Postnatal survival after endoscopic equatorial laser for the treatment of twin-to-twin transfusion syndrome

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Dual survival after equatorial laser for TTTS was lower in the presence of abnormal donor umbilical artery Doppler due to an increased intrauterine mortality of donor twins.

Abstract

Background: Endoscopic laser coagulation of placental anastomoses is the first-line treatment for severe twin-to-twin transfusion syndrome (TTTS). A recent randomized controlled trial reported that laser coagulation along the entire vascular equator was associated with a similar dual survival and survival of at least one twin compared to the group treated with the selective technique. In addition, there was a significantly lower incidence of postoperative recurrence of TTTS and development of twin anemia-polycytemia sequence (TAPS) in the equatorial group.

Objective: To report on neonatal survival in TTTS pregnancies treated with endoscopic laser using the equatorial technique and to examine the relationship between preoperative factors and twin loss.

Study design: Endoscopic equatorial laser was carried out as the primary treatment for TTTS in all consecutive monochorionic diamniotic twin pregnancies referred at a single fetal surgery Centre over a 4 years' period. All visible placental anastomoses were coagulated and additional laser ablation of the placental tissue between the coagulated vessels was carried out. Pre-laser ultrasound data, peri-procedural complications, pregnancy outcome and postnatal survival at hospital discharge were recorded and analysed.

Results: A total of 106 pregnancies were treated during the study period. Median gestational age at laser was 19.7 (range 15.1-27.6) weeks. There was postoperative recurrence of TTTS or development of TAPS in 2 (1.9%) and 2 (1.9%) cases, respectively. The survival rates of both and at least one twin were 56.6% and 83.0%, respectively. Donor survival was significantly lower compared to the recipient co-twin (64.2% vs 75.5%, respectively; $p<0.05$). The rate of fetal death, which was the most common cause of twin loss, was significantly higher in donors compared to recipient

fetuses (23.6% vs 10.4%, respectively; $p<0.05$). In cases with absent or reversed end-diastolic velocity in the donor umbilical artery, dual and donor survival rates were significantly lower compared to the remaining TTTS pregnancies (40.0% vs 64.8% and 40.0% vs 76.1%, respectively; $p<0.05$). There were no significant differences between the two groups in the survival of at least one twin and in the recipient survival.

Conclusions: Endoscopic equatorial laser was associated with a survival of both and at least one twin of about 55% and 83%, respectively, and with a low rate of recurrent TTTS and TAPS. In addition, the preoperative finding of abnormal donor umbilical artery Doppler identified a subgroup of TTTS pregnancies with a lower dual survival rate due to increased intrauterine mortality of donor twins.

Key words: monochorionic twins, twin-to-twin transfusion syndrome, equatorial laser, survival, Doppler

Introduction

Endoscopic laser coagulation of placental anastomoses is the first-line treatment for severe twin-to-twin transfusion syndrome[1] (TTTS), which affects 10-15% of monochorionic diamniotic twin pregnancies. Most of the studies examining the effects of laser therapy on postnatal survival have used the selective technique, by which only visible anastomoses are coagulated[2-10]. Additional laser ablation of the placental tissue between the anastomoses along the vascular equator has been proposed[11] to achieve a complete coagulation of all non-visible vascular connections between the two placental territories.

Only few studies have examined pregnancy and neonatal outcomes using equatorial laser for the treatment of TTTS[12-16]. A recent randomized controlled trial has shown that this approach, also called 'Solomon' technique, was associated with a similar dual survival and survival of at least one twin compared to the group treated with the selective technique. In addition, there was a significantly lower incidence of postoperative recurrence of TTTS and development of twin anemia-polycytemia sequence (TAPS) in the equatorial group[15].

The aim of this study is to report on neonatal survival in TTTS pregnancies treated with endoscopic equatorial laser and to examine the relationship between preoperative factors and twin loss.

Methods

Endoscopic equatorial laser was carried out as the primary treatment for TTTS in all consecutive monochorionic diamniotic twin pregnancies referred at a single fetal surgery Centre in Italy over a 4 years' period (2011-2014).

