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Fetoscopic Laser Ablation for Twin-to-Twin Transfusion Syndrome: A 15-year Review of Perinatal Survival

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Abstract

Objective

Twin to twin transfusion syndrome (TTTS) complicates 5-15% of monochorionic twin pregnancies and untreated is associated with a 90% mortality rate. The aim was to present the perinatal survival of patients with TTTS treated with laser ablation, by a national fetal medicine team.

Methods

This was a review of all cases of TTTS treated with fetoscopic laser ablation performed from March 2006 through to December 2020. All patients treated with fetoscopic laser were identified from the hospital database. The perinatal outcomes for the overall cohort and the individual Quintero stages were determined.

Results

A total of 155 cases of TTTS underwent fetoscopic laser ablation during the study period. The median gestational age at diagnosis was 19+1 weeks, with a mean growth discordance of 23.6%. The Quintero stage at diagnosis was: Stage 1 6.5% (10/155), Stage 2 49% (76/155), Stage 3 38.7% (60/155), Stage 4 5.8% (9/155).

There was at least one survivor in 83.2% (129/155) of pregnancies, with dual survival in 52.9% (82/155). An increase in the rate of any survivor was observed from 75% (2006-2014) to 94% (2014-2020) ($p<0.05$). Dual survival decreased with increasing Quintero Stage ($p<0.05$). 80.6% (125/155) of pregnancies delivered prior to 34+6 weeks gestation.

Conclusion

Fetoscopic laser ablation is the recommended first line treatment for severe TTTS. We observed a survival rate of at least one twin in 83.2% pregnancies which is comparable to internationally published data on single-centre outcomes.

Introduction

Fetofetal transfusion, or twin to twin transfusion syndrome(TTTS)[1], complicates approximately 5–15% of monochorionic twin pregnancies and is associated with a 90-95% mortality if left untreated[1-3]. Communicating placental vessels on the chorionic plate between the donor and recipient twin are responsible for an imbalance in blood flow[4] which results in hemodynamic alterations[2, 5, 6], where the recipient twin develops polyuria and polyhydramnios[2] and the donor twin develops anuria and oligohydramnios[2]. TTTS is defined on ultrasound by the presence of a maximum vertical pocket[2] of amniotic fluid of 8 cm or greater in one sac and 2 cm or less in the other, regardless of the gestational age at diagnosis[2]. The condition is staged using the Quintero staging system[2, 7].

Several options are available to parents when faced with a diagnosis of severe TTTS in a pregnancy and include conservative management, termination of pregnancy, or in utero treatments (amnioreduction and fetoscopic laser ablation). Fetoscopic laser has long been regarded as superior to serial amnioreduction[2, 8], and is considered the first-line therapy for TTTS[1]. There are continuous improvements in the performance of laser surgery and the overall survival ranges from 75% to greater than 90%[1, 4, 9].

The aim of this review was to determine the perinatal survival following fetoscopic laser ablation in a single institution. Secondly, we aim to compare these outcomes with other single-centre international experiences and with a previous audit performed in our unit[1].

Methods

This was an audit of all cases of TTTS treated with fetoscopic laser ablation over a 15-year period, from March 2006 to December 2020, by the Irish national fetal laser program, Dublin. The program was established in 2006, comprising of a single fetal medicine team from two large tertiary referral centers (one in the National Maternity Hospital and the other at the Rotunda Hospital), serving as a national referral service for all obstetric units in the country.

In the event of suspected TTTS, referring units have direct access to a member of the laser team, and suspected cases are generally reviewed within 24 h of referral in one of two fetal medicine units. The cases were entered prospectively into a Prenatal Diagnosis Registry. All patients provided verbal and written consent at the time of the procedure for use of their details for research purposes at a later stage. For analysis purposes all data was anonymized. For each case, prior to treatment, a comprehensive fetal medicine review was undertaken including confirmation of chorionicity, detailed anatomical assessment, placental assessment, and assessment of cardiac functional status[1]. All cases suitable for inclusion in this review were diagnosed using standard ultrasonographic features of TTTS and categorized according to Quintero Stage[7].

