ORIGINAL ARTICLE

Endoscopic Laser Surgery versus Serial Amnioreduction for Severe Twin-to-Twin Transfusion Syndrome

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ABSTRACT

BACKGROUND

Monochorionic twin pregnancies complicated by severe twin-to-twin transfusion syndrome at midgestation can be treated by either serial amnioreduction (removal of large volumes of amniotic fluid) or selective fetoscopic laser coagulation of the communicating vessels on the chorionic plate. We conducted a randomized trial to compare the efficacy and safety of these two treatments.

METHODS

Pregnant women with severe twin-to-twin transfusion syndrome before 26 weeks of gestation were randomly assigned to laser therapy or amnioreduction. We assessed perinatal survival of at least one twin (a prespecified primary outcome), survival of at least one twin at six months of age, and survival without neurologic complications at six months of age on the basis of the number of pregnancies or the number of fetuses or infants, as appropriate.

RESULTS

The study was concluded early, after 72 women had been assigned to the laser group and 70 to the amnioreduction group, because a planned interim analysis demonstrated a significant benefit in the laser group. As compared with the amnioreduction group, the laser group had a higher likelihood of the survival of at least one twin to 28 days of age (76 percent vs. 56 percent; relative risk of the death of both fetuses, 0.63; 95 percent confidence interval, 0.25 to 0.93; P=0.009) and 6 months of age (P=0.002). Infants in the laser group also had a lower incidence of cystic periventricular leukomalacia (6 percent vs. 14 percent, P=0.02) and were more likely to be free of neurologic complications at six months of age (52 percent vs. 31 percent, P=0.003).

CONCLUSIONS

Endoscopic laser coagulation of anastomoses is a more effective first-line treatment than serial amnioreduction for severe twin-to-twin transfusion syndrome diagnosed before 26 weeks of gestation.

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Monochorionic twin pregnancies complicated by severe twin-to-twin transfusion syndrome[1] before 26 weeks of gestation are associated with high risks of fetal loss, perinatal death, and subsequent handicap in the survivors.[2-5] The prognosis for untreated severe twin-to-twin transfusion syndrome is dismal,[6] with perinatal mortality rates of up to 90 percent.[7] The optimal initial treatment of this complication remains controversial. Uncontrolled series have suggested that two approaches reduce mortality. Serial amnioreduction is widely available and involves the repetitive removal of large volumes of amniotic fluid. The rationale for this technique is to prevent preterm delivery related to polyhydramnios and to improve fetal hemodynamics by decreasing pressure on the placental surface. Survival rates of 18 to 83 percent have been reported,[8-17] with rates of neurologic complications ranging from 5 to 58 percent.[12,14,15,18-21] Fetoscopic laser coagulation of placental vascular anastomoses responsible for the syndrome, a procedure performed in a few specialized centers, has been reported to result in survival rates between 55 and 69 percent,[22-25] with rates of subsequent neurologic complications ranging from 5 to 11 percent.[21,22,26,27]

Two nonrandomized studies comparing both techniques have suggested that endoscopic surgery results in lower mortality rates (with the survival of at least one twin in 71 to 83 percent of procedures) and lower rates of neurologic complications than serial amnioreduction[13,21]; however, these comparisons may be biased. We therefore conducted a randomized, controlled trial to compare the safety and efficacy of laser surgery and amnioreduction in severe twin-to-twin transfusion syndrome diagnosed before 26 weeks of gestation.

METHODS

DESIGN AND STUDY POPULATION

Women presenting between 15 and 26 weeks of gestation with severe twin-to-twin transfusion syndrome were invited to participate. Inclusion criteria were polyuric polyhydramnios in the recipient twin, with the deepest vertical pool measuring at least 8.0 cm at or before 20 weeks of gestation or 10.0 cm after 20 weeks of gestation and a distended fetal bladder, and oliguric oligohydramnios in the donor twin, with the deepest vertical pool measuring at most 2.0 cm. The Quintero staging system was used to describe the fetuses.[28] Exclusion criteria were fetal death, a major fetal anomaly, ruptured membranes, a maternal condition mandating delivery, and any previous invasive therapy for the syndrome. Placentas were assessed after delivery to confirm chorionicity.

