Twenty-Five Years of Fetoscopic Laser Coagulation in Twin-Twin Transfusion Syndrome: A Systematic Review

Joost Akkermans^a Suzanne H.P. Peeters^a Frans J. Klumper^a Enrico Lopriore^b
Johanna M. Middeldorp^a Dick Oepkes^a

^aDepartment of Obstetrics and ^bDivision of Neonatology, Department of Pediatrics, Leiden University Medical Center, Leiden, The Netherlands

Key Words

Laser therapy · Monochorionic twins · Neonatal outcome · Systematic review · Twin-twin transfusion syndrome

Abstract

Objective: The aim of this study was to assess the perinatal outcome of pregnancies with twin-twin transfusion syndrome (TTTS) treated with laser therapy over the past 25 years, and in relation to different techniques used in this time period. **Methods:** A systematic review of studies reporting on perinatal outcome according to the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines was conducted. The MEDLINE, Embase and Cochrane Library databases were systematically searched. Comparisons were made in respect to time period and laser technique and Quintero stages. **Results:** In total, 34 studies reporting on 3,868 monochorionic twin pregnancies were included. The mean survival of both twins increased from 35 to 65% ($p = 0.012$) and for at least one twin from 70 to 88% ($p = 0.009$) over the past 25 years. Mean gestational age at birth remained stable over the years at 32 weeks gestation. Also, we showed a significantly improved perinatal survival with the evolution of the laser technique from non-selective to selective, selective sequential and the Solomon technique ($p =$

0.010). **Discussion:** Since the introduction of laser therapy for TTTS more than two decades ago, perinatal survival improved significantly. Improved outcome is probably associated with several factors, including evolution of the laser technique, learning curve effect, better referral and improved early neonatal care.

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Introduction

Monochorionic twin pregnancies are at a 10% risk of developing twin-twin transfusion syndrome (TTTS) [1, 2] due to vascular anastomoses on a shared placenta. Before De Lia et al. [3] proposed fetoscopic laser coagulation of the placental vessels in 1990, serial amnioreduction was considered the only treatment option of polyhydramnios, the most prominent feature of TTTS. Serial amnioreduction was associated with mortality rates up to 60%, a median gestational age (GA) at delivery around 28 weeks and up to 50% severe neurodevelopment impairment in survivors [4].

J. Akkermans and S.H.P. Peeters contributed equally to this paper.

Survival significantly improved after the introduction of laser coagulation by addressing the cause of the problem, making it the accepted treatment of choice for TTTS [5]. However, results are still far from satisfactory, with mortality rates ranging from 20 to 48%, and significant complications, including iatrogenic preterm premature rupture of membranes (PPROM) [6] resulting in preterm delivery before 32 weeks gestation, twin anemia-polycythemia sequence (TAPS) [7], recurrence or reversal of TTTS [8] and adverse long-term neurodevelopmental outcome in 6–18% of survivors [9].

Since the first publications on fetoscopic laser surgery, several technical modifications have been described. Coagulation of all vessels crossing the inter-twin membrane was abandoned because it led to unnecessary placental loss [10]. In 1998, Quintero et al. [11] introduced the selective laser coagulation technique. This technique, which was rapidly adopted by most fetal therapy centers, aims to save as much functioning placenta tissue as possible by coagulating only true inter-twin vascular anastomoses instead of every vessel crossing the membranous equator. In 2007 the same group proposed the sequential selective laser coagulation technique [12].

Sequential selective laser is an adaptation whereby anastomoses are coagulated in a specific order. The aim is to obliterate the anastomoses in a sequence that allows, at least partly, an intraoperative correction of the hypoperfusion of the donor and hyperperfusion of the recipient. This is achieved by first closing the arteriovenous anastomoses from donor to recipient, starting with the largest ones, followed by the closure of the vein-to-artery anastomoses (e.g. the vessels with a blood flow towards the donor) as the last part of the procedure. In 2008 the Solomon trial [13] was started, introducing a new adaptation to the selective technique. The rationale of the Solomon technique is coagulation of the whole vascular equator from one placenta margin to the other. With the Solomon technique, all laser spots are connected by drawing a laser line, minimizing the chance of residual anastomoses. The study showed that this technique was associated with significantly less residual anastomoses, thereby reducing the risk for TAPS and recurrence of TTTS.