All patients received written informed consent prior to the fetoscopic laser ablation. Peri-operative antibiotics and tocolysis were administered as per protocol[1]. Selective fetoscopic laser treatment of placental vascular anastomoses was undertaken by a single team of three collaborative fetal medicine specialists, as previously described[1]. For each case the surgical team comprised of the primary operator and a second fetal medicine specialist, in addition to a sonography assistant and fetal medicine fellow. The procedures were performed in a similar fashion: a 10 or 12 French Cook Check-Flo Performer introducer sheath was introduced into the recipient sac under continuous ultrasound guidance[1]. For cases of an anterior placenta a 2mm Karl Storz 30^{o} curved fetoscope was used for the procedure and where there was a posterior placenta a 2 mm Karl Storz 0° straight fetoscope was used. The vascular equator was firstly identified in its entirety, and secondly, following a consensus regarding all potential anastomoses, sequential photocoagulation of anastomoses using a neodymium: YAG laser was performed[1]. A comprehensive review of all coagulated vessels ensured any anastomoses were re-examined and coagulated, with a Solomon technique being followed to ensure complete vascular separation between both fetuses. An amnio-reduction was performed to complete the procedure in all cases, and a karyotype routinely sent. Fetal survival was confirmed within 24 h of the procedure. All mothers were reviewed prior to discharge for any immediate procedure-related complications. Follow-up for survivors included serial biometry, assessment for recurrent TTTS, and targeted fetal and neonatal echocardiography with an affiliated consultant fetal cardiologist[1].

All patients treated with fetoscopic laser were identified from the hospital database. Triplet and monoamniotic pregnancies were excluded from the analysis. Information was obtained on gestational age at diagnosis, Quintero stage, percentage growth discordance and gestational age of the laser procedure. The survival for the overall cohort and the individual Quintero stages were determined. The gestational age at delivery was documented and the average number of days gained after the procedure were calculated for each patient. Statistical analysis was performed using the Chi-square test. The results obtained were compared to the outcomes with other single-centre international experiences and to the results of a previous audit performed in our unit[1].

Results

There were 155 pregnancies included for analysis. The median gestational age at diagnosis was 19 weeks+1 day (range 15 weeks+3 days to 27 weeks+1 day). The Quintero stage at the time of TTTS was: Stage 1 6.5%, Stage 2 49%, Stage 3 38.7%, Stage 4 5.8%. In 91/155(58.7%) the placenta was posterior and in 64/155(41.3%) was anterior. The median gestation of the laser procedure was 19 weeks+3 days (range 16 weeks+1 day to 27 weeks+1 day). One case was performed over 26 weeks, at 27 weeks+1 day. This was a late referral with stage 4 TTTS. Fetoscopic laser was performed but the twins were subsequently delivered the same day with resulting single fetal survival. There were 57/155 (36.8%) cases performed under local anaesthesia, and 98/155 (63.2%) performed under regional anaesthesia.

The mean percentage inter-twin growth discordance was 23.6% (range 0.7%-53.2%). 62.6% had a growth discordance of greater than 20%. In all cases an amnio-reduction was performed to complete the procedure, with a mean volume of 1673mls (range 300mls-4200mls) drained. In three cases, a repeat fetoscopic laser ablation was performed, resulting in recipient survival in one case, dual survival in the second case and in the other third case the second procedure was complicated by chorio-amnionitis, which ultimately required pregnancy termination via hysterotomy. Seven other women required repeat amniodrainage procedures for recurrent TTTS, with a mean amount of 2060mls drained(500mls-3100mls) and two of these had a third amniodrainage procedure.

For the overall population, the median gestational age at delivery was 30 weeks+4 days (range 17 weeks+1 day to 40 weeks+2 days), with 80.6% of pregnancies delivered prior to 34+6 weeks gestation and 26.5% delivered prior to 28 weeks. The overall PPROM rate was 16%. There was no significant difference in the gestation of the laser procedure between the PPROM group and the non-PPROM group. Those who did not have PPROM had a signifcantly greater volume of amniotic fluid removed at the time of amnioreduction($p<0.05$). For survivors the median gestational age at delivery was 33 weeks (range 23 weeks+5 days to 40 weeks+2 days).