The protocol was advertised to all fetal-medicine units on the Eurofoetus Web site (www.eurofoetus.org) and was approved by the institutional review board at each center. Each woman or couple gave written informed consent. Consenting women were allocated to laser surgery or amnioreduction with the use of a password-protected Web-based system, which assigned treatments according to an unrestricted random sequence of numbers.

Before randomization, termination of pregnancy was offered as an alternative to treatment. Once a woman underwent randomization, the possibility of termination of pregnancy was discussed when there was evidence of worsening fetal condition — the development of hydrops, critical pulmonary stenosis as defined by a fetal cardiologist, or brain lesions (grade 3 or 4 intraventricular hemorrhage, porencephaly, or hydrocephaly) — despite therapy. Women were also offered the opportunity to cross over to the other treatment options when any of the above conditions were present. Women who crossed over to the alternative therapy were analyzed according to the intention-to-treat principle.

INTERVENTIONS

All procedures were performed percutaneously, with the patient under local or regional anesthesia; laparotomy was not performed. The site of entry on the maternal abdomen was chosen to allow access to the intertwin membrane's insertion on the placental surface through the recipient's sac with the use of a 3.3-mm cannula with a trocar under continuous ultrasonographic guidance. A 2-mm fetoscope (50,000 pixels, model 11630, Karl Storz; developed in collaboration with Gèrard Barki) and a neodymium:yttrium–aluminum–garnet or diode laser with a fiber that had a diameter of 400 to 600 μm were used. Vessels crossing the membranes were followed to identify the anastomotic vessels in the recipient's sac. They were left intact when the examination could confirm that they belonged to just one twin but were otherwise coagulated with a nontouch technique with the use of an output of 30 to 60 W. Amniotic fluid was subsequently drained through the cannula until the deepest pool was a maximum of 5 to 6 cm on ultrasonography.

Amnioreduction was performed in the polyhy-

dramniotic sac, with the patient under local analgesia and continuous ultrasonographic guidance, with the use of an 18-gauge needle and either syringe aspiration or wall suction. Amniotic fluid was drained until the deepest pool was 5 to 6 cm. Amnioreduction was repeated whenever polyhydramnios recurred, according to the inclusion criteria.

Laser coagulation was performed at the three centers that had appropriate equipment and experience at the time of the study. Amnioreduction was performed by experienced operators at these 3 and 14 other fetal-medicine units. Prophylactic tocolytics and antibiotics were administered perioperatively. All women were kept in the hospital for 24 to 48 hours after the procedure and then treated as outpatients with weekly ultrasonographic follow-up. Treatment was considered ineffective when there was recurrence of polyhydramnios, as defined in the inclusion criteria. Subsequent antenatal care, delivery, and neonatal management were provided by the referring hospital. The decision to deliver was based on obstetrical indications and was made by the treating perinatologist, but all deliveries were performed no later than 37 completed weeks of gestation. For practical reasons, the treating perinatologist was not blinded to therapy. Perinatal and infant data were provided by the treating clinicians, and outcomes were assigned by one neonatologist who had no knowledge of the assigned treatment.

OUTCOME VARIABLES

The primary outcome measures, which were prespecified when the trial was initiated, included perinatal survival of at least one twin, survival of at least one twin to 7 to 12 months of age, and neurologic complications at 7 to 12 months of age. All outcome measures were evaluated on the basis of the number of pregnancies or the number of fetuses or infants, as appropriate. Other outcome measures included maternal complications (placental abruption, intraabdominal hemorrhage or leakage of amniotic fluid with peritoneal irritation, chorioamnionitis, and amniotic-fluid embolism) and fetal complications. The perinatal period was defined as the interval from randomization to 28 days of postnatal life. The present report includes data on perinatal mortality and outcomes to six months of age.

Pregnancy loss was defined as delivery before 24 weeks of gestation. Death was classified as intrauterine death after 24 weeks of gestation, death between delivery and 24 hours, death between 25 hours and less than 1 week, death from 1 week to less than 28 days, and death at 28 days or more. Clinically significant neurologic complications were defined in all infants as severe intraventricular hemorrhage (grade III or IV),[29] cystic periventricular leukomalacia,[30] blindness, and deafness. Brain ultrasonographic or magnetic resonance imaging (MRI) was performed at the perinatal centers where the infants received care when it was considered clinically indicated by the treating clinicians. All centers routinely performed brain ultrasonography twice in the first two weeks of life and MRI whenever the clinical examination, ultrasonography, or both were suggestive of an abnormality. Children free of any of the above complications at six months of age were reported to be "alive without major neurological morbidity."

