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Article

Neonatal Outcome in Twin-to-Twin Transfusion Syndrome *Not* Treated with Fetoscopic Laser Surgery

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Abstract

The aim of this study was to describe the neonatal management and outcome in monochorionic twins with twin-to-twin transfusion syndrome (TTTS) not treated with fetoscopic laser surgery. All consecutive live-born neonates with TTTS managed at our center between 2002 and 2021 were included in this retrospective study. Neonatal outcome was assessed in 44 twin pairs with TTTS not treated with laser (nonlaser group) compared to a control group of 88 twin pairs with TTTS successfully treated with laser (laser group), matched for gestational age at birth. Primary outcome was adverse neonatal outcome, a composite outcome including neonatal mortality or severe neonatal morbidity. The incidence of adverse neonatal outcome in the nonlaser group and laser group was 30% (26/88) and 11% (19/176), respectively (relative risk = 3.46, 95% CI [1.79, 6.71]). In the nonlaser group, 11% had necrotizing enterocolitis (vs. 2% in the laser group) and 24% had hypotension (vs. 10% in the laser group). Recipients in the nonlaser group had, compared to recipients in the laser group, significantly more severe cerebral injury (18% vs. 5%) and more polycythemia at birth (21% vs. 1%). Donors in the nonlaser group had, compared to donors in the laser group, more severe growth restriction (71% vs 42%), renal failure (11% vs 1%), and anemia at birth (25% vs. 7%). Thus, the risk for neonatal mortality and/or severe morbidity is three-fold higher in TTTS not treated with laser than in TTTS treated with laser, which highlights the fact that these neonates with TTTS are very sick at birth, requiring accurate and prompt intensive treatment.

Keywords: Twin-to-twin transfusion syndrome; amnioreduction; fetoscopic laser surgery; neonatal outcome; morbidity; mortality

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Twin-to-twin transfusion syndrome (TTTS) is a major complication that occurs in approximately 10−15% of monochorionic twin pregnancies (Bamberg & Hecher, 2019). TTTS results from an imbalanced blood flow through placental vascular anastomoses causing hypovolemia, oliguria and oligohydramnios in the donor twin, and hypervolemia, polyuria, and polyhydramnios in the recipient twin (Lewi et al., 2003). Rapid development of polyhydramnios can lead to maternal discomfort, premature rupture of membranes, and eventually (extreme) preterm delivery (Lewi et al., 2003). When left untreated, TTTS is associated with high mortality rates up to 80−90% (Bamberg & Hecher, 2019; Lewi et al., 2003).

The two main treatment options for TTTS are serial amnioreduction and fetoscopic laser occlusion of vascular anastomoses (Senat et al., 2004). The aim of amnioreduction is to prevent preterm delivery by reducing the intrauterine pressure and maternal discomfort. Amnioreduction is regarded as a symptomatic treatment as it does not treat the underlying cause of TTTS. The polyhydramnios may quickly return and the procedure must be repeated several times.

In contrast, fetoscopic laser surgery is regarded as a causal treatment since its aim is to occlude the anastomosing placental vessels and interrupt the intertwin transfusion of blood. In 2004, a randomized controlled trial showed a higher rate of perinatal survival and a lower rate of cerebral injury in the laser surgery group compared to the amnioreduction group (Senat et al., 2004). Since then, fetoscopic laser surgery is worldwide regarded as the optimal treatment for TTTS.

However, laser surgery is a complex procedure only performed in specialized centers and is not available in all countries (Rossi & D'Addario, 2008). In addition, not all twin gestations with TTTS are treated with laser surgery. For example, laser surgery is not routinely performed in TTTS cases with late presentation, in low stage TTTS, or when imminent delivery is required due to acute fetal distress. In these cases, conservative management with serial amnioreduction, expectant management, or induced delivery (depending of the gestational age at presentation) may be envisaged. Detailed information on the perinatal mortality and morbidity in this TTTS group not managed with laser surgery is sparse. Knowledge of the clinical course and outcome in TTTS not treated with laser is important to guide clinical management and in the counseling of parents in such circumstances.

The aim of this study is to describe the neonatal management and outcome in monochorionic twins with TTTS *not* treated with laser, and to characterize the neonatal morbidity including

cerebral, cardiovascular, hematological, gastrointestinal, pulmonal, and renal disorders.

Methods

All live-born monochorionic twin pairs with TTTS managed conservatively with either serial amnioreduction or expectant management, and delivered at the Leiden University Medical Center (LUMC) between May 2002 and May 2021 were included in this study (nonlaser group). Each twin pair was matched with a control group of two consecutive twin pairs with TTTS successfully treated with fetoscopic laser surgery and delivered at the same gestational age +/− 1 week (laser group). Monochorionic twins with major congenital abnormalities, with single or double fetal demise, and triplet pregnancies were excluded from the study. Fetoscopic laser surgery was the standard treatment at the LUMC in all TTTS cases presenting before 26 weeks with TTTS > stage 1, or stage 1 TTTS with symptomatic polyhydramnios.

