Part THREE

Brain injury

Chapter 2

Cerebral injury in twin-twin transfusion syndrome treated with fetoscopic laser surgery

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Abstract

Objective
To estimate the incidence and risk factors for cerebral lesions in monochorionic twins with twin-twin transfusion syndrome treated with fetoscopic laser surgery compared with dichorionic twins.

Methods
We performed a case-control study on cerebral injury detected by postnatal cranial ultrasonography in monochorionic twin neonates with twin-twin transfusion syndrome treated with laser compared with a control group of dichorionic twin neonates matched for gestational age at birth. Severe cerebral lesions were defined as the presence of at least one of the following: intraventricular hemorrhage grade III, periventricular hemorrhagic infarction, periventricular leukomalacia grade II or greater, porencephalic cysts, arterial stroke, ventricular dilatation, or a combination of these.

Results
From 2004 until 2011, 267 twin neonates with twin-twin transfusion syndrome could be included and matched with 267 dichorionic twin neonates. Incidence of severe cerebral lesions in the twin-twin transfusion syndrome group and control group was 8.6% (23/267) and 6.7% (18/267), respectively ($p = 0.44$). Multivariable analysis revealed that only gestational age at birth was independently associated with increased risk for severe cerebral lesions (odds ratio [OR] 1.35 for each week, 95% confidence interval [CI] 1.14 to 1.59, $p < 0.01$). In 52.2% (12/23), the cerebral lesions in the twin-twin transfusion syndrome group were of antenatal origin compared with 16.7% (3/18) in the control group (OR 8.00, 95% CI 1.42 to 45.06, $p = 0.02$).

Conclusion
Incidence of severe cerebral lesions in twin–twin transfusion syndrome treated with laser is similar to a matched control group and is independently associated with prematurity. In contrast to dichorionic twins, cerebral injury in twins with twin–twin transfusion syndrome most often occurs antenatally.

Introduction

Twin-twin transfusion syndrome is a major complication of monochorionic twin pregnancies and is the result of intertwin blood transfusion through placental vascular anastomoses. Fetoscopic laser coagulation of the anastomoses is today considered to be the treatment of choice in twin–twin transfusion syndrome.(1)

Despite improved short-term and long-term outcome after laser surgery, twin-twin transfusion syndrome is still associated with an increased incidence of cerebral injury and neurodevelopmental impairment. Incidence of severe cerebral lesions on cranial ultrasonography ranges from 3% to 16% whereas the incidence of neurodevelopmental impairment ranges from 8% to 18%.(1-5)

The cause of cerebral injury in twin-twin transfusion syndrome is not fully understood and may result from antenatal injury resulting from hemodynamic imbalance, postnatal injury resulting from prematurity, or both.(2, 6-8) To date, most studies on cerebral injury in twin-twin transfusion syndrome are limited by small numbers of included patients and lack of a control group. Our objective was to estimate the incidence and risk factors of severe cerebral injury on postnatal cranial ultrasonography in a large prospective series of twins with twin-twin transfusion syndrome treated with laser surgery compared with a control group of dichorionic twins matched for gestational age at birth.

Patients and methods

All consecutive monochorionic twins with twin-twin transfusion syndrome treated with fetoscopic laser surgery at the Leiden University Medical Center and delivered at our center between January 2004 and December 2011 were included in this study. Neonates in the twin-twin transfusion syndrome group were matched according to gestational age at birth (± 1 week of gestation) with a control group of dichorionic twins born at our center during the same 8-year study period. The control dichorionic twins were identified from the hospital's database and were the next twin pregnancy delivered at our hospital with a matched gestational age.

The Leiden University Medical Center is a tertiary medical center and serves as the national referral center for intrauterine laser treatment in twin-twin transfusion syndrome pregnancies in The Netherlands.

Pregnancies complicated by intrauterine fetal demise of both twins, major congenital anomalies, triplets, or severe perinatal asphyxia were excluded from the study. Twin-twin transfusion syndrome was diagnosed using standard prenatal ultrasonographic criteria and staged according to the criteria of Quintero.(9)

Neonatal cranial ultrasonographic scans were performed when indicated according to our cranial ultrasonographic protocol. The clinical protocol at our neonatal intensive care unit requires a minimum of three scans during the first week of life (days 1, 3, and 7) for premature neonates with gestational ages less than 32 weeks or birth weights less than 1500 g and scans are repeated biweekly until discharge. Premature neonates with gestational ages between 32 weeks and (near-)term neonates admitted to our unit are routinely scanned at least once during the first week of life. If cerebral abnormalities are detected, scanning frequency is intensified around the date of detection and repeated at the time of the estimated date of confinement. Cranial ultrasonographic scans in our unit are performed with an Aloka 5000 scanner with a multifrequency (5–10 MHz) transducer. The cerebral anatomy was visualized in the standard coronal and sagittal planes. Experienced neonatologists performed all cranial ultrasonographic scans.