STATISTICAL ANALYSIS

Local investigators entered all data prospectively in a Web-based database. Analyses were carried out on an intention-to-treat basis. For outcomes related to a single fetus or infant, methods were used that adjusted for the inherent correlation between twins.[31] Continuous variables were reported as means (±SD) or medians and interquartile ranges (25th and 75th percentiles); groups were compared with the use of the t-test or the Wilcoxon test, accordingly. The effect of the intervention was estimated in terms of the relative risk and 95 percent confidence interval. Proportions were compared with the use of the chi-square or Fisher's exact test. Kaplan–Meier time-to-event curves were compared with the log-rank test. In the analysis of the time to delivery, data were censored at the time of the termination of pregnancy. Data management and analysis were performed with the use of Epi Info (CDC). Analysis of clustered data was performed with the use of Acluster software (Update Software).

We calculated that 172 women would be needed in each group to demonstrate a 15 percent difference in survival between groups (70 percent vs. 55 percent) with an α of 0.05, a two-tailed analysis, and a β of 0.20. Two interim analyses were planned (after the inclusion of 72 and 144 women) to evaluate the rates of survival of at least one twin to discharge from the neonatal intensive care unit (NICU) — an end point that was considered to be more clinically relevant than survival at 28 days. The first interim analysis did not reveal significant differences between the groups, but the second interim analysis

(which involved 142 pregnancies, since 2 women were entered in the database twice) showed a significantly higher rate of survival of at least one twin to discharge from the NICU in the laser group than in the amnioreduction group (P=0.002), according to the O'Brien–Fleming rule, with adjustment for multiple evaluations of the data.[32] The industrial partner had no role in the study design, data analysis or interpretation, the writing of the report, or the decision to publish.

RESULTS

CHARACTERISTICS OF THE WOMEN

A total of 142 women — 72 in the laser group and 70 in the amnioreduction group — were enrolled in the study between January 1999 and March 2002. Women were recruited in six countries: France (122 women), Belgium (13), the Netherlands (3), Switzerland (2), Italy (1), and the United States (1). Data on the perinatal outcome were available for all pregnancies.

At inclusion, the groups were similar with respect to demographic, clinical, and ultrasonographic characteristics, except for an imbalance in placental location, with more anterior insertions in the amnioreduction group than in the laser group (57 percent vs. 42 percent) (Table 1). In both groups, the majority of fetuses were classified as Quintero stage 2 or 3.[28] Postnatal examination of the placenta confirmed monochorionicity in all but one case (dichorionic placenta) in the amnioreduction group.

INTERVENTIONS

Three women in the laser group did not undergo the procedure. Two of the women were not treated because they did not meet the criteria for treatment after evaluation. In the third woman, both fetuses died in utero 24 hours after randomization and before the procedure could be performed. The primary procedure failed within two weeks in three other women. Two of these underwent a second laser procedure, and amnioreduction was performed after 26 weeks of gestation in the third woman (since the study protocol did not allow laser coagulation after 26 weeks of gestation).

Two women in the amnioreduction group did not undergo the procedure. In one woman, both fetuses died in utero within hours after randomization and before the procedure was performed. The other woman withdrew her consent for amnioreduction and requested laser treatment, which was performed. Six women subsequently underwent a laser procedure for cardiac decompensation in the recipient fetus after two to six amnioreductions.

None of the women died or required a blood transfusion or admission to the intensive care unit. Placental abruption necessitating delivery occurred in one woman in the laser group and two women in the amnioreduction group (Table 2). No women had symptoms or signs of amniotic-fluid embolism. Abdominal pain related to intraperitoneal leakage of amniotic fluid through the uterine puncture was managed expectantly and resolved in two women in the laser group. The incidences of preterm rupture of the membranes and of fetal death within 7 days