TTTS was diagnosed and staged using standard prenatal ultrasound criteria (Bamberg & Hecher, 2019). Successful treatment with laser surgery was defined as the absence of recurrent TTTS or postlaser TAPS. Postlaser TAPS was defined as the presence of hemoglobin difference at birth > 8 g/dL and at least one of these two criteria: reticulocyte count ratio >1.7 or residual vascular anastomoses at placenta color dye injection (Slaghekke et al., 2010).

For both TTS groups, with and without laser surgery, we recorded the gestational age at first diagnosis (weeks), the interval between diagnosis and birth (weeks), mode of delivery, gestational age, and birth weight at delivery. In the group not treated with laser, we recorded the reason for which fetoscopic laser surgery was not performed and whether the resolution of TTTS occurred prior to birth (regression), or whether TTTS progressed to higher stages (progression). In addition, we recorded the following neonatal morbidities: respiratory distress syndrome, symptomatic patent ductus arteriosus requiring indomethacin therapy or surgical closure, right ventricular outflow tract obstruction (RVOTO), persistent pulmonary hypertension neonate (PPHN) requiring treatment with nitric oxide, hypotension requiring inotropic support, necrotizing enterocolitis (NEC) > stage II, renal failure (defined as oliguria and creatinine > 150 μmol/l), anemia at birth requiring blood transfusion, and polycythemia requiring partial exchange transfusion. Hemoglobin levels were routinely measured at birth from umbilical cord blood. Small for gestational age was defined as birth weight less than 10th centile.

We recorded the presence of severe cerebral injury on ultrasound scans defined as the presence of at least one of the following findings: intraventricular hemorrhage (IVH) ≥ grade III, cystic periventricular leukomalacia ≥ grade II, or posthemorrhagic ventricular dilation. Cerebral ultrasound scans were routinely obtained in all neonates on the first day of life and thereafter according to our unit protocol. The cerebral ultrasound protocol at our neonatal ward requires a minimum of three scans during the first week of life (days 1, 3, and 7), followed by weekly scans thereafter until discharge or transfer to another hospital.

The primary outcome measure was a composite outcome termed adverse neonatal outcome and defined as neonatal death within 28 days, severe cerebral lesions, NEC > stage 2, renal failure, RVOTO, or PPHN.

Outcome parameters were described as either absolute numbers and percentages for categorical variables, or mean and standard deviation (*SD*) for continuous and normally distributed variables. Results of categorical variables were compared using Fisher's exact test or Pearson chi square test, as appropriate. Results of

continuous normally distributed variables were compared using an independent *t* test. A statistical significant difference was defined as *p* < .05. Statistical analyses were carried out using SPSS version 27 (IBM, Armonk, NY, USA).

Results

A total of 44 twin pairs with TTTS managed without laser surgery were included in our study. Fetoscopic laser surgery was not performed in these twin pregnancies for the following reasons: 16 (36%) presented with TTTS after 26 weeks of gestation, 12 (27%) twin pairs had asymptomatic stage 1 TTTS, in 9 (20%) cases laser surgery was deemed technically impossible and in 7 (16%) cases an emergency cesarean section had to be performed due to fetal distress. Serial amnioreduction was performed in 28 (63%) cases. In the TTTS group not treated with laser, 32 (73%) TTTS cases had the same TTTS stage at diagnosis and at birth, 8 (18%) TTTS cases progressed to higher stages after diagnosis, 4 (9%) TTTS cases regressed to lower stages (of which 1 resolved spontaneously).

The baseline and perinatal characteristics in the nonlaser group and the control group of TTTS cases treated with laser are presented in Table 1. Median gestational age at birth was 30.4 weeks in both groups. The percentage of Quintero stage 1 at diagnosis was higher in the nonlaser group (48% vs. 19%, *p* = .001) as well as the percentage of cesarean section (71% vs. 44%, *p* < .001).

Donor twins in the nonlaser group were more often small for gestational age (71%) than donors in the laser group (42%; *p* = .002). Donors in the nonlaser group also had lower hemoglobin levels than donors in the laser group, 14.3 versus 16.6 g/dL (*p* = .001), whereas recipient twins in nonlaser group had higher hemoglobin levels than recipient twins in the laser group, 17.9 versus 16.6 dg/dL (*p* = .033).