In all cases, a detailed ultrasound examination (RAB 4-8 transducer, Voluson E8, GE Medical Systems, Milwaukee, WI, USA) was performed within 48 hours before laser treatment. The minimum required criteria for the diagnosis of TTTS were oligohydramnios in the sac of the donor, defined as a maximum vertical pocket of amniotic fluid of $\leq$ 2 cm, and polyhydramnios in the sac of the recipient twin, defined as a maximum vertical pocket of $\geq$ 8 cm before 20 weeks' gestation and $\geq$ 10 cm thereafter. The estimated fetal weight was derived from the appropriate reference ranges for gestation[17,18] and the inter-twin discordance in estimated fetal weight was calculated as the weight difference divided by the weight of the large twin. Doppler assessments of the umbilical arteries and the ductus venosus of both twins were carried out in all cases.

Endoscopic laser surgery was performed using a semi-rigid 2.0-mm diameter fetoscope (Karl Storz GmbH, Tuttlingen, Germany) through a 3.3-mm diameter cannula (Cook Medical, Bloomington, Ind., USA), which was introduced transabdominally into the sac of the recipient twin after the administration of prophylactic antibiotics and local anaesthesia. A 400-µm diameter diode laser fibre (Dornier Med Tech, Wessling, Germany) with a power output of 20-30 W was used for coagulation of the placental surface. All visible inter-twin vascular anastomoses were coagulated with additional laser ablation of the placental tissue between the coagulated vessels, as previously described[11]. Subsequently, amnioreduction of the polyhydramnios was undertaken through the cannula over a period of 10–15 min to obtain subjective normalisation of the amniotic fluid volume on ultrasonographic examination. All patients underwent a period of observation in the hospital of about 48 hours. Weekly follow-up was undertaken at our Centre for the first 4 weeks postoperatively and at the referring hospitals thereafter.

Maternal demographic characteristics, ultrasound findings and details of intrauterine intervention were recorded in a database. Pregnancy outcome and neonatal survival at hospital discharge were collected when they became available from the referring hospitals or from the patients.

The study did not require formal ethical approval as data collection did not alter clinical management or standard of care and information on postnatal outcome is routinely recorded for each case undergoing intrauterine treatment at our Centre. Informed consent to the use of confidential information according to the Hospital privacy policy was obtained for each patient.

Statistical analysis

Comparisons in the examined parameters between different groups were performed using the Chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. The tests were considered significant at a p value of <0.05 using two-tailed tests.

Logistic regression analysis was used to determine the variables providing a significant contribution in predicting postnatal twin survival. Univariate analysis was carried out to examine the individual variables contributing to survival by assessing their odds ratios and 95% confidence intervals. Subsequently, multivariate logistic regression analysis with backward stepwise elimination was performed to determine which of these variables provide a significant independent contribution in the logistic model.

The data were analysed using the statistical software package IBM SPSS 19.0 (IBM Corp., Armonk, N.Y., USA) and Excel for Windows 2010 (Microsoft Corp., Redmond, WA, USA).

Results

Endoscopic equatorial laser was carried out at our Centre in 106 cases of TTTS during the study period. Table 1 shows the main obstetric and fetal characteristics of the study population. Complications within 14 days postoperatively included preterm premature rupture of membranes (p-PROM) in 4 (3.8%) cases, preterm labor in 5 (4.7%) and maternal bleeding in 3 (2.8%) cases. In 1 (0.9%) patient, bleeding at the site of trocar entry required maternal blood transfusion, with no further complications. In 2 (1.9%) cases, there was recurrence of TTTS which was treated with repeat laser. In additional 2 (1.9%) pregnancies, there was development of TAPS that was treated with fetal blood transfusion of the anemic twin.

Details on pregnancy outcome and neonatal survival are shown in Table 2. The survival rates of both and at least one twin at neonatal hospital discharge were 56.6% and 83.0%, respectively. Donor survival was significantly lower compared to the recipient co-twin (64.2% vs 75.5%, respectively; $p<0.05$). The prevalence of fetal death, which was the most common cause of twin loss, was significantly higher in donors compared to recipient fetuses (23.6% vs 10.4%, respectively; $p<0.05$).

