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Fetoscopic laser coagulation in 1020 pregnancies with twin–twin transfusion syndrome demonstrates improvement in double-twin survival rate

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KEYWORDS: laser coagulation; learning curve; monochorionic twins; TTTS

ABSTRACT

Objective *To investigate the growing experience and learning curve of fetoscopic laser coagulation of the placental vascular anastomoses in severe mid-trimester twin–twin transfusion syndrome (TTTS) and its influence on perinatal outcome in a single-center setting.*

Methods *Between January 1995 and March 2013 we performed laser therapy in 1020 consecutive pregnancies with TTTS between 15.1 and 27.4 weeks' gestation. We compared perinatal outcome in blocks of five sequential groups of 200 cases, taking into account several covariates in order to adjust for case mix and to demonstrate learning curves and success rates.*

Results *The percentage of pregnancies with survival of both fetuses increased from 50.0% (*n = *100) in the first 200 cases to 69.5% (*n = *153) in the last 220 cases (*P = *0.018 for trend) and the overall survival rate for both fetuses in the complete series of 1019 cases with known outcome was 63.3% (*n = *645). The survival rate of at least one fetus increased from 80.5% (161/200) in the first group to 91.8% (202/220) in the last group (*P = *0.072 for trend) and the overall survival rate of at least one fetus in the complete series was 86.7% (883/1019). In the total population, the mean gestational age at delivery of pregnancies with at least one liveborn neonate was 33.7 ± 3.2 weeks, with a mean interval of 12.9 ± 4.0 weeks between intervention and delivery. Among the first two groups, 124 pregnancies had anterior placentae and were treated with a 0° fetoscope. These cases had the poorest overall outcome, with a double-twin survival rate of 44.4% (55/124), which increased to 65.1% (207/318;* P = *0.001) after the introduction of a 30° fetoscope for cases with anterior placenta. The success rate for double-twin survival reached a plateau of 69% at 600 procedures, a rate equalled by a new operator who was trained hands-on and performed 174 of the last 400 procedures.*

Conclusions *We report the largest single-center experience of laser coagulation in TTTS. We observed a continuous increase in double-twin survival rate owing to the growing experience based on the learning curve and refinements in fetoscopic instruments and techniques. These data provide strong arguments for the centralization of minimally invasive intrauterine surgery in specialized high-volume centers.* Copyright © 2017 ISUOG. Published by John Wiley & Sons Ltd.

INTRODUCTION

The feasibility of fetoscopic laser coagulation of placental vascular anastomoses in twin–twin transfusion syndrome (TTTS) was first shown by De Lia *et al.*[1] in 1990 after laparotomy and under general anesthesia. In contrast to serial amnioreduction, this treatment addresses directly the underlying cause of TTTS. Subsequently, Ville *et al.*[2] introduced the direct transcutaneous fetoscopic approach under local anesthesia. The superiority of laser coagulation therapy over serial amnioreduction regarding survival rates has subsequently been demonstrated in a population-based trial and a randomized controlled trial (RCT)[3,4]. Furthermore, laser therapy of TTTS leads to an improvement in long-term neurodevelopmental outcome[5–8]. However, laser therapy may lead to complications such as iatrogenic preterm prelabor rupture of membranes[9], twin anemia–polycythemia

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sequence (TAPS)[10], reversal or recurrence of TTTS[11] and intrauterine fetal death.

Since laser coagulation for TTTS was introduced in the early 1990s, almost 4000 TTTS procedures have been reported worldwide[12]. However, most reports from single centers have included fewer than 200 cases. While overall there is a significant trend of improvement in perinatal survival rates over the last 25 years, the reported outcomes show a large variation between individual centers. We hypothesized that the outcome of laser therapy for TTTS depends on the experience and caseload of a center and that there is a continuous learning curve for centers performing this procedure, including further developments in the technique of fetoscopic laser surgery.

METHODS

We report the perinatal outcome of 1020 consecutive pregnant women with severe mid-trimester TTTS who were referred to our center for endoscopic laser coagulation of placental vascular anastomoses between January 1995 and March 2013. Outcome data for the first 400 patients of this population have been reported previously by our group[13,14]. For these studies, ethical committee approval had been obtained but was no longer necessary when laser therapy became the standard medical treatment for TTTS. All patients gave written informed consent for the procedure and consented to their clinical data being used for research purposes. All fetal and procedural data were entered prospectively into a fetal database (ViewPoint Bildverarbeitung GmbH, Wessling, Germany) as were follow-up data as soon as they were available from the referral centers, which were located all over Germany, in other European countries and in the Middle East, and where further care of pregnancy was managed and delivery took place. For blockwise comparison of data, the whole population was divided into five sequential groups, of 200 patients for the first four and 220 for the last one.