This study focuses on perinatal outcome after laser therapy over the past 25 years and on the impact of the above-mentioned changes in laser treatment strategies on the outcome results. We systematically reviewed all published series since the introduction of laser treatment of TTTS with respect to survival, GA at birth and procedural or postoperative complications in relation to the time and the laser technique used.

Methods

Data Sources

Before conduct of the systematic review a detailed protocol that included the search strategies, inclusion and exclusion criteria, outcome parameters and methods of statistical analysis was created. This systematic literature review was performed according to the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) [14], and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15] where applicable.

Literature Search

An initial literature search on survival after laser coagulation for TTTS was conducted in MEDLINE, Embase and the Cochrane Library using the PubMed and OVID search engines without restriction on the language or type of publication. Key words and free text searches were performed with combinations of the following key words: survival, perinatal survival, twin-to-twin transfusion syndrome, TTTS, twin-twin transfusion syndrome, fetofetal transfusion, placental anastomoses, laser, laser therapy, laser ablation, SLPCV, SQLPCV, sequential laser, selective laser, fetoscopy, FLOC and photocoagulation. Additionally, reference sections of eligible studies were hand-reviewed for potential eligible studies. Our search included articles published up to May 2014 that reported on pregnancy outcomes after fetoscopic laser coagulation of placental vascular anastomoses.

Inclusion and Exclusion Criteria

Randomized trials and comparative studies as well as prospective and retrospective case series were considered eligible for inclusion. Reasons for exclusion were studies with insufficient or overlapping data, letters, conference abstracts, review articles and case reports.

Selection and Data Extraction

All references were independently screened by two reviewers (J. Akkermans and S.H.P. Peeters). Disagreement on the eligibility of a study was resolved by discussion until consensus was reached.

Studies presenting data on twin pregnancies with confirmed monochorionicity by first trimester ultrasound, affected by TTTS according to the Eurofoetus criteria [5] or the Quintero criteria [16] treated with fetoscopic laser coagulation of vascular anastomoses were included.

Studies were selected when presenting at least the number of patients treated and either survival rate of both twins, survival rate of one twin, survival rate of at least one twin or GA at birth. Other important parameters were complications, such as PPROM, GA at laser and laser technique used. In the sporadic event that study results contained also outcomes of triplets (e.g. monochorionic twins affected by TTTS and a singleton), we used the perinatal outcome results of the twins for analysis.

To prevent double counting of cases, we excluded studies reporting outcomes from pregnancies that were treated in overlapping years with other published series from the same centers.

Differences in dual survival, single survival and at least one survival as well as GA at birth were analyzed on a timeline. Five-year intervals were chosen to analyze studies over time. For categorization we used the year the study was concluded as a cut-off value. Survival was analyzed per laser technique used in the series to show the impact of the proposed technical adaptations of the laser treatment.

