Fetal Doppler changes one week after endoscopic equatorial laser for twin-to-twin transfusion syndrome: a longitudinal study.

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What's already known about this topic?

- In twin-to-twin transfusion syndrome requiring laser treatment, preoperative umbilical artery abnormalities in donor fetuses are associated with an increased risk of postoperative fetal demise. Less is known about changes in fetal Dopplers one week post-laser and their clinical significance.

What does this study add?

- In about 70% of TTTS donors with abnormal umbilical artery Doppler, there was normalization of flow one week after endoscopic laser.
- In our series, the incidence of fetal growth restriction was not significantly different in donors with persistence of Doppler abnormalities compared to those with normalized findings.

Abstract

Objective: To investigate sequential Doppler changes in donors and recipients before and one week after endoscopic laser for twin-to-twin transfusion syndrome (TTTS) and to examine factors that may be associated with such changes.

Methods: In TTTS pregnancies undergoing laser treatment, we examined fetal Doppler changes before and one week post-intervention. Intrauterine death rates and preoperative factors were analysed in relation to Doppler changes.

Results: Among 129 (85.4%) of 151 donors surviving at one week after laser, there was normalization of umbilical artery flow in 26 (72.2%) out of 36 cases with preoperative abnormal Dopplers. In the remaining 10 (27.8%) fetuses abnormal findings persisted. The rate of later intrauterine death was significantly higher in the latter group (6 of 10, 60.0%) compared to fetuses in which Doppler findings normalized (4 of 26, 15.4%; $p<0.05$), with no difference in the rate of severe growth restriction in the donor between the two groups (80.0% vs. 65.4%, respectively; $p=0.688$).

Conclusions: In about 70% of TTTS donors with preoperative abnormal umbilical artery Doppler, there was normalization one week after endoscopic laser. The incidence of fetal growth restriction was not significantly different in donors with persistence of Doppler abnormalities compared to those with normalized findings.

Key words: monochorionic twins, twin-to-twin transfusion syndrome, fetal growth restriction, placental laser, Doppler ultrasound

Introduction

Twin-to-twin transfusion syndrome (TTTS) is caused by preferential passage of blood through placental vascular anastomoses, which leads to hypervolemia and polyuria in the recipient fetus and hypovolemia with oligo-anuria in the donor twin[1]. These hemodynamic changes can be detected on obstetric ultrasound by demonstrating the co-existence of polyhydramnios in the sac of the recipient and oligo-anhydramnios in the donor. These findings are diagnostic criteria for the clinical diagnosis of TTTS. In a proportion of pregnancies with TTTS, there are additional signs of hemodynamic imbalance that can be demonstrated with the use of Doppler technology and the most common findings are absent or reversed end-diastolic flow (AREDF) in the donor umbilical artery and absent or reversed a-wave in the ductus venosus of the recipient twin[2].

Endoscopic laser coagulation of placental anastomoses is the first-line treatment for TTTS[3]. Preoperative Doppler abnormalities have been examined in relation to fetal survival and most studies showed concordant results on the increased rate of donor demise in cases with AREDF in the umbilical artery[4-7]. In contrast, several cross-sectional studies have shown that abnormal donor umbilical artery Doppler and recipient ductus venosus flow, assessed in the postoperative period between 24 hours and 4 weeks after laser, were not significantly associated with an increased mortality[8-12]. However, longitudinal assessment of fetal Doppler findings across the perioperative period and investigation into the possible causes for non-improvement in fetuses surviving beyond the early postoperative phase have not been systematically carried out.

The aim of this study was to investigate sequential changes in donor and recipient Doppler findings before and one week after endoscopic equatorial laser for TTTS and to examine preoperative factors that may be associated with such changes.