The diagnosis of TTTS was made according to established criteria[15], with polyhydramnios of the recipient fetus and anhydramnios of the stuck donor fetus, and staging was according to that of Quintero *et al.*[16]. Chorionicity was established by first-trimester sonographic examination at the referring center and confirmed during detailed sonographic examination at our center. The parents were counseled extensively regarding expectant management, endoscopic laser ablation of the communicating vessels, amniodrainage and termination of pregnancy.

All procedures were performed under local anesthesia as previously reported[13,14,17]. Briefly, the fetoscope (0° telescope, Olympus, Hamburg, Germany and Hopkins telescope, 26 008 AA with sheath 26 161 UK; and for anterior placenta since June 2001, Hopkins 30° telescope 26 008 BUA with operating sheath and working insert with steering lever 26 161 UFK and UH, Storz, Tuttlingen, Germany) was introduced into the amniotic cavity of the recipient and endoscopic ablation of the vessels was performed selectively along the whole vascular equator with a 0.4-mm fiber and a Nd:YAG laser (Dornier MedTech GmbH, Wessling, Germany). Before the availability of the 30° fetoscope in June 2001, the 0° fetoscope was also used in 124 twin pregnancies with anterior placentae. At the end of the laser procedure, the amniotic fluid was drained until a normal amount remained.

All laser procedures in the first two groups ($n = 400$) were performed by two operators at Barmbek Hospital, Hamburg, Germany, between 1995 and 2003. The vast majority were performed by the same surgeon (K.H.), who was part of the original team that developed the transcutaneous fetoscopic technique for laser coagulation at King's College in London[2,18]. The following three groups were treated at the University Medical Center Hamburg-Eppendorf, Hamburg, when K.H. moved there in January 2004. In the third group, another operator was trained hands-on and performed 33 procedures before he moved to another center, while in Groups 4 and 5 a fourth operator (W.D.) was trained and performed 174 procedures during that period under the supervision of the senior operator.

The primary outcome was survival of two fetuses and secondary outcome variables were survival of at least one fetus, gestational age at delivery, interval between laser treatment and delivery in pregnancies with at least one liveborn neonate, birth weight and neonatal morbidity. Survival was defined as survival of the neonatal period at discharge from hospital. Severe prematurity was defined as delivery before 32 completed weeks' gestation, and neonatal morbidity as intracerebral hemorrhage (Grades 3 and 4), periventricular leukomalacia, sepsis, bronchopulmonary dysplasia, necrotizing enterocolitis or any other severely debilitating disease, or need for blood transfusion.

Continuous variables are reported as mean ± SD and categorical variables as *n* (%). Depending on scale type of the dependent variable, linear or logistic regression analysis was performed for baseline variables as well as for outcomes, adjusted for type of fetoscope, gestational age at laser treatment, Quintero stage and surgeon. Model-based marginal means with corresponding 95% CIs were tested using F-tests, linear contrast tests or corresponding likelihood ratio tests, as appropriate. The learning curve of the surgeons was estimated by the application of locally weighted scatterplot smoothing (Lowess) with a bandwidth of 0.8[19]. Nominal *P*-values are reported without correction for multiplicity, and two-sided $P < 0.05$ was considered to indicate statistical significance. Statistical analysis was conducted using STATA (Version 14.0, StataCorp, College Station, TX, USA).

RESULTS

Baseline characteristics and outcomes for the total population and the five subgroups are given in Tables 1 and 2. The yearly caseload more than doubled during the

Table 1 Clinical and procedural data at treatment by fetoscopic laser coagulation in sequential groups of fetuses with twin–twin transfusion syndrome

Parameter	*Group 1* (n = *200*)	*Group 2* (n = *200*)	*Group 3* (n = *200*)	*Group 4* (n = *200*)	*Group 5* (n = *220*)	*Total* (n = *1020*)	P*	P†
GA at laser (weeks)	20.8 ± 2.0	20.7 ± 2.0	20.8 ± 2.1	20.9 ± 2.2	20.7 ± 2.5	20.8 ± 2.2	0.835	0.994
Quintero stage							0.003	0.001
I	36 (18.0)	29 (14.5)	20 (10.0)	42 (21.0)	57 (25.9)	184 (18.0)		
II	56 (28.0)	81 (40.5)	77 (38.5)	75 (37.5)	71 (32.3)	360 (35.3)		
III	94 (47.0)	80 (40.0)	93 (46.5)	76 (38.0)	84 (38.2)	427 (41.9)		
IV	14 (7.0)	10 (5.0)	10 (5.0)	7 (3.5)	8 (3.6)	49 (4.8)		
Type of fetoscope								
0° for posterior placenta	118 (59.0)	126 (63.0)	106 (53.0)	102 (51.0)	125 (56.8)	577 (56.6)		
0° for anterior placenta	82 (41.0)	42 (21.0)	0 (0.0)	0 (0.0)	0 (0.0)	124 (12.2)		
30° for anterior placenta	0 (0.0)	32 (16.0)	94 (47.0)	98 (49.0)	95 (43.2)	319 (31.3)		
Fetoscopy time (min)	32.2 ± 12.0	30.6 ± 10.8	30.1 ± 11.7	25.3 ± 8.9	27.4 ± 11.1	29.1 ± 11.2	< 0.001	< 0.001
Cases/year	43	48	49	73	91			