Table 1. Studies included in the review

Reference (first author)	n	Inclusion period	Type of study	Dual survival	GA at birth, weeks	Comments
De Lia, 1995 [18]	26	1988–1994	prospective single-center cohort	35%	32.2±2.8	
Ville, 1995 [10]	45	1992–1994	prospective single-center cohort	36%	35.0±3.8	
De Lia, 1999 [19]	67	1995–1998	prospective single-center cohort	57%	30.0±5.0	
Hecher, 2000 [20] ^{a, b}	200	1995–1999	prospective single-center cohort	48%	34.0±2.7	early vs. late series to show learning curve effect
Quintero, 2000 [21] ^{a, b}	89	1994–1999	prospective multicenter cohort	39%	32.0±2.5	non-selective laser vs. selective laser
Gray, 2006 [22]	31	2002–2003	prospective single-center cohort	39%	34.0±4.5	
Huber, 2006 [23]	200	1999–2003	prospective single-center cohort	60%	34.3±2.9	
Ierullo, 2007 [24]	77	2002–2006	prospective single-center cohort	40%	NA	
Middeldorp, 2007 [25]	100	2000–2004	prospective single-center cohort	58%	33.0±3.7	
Quintero, 2007 [12] ^b	193	2003–2005	prospective single-center cohort	65%	33.7±4.0	sequential laser vs. standard selective laser
Sepulveda, 2007 [26]	33	2003–2006	prospective single-center cohort	27%	32.0±3.8	
Stirneman, 2008 [27]	287	1999–2005	retrospective single-center cohort	42%	32.0±3.6	
Cincotta, 2009 [28]	100	2002–2007	prospective single-center cohort	66%	31.0±3.2	
Nakata, 2009 [58] ^b	52	2002–2006	prospective multicenter cohort	50%	32.0±4.2	excluded for time-based analysis but included for technique-based analysis due to overlap
Ruano, 2009 [29]	19	2006–2008	retrospective single-center cohort	26%	32.1±3.0	
Chmait, 2010 [30] ^b	99	2006–2008	prospective single-center cohort	68%	32.2±4.5	sequential laser vs. standard selective laser
Meriki, 2010 [31]	75	2003–2008	retrospective single-center cohort	60%	32.0±2.7	
Morris, 2010 [32]	164	2004–2009	prospective single-center cohort	38%	33.2±1.3	
Yang, 2010 [33]	30	2002–2008	retrospective single-center cohort	60%	32.0±4.0	
Delabaere, 2011 [34]	49	2006–2008	retrospective single-center cohort	59%	32.0±2.6	article in French
Hernandez-Andrade, 2011 [35]	35	2008–2009	retrospective single-center cohort	49%	32.0±3.7	article in Spanish
Lombardo, 2011 [36]	70	2000–2010	retrospective single-center cohort	59%	32.1±NA	
Tchirikov, 2011 [37]	80	2006–2011	retrospective single-center cohort	78%	33.8±3.2	use of 1 mm optic vs. 2 mm optic
Weingertner, 2011 [38]	100	2004–2010	retrospective single-center cohort	52%	32.6±3.8	
Chang, 2012 [39] ^a	44	2005–2010	retrospective single-center cohort	50%	30.6±5.9	
Liu, 2012 [40]	33	2003–2010	retrospective single-center cohort	52%	31.0±6.0	excluded in technique-based analysis due to unclear technique; article in Chinese
Murakoshi, 2012 [41]	152	2002–2010	retrospective single-center cohort	63%	33.0±NA	
Rustico, 2012 [42] ^a	150	2004–2009	retrospective single-center cohort	41%	32.1±2.2	
Sundberg, 2012 [43]	55	2004–2010	retrospective single-center cohort	35%	34.8±4.0	
Swiatkowska-Freund, 2012 [44]	85	2005–2010	retrospective single-center cohort	45%	32.0±2.5	
Valsky, 2012 [45]	334	2006–2009	retrospective multicenter cohort	68%	33.2±3.0	GA at laser 16–26 weeks vs. >26 weeks
Baschat, 2013 [46] ^b	147	2005–2011	retrospective single-center cohort	60%	32.6±3.5	selective laser vs. Solomon laser
Baud, 2013 [47]	325	1999–2012	retrospective single-center cohort	63%	31.3±4.0	GA at laser <16 weeks vs. 16–26 weeks vs. >26 weeks
Ruano, 2013 [48] ^b	102	2010–2012	retrospective multicenter cohort	65%	31.6±4.4	selective laser vs. Solomon laser
Slaghekke, 2014 [13] ^b	272	2008–2012	multicenter RCT	62%	32.3±3.3	selective laser vs. Solomon laser

Figures for GA at birth are mean ± SD. NA = Not assessed; RCT = randomized controlled trial.

^aThese studies described more series over different time periods and were split up in the time-based analyses.

^bThese studies described comparisons between different techniques.

Statistical Analysis

Continuous variables were reported as median (range) or mean ± standard deviation (SD); for synthesis of data, medians (range) were recalculated as means ± SD using the method described by Hozo et al. [17].

For comparing survival outcomes of different techniques, a cumulative survival rate was calculated and the 95% confidence intervals (CIs) were estimated using binomial distribution. The survival rates were pooled using the DerSimonian and Laird random-effects models with heterogeneity estimated from the Mantel-Haenszel model.

The results of multiple groups were compared using analysis of variance (ANOVA) statistics. Results of categorical variables were compared using Fisher's exact test or χ^2 test, as appropriate. Student's t test was used to compare normally distributed values between two groups. The Mann-Whitney U test was used to compare non-parametric variables. A p value <0.05 was considered to indicate statistical significance.

Statistical analysis was performed using SPSS (IBM SPSS Statistics 20 for Windows; IBM, New York, N.Y., 2011) and MS Excel (Microsoft Excel 2010; Microsoft, Redmond, Wash., 2010). This being a literature review, no approval from our Ethics Committee was needed before performing this study.