Intraventricular hemorrhages were classified according to Volpe, and periventricular leukomalacia was graded according to de Vries et al.(10, 11) Severe cerebral lesions on cranial ultrasound scans were defined as the presence of at least one of the following findings: intraventricular hemorrhage grade III, periventricular hemorrhagic infarction, periventricular leukomalacia grade II or greater, porencephalic cysts, arterial stroke, ventricular dilatation, or a combination of these. Diagnosis of arterial stroke was reached when a wedge-shaped area of echogenicity was detected on coronal and parasagittal views, in the region supplied by the middle or anterior or posterior cerebral artery with a linear demarcation line, followed by cystic evolution of this area of increased echogenicity after 2–4 weeks. Ventricular dilatation was present when the width of one or both lateral ventricles exceeded the 97th percentile.(12) Other severe cerebral abnormalities such as parenchymal hemorrhage, infarction, or both, which are associated with adverse neurological outcome, were also recorded and classified as severe cerebral lesions. Severe cerebral lesions were considered to be of antenatal onset if present on the first cranial ultrasonographic scan on day 1. Periventricular white matter cysts detected within 2 weeks after birth were also considered to be of antenatal onset. Magnetic resonance imaging of the brain was performed in cases with suspected severe cerebral lesions.

The following data were recorded in the twin-twin transfusion syndrome group and control group: stage of twin-twin transfusion syndrome, treatment failure (defined as recurrent twin-twin transfusion syndrome or twin anemia-polycythemia sequence after laser surgery), gestational age at delivery, mode of delivery, birth weight, gender, and small for gestational age.(13)

The primary outcome measure was presence of severe cerebral lesions detected on cranial ultrasonographic scans. Outcome of the twin-twin transfusion syndrome group was compared with the matched control group of dichorionic twin neonates.

The following potential predictors for cerebral injury in the twin-twin transfusion syndrome group were studied in a univariable and multivariable logistic regression model: gestational age at birth, Quintero stage, donor (compared with recipient), treatment failure (defined as recurrent twin-twin transfusion syndrome or twin anemia-polycythemia sequence), and year of the laser procedure (assessed as a continuous variable to study the effect of the learning curve). Selection of the potential risk factors was based on previous studies.(14)

Based on previous studies (including our own data), we estimated that group sizes of at least 250 neonates were required to demonstrate a 10% difference (15% in the twin-twin transfusion syndrome group compared with 5% in the control group) in severe cerebral lesions with a significance of .05, a power of 90%, and an intracluster correlation coefficient ρ of 0.33 by two-tailed analysis. To take into account the dependence between siblings, we used the method of generalized estimating equations for all analyses.(15) The results of the logistic models were expressed as an odds ratio (OR) and 95% confidence intervals (CIs). A value of $p<.05$ was considered to indicate statistical significance. Analyses were performed using SPSS 17.0.

Results

During the 8-year study period (2004 - 2011), 313 twin-twin transfusion syndrome twin pregnancies were treated with laser surgery at our center. Overall perinatal survival was 77% (480/626). Of these 313 twin-twin transfusion syndrome pregnancies, 46% (144/313) were delivered at our center with at least one liveborn neonate (n=267 liveborn neonates). All 267 liveborn neonates were admitted to our neonatal intensive care unit and included in the study (twin-twin transfusion syndrome group). Patients' characteristics in the twin-twin transfusion syndrome group and the matched control group of dichorionic twins are presented in **table 1**. The neurologic outcome in twin-twin transfusion syndrome survivors delivered at our center between June 2002 and September 2005 has been published before.(2)

Table 1. Baseline characteristics in neonates included in the twin-twin transfusion group and the control group

	TTTS Group (n = 267)	Control Group (n = 267)	*p value*
Gestational age at birth (wk)	32 (29-34)	32 (29-34)	0.71
Female	144 (53.9)	130 (48.7)	0.26
Vaginal delivery	135 (50.6)	191 (71.5)	< 0.01
Birth weight (g)	1634 ± 532 (683-3421)	1711 ± 540 (590-3785)	0.180
Small for gestational age	18 (6.7)	14 (5.2)	0.53
Quintero stage	3 (2-3)		
Recurrent TTTS after laser	2 (0.7)		
TAPS after laser	46 (17.2)		
Treatment failure*	48 (18.0)		

TAPS, twin anemia–polycythemia sequence.
Data are median (interquartile range), n (%), or mean ± standard deviation (range) unless otherwise specified.
* Treatment failure was defined as recurrent TTTS or TAPS after laser.

