevelopmental outcome, Solomon, twin-twin transfusion syndrome

Twin-twin transfusion syndrome (TTTS) is a major complication of monochorionic twin pregnancies and is the result of unbalanced inter-twin blood flow through placental vascular anastomoses. The preferred treatment for TTTS is fetoscopic laser coagulation of the anastomoses, with an overall survival rate of up to 74%.[1] Although the goal of fetoscopic laser surgery is to coagulate all anastomoses, in up to 33% of pregnancies some vascular connections remain patent.[2,3] These residual anastomoses can cause severe complications such as twin-anemia polycythemia sequence (TAPS) or recurrent TTTS.[1,4] To minimize the occurrence of residual anastomoses and their associated complications, a modified fetoscopic laser surgery technique was developed called the "Solomon technique," in which a coagulation line is drawn along the entire vascular equator.[1] In the Solomon randomized controlled trial, this technique was associated with a significant reduction in TAPS and recurrence of TTTS when compared with the standard laser surgery technique.[1] Although a significant improvement in perinatal outcome was shown after the Solomon technique, the clinical importance should also be ascertained with long-term follow-up evaluation of the surviving children. The aim of this study was to compare the long-term neurodevelopmental outcome in the surviving children who were included in the Solomon randomized trial.

Materials and Methods

The Solomon trial was an open-label, international, multicenter, randomized

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controlled trial (NTR1245). The background of the trial, methods, baseline characteristics, and perinatal outcome have been reported previously.[1,5] The protocol of the trial can be found on http://www.studies-obsgyn.nl/solomon/page.asp?page_id=791. In brief, the trial included 274 women with monochorionic twin pregnancies up to 26 weeks gestation that were complicated by TTTS. Women were assigned randomly to the Solomon technique or standard technique. All fetoscopic laser procedures were undertaken by experienced operators, each of whom had done at least 60 previous laser procedures and were competent to undertake the Solomon technique. Routine standardized follow-up evaluation in survivors at least 2 years of age was performed at 2 of the 5 centers that participated in the Solomon trial: Buzzi Hospital Milan (Italy) and Leiden University Medical Center (The Netherlands). Of the 274 patients who were included in the Solomon trial, 156 patients (57%) were assigned randomly in 1 of these 2 centers. The follow-up study was approved by the Institutional Review Board of both centers. All parents gave written informed consent for their children.

The following antenatal and neonatal data were recorded: gestational age at laser surgery, Quintero stage, fetal death, antenatal and/or postnatal TAPS, recurrence of TTTS, gestational age at birth, birthweight, severe neonatal morbidity, cerebral injury, and neonatal death (death of a live-born baby within the first 4 weeks of life). The presence of TAPS was identified according to previously published antenatal and postnatal criteria.[6] In brief, antenatal TAPS was diagnosed when Doppler ultrasound examination revealed an increase in peak systolic velocity in the middle cerebral artery of >1.5 multiples of the median in 1 fetus that coincided with a decreased velocity of <1.0 multiples of the median in the co-twin, in the absence of twin oligo-polyhydramnios sequence. Postnatal TAPS diagnosis is based on intertwin hemoglobin difference ≥8.0 g/dL and at least 1 of the following criteria: reticulocyte count ratio >1.7 or small anastomoses (<1 mm) at the placental surface.[6]

Severe neonatal morbidity was defined as respiratory distress syndrome, chronic lung disease (defined as oxygen dependency at 36 weeks gestational age), patent ductus arteriosus that needs medical therapy or surgical closure, necrotizing enterocolitis grade ≥2, retinopathy of prematurity stage ≥3, ischemic limb injury, amniotic band syndrome, or severe cerebral injury. Severe cerebral injury includes intraventricular hemorrhage grade ≥3,[7] cystic periventricular leukomalacia grade ≥2,[8] ventricular dilation ≥97th percentile,[9] porencephalic or parenchymal cysts, or other severe cerebral lesions that are associated with adverse neurologic outcome.[10] Neuroimaging was performed with either fetal or neonatal ultrasound scanning. In case of suspected cerebral injury, magnetic resonance imaging was performed. Maternal educational level was recorded and divided into 3 levels. A score of 1 was given when the mother's education was low (primary school); a score of 2 was given for an intermediate educational level (secondary school and intermediate vocational school), and a score of 3 was given for higher levels of education (higher vocational school and university).

Follow-up assessments were performed by trained psychologists and pediatricians who were unaware of the treatment allocations. A follow-up visit was performed at age 2 years corrected for prematurity (that is, 2 years after the estimated date of delivery) and included a physical and neurologic examination and an assessment of cognitive and motor development with the use of the Bayley scales of Infant and Toddler Development third edition (Bayley-III).[11] The Bayley-III provides cognitive and motor composite scores with a normed mean of 100 and a standard deviation (SD) of 15. *Cerebral palsy* was defined according to the European CP Network and classified as spastic bilateral, spastic unilateral, dyskinetic (dystonic or choreoathetotic), ataxic, or mixed.[12] The functional severity was classified according to the Gross Motor Function Classification System (GMFCS) for cerebral palsy.[13]

The primary outcome of this follow-up study was survival without neurodevelopmental impairment (NDI). *NDI* was defined as the presence of at least 1 of the following items: cerebral palsy (GMFCS II-V), a cognitive composite score of <85 (>−1 SD), a motor composite score of <85 (>−1 SD), bilateral blindness, or bilateral deafness requiring hearing aids. *Severe NDI* was defined as cerebral palsy (GMFCS II-V), a cognitive composite score of <70 (>−2 SD), a motor composite score of <70 (>−2 SD), bilateral blindness, or bilateral deafness that required hearing aids.

Data are reported as means with SD or as medians with range, as appropriate. Baseline characteristics were compared with the use of the *t*-test and Mann-Whitney test for continuous variables. Chi-square test and Fisher exact test were used for categoric variables, as appropriate. All analyses per fetus, neonate, or child were conducted with the generalized estimated equation module to account for the effect that observations between co-twins are not independent. A 2-sided probability value of <.05 was considered significant. Statistical data were analyzed using SPSS software (version 20.0; (IBM, Armonk, NY).

Results

A total of 76 pregnancies (152 fetuses) were treated with the Solomon, and 77 pregnancies (154 fetuses) were treated with the standard laser surgery technique for TTTS (Figure). Overall survival did not differ significantly between the Solomon (118/152; 78%) and the standard group (117/154; 76%; $P = .77$). Cord occlusion of 1 of the twins was performed in 4 cases because of severe cerebral injury (Solomon group, 1; standard group, 1) or life-threatening condition of the co-twin (Solomon group, 1; standard group, 1). After treatment with Solomon laser surgery, 1 pregnancy was terminated after the diagnosis of trisomy 21. In both groups, neonatal death within 28 days of birth