Neonatal mortality and morbidity are presented in Table 2. Overall, the rate of adverse neonatal outcome was higher in the nonlaser group compared to the laser group, 30% versus 11% (*OR* 3.465; 95% CI [1.790, 6.708]). Severe cerebral injury was detected more often in the nonlaser group (14% vs. 5%) and was primarily due to a higher risk of cerebral injury in the recipient twins (18%). Hypotension requiring inotropic support occurred more often in the nonlaser group (24% vs. 10%) and was present in both donors and recipients. Similarly, severe NEC (> grade 2) occurred more frequently in the nonlaser group (11% vs. 2%), both in donors as in recipients.

Specific conditions were particularly more prominent in donor twins in the nonlaser group, such as a higher risk of anemia (25% vs. 7% in the laser group) and renal failure (11% vs. 1% in the laser group), whereas recipient twins in the non-laser group had more often polycythemia at birth (21% vs. 1% in the laser group) and more often severe cerebral injury (18% vs. 5% in the laser group).

The rate of adverse neonatal outcome in the nonlaser group divided in subgroups depending on the indication for not treating with laser surgery was 34% (11/32) for the group presenting with TTTS after 26 weeks of gestation, 33% (8/24) for the group with TTTS stage 1, 29% (4/14) for the group undergoing an emergency cesarean section due to fetal distress, and 17% (3/18) in the subgroup for which laser surgery was deemed technically impossible.

Discussion

This is the first study reporting in detail the neonatal outcome in the small group of TTTS twins not treated with laser surgery. We found that twins with TTTS not treated with laser surgery had a high rate of adverse neonatal outcome (30%), with a three times higher relative risk compared to twins in the laser group. The

Table 1. Patients' characteristics during pregnancy and at delivery

	Nonlaser group (n = 44 twin pregnancies; 88 live-born twins)	Laser group (n = 88 twin pregnancies; 176 live-born twins)	p value
Quintero stage – n (%)			.001
Stage 1	21 (48%)	16 (19%)	
Stage 2	5 (11%)	22 (26%)	
Stage 3	14 (32%)	44 (51%)	
Stage 4	4 (9%)	4 (5%)	
GA at TTTS diagnosis — wks	27.6 ± 3.1	20.2 ± 3.4	<.001
Interval between diagnosis and birth — weeks	2.6 ± 3.6	10.0 ± 3.4	<.001
Cesarean section – n (%)	31 (71%)	38 (44%)	<.001
Gestational age at birth – weeks	30.4 ± 2.9	30.4 ± 2.9	.993
Female — n (%)	46 (52%)	92 (53%)	.927
Birth weight – g	1442 ± 610	1432 ± 510	.889
Donor	1289 ± 570	1345 ± 503	.564
Recipient	1595 ± 616	1519 ± 504	.450
Birth-weight difference — %	20 ± 13	15 ± 14	.047
SGA — n (%)	34 (39%)	49 (29%)	.075
Donor	31 (71%)	37 (42%)	.002
Recipient	3 (7%)	12 (14%)	.245
Hb – g/dL	16.1 ± 4.0	16.6 ± 2.7	.330
Donor	14.3 ± 3.9	16.6 ± 2.7	.001
Recipient	17.9 ± 3.4	16.6 ± 2.9	.033
Intertwin Hb difference – g/dL	5.0 ± 4.5	2.7 ± 3.1	0.004

Note: Results show mean ± *SD* or number (%). GA, gestational age; SGA, small for gestational age.

neonates not treated with laser had high rates of mortality (10%), NEC (11%), severe cerebral injury (14%), and hypotension (24%), highlighting the fact that these neonates with TTTS are very sick at birth and require accurate and prompt intensive treatment. Severe cerebral injury was mainly present in recipient twins (18%), whereas donors had more renal failure (11%). Interestingly, donors in the nonlaser group were often small for gestational age (71% vs. 42%). This could be due to compensatory fetal growth in donors in the laser group due to interruption of TTS after successful laser surgery. Alternatively, growth restriction in donors in the nonlaser group could be more prominent due to persistent and ongoing TTS. Anemia and polycythemia occurred more frequently in the nonlaser group due to the persisting intertwin transfusion through the placental anastomoses. Of note, the rate of anemia and polycythemia in the nonlaser group was only approximately 25%, emphasizing the fact that these hematologic abnormalities are not as predominant in TTTS as sometimes incorrectly assumed.

From a pathophysiologic point of view, it should not come as a surprise that twins with TTTS are sicker and more instable during the neonatal period and have an increased of various neonatal morbidities. After all, these neonates were already instable before birth and their adverse fetal condition continued until delivery due to the persistent intertwin transfusion through the patent anastomoses. Disorders such as hypotension, hemorrhages (IVH), NEC, and renal failure are known to be associated with circulatory imbalance and end-organ hypoperfusion and could be related to the chronic hypo- and hypervolemia during fetal life.

