Twin-to-twin transfusion syndrome : from placental anastomoses to long term outcome

Lopriore, E.

Chapter 12

Long-term neurodevelopmental outcome in twin-to-twin transfusion syndrome treated with fetoscopic laser surgery

Enrico Lopriore MD
Johanna M Middeldorp MD
Marieke Sueters MD
Dick Oepkes MD PhD
Frank PHA Vandenbussche MD PhD
Frans J Walther MD PhD

Submitted

Abstract

Objective: To determine the long-term neurodevelopmental outcome in twin-to-twin transfusion syndrome (TTTS) treated with fetoscopic laser surgery.

Methods: All TTTS-cases treated at our center with laser between August 2000 and December 2003 were included in the study. Neurological, mental and psychomotor development at 2 years of age corrected for prematurity was assessed in all TTTS survivors. Neurodevelopmental impairment was defined as any of the following: cerebral palsy, deafness, blindness, mental or psychomotor development index of the Bayley Scales of Infant Development II < 2 SD.

Results: A total of 82 TTTS pregnancies were treated with fetoscopic laser surgery during the study period. Perinatal survival was 70% (115/164). The incidence of neurodevelopmental impairment was 17% (19/115) and was due to cerebral palsy (n = 8), mental developmental delay (n = 9), psychomotor developmental delay (n = 12) and deafness (n = 1).

Conclusions: The incidence of neurodevelopmental impairment in TTTS survivors treated with laser is high and warrants long-term follow-up.

Introduction

Monochorionic twinning predisposes to cerebral damage due to complications caused by twin-to-twin transfusion (TTTS). TTTS occurs in approximately 15% of monochorionic pregnancies and results from shunting of blood from one twin, the donor, to the other twin, the recipient, through placental vascular anastomoses. Untreated, TTTS is associated with high perinatal mortality and morbidity[130]. The two current treatment options in TTTS are serial amnioreduction and fetoscopic laser occlusion of vascular anastomoses[27;93;129;130]. In a recent randomized trial comparing serial amnioreduction and laser treatment, perinatal survival and neurological outcome at six months of age was significantly better in the group treated with laser[10]. Although fetoscopic laser occlusion of vascular anastomoses is increasingly being advocated as the preferred treatment for TTTS, only a few studies have been published on the long-term neurodevelopmental outcome following such treatment. The incidence of major neurological abnormalities in these reports varied from 6% to 11%[151;152;254].

The main objective of our study was to evaluate long-term neurodevelopmental outcome in a large group of TTTS survivors after treatment with fetoscopic laser surgery.

Patients and methods

All survivors of consecutive TTTS-cases treated with fetoscopic laser surgery between August 1, 2000 and December 31, 2003 at the Leiden University Medical Center were included in the study. The Leiden University Medical Center serves as the national referral center for intrauterine laser treatment in TTTS pregnancies in the Netherlands. TTTS was diagnosed using standard prenatal ultrasound criteria[105], and staged according to the criteria of Quintero[9]. The following perinatal data were recorded: gestational age at the time of laser treatment, stage of TTTS, gestational age at delivery, mode of delivery and birth weight. Inter-twin birth weight discordance was assessed and calculated as follows: ((birth weight larger twin – birth weight smaller twin)/ birth weight larger twin) x 100%. Birth

weight discordance was defined as more than 20% difference in birth weight.
The follow-up visit was assessed at 2 years of age (corrected for prematurity) and included a physical and neurological examination and an assessment of cognitive and neuromotor development using the Dutch version of the Bayley Scales of Infant Development, 2nd edition (BSID-II) (both by certified examiners). Bayley scale scores provide mental development indexes (MDI) and psychomotor development indexes (PDI). The mean score for both MDI and PDI is 100. A score below 70 is more than 2 SD below the mean score and indicates a severe delay. Infants with very low MDI or PDI scores (< 50) were assigned a score of 49 in the database. Cerebral palsy (CP) was defined according to the European CP Network and classified as diplegia, hemiplegia, quadriplegia, dyskinetic or mixed[255].
A composite outcome, termed neurodevelopmental impairment (NDI), was defined as any of the following: CP, MDI score of less than 70, PDI score of less than 70, bilateral blindness, or bilateral deafness requiring amplification. Overall adverse outcome was defined as intrauterine fetal death, neonatal death, infant death or NDI. Outcome was compared between donor and recipient twins.
The institutional review board of the Leiden University Medical Center approved the study and all parents gave written informed consent for their children.