Data are shown as mean ± SD, *n* or *n* (%). *Global F-test for group comparison. †Linear contrast test for linear trend. GA, gestational age.

Table 2 Perinatal outcome of sequential groups of fetuses with twin–twin transfusion syndrome treated by fetoscopic laser coagulation

Parameter	*Group 1* (n = *200*)	*Group 2* (n = *200*)	*Group 3* (n = *200*)	*Group 4* (n = *199*)*	*Group 5* (n = *220*)	*Total* (n = *1019*)	P†	P‡
Survival								
Two survivors	100 (50.0)	119 (59.5)	138 (69.0)	135 (67.8)	153 (69.5)	645 (63.3)	0.136	0.018
At least one survivor	161 (80.5)	167 (83.5)	179 (89.5)	174 (87.4)	202 (91.8)	883 (86.7)	0.269	0.072
One survivor	61 (30.5)	48 (24.0)	41 (20.5)	39 (19.6)	49 (22.3)	238 (23.4)	0.511	0.193
Surviving recipient	143 (71.5)	145 (72.5)	171 (85.5)	166 (83.4)	188 (85.5)	813 (79.8)	0.056	0.022
Surviving donor	118 (59.0)	141 (70.5)	146 (73.0)	143 (71.9)	167 (75.9)	715 (70.2)	0.225	0.083
Intrauterine death								
Both twins	7 (3.5)	14 (7.0)	6 (3.0)	2 (1.0)	2 (0.9)	31 (3.0)	0.158	0.991
One twin	54 (27.0)	45 (22.5)	42 (21.0)	34 (17.1)	46 (20.9)	221 (21.7)	0.512	0.181
Recipient	21 (10.5)	37 (18.5)	14 (7.0)	11 (5.5)	13 (5.9)	96 (9.4)	< 0.001	0.007
Donor	47 (23.5)	36 (18.0)	40 (20.0)	27 (13.6)	37 (16.8)	187 (18.4)	0.222	0.088
TOP after laser	7 (3.5)	4 (2.0)	3 (1.5)	1 (0.5)	2 (0.9)	17 (1.7)	0.770	0.299
Miscarriage	21 (10.5)	7 (3.5)	11 (5.5)	16 (8.0)	11 (5.0)	66 (6.5)	0.110	0.808
Interval between laser and delivery (weeks)	10.6 ± 5.8	11.4 ± 5.9	12.0 ± 5.0	11.3 ± 5.4	12.0 ± 5.0	11.4 ± 5.4	0.183	0.100
Interval between laser and delivery in cases with at least one LB (weeks)	12.7 ± 4.1	13.3 ± 4.0	13.2 ± 3.6	12.6 ± 4.2	12.8 ± 4.2	12.9 ± 4.0	0.221	0.709
GA at delivery in cases with at least one LB (weeks)	33.5 ± 3.2	34.0 ± 3.4	34.0 ± 2.8	33.5 ± 3.3	33.5 ± 3.1	33.7 ± 3.2	0.193	0.656
Severe prematurity in cases with at least one LB§	53/165 (32.1)	55/175 (31.4)	41/180 (22.8)	52/180 (28.9)	61/205 (29.8)	262/905 (29.0)	0.189	0.584
BW of liveborns (g)								
Recipient	2041 ± 599	2106 ± 600	2107 ± 561	2030 ± 660	2007 ± 588	2056 ± 601	0.341	0.380
Donor	1749 ± 586	1852 ± 601	1802 ± 539	1691 ± 604	1752 ± 566	1769 ± 580	0.104	0.343
Neonatal death								
Recipient	7 (3.5)	9 (4.5)	1 (0.5)	5 (2.5)	6 (2.7)	28 (2.7)	0.411	0.557
Donor	8 (4.0)	10 (5.0)	0 (0.0)	12 (6.0)	3 (1.4)	33 (3.2)	0.104	0.912
Morbidity of neonate with known outcome¶								
Recipient	NA**	NA	16/161 (9.9)	10/166 (6.0)	10/188 (5.3)	36/515 (7.0)	0.949	0.749
Donor	NA**	NA	12/139 (8.6)	9/143 (6.3)	10/165 (6.1)	31/447 (6.9)	0.956	0.971