Materials and Methods

In this prospective observational study, endoscopic equatorial laser was carried out as the primary treatment for TTTS in all consecutive monochorionic diamniotic twin pregnancies referred to our fetal surgery centre over a 5-year period (2011-2015). 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 deepest 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[13,14] and the inter-twin discordance in estimated fetal weight was calculated as the weight difference divided by the weight of the large twin. Fetal growth restriction (FGR) was defined as an estimated fetal weight at or below the 5th percentile. Fetal Dopplers were considered abnormal if the end-diastolic flow (EDF) and the a-wave were absent or reversed in the umbilical arteries and in the ductus venosus, respectively.

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 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[15-17]. Subsequently, amnioreduction of the polyhydramnios was undertaken through the cannula over a period of 10–15 min to obtain subjective normalization of the amniotic fluid volume on ultrasound. All patients remained admitted for observation for about 48 hours. Weekly ultrasound follow-up, including re-assessment of fetal Dopplers, was undertaken at our centre for the first 4 weeks postoperatively and at the referring hospitals thereafter.
Maternal demographic characteristics, pre- and post-laser 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 main study outcome was the change in fetal Dopplers one week after laser treatment with respect to preoperative findings. Fetuses surviving at one week post-intervention were divided into three groups according to Doppler changes as follows (donor side, recipient side): normal-normal, abnormal-normal, abnormal-abnormal. Several variables, such as intrauterine death later than one week postoperatively, gestational age at laser, cervical length, placenta position, FGR, fetal Dopplers and co-twin death within one week from intervention were analysed and compared between the three groups.

This study was approved by the Institutional Review Board of Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy.

Statistical analysis

Comparisons of 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.

The data were explored and 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 laser treatment was carried out in 151 twin pregnancies with TTTS during the study period. Table 1 shows the main obstetric and fetal characteristics of the study population. Survival rates at hospital discharge of both twins, at least one twin, donors and recipients were 56.3%, 81.5%, 62.9% and 74.2%, respectively. The respective percentages at one week after laser treatment were 79.5%, 95.4%, 85.4% and 90.1%. The causes of twin loss are reported in Table 2. In 10 (6.6%) out of 151 pregnancies, selective fetocide was performed at least 3 weeks post-intervention following the diagnosis of a major brain injury. Table 3 shows the distribution of cases in relation to changes in fetal Doppler findings across the perioperative period. In 36 (27.9%) of 129 donors there was pre-laser abnormal umbilical artery Doppler. The EDF normalized at one week after treatment in 26 (72.2%) of these cases and it was persistently absent or reversed in the remaining 10 (27.8%) fetuses. The rate of subsequent intrauterine fetal death (IUFD) was significantly higher in the latter group (6 of 10, 60.0%) compared to cases with normalized findings (4 of 26, 15.4%; p<0.05) and to those with positive EDF before and after laser treatment (5 of 93, 5.4%; p<0.05). Among the 135 recipient fetuses surviving at one-week post-intervention, ductus venosus flow was preoperatively abnormal in 23 (17.0%) cases and only 1 (4.3%) of these showed persistence of absent or reversed a-wave (Table 3). There was no significant difference in the rate of IUD between recipients with normalization of ductus venosus flow (0 of 22, 0%) and those with normal findings before and after treatment (8 of 112, 7.1%; p=0.352).

Preoperative characteristics in relation to changes in donor umbilical artery Doppler are shown in Table 4. The incidence of oligohydramnios, as opposed to anhydramnios, was significantly higher in donors who subsequently showed persistently abnormal findings (8 of 10, 80%) compared to those with Doppler normalization (8 of 26, 30.8%; p<0.05). No difference between these groups was observed in the rate of severe FGR and 17 (68.0%) of 25 donors with FGR and preoperatively abnormal Doppler showed a positive EDF after laser treatment.

Discussion

The findings of this study showed that in about 70% of TTTS donors with preoperative umbilical artery AREDF, there was normalization of flow one week after laser treatment and the rate of subsequent IUFD in this group was significantly lower compared to cases with persistence of abnormal Dopplers. In our series, the incidence of fetal growth restriction was not significantly different in donors with persistence of Doppler abnormalities compared to those with normalized findings.