Fetal survival is presented in Table 1 for both the overall population and by Quintero stage. Overall fetal survival was 68.1% (211/310 of fetuses). At least one survivor was recorded in 83.2% (129/155) of pregnancies. In one case of dual demise a karyotype confirmed a diagnosis of Turner syndrome. Dual survival was significantly decreased with increasing Quintero Stage ($p<0.05$). Table 2 compares our results with reported survival outcomes from other single centre fetoscopic laser programs.

Table 1. *Survival for the overall cohort and for each individual Quintero Stage.*

Median gestational age and days gained for the overall group	
Median gestational age at delivery	30 weeks + 4 days gestation (range 17+1 weeks to 40+2 weeks)
Average number of days gained for survivors following procedure	86.7 days (range 0–162 days)

Overall Survival Outcomes	
At least one survivor	83.2% (129/155)
Single fetal survival	30.3% (47/155)
Dual fetal survival	52.9% (82/155)
Dual demise	16.8% (26/155)

Survival Outcome by Stage	Stage 1	Stage 2	Stage 3	Stage 4
At least one survivor	10/10 (100%)	67/76 (88.2%)	44/60 (73.3%)	8/9 (88.9%)
Single fetal survival	2/10 (20%)	19/76 (25%)	21/60 (35%)	5/9 (55.6%)
Dual fetal survival	8/10 (80%)	48/76 (63.2 %)	23/60 (38.3%)	3/9 (33.3%)
Dual Demise	0/10 (0%)	9/76 (11.8%)	16/60 (26.7%)	1/9 (11.1%)

The overall survival for the group (N=155) is presented in this Table, with the survival rates subdivided by each individual Quintero Stage (7). No significant difference in the overall survival was observed between the groups. A significant difference was noted in the number of dual survivors between the Quintero groups P<0.05.

Table 2. *A comparison of single center survival outcomes following selective fetoscopic laser ablation.*

	Total number of cases	**Dual survival**	**Single fetal survival**	**At least one survivor**	**Dual demise**
Irish fetal laser program (2006-2020)	155	52.9%	30.3%	83.2%	16.8%
Mullers et al, 2015 [1] Irish fetal laser program (2006-2014)	105	47%	28%	75%	25%
Diehl et al., 2017 [11]	1019	63.3%	23.4%	86.7%	13.3%
Persico et al., 2015 [12]	106	53.7%	*	83%	17%
Has et al., 2014 [13]	85	26%	32%	58%	42%
Peeters et al., 2013 [14]	340	59%	27%	86%	14%
Baschat et al., 2013 [15]	147	60%	28%	88%	12%
Stirnemann, 2013 [16]	507	46%	32%	78%	22%
Rustico et al., 2012 [17]	150	41%	33%	74%	26%
Morris et al., 2010 [18]	164	38%	46%	85%	15%

This Table compares the outcomes of the Irish fetal laser program with other single center outcomes.
** Denotes where data on dual or single survival was not published.*

We subsequently compared the results of the initial years (March 2006- Sept 2014) of the Irish fetal laser program[1] with the outcomes of the more recent years (Oct 2014- Dec 2020). A significant increase in the rate of any survivor was observed, increasing from 75% (2006-2014) to 94% in the most recent audit($p<0.05$), with a notable decrease in dual demise, 25% to 6% ($p<0.05$).

Discussion

TTTS is a complex condition with significant mortality in affected pregnancies. We present the perinatal survival of 155 TTTS cases treated with fetoscopic laser ablation by a single national collaborative fetal medicine team. There was at least one survivor in 83.2% of pregnancies, which is comparable to internationally published data for other single centre studies[11, 12, 15, 16, 18, 19].