Data are shown as mean ± SD, *n* (%) or *n*/*N* (%). *Outcome missing in one case. †Global F-test for group comparison and ‡linear contrast test for linear trend from logistic regression model, adjusted for type of fetoscope, gestational age at laser, Quintero stage and surgeon. §Delivery ≤ 32.0 weeks. ¶Defined as intraventricular hemorrhage (Grade 3 to 4), periventricular leukomalacia, sepsis, bronchopulmonary dysplasia, necrotizing enterocolitis or other severe debilitating disease, or need for transfusion. **For neurodevelopmental outcome of Group 1 see Banek *et al.*[5] and Graef *et al.*[6]. BW, birth weight; GA, gestational age; LB, live birth; NA, not applicable; TOP, termination of pregnancy.

study period, from 43 cases in the first group to 91 in the last group. Gestational age at laser therapy did not show a significant difference between the subgroups, the mean gestational age for all 1020 cases being 20.8 ± 2.2 weeks. Significant differences between the treatment groups were observed for Quintero stages. More cases with Quintero stage I were treated in the later than in the earlier groups and there was a significant reduction in the time needed for fetoscopy (Table 1).

To avoid potential confounders for perinatal outcome, adjustment for Quintero stage, fetoscope, gestational age at laser treatment and surgeon was performed in the subsequent outcome analysis. Perinatal outcomes were obtained for all cases except one (in Group 4). Table 2 and Figure 1 show the percentages of double-twin survival for intergroup comparison of the five chronological treatment subgroups and for the total study group. The percentage was 50.0% (100/200) in the first and increased to 69.5% (153/220) in the last group, reaching a plateau after the third group. After adjusting for confounders, the linear trend was significant (linear $P = 0.018$). There was a significant increase in survival of recipients, from 71.5% to 85.5% ($P = 0.022$) and a significant decrease in intrauterine deaths of recipients ($P = 0.007$). Survival of donors increased non-significantly, from 59.0% to 75.9% ($P = 0.083$).

Table 2 and Figure 2 show the percentages of at least one survivor for intergroup comparison and for the total study population. There was a non-significant trend, with an increase from 80.5% (161/200) to 91.8% (202/220) ($P = 0.072$).

In the first two groups, 124 twin pairs had anterior placenta and were treated using 0° fetoscopes. These cases showed a double-twin survival rate of 44.4% (55/124). After the 30° fetoscope became available, it was used for anterior placentae. This led to a significant increase in double-twin survival, to 65.1% (207/318) (over all groups $P = 0.001$). Figure 3 shows double-twin survival rates before and after introduction of the 30° fetoscope. There was no longer a significant difference in survival rate between anterior and posterior placental location.

For all pregnancies with at least one liveborn neonate, the mean gestational age at delivery was 33.7 ± 3.2 weeks, with a time interval between laser treatment and delivery of 12.9 ± 4.0 weeks, and an incidence of severe prematurity with delivery at or before 32 weeks of 29.0% (262/905). The mean birth weight of recipients was 2056 ± 601 g and for donors it was 1769 ± 580 g, without any significant difference between groups. Furthermore, there was no significant difference in rates of severe neonatal morbidity between Groups 3, 4 and 5. Overall, severe neonatal morbidity occurred in 7% of both surviving recipients and donors for which neonatal follow-up reports were available. Recurrent TTTS or TAPS was reported in 2.7% (17/619) of the patients in these groups. Data on composite morbidity were not consistently available for Groups 1 and 2.

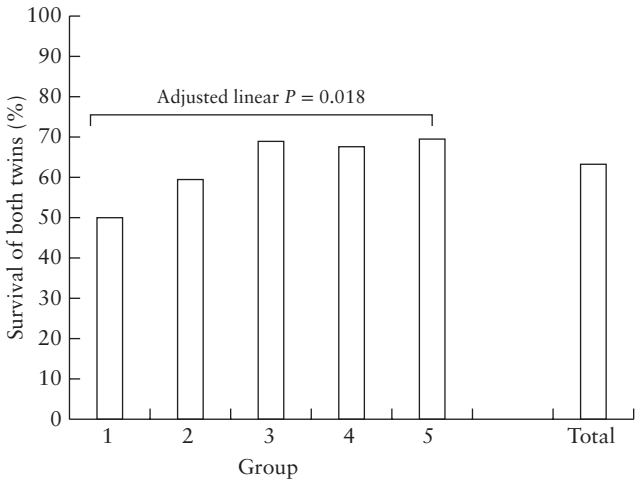

Figure 1 Survival of both twins in pregnancies with twin–twin transfusion syndrome treated by fetoscopic laser coagulation according to sequential groups of 200 cases.