Statistics

Results of categorical variables were compared using Fisher's exact test or Chi-square test, as appropriate. Unpaired Student's *t* test was used to compare normally distributed values between two groups. For comparisons between donors and recipients, the paired Student t test was used for normally distributed continuous variables and the Mc Nemar test for analysis of paired nominal variables. Multiple logistic regression analysis with "random twin effect" was used to measure the independent effects of potential prognostic factors on outcome. A model with "random twin effect" was applied to adjust for possible correlated effects within twins. The results of the logistic models were expressed as an odds ratio (OR) and

95% confidence intervals (CI). Chi-square test for trend was used in order to evaluate the relationship between stage of TTTS and outcome. A p-value < 0.05 was considered to indicate statistical significance. Analysis was performed using SPSS version 11 (SPSS Inc., Chicago, IL, USA). Multiple logistic regression analysis was performed with EGRET version 2.0.1 for Windows (Cytel Software Corporation, Cambridge, Massachusetts, USA).

Results

During the study period, 82 TTTS pregnancies were treated with fetoscopic laser surgery at our center. Quintero stage was I in 9 cases, II in 35 cases, III in 32 cases and IV in 6 cases. Laser surgery treatment for Quintero stage I was only performed when symptomatic polyhydramnios warranted intervention. Mean gestational age at laser surgery was 20.0 weeks. Intrauterine fetal demise occurred in 41 fetuses (single intrauterine fetal demise, n = 15; double intrauterine fetal demise, n = 26). Mean gestational age at birth of the surviving infants was 33.9 ± 3.1 weeks (range: 27 to 40 weeks). Neonatal death occurred in 8 neonates. Overall perinatal survival was 70% (115/164). We were able to follow-up all 115 surviving twins. Four families refused to travel to our center for follow-up visit due to the long travel distance, but agreed to allow the complete follow-up examination (including BSID-II test) at their own home. Baseline characteristics of the TTTS survivors are presented in Table 1.

TABLE 1 Baseline characteristics in the 115 TTTS long-term survivors.

	Long-term survivors (n = 115 infants)
Gestational age at laser surgery - wk[a]	20.2 ± 3.0
Median Quintero stage (range)	2 (1-4)
Gestational age at birth - wk[a]	33.9 ± 3.1
Female - no. (%)	55 (48%)
Vaginal delivery - no. (%)	80 (70%)
Birth weight - g[a]	2015 ± 678

[a]*Value given as mean ± SD*

The incidence of NDI was 17% (19/115) and was due to cerebral palsy (n = 8), severe mental developmental delay (n = 9), severe psychomotor developmental delay (n = 12) and deafness (n = 1). Cerebral palsy was classified as quadriplegia (n=4), diplegia (n= 2) and hemiplegia (n= 2). The incidence of adverse outcome (death or NDI) was 41% (68/164). Details on long-term outcome are presented in Table 2.

TABLE 2 Long-term outcome in 115 TTTS survivors after fetoscopic laser surgery.

	Long-term survivors (n = 115 infants)
Cerebral palsy[a] - no. (%)	8 (7%)
Mental development index < 2 SD - no. (%)	9 (8%)
Psychomotor development index < 2 SD - no. (%)	12 (10%)
Bilateral deafness - no. (%)	1 (1%)
Bilateral blindness - no. (%)	0 (0%)
Neurodevelopmental impairment[b] - no. (%)	19 (17%)

[a]*Cerebral palsy included spastic quadriplegia (n = 4), spastic diplegia (n = 2) and spastic hemiplegia (n = 2)*
[b]*Neurodevelopmental impairment is defined as any of the following: cerebral palsy, mental development index < 2 SD, psychomotor development index < 2 SD, bilateral deafness or blindness.*