Detailed information in the literature on neonatal outcome in TTTS not treated with laser surgery is sparse. In a randomized trial, Senat et al. (2004) also reported higher mortality rates (29%) and higher rates of severe cerebral injury (20%) in patients treated without laser compared with the patients treated *with* laser. The focus in this randomized trial was on perinatal survival and on the occurrence of cerebral injury. The strength of our study is that we did not only focus on neonatal mortality and cerebral injury, but expanded our evaluation to other important neonatal morbidities. Another strength was that we were able to precisely match our study group with a control group with similar gestational age to eliminate prematurity as a major confounder for adverse neonatal outcome.

Nevertheless, the groups were significantly different on several levels that could have potentially affected this outcome. The twins in the nonlaser group had more Quintero stage 1 and were more often delivered through cesarean section. This difference is explained by the reasons not to perform laser surgery being TTTS stage 1, late gestational age at presentation of TTTS and emergency cesarean sections due to fetal distress. This study was obviously not designed to compare different antenatal management and our results should thus be interpreted according to our study aim, which is to describe the outcome in TTTS not treated with laser surgery. In a recent randomized trial in stage 1 TTTS in asymptomatic pregnant women with a long cervix, no difference was found between immediate laser surgery or expectant follow-up (Stirnemann et al., 2021).

A limitation of our study was the relatively small study group, since only 44 twin pairs with TTTS over the past 20 years were not

Table 2. Neonatal mortality and morbidity rates

	Non-laser group (*n* = 88)	Laser group (*n* = 176)	*p* value
Neonatal death — *n* (%)	**9 (10%)**	**9 (5%)**	.120
Donor	3 (7%)	6 (7%)	1.000
Recipient	6 (14%)	3 (3%)	.059
Severe cerebral injury — *n* (%)	**12 (14%)**	**9 (5%)**	.016
Donor	4 (9%)	5 (6%)	.480
Recipient	8 (18%)	4 (5%)	.020
Patent ductus arteriosus — *n* (%)	**10 (11%)**	**7 (4%)**	.021
Donor	5 (11%)	3 (3%)	.116
Recipient	5 (11%)	4 (5%)	.159
RVOTO — *n* (%)	**1 (1%)**	**1 (1%)**	1.000
Donor	0 (0%)	0 (0%)	–
Recipient	1 (2%)	1 (1%)	1.000
PPHN — *n* (%)	**8 (9%)**	**17 (10%)**	.882
Donor	5 (11%)	9 (10%)	1.000
Recipient	3 (7%)	8 (9%)	.751
Hypotension — *n* (%)	**21 (24%)**	**17 (10%)**	.002
Donor	11 (25%)	9 (10%)	.026
Recipient	10 (23%)	8 (9%)	.031
Anemia at birth — *n* (%)	**13 (15%)**	**10 (6%)**	.014
Donor	11 (25%)	6 (7%)	.003
Recipient	2 (5%)	4 (5%)	1.000
Polycythemia at birth — *n* (%)	**9 (10%)**	**3 (2%)**	.003
Donor	0 (0%)	2 (2%)	.314
Recipient	9 (21%)	1 (1%)	<.001
Necrotizing enterocolitis — *n* (%)	**10 (11%)**	**3 (2%)**	.001
Donor	6 (14%)	2 (2%)	.017
Recipient	4 (9%)	1 (1%)	.042
Respiratory distress syndrome — *n* (%)	**44 (50%)**	**68 (39%)**	.078
Donor	20 (46%)	33 (38%)	.379
Recipient	24 (55%)	35 (40%)	.108
Renal failure — *n* (%)	**7 (8%)**	**1 (1%)**	.002
Donor	5 (11%)	1 (1%)	.016
Recipient	2 (5%)	0 (0%)	.109
Adverse neonatal outcome — *n* (%)	**26 (30%)**	**19 (11%)**	<.001
Donor	11 (25%)	11 (13%)	.069
Recipient	15 (34%)	8 (9%)	0.001

Note: RVOTO, right ventricular outflow tract obstruction; PPHN, persistent pulmonary hypertension of the neonate.

treated with laser surgery in the LUMC. Therefore, other potential risk factors for adverse neonatal outcome could not be studied properly due to the relatively small sample size. For this same reason, we could not perform a subgroup risk analysis based on indication for not treating with laser. Furthermore, due to the retrospective nature of the study, information on maternal risk factors could not be obtained. Further research with a larger multicentered international study group is needed to obtain and more clearer information on risk factors for adverse neonatal outcome in TTTS twins *not* treated with laser, so that physicians can be even more precisely prepared and informed in the management of this specific group of TTTS twins.

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