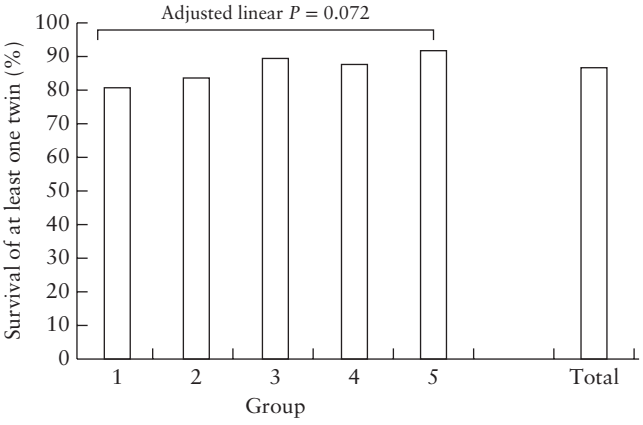

Figure 2 Survival of at least one twin in pregnancies with twin–twin transfusion syndrome treated by fetoscopic laser coagulation according to sequential groups of 200 cases.

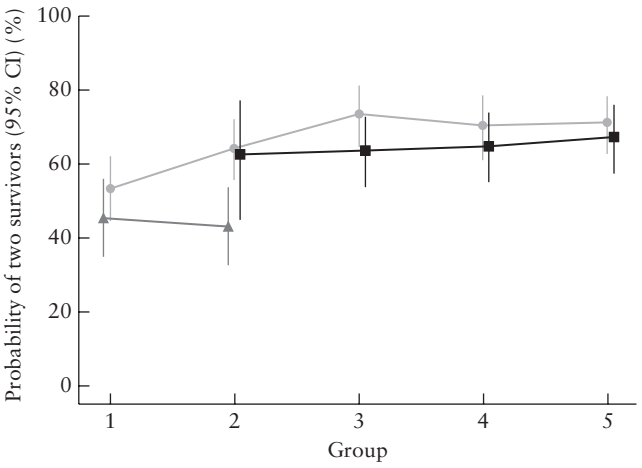

Figure 3 Impact of 30° fetoscope on double-twin survival rate in cases of twin–twin transfusion syndrome with anterior placenta treated by fetoscopic laser coagulation according to sequential groups of 200 cases. ●, 0° rod lens for posterior placenta; ▲, 0° rod lens for anterior placenta; ■, 30° lens with lever for anterior placenta.

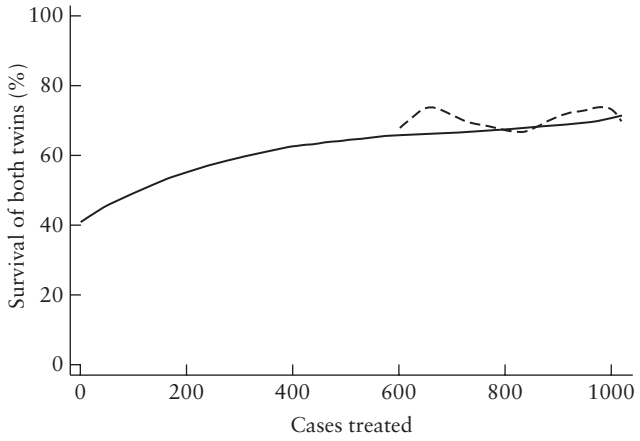

Figure 4 Operator-dependent success rate for survival of both twins in pregnancies with twin–twin transfusion syndrome treated by fetoscopic laser coagulation. ——, Operator 1 (K.H.); – – –, Operator 2 (W.D.).

Figure 4 shows the success rate of double-twin survival for the lead surgeon, which reached a plateau in the third group. In addition, the learning curve of another operator, who was trained hands-on and performed 174 procedures in the last two groups, is shown. There was no difference between the success rates of the experienced surgeon and the trainee, which was 70% overall. This was also the case for the operator who performed only 33 procedures.