The incidence of severe cerebral lesions in the twin-twin transfusion syndrome group and control group was 8.6% (23/267) and 6.7% (18/267), respectively (p = 0.44). The majority of severe cerebral lesions in the twin-twin transfusion syndrome group were of antenatal origin. The incidence of antenatally acquired severe cerebral lesions in the twin-twin transfusion syndrome group and control group was 52.2% (12/23) and 16.7% (3/18), respectively (OR 8.00, 95% CI 1.42 to 45.06, p = 0.02). Details of the type of mild and severe cerebral lesions are presented in **table 2**.

In the twin-twin transfusion syndrome group, four neonates had a large parenchymal defect after an arterial stroke of the middle cerebral artery. All were ex-recipients and, in all cases, the stroke was localized in the left hemisphere (**figure 1**). None of the neonates in the control group had an arterial stroke.

Multiple logistic regression analysis was carried out to measure the independent associations between severe cerebral lesions and various possible risk factors in the twin-twin transfusion syndrome group (Quintero stage, treatment failure [either recurrent twin-twin transfusion syndrome or twin anemia–polycythemia sequence], donor compared with recipient status, gestational age at birth, and treatment year). After multivariable analysis, lower gestational age at birth was the only factor independently associated with increased risk for severe cerebral lesions (OR 1.35 for each week less, 95% CI 1.14 to 1.59; $p < 0.01$) (**table 3**). The incidence of cerebral lesions decreased over the years, but the reduction did not reach statistical significance (OR 1.15, 95% CI .94 to 1.41, p = 0.16).

Table 2. Cerebral lesions detected by cranial ultrasound in the twin-twin transfusion group and the control group

	TTTS Group (n = 267)	**Control Group (n = 267)**	***p value***
Intraventricular hemorrhage grade III	10 (3.7)	10 (3.7)	0.95
Periventricular hemorrhagic infarction	9 (3.4)	7 (2.6)	0.63
PVL grade II	2 (0.7)	4 (1.5)	0.49
PVL grade III	5 (1.9)	3 (1.1)	0.81
Ventricular dilatation	8 (3.0)	7 (2.6)	0.77
Arterial stroke	4 (1.5)	0 (0.0)	0.12†
Other*	1 (0.4)	0 (0.0)	0.50†
Severe cerebral lesions	23 (8.6)	18 (6.7)	0.44
Antenatally acquired severe cerebral lesions	12/23 (52.2)	3/18 (16.7)	0.02

PVL, periventricular leukomalacia.
Data are n (%) or n/N (%) unless otherwise specified.
* Large venous hemorrhagic infarction of the right temporal lobe with parenchymal loss.
† Calculated with Fisher's exact test.

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Table 3. Analysis of risk factors for severe cerebral injury in the twin-twin transfusion syndrome group

Characteristic	Cerebral Injury (n=23)	No Cerebral Injury (n=244)	Univariable OR (95% CI)	*p value*	Multivariable OR (95% CI)	*p value*
Gestational age at birth (wk)*	29.4 ± 3.1	31.9 ± 2.9	1.35 (1.15-1.59) for each week less	< 0.01	1.35 (1.14–1.59) for each week less	< 0.01
Stage 1	1 (4)	22 (9)	1			
Stage 2	8 (35)	82 (34)	2.17 (0.23–20.39)†	0.50	1.83 (0.21–16.07)	0.57
Stage 3	13 (57)	130 (53)	2.19 (0.24–19.61)†	0.48	1.74 (0.21–14.25)	0.60
Stage 4	1 (4)	10 (4)	2.45 (0.13–46.94)†	0.55	1.99 (0.10–37.87)	0.65
Treatment failure	6 (26)	42 (17)	1.69 (0.60–4.74)	0.32	1.34 (0.45–3.97)	0.60
Donor	12 (52)	122 (50)				
Recipient	11 (48)	122 (50)	0.93 (0.41–2.09)	0.86	0.92 (0.37–2.27)	0.86
Treatment year‡	2008 (2005-2010)	2009 (2007-2010)	1.19 (0.96–1.46)	0.12	1.15 (0.94–1.41)	0.16

OR, odds ratio; CI, confidence interval.