Preoperative findings in survivors, compared to cases with fetal or neonatal death, are shown in Table 3. In donor fetuses that died there was a significantly higher prevalence of estimated fetal weight discordance with the co-twin $\geq$ 25% and abnormal umbilical artery Doppler. No difference in the examined parameters was observed in recipient twins according to postnatal survival.

Donor survival was significantly lower in Quintero stage III cases compared to stage I and II (47.1% vs 85.2% and 47.1% vs 74.1%, respectively; $p<0.05$), with no difference between stage I and II pregnancies ($p=0.501$). No significant difference in recipient survival was observed according to Quintero stages.

Logistic regression analysis demonstrated that significant predictors of donor survival were estimated fetal weight discordance ≥ 25% and absent or reversed end-diastolic velocity in the umbilical artery. In the multivariate analysis, the only independent contribution to donor survival was provided by abnormal umbilical artery Doppler (Table 4).

Table 5 shows the differences in preoperative factors, fetal and neonatal outcome between TTTS cases with absent or reversed end diastolic velocity in the umbilical artery of the donor (Group A) and the remainder pregnancies (Group B). Dual and donor survival rates were significantly lower in Group A compared to Group B (40.0% vs 64.8% and 40.0% vs 76.1%, respectively; $p<0.05$). There were no significant differences between the two groups in the survival of at least one twin and in the recipient survival.

Discussion

This study shows that, in our experience, equatorial laser was associated with a survival of both and at least one twin of about 55% and 83%, respectively, and with a low rate of recurrent TTTS and TAPS. In addition, the preoperative finding of abnormal donor umbilical artery Doppler identified a subgroup of TTTS pregnancies with a lower dual survival rate due to increased intrauterine mortality of donor twins.

Recent studies on treatment of TTTS using the equatorial laser technique reported survival rates of both and at least one twin ranging between 64% and 85% and between 84% and 91%, respectively[12-16]. A recent randomised controlled trial showed no significant difference in postnatal survival after equatorial laser compared to the more widely used selective approach[15]. In contrast, observational studies reported a trend towards a higher dual survival rate using equatorial laser, with a

similar survival of at least one twin between the two techniques[12,13]. A review of studies comparing equatorial and selective laser suggested an overall improved survival with equatorial laser, but addressed the need for an appropriately powered randomised controlled trial in order to confirm these results and to assess the impact of laser technique on long-term neurological morbidity[19]. However, it will be difficult for such a study to be carried out because the recently published randomised trial showed significant benefits of equatorial laser, with no disadvantages in terms of survival compared to the selective technique, on the rate of postoperative complications such as recurrence of TTTS and TAPS[15].

The survival rate of donor twins in our cohort was about 10% lower than that of the recipients and this has been previously reported[20]. The most common cause of twin loss in our study was spontaneous intrauterine death, which accounted for about 60% of all losses and was significantly more common in donor fetuses (Table 2). Among the preoperative factors included in our protocol, donor survival was significantly associated with the presence or absence of severe inter-twin fetal weight discordance and abnormal umbilical artery Doppler. However, in the multivariate analysis the only independent contribution to donor survival was provided by absent or reversed end-diastolic velocity in the umbilical artery and these results are consistent with previous studies using the selective laser technique[6-9]. Donor umbilical artery Doppler abnormalities may be a sign of severe hypovolemia or they can be associated with selective placental insufficiency, especially in the presence of a large inter-twin fetal weight discordance, which in our series occurred more frequently for cases with abnormal donor Dopplers (Table 5). However, in this study the degree of fetal weight discordance did not provide an independent contribution to neonatal outcome when Doppler assessment was included in the prediction model.

This may be explained by the fact that, in the context of TTTS, it is difficult to distinguish between hypovolemic and hypoxemic donors with a small placental territory based on the preoperative ultrasound evaluation used in our study.

We did not find any significant relationship between preoperative Doppler assessment of umbilical artery or ductus venosus flows of recipient twins and neonatal survival. Previous studies have shown that additional echocardiographic findings, such as cardiac hypertrophy and dilatation, atrioventricular flow abnormalities, increased myocardial performance index, abnormal cardiac output and others, can identify a group of TTTS recipients with a worsened cardiovascular function[21-23]. However, there are discordant results among the published studies on the value of a detailed cardiovascular assessment in the prediction of recipient survival[24-28] and therefore, further investigation into this topic is required.