DISCUSSION

To our knowledge, this is the largest single-center study of perinatal outcome after laser therapy for severe TTTS, with practically 100% (1019/1020) follow-up. We report our experience of almost 20 years, including the learning curve, new technical developments and training. The caseload per year doubled over the study period, during which there was a significant improvement in double-twin survival rates. Furthermore, after the introduction of a special fetoscope for cases with anterior placenta, differences in survival rate according to placental location were eliminated and, with an experienced surgeon supervising hands-on training, trainees achieved the same double-twin survival rate from soon after starting to perform the procedure.

Most outcome data on laser coagulation for TTTS published between 1995 and 2014 were derived from smaller studies, with the vast majority of these studies reporting on fewer than 200 cases. Double-twin survival rates increased significantly, from 31% to 62%, reflecting learning-curve effects, heterogeneity of the study populations and evolution of the technique[12]. Survival rates for at least one twin increased significantly, from 70% to 88%. The largest population, including 682 cases with laser surgery performed between 2002 and 2010 at two centers, reported a survival rate of 67% for both twins, which differed significantly according to stage, and 91% for at least one twin[20].

In a meta-analysis of studies published between 1995 and 2009 focusing on survival of at least one twin, Ahmed *et al.*[21] found no significant impact of experience and improvements in technique (represented by date of publication), caseload or stage distribution. However, they did not analyze the influence of these parameters on double-twin survival, which is the primary aim of intrauterine therapy for TTTS, as there are two severely affected fetuses. In contrast, Morris *et al.*[22] reported a significant improvement in perinatal survival of at least one twin with increasing operator experience in a single-center setting with 164 consecutive cases treated by laser coagulation. However, they did not evaluate the effects of operator experience on double-twin survival either.

In our population we found a significant increase in double-twin survival rate, from 50% to 70% in the first and last groups, respectively, and a non-significant increase in the rate of survival of at least one fetus, from 81% to 92%. A plateau was reached after 600 cases had been treated. The increase in double-twin survival rate in the first three groups reflects the growing experience and learning curve of the lead operator, the development of a selective technique, the introduction of the 30° fetoscope for anterior placentae in the second group and training of a new operator in the third group. The new fetoscope for anterior placentae led to a significant improvement in double-twin survival rates in these cases, which was comparable with that of cases with posterior or lateral placentae.

The differences in stage distribution between groups, with an increase in Stage I cases in Groups 4 and 5, may have contributed to the increase in double-twin survival rates. However, this is unlikely, as the plateau had already been reached after the first three groups and *P*-values were adjusted for Quintero stage. Furthermore, the largest study analyzing stage-dependent survival rates showed no significant differences in double-twin survival between Stages I and II, but differences were primarily due to decreased donor-twin survival in Stage-III cases[20]. A recent paper from the North American Fetal Therapy Network reported that the majority (60%) of expectantly managed Stage-I cases progressed, and only laser therapy was protective against poor outcome, which was defined as double fetal demise or delivery before 26.0 weeks' gestation[23]. The increase in Stage-I cases in our population may be a consequence of either earlier referral or increased awareness of minimal bladder filling in the donor twin.

Of two studies using the cumulative summation (CUSUM) test to determine the learning curve of individual surgeons, one analyzed the success rate for at least one survivor[24] and the other for double-twin survival[25]. In the first study, of 171 consecutive cases, an observer-trained operator needed 60 procedures, whereas hands-on trained operators needed only 20 procedures to reach an acceptable success rate. In the second study, of 340 consecutive cases, four operators reached an acceptable level of competence

after 25–35 procedures. In our study, the learning curve for double-twin survival of the fourth operator, who performed 39.5% (174/440) of procedures in Groups 4 and 5, showed the same success rate as for the lead operator. This may be explained by his starting with the first procedures in technically easier cases with posterior placentae, the possibility of immediate intervention by the supervising experienced operator if technical difficulties occurred and a final check as to whether all anastomoses had been coagulated. It is possible that in the future a recently developed procedure-specific evaluation tool to assess the performance of trainees may be helpful in ensuring that they have reached a sufficient level of competence to perform the procedure unsupervised[26].

Our study supports the view that laser coagulation for TTTS and other intrauterine surgical interventions should be concentrated, nationwide as well as internationally, in specialized high-volume centers in which all procedures are registered prospectively. Two recent studies, one from Norway and one from Finland, have shown substantial improvement in survival and immediate and longer-term outcomes after congenital-heart-defect surgery and among pediatric cardiac surgery patients[27,28]. In addition to advances in diagnostics and surgical methods as well as postoperative intensive care, in both countries operations have been fully centralized to, and performed only by highly experienced teams at, the Oslo University Hospital since 2003 and the Helsinki University Hospital since 1997. For outcome assessment, both centers obtained status and mortality data from their respective national population registry.