* Data are mean ± standard deviation or n (%) unless otherwise specified.

† Compared with the reference category = stage 1.

‡ Data are median (interquartile range).

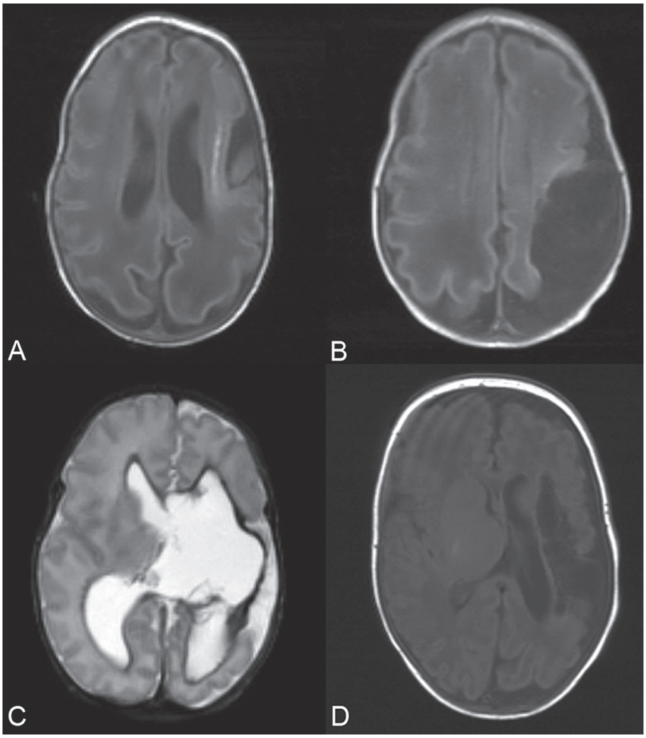

Figure 1. Four neonates from the twin-twin transfusion group with arterial ischemic stroke

A. Female neonate, ex-recipient, born at 29 weeks of gestation. T1-weighted magnetic resonance image (MRI) shows left-sided middle cerebral artery infarction with parenchymal destruction in the region of the left insula and operculum.
B. Female neonate, ex-recipient, born at 31 weeks of gestation. T1-weighted MRI shows left-sided middle cerebral artery infarction with extensive parenchymal destruction of the left hemisphere.
C. Male neonate, ex-recipient, born at 38 weeks of gestation. T2-weighted MRI shows a large parenchymal defect with a hemorrhagic component, contiguous with the lateral ventricle and involving both deeper and superficial structures of the left hemisphere. There was also severe parenchymal loss of both cerebellar hemispheres and vermis (not shown).
D. Female neonate, ex-recipient, born at 28 weeks of gestation. T1-weighted MRI shows left-sided middle cerebral artery infarction with parenchymal destruction of the temporal and parietal lobe and compensatory enlargement of the left lateral ventricle.

Discussion

In this study we compared the results of neonatal cranial ultrasonographic examination in 267 neonates with twin-twin transfusion syndrome treated with fetoscopic laser surgery with a matched control group of dichorionic twins and found the incidence of severe cerebral lesions to be similar in the two groups. These data suggest that twin-twin transfusion syndrome survivors after laser surgery are not at increased risk for cerebral injury compared with matched control participants.

The incidence of cerebral lesions reported in twin-twin transfusion syndrome survivors in our study was relatively low, 8.6%. In a previous study performed in the first cohort of twin-twin transfusion syndrome survivors born and examined at our center, the incidence of severe cerebral lesions in twin-twin transfusion syndrome survivors was 14.3%.(2) The methodology and definitions for severe cerebral lesions used in our studies remained the same during the last decade. One of the possible explanations for the lower incidence of cerebral injury detected in the present study could be related to the learning curve associated with improvement in laser surgery.(16) In this study, we detected a slight reduction in incidence of severe cerebral injury during the years. However, this difference did not reach statistical significance likely as a result of the relatively small numbers of patients.