Table 1. Baseline Characteristics.*

Characteristic	Laser Group (N=72)	Amnioreduction Group (N=70)
Maternal		
Age — yr	31.8±5.1	31.5±5.1
Nulliparity — no. (%)	28 (39)	23 (33)
Gestational age at randomization — wk	20.6±2.4	20.9±2.5
Location of placenta — no. (%)		
Anterior	30 (42)	40 (57)
Posterior	42 (58)	30 (43)
Fetal		
Size of deepest pool of amniotic fluid — cm		
Recipient		
Mean	12.2±2.8	12.5±2.5
Range	8–24	8–19
Donor		
Mean	0.4±0.6	0.4±0.6
Range	0.0–2.0	0.0–1.8
Distended bladder in recipient — no. (%)	72 (100)	70 (100)
Collapsed bladder in donor — no. (%)	58 (81)	59 (84)
>20% Discrepancy in AC — no./total no. (%)†	33/68 (48)	25/66 (38)
Quintero stage — no. (%)		
Stage 1 (abnormal amniotic-fluid levels alone)	6 (8)	5 (7)
Stage 2 (collapsed bladder in donor)	31 (43)	31 (44)
Stage 3 (abnormal Doppler flow in either twin)	34 (47)	33 (47)
Stage 4 (hydrops in either twin)	1 (1)	1 (1)

* Plus–minus values are means ±SD. There were four missing values for abdominal circumference (AC) in each group. The AC ratio was calculated according to the following equation: (recipient's AC–donor's AC)÷recipient's AC.

Table 2. Procedures and Complications.*

Variable	Laser Group (N=69)	Amnioreduction Group (N=68)	P Value
No. of procedures	NA†	2.6±1.9	—
No. of anastomoses detected endoscopically	5.8±2.7	NA	—
Volume of amniotic fluid drained per procedure — ml‡			—
Median	1725	2000	
Range	500–5500	243–4000	
Total volume of amniotic fluid drained — ml‡			<0.001
Median	1725	3800	
Range	500–5500	600–18,000	
Maternal complications — no. of women (%)			
Intraabdominal leakage of amniotic fluid	2 (3)	0	0.50
Placental abruption	1 (1)	2 (3)	0.62
Pregnancy loss within 7 days after the initial procedure — no. of women (%)	8 (12)	2 (3)	0.10
Premature rupture of membranes within 7 days after the initial procedure — no. of women (%)	4 (6)	1 (1)	0.37
Premature rupture of membranes within 28 days after the initial procedure — no. of women (%)	6 (9)	6 (9)	0.98
Intrauterine death within 7 days after the initial procedure — no./total no. of fetuses (%)	16/138 (12)	9/136 (7)	0.23§

* Five women who did not undergo the assigned procedure were excluded: three in the laser group and two in the amnioreduction group. Plus–minus values are means ±SD. NA denotes not applicable.
† Only two women in the laser group had a second laser procedure.
‡ The value in the laser group is the median volume drained at the end of a single procedure.
§ The P value was adjusted for clustering.

and 28 days after the procedure were similar in the two groups (Table 2).

PREGNANCY OUTCOMES

During the perinatal period, the rate of survival of at least one twin was significantly higher in the laser group than in the amnioreduction group (76 percent vs. 56 percent of pregnancies; relative risk of the death of both fetuses, 0.63; 95 percent confidence interval, 0.25 to 0.93; P=0.009). The rate of survival of at least one twin was also significantly higher at six months in the laser group than in the amnioreduction group (76 percent vs. 51 percent of pregnancies; relative risk of the death of both fetuses, 0.51; 95 percent confidence interval, 0.07 to 0.86; P=0.002) (Table 3).

In the subgroup of women with an anterior placenta, 87 percent of those in the laser group had at least one twin alive at six months, as compared with 48 percent of those in the amnioreduction group; the respective values for women with a posterior placenta were 69 percent and 57 percent. Adjustment for placental location did not change the likelihood of survival of at least one twin to six months of age in the laser group, as compared with the amnioreduction group (relative risk of the death of both fetuses, 0.51; 95 percent confidence interval, 0.07 to 0.85). The rate of survival of at least one twin at the age of six months was higher among women whose pregnancies had been classified as Quintero stage 1 or 2 (53 of 73 [73 percent]) than among those whose pregnancies were classified as stage 3 or 4 (38 of 69 [55 percent]). However, the survival rate was higher in the laser group than in the amnioreduction group for all Quintero stages.