The introduction of minimum volume standards for hospitals performing specific complex surgical interventions and transplantation in Germany seems not to have been completely effective[29]. In contrast, as our significant increase in caseload over the study period shows, for laser coagulation in pregnancies with TTTS, centralization seems to have been driven mainly by referring fetal medicine specialists and patient demand. However, we do not have any nationwide data for comparison, as there is no national population registry in Germany, and intrauterine surgery is not listed in German hospital quality reports. Our study also shows that, for small countries, international centralization may be an alternative, which avoids patients having to go through a local learning curve (smaller national centers that started performing laser therapy have described similar learning curves to ours[30–32]). This is emphasized by our referral pattern from several European countries, the majority from Norway, but also from countries which are further away, for example in the Middle East. A small case series has shown that even long-distance air travel is safe for women before and after laser treatment[33].

A limitation of this study is the fact that follow-up data of surviving neonates are not complete. This is due to several reasons, the most important being the lack of a systematic registration of long-term follow-up for the whole population over a time period of more than 20 years. Furthermore, studies on specific complications after laser therapy, such as TAPS[34,35], have only recently been published and, therefore, standardized reports on these complications were not requested from referral centers. As a consequence, the incidence of long-term morbidity may be underreported. However, we have published several studies on long-term morbidity of subpopulations of the first two blocks of patients, focusing on neurodevelopmental follow-up and on the cardiovascular system[5,6,36–39]. In two consecutive series investigating neurodevelopmental outcome at a median age of 2 and 3 years, respectively, 11% and 7% showed minor and 11% and 6% major neurological abnormalities, and at a median age of 6 years the results were not significantly different (overall 11% and 9%, respectively)[5,6,36]. This is in accordance with a study by van Klink *et al.*[40], who reported a decrease in neurodevelopmental impairment from 18% to 6% with a concomitant increase in fetal survival in two consecutive cohorts of TTTS treated with laser surgery, which was explained by different factors, mainly improvements in prenatal care strategies, learning-curve effects and the development of new techniques. Follow-up studies investigating cardiovascular development in survivors of our first group have shown that cardiac dysfunction regressed after laser therapy and vascular programming resembled that seen in dichorionic twins[37]. However, there was an increased incidence of pulmonary stenosis (8%), affecting both former recipients and donors, at 10 years of age[38].

Another limitation of our study is that, apart from the introduction of the 30° fetoscope for anterior placentae, we were not able to investigate the influence of different techniques, such as the selective sequential and the Solomon techniques[12]. The former has not been applied systematically by our group, apart from to placentae with large arteriovenous anastomoses in the direction of recipient to donor, in which case we aimed at coagulating them at the end of the laser procedure. The results of a multicenter RCT comparing laser coagulation of the entire vascular equator with selective coagulation of anastomoses was published after our study period in 2014 by Slaghekke *et al.*[41]. They found a significantly lower incidence of TAPS or recurrent TTTS in the Solomon group as compared with the standard group (4% *vs* 21%), whereas no difference was found in mortality and severe neonatal morbidity as well as survival without neurodevelopmental impairment at 2 years of age (67% *vs* 68%)[41,42]. However, the trial was not powered to detect differences in long-term outcome, and not all centers participated in the follow-up study. Therefore, an appropriately powered RCT with long-term neurodevelopmental follow-up has been suggested[43]. The concern that follow-up data on complications, such as TAPS and recurrent TTTS, may be underestimated in our study has already been expressed. However, we did apply the Solomon technique, to a certain extent, long

before it was formally introduced in a study protocol by coagulating an area of neighboring anastomoses along a line on the vascular equator of the placenta. Furthermore, we always aimed to inspect the whole vascular equator from margin to margin to avoid missing thin anastomoses.

In conclusion, more than 20 years of experience with laser therapy in TTTS shows a significant increase in double-twin survival rate. Several factors, such as the learning-curve effect, technical developments and improvements in ultrasound monitoring and early referrals of monochorionic pregnancies with signs of TTTS, may have contributed to this success. Our data provide strong arguments for the centralization of minimally invasive intrauterine surgery, such as laser therapy, in specialized high-volume centers with an experienced team that also supervises hands-on training, thus allowing trainees to achieve the same double-twin survival rate as an experienced operator from the start of their use of the technique.

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This article has been selected for Journal Club.

A slide presentation, prepared by Dr Maddalena Morlando, one of UOG's Editors for Trainees, is available online.

Chinese translation by Dr Yang Fang. Spanish translation by Dr Masami Yamamoto.