Dual survival is the main objective of intrauterine treatment of TTTS and our data showed that this is strongly influenced by the presence or absence of umbilical artery Doppler abnormalities of donor twins. In this group, which accounted for about 30% of all TTTS cases in our population, dual survival was substantially lower compared to what was observed in the remaining pregnancies, with a similar survival of at least one twin between the two groups (Table 5). Survival analysis taking into account the prevalence of donor Doppler abnormalities may be useful for a better understanding of the effects of endoscopic laser on the natural history of the donor and recipient diseases under different preoperative conditions and for making meaningful comparisons between different studies. For example, two previous series[5,8] reported a similar survival of at least one twin, after endoscopic laser, of about 85% and 82%, respectively, and a wider difference in dual survival (38% and 54%, respectively) due to a higher donor mortality in one study[5]. It is likely that a major contribution to these

results was given by the large difference in the proportion of donors with abnormal umbilical artery Doppler between the two studies (84% and 33%, respectively). From a clinical perspective, our results may have an impact on parents' expectations before laser surgery about the chance for both babies to survive but would not change the clinical management and the treatment choice, which has been widely agreed to be endoscopic laser in cases presenting with TTTS.

One limitation of this study is the unavailability of placental injection studies, which could have been used to assess measures of placental sharing in relation to preoperative ultrasound factors. In addition, we did not report data on postnatal neurological morbidity, which requires a longer follow-up period.

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cardiovascular profile score predicts recipient twin outcome in twin-twin transfusion syndrome. J Am Soc Echocardiogr 2008;21:1105-8.

Table 1. Obstetric and fetal preoperative characteristics of the study population.

	N=106
Obstetric characteristics	
Gestational age at laser (weeks)	19.7 (15.1-27.6)
Cervical length (mm)	34.5 (12-45)
Placenta location	
Anterior	51 (48.1)
Posterior	55 (51.9)
Fetal characteristics	
Estimated fetal weight (g)	
Donor	232 (112-992)
Recipient	316 (145-1176)
EFWD $\geq$ 25%	45 (42.5)
Donor smaller than recipient	105 (99.1)
Umbilical artery absent or reversed EDV	
Donor	35 (33.0)
Recipient	2 (1.9)
Ductus venosus absent or reversed a-wave	
Donor	9 (8.5)
Recipient	20 (18.9)
Quintero stage	
I	27 (25.5)
II	27 (25.5)
III	51 (48.1)
IV	1 (0.9)

Numbers are presented as median (range) or n (%).

EFWD = estimated fetal weight discordance; EDV = end-diastolic velocity

Table 2. Details on pregnancy and neonatal outcomes of the study population.

	N=106
Pregnancy outcome	
Gestational age at delivery (weeks)	30.6 (16.3-40.3)
Delivery < 24 weeks	16 (15.1)
Delivery 24-28 weeks	17 (16.0)
Delivery 29-32 weeks	40 (37.8)
Delivery >32 weeks	33 (31.1)
Neonatal outcome	
Dual survival	60 (56.6)
At least 1 survivor	88 (83.0)
Individual twin survival	
Donor	68 (64.2)
Recipient	80 (75.5)*
Birthweight of live births (g)	
Donor	1399 (490-2460)
Recipient	1600 (530-3320)*
Causes of twin loss	
Intrauterine death	
Donor	25 (23.6)
Recipient	11 (10.4)*
PROM < 24 wks - Miscarriage	9 (8.5)
Selective fetocide	5 (4.7)
Neonatal death	4 (3.8)

Numbers are presented as median (range) or n (%).

* P<0.05 compared to donor co-twins

Table 3. Preoperative findings in donor and recipient fetuses that survived compared to those that died.