There was no significant difference in the rate of pregnancy loss before 24 weeks of gestation in the laser group as compared with the amnioreduction group (17 percent vs. 11 percent, P=0.37). Two pregnancies in the laser group resulted in the intrauterine death of both fetuses, as compared with five in the amnioreduction group (P=0.27). The median gestational age at delivery was significantly older in the laser group than in the amnioreduction group (33.3 weeks vs. 29.0 weeks, P=0.004), with 30 women (42 percent) and 48 women (69 percent), respec-

tively, delivering before 32 weeks of gestation (Table 3). The interval between randomization and delivery was longer in the laser group (P=0.006) (Fig. 1).

PERINATAL AND PEDIATRIC OUTCOMES

The rate of perinatal survival was significantly higher in the laser group than in the amnioreduction group (57 percent vs. 41 percent, P=0.02). The rate of survival to six months of age was also higher in the laser group (P=0.01) (Table 3). Among the liveborn infants, those in the laser group had a higher birth weight than those in the amnioreduction group (1757 g vs. 1359 g, P<0.001); the differences between groups were significant for both recipients (P=0.02) and donors (P=0.01).

Eleven women in the amnioreduction group, as compared with none in the laser group, requested and underwent termination of pregnancy at 21 to 25 weeks of gestation for the following indications: worsening of the syndrome after one to four amnioreductions in four women, ultrasonographic evidence of severe intracranial hemorrhage or porencephalic cysts in the surviving twin after the intrauterine death of one twin in six women, and critical pulmonary stenosis and tricuspid atresia in the surviving recipient twin after the intrauterine death of the donor twin in one woman. Two fetuses in the laser group had grade 3 intraventricular hemorrhage, and eight (two in utero and six in the postnatal period) had cystic periventricular leukomalacia, respectively. These findings were therefore considered indicative of treatment failure. Overall, a significantly higher percentage of infants were alive without major neurologic complications at the age of six months in the laser group than in the amnioreduction group (P=0.003) (Table 4).

Cystic periventricular leukomalacia was diagnosed in the neonatal period in 12 infants (4 in the laser group and 8 in the amnioreduction group), which resulted in spontaneous neonatal death in 3 and the withdrawal of intensive care in 9 within the first six months of life. Among infants who were alive at six months, 4 of 88 in the laser group (5 percent) and 6 of 58 in the amnioreduction group (10 percent) had overt cystic periventricular leukomalacia. Other major neurologic complications were present in two infants (2 percent) in the laser group at six months (grade 3 intraventricular hemorrhage and blindness) and four (7 percent) in the amnioreduction group (blindness in one and gross motor impairment in three). In the subgroup of twins in which one twin died in utero, cerebral lesions (intraventricular hemorrhage or periventricular leukomalacia) were diagnosed in 7 percent of the surviving twins in the laser group, as compared with 35 percent of those in the amnioreduction group (2 of 29 vs. 7 of 20; relative risk of cerebral lesions, 0.20; 95 percent confidence interval, 0.05 to 0.85; P=0.02).

Table 3. Obstetrical Outcomes and Interventions.

Variable	Laser Group (N=72)	Amnioreduction Group (N=70)	P Value
Survival at 6 mo — no./total no. of pregnancies (%)			
0 Survivors	17/72 (24)	34/70 (49)	
1 Survivor	29/72 (40)	18/70 (26)	
2 Survivors	26/72 (36)	18/70 (26)	
At least 1 survivor	55/72 (76)	36/70 (51)	0.002
Quintero stage 1 or 2*	32/37 (86)	21/36 (58)	0.007
Quintero stage 3 or 4*	23/35 (66)	15/34 (44)	0.07
Gestational age at delivery — wk			0.004
Median	33.3	29.0	
Interquartile range	26.1–35.6	25.6–33.3	
Gestational age at delivery — no. of pregnancies (%)			0.003†
<24 wk	12 (17)	8 (11)	
24 to <27 wk	9 (12)	22 (31)	
28 to 31 wk	9 (12)	18 (26)	
32 to <33 wk	9 (12)	7 (10)	
34 to 35 wk	17 (24)	11 (16)	
≥36 wk	16 (22)	4 (6)	
Cesarean section — no./total no. of pregnancies‡	34/60 (57)	34/49 (69)	0.17

* The Quintero staging system is defined as follows: stage 1, abnormal amniotic-fluid levels alone, with bladder filling in the donor; stage 2, collapsed bladder in the oliguric donor; stage 3, abnormal Doppler flow in the umbilical artery or the ductus venosus of either twin (suggesting the presence of impaired fetal hemodynamics); stage 4, hydrops (suggesting cardiac failure) in either twin; and stage 5, intrauterine death of either twin.