Intrauterine fetal demise in donors and recipients occurred in 21% (17/82) and 29% (24/82), respectively (p = 0.12). Neonatal death occurred in 5% (4/82) of donors and 5% (4/82) of recipients (p = 1.0). Characteristics and outcome in surviving donor and recipient twins at 2 years of age are presented in Table 3.
We found a direct relationship between stage of TTTS and death (Chi-square test for trend = 5.8, df = 1, p = 0.016) as well as stage of TTTS and adverse outcome (Chi-square test for trend = 9.2, df = 1, p = 0.002) (Table 4).
Multiple logistic regression was carried out to measure the independent associations between NDI and various clinical parameters (gestational age at laser, gestational age at birth, birth weight, Quintero stage and donor versus recipient status). We found a trend towards an independent association between higher Quintero stages and NDI (OR 6.6 for each stage, 95% CI 0.7 – 66.0, p = 0.079) and lower gestational age at birth and NDI (OR 1.6 for each week, 95% CI 0.8 – 3.0, p = 0.080).

TABLE 3 Characteristics and outcome in donor and recipient twins.

	Donor (n = 61)	Recipients (n = 54)	p-value
Birth weight - g[a]	1773 ± 608	2076 ± 567	< 0.001
Weight at 2 years of age - kg[a]	11.7 ± 1.3	12.3 ± 1.3	< 0.001
Length at 2 years of age - cm[a]	86.8 ± 4.1	87.6 ± 3.8	0.005
Head circumference at 2 years of age - cm[a]	48.5 ± 1.4	48.9 ± 1.4	0.006
Cerebral palsy - no. (%)	3 (5%)	5 (9%)	0.25
Mental development index[a]	96 ± 16	96 ± 18	0.90
Psychomotor development index[a]	91 ± 13	89 ± 18	0.52
Neurodevelopmental impairment[b] - no. (%)	10 (16%)	9 (17%)	1.0

[a]*Value given as mean ± SD*

[b]*Neurodevelopmental impairment is defined as any of the following: cerebral palsy, mental development index < 2 SD, psychomotor development index < 2 SD, bilateral deafness or blindness.*

TABLE 4 Mortality rate and adverse outcome (neurodevelopmental impairment or death) by stage of TTTS.

TTTS stage	Death[a]	Adverse outcome[b,c]
I	6% (1/18)	6% (1/18)
II	29% (20/70)	40% (28/70)
III	36% (23/64)	52% (33/64)
IV	42% (5/12)	50% (6/12)

[a]*Chi-square test for trend = 5.8, df = 1, p = 0.016*

[b]*Chi-square test for trend = 9.2, df = 1, p = 0.002*

[c]*Adverse outcome = Intrauterine fetal demise, neonatal death or neurodevelopmental impairment.*

Comment

The main objective of our study was to evaluate the long-term neurodevelopmental outcome in TTTS survivors treated with fetoscopic laser surgery. We were able to follow-up all (100%) TTTS survivors and report a high incidence (17%) of NDI. The long-term neurolodevelopmental outcome found in this study is in agreement with the short-term neurological outcome reported previously by our research group, in which we found a similar incidence (14%) of severe cerebral lesions in TTTS survivors after laser treatment[206].