Furthermore, when we compared our results to the results of a previous audit from the initial years of the Irish fetal laser program, we observed a significant improvement in our overall survival rates[1]. Similar findings have been reported in other studies. A large series of 1020 cases observed a significant increase in double-twin survival rate comparing the first 200 cases to the last 220 cases[11]. Another large review of 34 studies also reported improvements in the mean survival of both twins from 35 to 65%[19] and for at least one twin from 70 to 88%[19] over a 25 year period. Improvement in perinatal survival of at least one twin has been associated with increasing operator experience[11, 18]. We observed a decrease in dual survival with increasing Quintero Stage in this study. Dual survival for Stage 3 and Stage 4 (38.3% and 33.3% respectively), was slightly lower than other reports, 45-65%[9, 20].

Most of the pregnancies were delivered preterm, at a median gestation of 30 weeks+4 days. This is similar to other studies, including a large systematic review of 2699 twin pregnancies[9] reported a mean gestational age at delivery of 31.1 weeks[9]. We report a PPROM rate of 16%, a slight increase from the previously reported 10%[1]. While this remains comparable to published figures where PPROM rates have been described in some series to be as high as 26-43%[21, 22], it is an area for examination in future audits.

Recurrent TTTS is thought to occur because of incomplete coagulation of placental anastomoses during the laser procedure[3, 23]. Studies have reported an association between recurrence of TTTS and residual large AV anastomoses[24] while the development of twin anaemia polycythaemia sequence is more closely associated with missed smaller AV anastomoses[4]. It has been suggested that it may be more accurately described as a persistence of the disease process, rather than a true recurrence. A systematic review of 2447 fetoscopic laser procedures reported the recurrence rate to range from 0 to 16%[3]. In our series we observed recurrent TTTS in 6.5% (10/155) of cases and TAPS in 1.3% (2/155). The use of the “Solomon” technique has shown a significant reduction in recurrent TTTS and TAPS in comparison to the selective laser method[4]. While this technique is performed in most cases in the Irish fetal laser program it is not always documented at the time of the procedure. As such, there is a paucity of data to confirm whether it was performed in all cases with recurrent TTTS, and a limitation of this review. While there is a standardised operative technique, as described above, the development of a surgical pro-forma may assist in more detailed analysis of cases, particularly when TTTS recurs. While we acknowledge the numbers referred to the centre are small in comparison to some larger international units, a team-based approach has been adopted to allow maximin exposure of the operators to fetoscopic laser surgery, allowing both improvement of operator technique and training of new operators in the procedure.

Over the study period approximately 11 cases of TTTS per annum underwent fetoscopic laser. This is lower than the national expected incidence of 50 cases of TTTS per annum, acknowledged in the previous review[1]. During the study period, patients were referred from 14/19 maternity units.

Some limitations of the study include that we have no data on patients that may have been referred outside of Ireland for treatment, on patients referred at stage I or stage IV where laser was not performed or where the parents may have opted not to have fetoscopic laser. It is also possible that patients with TTTS are not being referred in a timely manner. There is a need for ongoing awareness and education at a National Level with an appreciation of the complex nature of monochorionic twin pregnancies, with early and serial monitoring of multiple pregnancies, and appropriate assignment of chorionicity[1]. In this cohort 10 patients with stage 1 TTTS had fetoscopic laser performed. While all patients in this group were managed on an individualised basis, a recent randomised trial that of 117 pregnancies with stage 1 TTTS concluded that there was no difference in the intact survival between surgery and expectant management overall[25] and will likely influence the management of this group in the future. From the early years of the Irish fetal laser program, 86% of survivors were reported to have normal neurodevelopmental outcome[1], comparable to the available literature[4]. A limitation of this study is that follow-up data on surviving neonates are not complete for the most recent years of the program and is an area of ongoing review.

In our National Fetal Therapy Unit, we report improved survival rates over time in cases of TTTS treated by fetoscopic laser ablation. Moreover, this series is comparable to survival rates published in other single centres internationally. Additional technological innovations in laser procedures, refinement of operator technique and the development of noninvasive treatment such as high-intensity focused ultrasound are areas that may enhance the future treatment of TTTS. The development of novel less invasive techniques, in conjunction with routine audit, can continue to advance the care in high-risk fetal therapy and result in improved in survival in these complex pregnancies.

Declaration of Conflicts of Interest:
The authors have no conflict of interest to declare.

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