† The chi-square test was used, with 5 degrees of freedom.

‡ Calculations excluded women in whom both fetuses died in utero (2 in the laser group and 7 in the amnioreduction group), those who had the pregnancy terminated (0 and 11, respectively), and those who delivered before 24 weeks of gestation (12 and 8, respectively).

DISCUSSION

This multicenter randomized trial showed that in severe twin-to-twin transfusion syndrome treated before 26 weeks of gestation, laser therapy resulted in higher survival rates and better neurologic out-

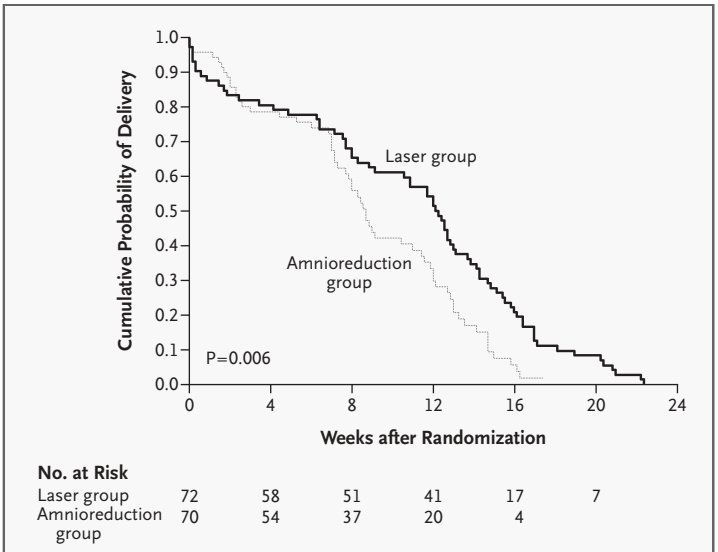

Figure 1. Interval between Randomization and Delivery.
Data on women whose pregnancies were terminated were censored.

comes than did amnioreduction, both in the perinatal period and during the first six months of life.

The rate of pregnancy loss within seven days after the procedure was higher in the laser group than in the amnioreduction group, but not significantly so. Pregnancy losses shortly after laser therapy may be explained by damage to the placental vessels during the procedure. There were more terminations of pregnancy in the amnioreduction group. These were requested after the diagnosis of severe fetal complications, which occurred more frequently in the amnioreduction group than in the laser group. The number of live births was similar in the two groups, but neonatal death was more frequent in the amnioreduction group; this difference is likely to be attributable to the older gestational age at delivery in the laser group. Repeated invasive procedures and recurrence of polyhydramnios may explain the higher rate of preterm delivery in the amnioreduction group. The difference in cumulative delivery rates was particularly prominent 4 to 8 weeks after the initial procedure, which corresponds to 24 to 28 weeks of gestation, a critical period of extreme prematurity.

Recruitment for the study was terminated after the planned interim analysis showed that laser therapy was associated with a significantly higher rate of the survival of at least one infant to discharge from the NICU. This outcome is considered to be more clinically relevant than the perinatal mortality rate, a prespecified primary outcome; in our study group, one neonate in the laser group and four in the amnioreduction group survived to 28 days but not to discharge from the NICU. It is unlikely that the results would have changed with the inclusion of more women.

None of the infants died after being discharged from the NICU, and thus, the survival rate at six months is likely to be representative of those obtained with longer follow-up. Reliable assessment of neurologic abnormalities will require longer follow-up, since cerebral palsy cannot be diagnosed reliably before the age of two years. However, the presence of cystic periventricular leukomalacia or grade 3 or 4 intraventricular hemorrhage in the neonatal period is a strong predictor of the subsequent diagnosis of this condition.[3] These complications are believed to develop as a result of severe hemodynamic imbalance, especially when one twin dies in utero and patent intertwin vascular communications on the placenta allow extensive transfer of blood from the surviving twin to the dead twin.[33] We found a significantly lower risk of cystic periventricular leukomalacia in the laser group, both overall and in instances in which one twin had died in utero.