Only two previous studies assessed fetal Doppler findings at one week after laser treatment, which was carried out mainly using the selective technique, and reported no significant association between postoperative abnormal umbilical artery Doppler and donor survival at 30 days and 6 months of age, respectively[11-12]. The main differences with our study are that firstly, we considered as the main outcome spontaneous IUFD, rather than postnatal survival, to remove other causes of death, such as miscarriage before 24 weeks, selective fetocide and neonatal death (Table 2), which more are difficult to relate to early post-laser Doppler findings. Secondly, in our study laser treatment was carried out using the equatorial technique in all cases and it is possible that, using the selective approach, a longer postoperative time may be needed to achieve normalization of umbilical artery EDF. Thirdly, we took into consideration changes in Dopplers across the perioperative period in the same fetuses, showing that donors with normalization of flow have a similarly low rate of IUFD as those with normal Dopplers before and after treatment, compared to the 60% rate of IUFD in cases with persistent AREDF. Only one previous study used a similar approach in data analysis and reported no significant difference in the rate of IUFD in donors with normalization of umbilical artery EDF at 24 hours after selective laser treatment compared to cases with persistence of Doppler abnormalities. However, the study included only 9 donors with postoperative normalization and 2 with persistently abnormal Dopplers[8].

The preoperative finding of umbilical artery AREDF in TTTS donors can be considered as a sign of severe hypovolemia, placental insufficiency, or both[18]. The co-existence of severe FGR was found to be an additional risk factor of donor's demise in previous studies[4,6,12,19]. Our data showed that, among donors surviving at one week after laser treatment, the incidence of FGR was similarly high in the group with Doppler normalization and in cases with persistently abnormal findings (Table 4), and that in 68% of growth restricted donors with pre-laser Doppler abnormalities there was normalization after treatment, suggesting a hypovolemic cause of preoperative findings in these cases more than a hypoxic mechanism. However, we cannot exclude that the lack of association between donor FGR and

persistence of Doppler abnormalities may have also been influenced by the small sample size and therefore, future studies should investigate this finding further.

In this study, the proportion of cases with oligohydramnios, as opposed to anhydramnios, was higher in the group with persistently abnormal Doppler findings compared to cases with post-laser normalization (Table 4). The possible explanation for this finding is that, in donors with anhydramnios, AREDF in the umbilical artery is more likely to reflect a progression in the severity of hypovolemia into anuria, which can be improved by laser treatment with consequent re-appearence of a positive EDF. In contrast, the presence of some amniotic fluid in the sac of the donor, which was more common in the group with persistence of abnormal Dopplers, may suggest that preoperative AREDF in these cases was more likely due to the co-existence of placental insufficiency and, in this respect, laser coagulation of the vascular anastomoses would not be able to restore a normal placental function in these donors.

The incidence of persistent Doppler abnormalities in recipient fetuses was very low and, in the vast majority of survivors one week after treatment, there was normalization of ductus venosus flow. This finding confirms that endoscopic equatorial laser is effective in reversing recipient's hypervolemia and it supports the concept that donor persistent umbilical artery AREDF may be due to other causes than hypovolemia.

The strengths of our study are that we analysed a large consecutive series of TTTS pregnancies undergoing endoscopic laser as the primary treatment with complete follow-up and using in all cases the equatorial technique, also known as 'Solomon' technique, which has been recently shown to be preferable to the selective approach because it is associated with a lower rate of postoperative recurrence of TTTS and development of twin anemia-polycytemia sequence[16]. The main limitation of our study is the small number of donors with persistently abnormal Dopplers and therefore, our results should be confirmed in larger series. In addition, we did not report any information about long-term neurological development, which requires a longer follow-up period.

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Table 1. Obstetric and fetal characteristics and pregnancy outcome of the study population.