	Donor fetus			**Recipient fetus**		
	Alive (n=68)	**Demise (n=38)**	**P-value**	**Alive (n=80)**	**Demise (n=26)**	**P-value**
Obstetric factors						
Gestational age at laser (weeks)	20.2 (16.3-27.6)	18.9 (15.1-26.3)	0.140	19.4 (15.0-26.9)	20.1 (15.7-27.6)	0.665
Cervical length (mm)	35.0 (18-45)	33 (12-41)	0.263	35.0 (12-45)	33.0 (16-40)	0.268
Anterior placenta	34 (50.0)	21 (55.3)	0.687	45 (56.3)	10 (38.5)	0.175
Fetal factors						
EFWD $\geq$ 25%	23 (33.8)	22 (57.9)	0.024	31 (38.8)	14 (53.8)	0.253
Donor UA absent or reversed EDV	14 (20.6)	21 (55.3)	<0.01	25 (31.3)	10 (38.5)	0.632
Donor DV absent or reversed a-wave	3 (4.4)	6 (15.8)	0.067	5 (6.3)	4 (15.4)	0.218
Donor visible bladder	31 (45.6)	16 (42.1)	0.839	43 (53.8)	16 (61.5)	0.507
Recipient UA absent or reversed EDV	1 (1.5)	1 (2.6)	1	1 (1.3)	1 (3.8)	0.432
Recipient DV absent or reversed a-wave	12 (17.6)	8 (21.1)	0.796	12 (15.0)	8 (30.8)	0.088

Numbers are presented as median (range) or n (%).

EFWD = estimated fetal weight discordance; UA = umbilical artery; DV = ductus venosus; EDV = end-diastolic velocity

Table 4. Logistic regression analysis for predicting donor survival after equatorial laser based on preoperative findings.

Variable	Univariate analysis			Multivariate analysis		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Gestational age at laser (weeks)	1.151	0.994 – 1.334	0.061	-	-	-
Cervical length (mm)	1.033	0.963 – 1.108	0.369	-	-	-
Anterior placenta	0.810	0.365 – 1.796	0.603	-	-	-
EFWD ≥ 25%	0.372	0.164 – 0.841	0.018	-	-	-
Visible bladder	0.868	0.389 – 1.935	0.729	-	-	-
Donor UA absent or reversed EDV	0.210	0.088 – 0.500	<0.001	0.249	0.101 – 0.610	0.002
Donor DV absent or reversed a-wave	0.246	0.058 – 1.048	0.058	-	-	-

EFWD = estimated fetal weight discordance; UA = umbilical artery; DV = ductus venosus; EDV = end-diastolic velocity; OR = odds ratio; CI = confidence interval

Table 5. Obstetric and fetal characteristics, neonatal outcome and causes of twin loss in TTTS cases with absent or reversed end diastolic velocity in the umbilical artery of the donor (Group A) compared to the remainder pregnancies (Group B).

	Group A n=35	**Group B n=71**	**P-value**
Obstetric characteristics			
Gestational age at laser (weeks)	19.4 (15.1-26.7)	20.0 (16.1-27.6)	0.161
Cervical length (mm)	34.0 (20-41)	35.0 (12-45)	0.988
Gestational age at delivery (weeks)	29.9 (16.3-40.3)	31.3 (16.3-38.3)	0.367
Fetal characteristics			
EFWD $\geq$ 25%	22 (62.9)	23 (32.4)	<0.01
Recipient UA absent or reversed EDV	2 (5.7)	0	0.107
Recipient DV absent or reversed a-wave	5 (14.3)	15 (21.1)	0.443
Neonatal outcome			
Dual survival	14 (40.0)	46 (64.8)	0.02
At least 1 survivor	25 (71.4)	63 (88.7)	0.06
Individual twin survival			
Donor	14 (40.0)	54 (76.1)	<0.01
Recipient	25 (71.4)	55 (77.5)	0.632
Causes of twin loss			
Intrauterine death			
Donor	15 (42.9)	10 (14.1)	0.02
Recipient	3 (8.6)	8 (11.3)	1
PROM < 24 wks - Miscarriage	5 (14.3)	4 (5.6)	0.153
Selective fetocide	1 (2.9)	4 (5.6)	1
Neonatal death	1 (2.9)	3 (4.2)	1

Numbers are presented as median (range) or n (%).

EFWD = estimated fetal weight discordance; EDV = end-diastolic velocity