Four studies from three different research groups have reported on long-term outcome in TTTS after laser surgery. The incidence of NDI found in this study is somewhat higher than in these other reports. However, special care must be taken when comparing results from various studies, as discrepant results may partly be due to different methodology, selection criteria and definitions of NDI. De Lia *et al* report a 6% (6/93) incidence of severe handicaps in TTTS survivors after laser surgery[131]. Mean age at follow-up was 14 months (range 1 to 34 months), which may be too soon for accurate assessment of CP or major developmental delay. Most importantly, the methods used to determine neurodevelopmental outcome were not specified, suggesting that accurate assessment of mental and psychomotor development was not performed. Sutcliffe *et al* found a 9% (6/66) incidence of CP in a cohort of TTTS survivors treated with laser[152]. Follow-up was however incomplete (81%) and in 47% (31/66) of patients neurological outcome was assessed using information from the general practitioner. In the group assessed by a pediatrician, 14% (5/36) had CP. Children assessed by pediatricians were also tested with a standardized developmental test (Griffiths' Developmental Test Scales). However, details on the number of infants with severe developmental delay (defined as a score < 2 SD) were not reported or scored as primary outcome, as opposed to the definition used in this study. The two largest follow-up cohorts have been reported by a research group from Germany. Using standardized developmental test and neurological examination, Banek *et al* and Graef *et al* report an incidence of major neurological deficiencies of 11% (10/89) and 6% (10/167), respectively[151;254]. In both studies, the definition of major neurological deficiencies did not include severe developmental delay. Therefore, as opposed to this study, infants with severe developmental delay but without CP were not included in the group with major abnormalities. Also, developmental outcome in the majority of children (112/167) in the study from Graef *et al* was only assessed by the Snijders-Oomen Non-Verbal-Intelligence Test and therefore motor abilities were not tested[254]. The incidence of CP in the studies from Banek *et al* and Graef *et al*, respectively 11% and 6%, was nevertheless similar to the 7% incidence of CP found in this study[151;254].

After treatment of TTTS with amniodrainage, most studies on long-term outcome report a high incidence of NDI, ranging from 22 to 26%[12;147;148;226].

Only one study in TTTS treated with amniodrainage reported a lower incidence of CP or multicystic encephalomalacia of 7% (3/42)[150], without assessment of neurodevelopmental delay. Overall, the reported incidence of NDI appears to be higher in TTTS survivors treated with serial amniodrainage than with laser surgery. However, different methodology may also explain the discrepancy in results between various follow-up studies. To assess the true difference in NDI in TTTS survivors treated with either laser surgery or serial amnioreduction, results of the long-term follow-up in the first randomized control trial comparing both treatments must be awaited[10].

Absence of a control group is an important limitation of this study. A case-control study comparing the long-term outcome in monochorionic twins with TTTS treated with laser and monochorionic twins without TTTS is currently being performed at our institution[153].

We found no difference in NDI between donor and recipient twins, suggesting that both are equally at risk for adverse neurodevelopmental outcome. These results are in agreement with previous studies[12;151;254]. Donor twins are significantly smaller at birth than recipient twins, and remain smaller and shorter at 2 years of age. These findings are in agreement with previous reports[12]. According to the 'fetal origins of adult disease' or 'Barker hypothesis', lower birth weight is associated with an increased risk for coronary heart disease, diabetes, hypertension and stroke in adulthood[256]. Whether reduced birth weight in donor twins in TTTS may also lead to increased incidence of adult diseases is not known yet.

We also found increasing Quintero stage to be associated with combined adverse outcome (death or NDI). Our results confirm previous findings[9;12;126;257]. Although the prognostic value of Quintero stages is subject of debate[93;258], our results suggest an important prognostic value of Quintero staging. Multivariate analysis also showed that higher Quintero stages are almost independently associated with NDI. Similarly, we found a trend towards an independent association between lower gestational age at birth and NDI. Prematurity is a well recognized risk factor for adverse neurodevelopmental outcome in twins as well as in singletons[239;258].

The objective of fetal therapy should be to reach a high percentage of intact-survival. Even though fetoscopic laser surgery appears to be the best available treatment option for TTTS, the idealistic goal of high intact-

survival rate has not yet been reached. Timing of cerebral injury leading to NDI in TTTS treated with fetoscopic laser surgery is not clear. Cerebral injury may occur before, during or after laser surgery. Therefore, whether cerebral injury and subsequent NDI could be prevented by advances in laser surgery techniques such as more selective or more complete coagulation of anastomoses, or by adaptation of inclusion criteria for laser surgery is not known. Considering the high incidence of adverse neurodevelopmental outcome in TTTS, we recommend that all surviving twins be thoroughly followed up.