	N=151
Obstetric characteristics	
Gestational age at laser (weeks)	19.7 (15.1-27.6)
Cervical length (mm)	33.0 (10-45)
Placenta location	
Posterior	77 (51.0)
Anterior	74 (49.0)
Fetal characteristics	
Estimated fetal weight ≤ 5th percentile	
Donor	68 (45.0)
Recipient	3 (2.0)
EFWD ≥ 25%	59 (39.1)
Umbilical artery absent or reversed EDF	
Donor	50 (33.0)
Recipient	7 (4.6)
Ductus venosus absent or reversed a-wave	
Donor	12 (7.9)
Recipient	29 (19.2)
Quintero stage	
I	41 (27.2)
II	35 (23.2)
III	73 (48.3)
IV	2 (1.3)
Pregnancy outcome	
Gestational age at delivery (weeks)	31.2 (16.3-40.3)
Delivery < 24 weeks	20 (13.2)
Delivery 24-28 weeks	27 (17.9)
Delivery 29-32 weeks	59 (39.1)
Delivery >32 weeks	45 (29.8)
Birthweight of live births (g)	
Donor	1400 (485-2460)
Recipient	1600 (520-2550)

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

EFWD = estimated fetal weight discordance; EDF = end-diastolic flow

Table 2. Details on the causes and timing of twin loss in the study population.

	Total (n=151)	**> 1 week post-laser laser**
Cause of twin loss		
Intrauterine death		
Donor	33 (21.9)	15 (45.5)
Recipient	20 (13.2)	9 (45.0)
PROM < 24 wks - Miscarriage	11 (7.3)	7 (63.6)
Selective fetocide	10 (6.6)	10 (100)
Neonatal death		
Donor	6 (4.0)	6 (100)
Recipient	5 (3.3)	5 (100)

Numbers are presented as n (%).

PROM = premature rupture of membranes

Table 3. Sequential Doppler changes in donors and recipient before and one week after laser treatment.

	Donors (n=129)	**Recipients (n=135)**
Umbilical artery Doppler		
Normal-Normal	93 (72.1)	133 (98.5)
Abnormal-Normal	26 (20.1)	2 (1.5)
Abnormal-Abnormal	10 (7.8)	0
Ductus venosus Doppler		
Normal-Normal	122 (94.6)	112 (83.0)
Abnormal-Normal	6 (4.6)	22 (16.3)
Abnormal-Abnormal	1 (0.8)	1 (0.7)

Numbers are presented as n (%).

Table 4. Preoperative obstetric and fetal factors according to changes in donor umbilical artery Doppler before and one week after laser treatment.

	Donor umbilical artery Doppler		
	Normal-Normal (n=93)	**Abnormal-Normal (n=26)**	**Abnormal-Abnormal (n=10)**
Obstetric factors			
Gestational age at laser (weeks)	20.0 (16.0-27.6)	19.8 (16.1-27.4)	19.4 (17.0-23.4)
Cervical length (mm)	33 (10-45)	33 (23-40)	35 (20-41)
Anterior placenta	50 (53.8)	10 (38.5)	3 (30.0)
Fetal factors			
Donor EFW $\leq$ 5th percentile	27 (29.0)	17 (65.4)	8 (80.0)*
EFWD $\geq$ 25%	26 (28.0)	13 (50.0)	6 (60.0)
Donor DV absent or reversed a-wave	3 (3.2)	4 (15.4)	0
Donor visible bladder	41 (44.1)	8 (30.8)	6 (60.0)
Donor oligohydramnios vs anhydramnios	44 (47.3)	8 (30.8)	8 (80.0)¥
Recipient UA absent or reversed EDF	5 (5.4)	1 (3.8)	0
Recipient DV absent or reversed a-wave	17 (18.3)	5 (19.2)	0
Recipient IUD	7 (7.5)	1 (3.8)	0

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

EFW = estimated fetal weight; EFWD = estimated fetal weight discordance; UA = umbilical artery; DV = ductus venosus; EDF = end-diastolic flow; IUD = intrauterine death

*p<0.05 compared to the 'Normal-Normal' group

¥ p<0.05 compared to the 'Abnormal-Normal' group