Quintero et al. reported that the fetal status is an important prognostic factor when therapy involves amnioreduction, but not when laser therapy is used.[21] In contrast, we observed that fetuses in Quintero stage 1 or 2 had better outcomes than those with higher stages in both treatment groups. Whereas previous data suggested a benefit for laser therapy only for fetuses in stage 3 or 4,[21] we found that laser therapy was also beneficial for fetuses in stage 1 or 2 and conclude that staging should not influence the choice of treatment.

Our study has potential limitations. One is the imbalance in placental location between the two groups despite the randomized design. However, subgroup analyses according to the placental location and adjustment for placental location in multivariate analysis suggest that this imbalance does not account for the differences in outcomes between the two groups. Perinatal management was not standardized, but the level of care was similar in all perinatal units involved in the care of the preterm babies. The neonates were assessed at their local perinatal center, where clinicians were aware of the treatment received in utero. However, outcomes were assigned by one neonatologist who was blind-

Table 4. Perinatal and Infant Outcomes.

Outcome	Laser Group (N=144)	Amnioreduction Group (N=140)	Relative Risk (95% CI)*	P Value
All deaths — no./total no. of infants or fetuses (%)	63/144 (44)	86/140 (61)	0.71 (0.55–0.92)†	0.01†
Donor	33/72 (46)	42/70 (60)	0.76 (0.56–1.05)	0.09
Recipient	30/72 (42)	44/70 (63)	0.66 (0.48–0.92)	0.01
Delivered before viability (<24 wk of gestation) — no./total no. of fetuses (%)	24/144 (17)	16/140 (11)		
Intrauterine death at ≥24 wk of gestation — no./total no. of fetuses (%)	27/144 (19)	29/140 (21)		
Neonatal or infant death — no./total no. of infants (%)	12/144 (8)	41/140 (29)		0.009
Within 24 hr after delivery	6/144 (4)	26/140 (19)		
2–7 days after delivery	4/144 (3)	6/140 (4)		
8–28 days after delivery	1/144 (1)	5/140 (4)		
>28 days after delivery	1/144 (1)	4/140 (3)		
Intraventricular hemorrhage (grade III or IV) — no./total no. of fetuses (%)‡	2/144 (1)	8/140 (6)	0.24 (0.05–1.11)†	0.10†
Donor	2/72 (3)	2/70 (3)	0.97 (0.14–6.71)	1.0
Recipient	0/72	6/70 (9)	—	0.02
Cystic periventricular leukomalacia — no./total no. of fetuses (%)§	8/144 (6)	20/140 (14)	0.39 (0.18–0.86)†	0.02†
Donor	2/72 (3)	5/70 (7)	0.39 (0.08–1.94)	0.27
Recipient	6/72 (8)	15/70 (21)	0.39 (0.16–0.94)	0.03
Alive without major neurologic complications at 6 mo — no./total no. of infants (%)	75/144 (52)	44/140 (31)	1.66 (1.17–2.34)†	0.003†
Donor	36/72 (50)	25/70 (36)	1.40 (0.95–2.07)	0.09
Recipient	39/72 (54)	19/70 (27)	2.00 (1.29–3.09)	0.001

* CI denotes confidence interval.
† The analysis was adjusted for clustering between twins.
‡ Severe intraventricular hemorrhage was defined as ventricular bleeding with dilatation of the cerebral ventricles (grade III) or parenchymal hemorrhage (grade IV).[29]
§ Cystic periventricular leukomalacia was defined as periventricular densities evolving into extensive cystic lesions (grade III) or extending into the deep white matter and evolving into cystic lesions (grade IV).[30]

ed to treatment allocation. Laser therapy was performed by experienced operators at three specialized centers, and further study is needed to assess whether these results will be generalizable.

Our results show that selective endoscopic laser coagulation of the chorionic-plate communicating vessels results in higher survival rates and lower rates of neurologic complications at 6 months of age than serial amnioreduction in severe twin-to-twin transfusion syndrome presenting before 26 weeks of gestation. Better understanding of the long-term outcomes of this therapy awaits follow-up assessments of the survivors.

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APPENDIX

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