Several large studies reported on the incidence of severe cerebral lesions in twin-twin transfusion syndrome treated with laser. In the study from Senat et al., the incidence of cerebral lesions seems to be lower (6%) compared with our study.(1) However, their definition of severe cerebral lesions was limited to the most severe form of leukomalacia (cystic periventricular leukomalacia grade 3 or greater) and intraventricular hemorrhage grade 3 or greater. In addition, other severe lesions such as arterial strokes or porencephalic cysts were not included in the definition, suggesting that the true incidence of severe cerebral lesions could be higher than reported. In addition, the denominator in the study from Senat et al. was the total number of fetuses instead of the total number of liveborn neonates in which a cranial ultrasonography was performed. The incidence of cystic periventricular leukomalacia (grade 3 or greater) in liveborn neonates was higher (8.6% [8 of 93]) compared with our findings (1.9% [5 of 267]).

In a recent study in 99 twin-twin transfusion syndrome survivors after laser surgery, Lenclen et al. reported a higher rate (16%) of cerebral lesions compared with our results.(3) However, they included only twin-twin transfusion syndrome survivors delivered before 34 weeks of gestation. Their studied cohort was therefore more premature and consequently more at risk for cerebral injury.

As shown in this study, lower gestational age at birth is the strongest predictor for cerebral damage in neonates. This is also in accordance with long-term outcome data in twin-twin transfusion syndrome showing that prematurity is the only independent predictor of adverse neurodevelopmental outcome.(14)

In another recent study in 143 twin-twin transfusion syndrome survivors from Cincotta et al., the authors reported an extremely low rate, only 2.8%, of severe cerebral abnormalities.(4) The discrepancies in reported rate may partly be the result of several methodological differences between the studies such as the use of different protocols for ultrasonographic scans, the criteria for cerebral injury, and the size of the various studies. Detection of cystic lesions is known to be less accurate when a restrictive scan regimen is used during the neonatal period. A restricted ultrasonographic regimen may lead to an underestimation of adverse outcome in twin-twin transfusion syndrome survivors because up to 33% of severe cerebral lesions may be missed.(17, 18)

Slightly more than half of severe cerebral lesions in the twin-twin transfusion syndrome group were present at birth, suggesting that the onset of brain injury in neonates with twin-twin transfusion syndrome is often of antenatal origin. The incidence of antenatally acquired cerebral lesions in the twin-twin transfusion syndrome group was eightfold higher than in the control group, which is accordance with our previous study.(2) The exact mechanism responsible for antenatal cerebral injury in twin-twin transfusion syndrome is not clear and may result from impaired cerebral perfusion resulting from hemodynamic imbalance and intertwin blood shifts. Impaired cerebral perfusion may then lead to hypoxic-ischemic insults and may occur before fetoscopic laser surgery. Previous studies have shown that severe cerebral injury in twin-twin transfusion syndrome may be detected before laser treatment.(19) Nevertheless, the timing of cerebral injury in twin-twin transfusion syndrome remains unclear and may occur before, during, or after fetoscopic laser surgery. This urgently requires further study, because more insight in the etiology of cerebral injury may lead to adaptation of treatment protocols, eg, earlier intervention in case of prelaser origin or altered technique if injury occurs during laser surgery.

Interestingly, we also detected rare cerebral lesions in the twin-twin transfusion syndrome group, such as perinatal arterial stroke. All arterial strokes occurred in ex-recipients and involved the left middle cerebral artery. Twin-twin transfusion syndrome has been shown to be the main risk factor for perinatal arterial strokes in preterm neonates.(20) The etiology of the focal ischemic stroke in the recipient is still obscure but could theoretically be related to sludging of polycythemic blood, hypoxia-ischemia, coagulation disorders, or all of these.(21)

The data on incidence of cerebral injury reported in this study should be interpreted with care because a selection bias may have been introduced as a result of the specific nature of our tertiary referral center. It is conceivable that the more complicated or more premature cases (particularly in the twin-twin transfusion syndrome group) may have been delivered at our center, whereas the less complicated or less premature cases were born elsewhere. However, by matching the twin-twin transfusion syndrome group with a control group of dichorionic twins, we eliminated the potential confounding bias resulting from prematurity.

In addition, although the predictive value of sequential cranial ultrasonography, magnetic resonance imaging, or both for detecting neurologic morbidity is increasing, the predictive accuracy of cerebral imaging remains controversial.(17) Neurodevelopmental impairment can only reliably be ascertained by adequate long-term evaluation up until childhood.

In conclusion, the risk of severe cerebral lesions in twin-twin transfusion syndrome treated with laser is similar to a matched control group of dichorionic twins. Cerebral injury in the twin-twin transfusion syndrome group is mainly of antenatal origin and is associated with premature delivery.

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