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La coagulación fetoscópica láser en 1020 embarazos con síndrome de transfusión feto fetal demuestra una mejoría en la tasa de supervivencia de gemelos

RESUMEN

Objetivo Investigar la experiencia creciente y la curva de aprendizaje de la coagulación fetoscópica láser de anastomosis vasculares placentarias en el síndrome de transfusión feto fetal (TTTS, por sus siglas en inglés) de carácter severo a mitad de trimestre y su influencia en el resultado perinatal en el contexto de un solo centro.

Métodos Entre enero de 1995 y marzo de 2013 se realizó terapia con láser en 1020 embarazos consecutivos con TTTS entre las semanas de gestación 15.1 y 27.4. Se comparó el resultado perinatal en bloques de cinco grupos secuenciales de 200 casos, teniendo en cuenta varias covariables con el fin de hacer ajustes según la mezcla de casos, y para demostrar las curvas de aprendizaje y las tasas de éxito.

Resultados El porcentaje de embarazos con supervivencia de ambos fetos aumentó del 50,0% (n=100) en los primeros 200 casos al 69,5% (n=153) en los últimos 220 casos (P=0,018 para la tendencia) y la tasa de supervivencia general para ambos fetos en la serie completa de 1019 casos con resultado conocido fue del 63,3% (n=645). La tasa de supervivencia de al menos un feto aumentó del 80,5% (161/200) en el primer grupo al 91,8% (202/220) en el último grupo (P=0,072 para la tendencia) y la tasa de supervivencia general de al menos un feto en la serie completa fue del 86,7% (883/1019). En la población total, la edad de gestación media al momento del parto con al menos un neonato vivo fue de 33,7 ± 3,2 semanas, con un intervalo promedio de 12,9 ± 4,0 semanas entre la intervención y el parto. Entre los primeros dos grupos, 124 embarazos tenían placenta anterior y fueron tratados con un fetoscopio de 0°. Estos casos tuvieron el peor resultado en general, con una tasa de supervivencia de gemelos del 44,4% (55/124), que aumentó al 65,1% (207/318; P=0,001) después de la introducción de un fetoscopio de 30° para casos con placenta anterior. La tasa de éxito para la supervivencia de gemelos alcanzó un nivel estable del 69% al alcanzar los 600 procedimientos, siendo ésta tasa igualada por una nueva persona que recibió capacitación práctica y realizó 174 de los últimos 400 procedimientos.

Conclusiones Se reporta la mayor experiencia hasta la fecha en un solo centro en cuanto a coagulación con láser en TTTS. Se observó un aumento continuo en la tasa de supervivencia de gemelos debido a la experiencia cada vez mayor en función de la curva de aprendizaje y los avances en los instrumentos y técnicas fetoscópicas. Estos datos proporcionan argumentos sólidos para la centralización de la cirugía intrauterina mínimamente invasiva en centros especializados de alto volumen.

采用胎儿镜下激光凝固治疗1020例双胎输血综合征妊娠能够提高双胎存活率

目的：单中心研究采用胎儿镜下激光凝固胎盘吻合血管术治疗重度孕中期双胎输血综合征（twin–twin transfusion syndrome，TTTS）的成长经验和学习曲线以及其对围产结局的影响。

方法：1995年1月至2013年3月间，我们采用激光手术治疗1020例孕15.1~27.4周的连续TTTS孕妇。比较5个序贯组（每组200例）的围产结局，考虑几个协变量，以校正病例混合，来证实学习曲线和成功率。

结果：双胎存活的妊娠比例从前200例的50.0%（n=100）升高至最后220例的69.5%（n=153）（趋势P值=0.018），已知结局的全部1019例中双胎总存活率为63.3%（n=645）。至少一胎存活率从第一组的80.5%（161/200）升高至最后一组的91.8%（202/220）（趋势P值=0.072），全部病例中至少一胎存活率为86.7%（883/1019）。总人群中，至少一胎活产的孕妇平均分娩孕周为33.7 ± 3.2周，治疗与分娩平均间隔2.9 ± 4.0周。前两组中，124例妊娠为前置胎盘，接受0°胎儿镜治疗。这些病例的总体结局最差，双胎存活率为44.4%（55/124），采用30°胎儿镜治疗前置胎盘病例后，双胎存活率升高至65.1%（207/318；P=0.001）。治疗600例后双胎存活治疗成功率达到平稳，为69%，与接受实践培训的新操作者对后400例中174例进行治疗取得的成功率相似。

结论：我们报道了采用激活凝固治疗TTTS的最大单中心经验。我们发现，根据学习曲线取得越来越多的经验以及胎儿镜仪器和技术的成熟，双胎存活率持续升高。这些结果为在专科、患者量大的医疗中心集中进行微创宫内手术提供了有力证据。