Fig. 1. Flow chart of study selection according to the MOOSE guideline.

Results

Flow of Study Inclusion

Figure 1 shows a flow diagram according to the PRISMA statement [15] with the total number of citations retrieved by the search strategy and the number included in the review. After full-text analysis a total of 34 studies were included in the time-based analysis [10, 12, 13, 18–48]. Twelve studies [5, 49–59] presented data overlapping other series, of which one presented data relevant for the technique-based analysis [58].

Study Characteristics

The characteristics of all included studies are shown in table 1. One of the studies enrolled was a randomized controlled trial [13]; there were 13 prospective single-center cohort studies [10, 12, 18–20, 22–26, 28, 30, 32], 18 retrospective single-center cohort studies [27, 29, 31, 33–44, 46, 47, 59], 2 prospective multicenter cohort studies [21, 58] and 3 retrospective multicenter cohort studies [45, 48, 55].

The studies were from the United States, Belgium, Australia, Canada, Spain, Poland, Italy, Taiwan, Germany, The Netherlands, Denmark, the United Kingdom, France, Japan, Mexico, Brazil, China and Chile. The pri-

mary outcomes – perinatal survival of at least one or both twins and GA at birth – were well defined in all included studies.

There were three non-English language articles [34, 35, 40]. The language skills of the authors and co-workers (Chinese) were sufficient to analyze these articles.

Three authors described their series in two separate cohorts in order to display their learning curve [20, 39, 42]. Eight studies compared different (adaptations of) laser techniques [12, 13, 20, 21, 30, 46, 48, 58].

Baud et al. [47] compared the outcomes of early, late and conventional selective laser surgery defined as performed before 17 weeks gestation, after 26 weeks gestation and between 17 and 26 weeks.

For the overlapping series of Nakata et al. [58] and Murakoshi et al. [41], we used the latter for the time-based analysis and the former for the technique-based analysis. For the study of Liu et al. [40] it was unclear what technique was used and therefore it was excluded in the technique-based analysis.

Primary Outcome

A total of 3,868 women with a monochorionic twin pregnancy complicated by TTTS treated with fetoscopic laser coagulation were included in the time-based analysis; the sample size per study ranged from 19 to 334 women. The median time span of study inclusion for all studies was 4 years (interquartile range 2–6).

The mean GA at the time of surgery was 20.9 ± 1.9 weeks. Combining all series, the mean perinatal survival of both twins, one twin and at least one twin was $52 \pm 14.8\%$, $29 \pm 10.5\%$ and $81 \pm 8.3\%$, respectively. The overall survival of fetuses was 5,348/7,736 (69.1%). Figure 2a displays a forest plot with double twin survival rates in all included studies subdivided into time groups based on their study period, and the difference between the time periods. Figure 2b displays the forest plot of single twin survival rates.

For both twins survival rates significantly increased from 31% (1990–1995) to 62% (2011–2014) ($p < 0.001$), and survival rates for at least one twin significantly increased from 70% (1990–1995) to 88% (2011–2014) ($p = 0.009$). No significant change in survival of one twin was

Fig. 2. a Forest plot showing double twin survival rates over 25 years of laser therapy for TTTS subdivided into 5-year time periods. **b** Forest plot showing single twin survival rates over 25 years of laser therapy for TTTS subdivided into 5-year time periods.

(For figures 2a and b see next pages.)

Fig. 3. a Forest plot showing double twin survival rates subdivided by the laser technique used.

(For second part of figure 3a see next page.)

seen between 1990 and 1995 (39%) and between 2011 and 2014 (26%) ($p = 0.09$).

The overall mean GA at birth of all series was 32.4 ± 1.3 weeks. GA at birth did not change in time for the included series ($p = 0.226$).

Laser Technique

Thirty-four studies clearly specified their laser technique and eight of these studies compared two groups for which different laser techniques were used [12, 13, 20, 21,

30, 46, 48, 58]. These groups were analyzed separately, resulting in 41 subgroups describing survival results for different laser techniques. The non-selective laser technique was used in five series [10, 18–21], 28 series used the selective laser technique [12, 20–39, 42, 43, 45–48, 58], the selective sequential technique was used in five series [12, 13, 30, 41, 44], and three series used the Solomon technique [13, 46, 48].

Figure 3a shows a forest plot with the individual studies and the inter-study heterogeneity per technique as

well as the subgroup difference and heterogeneity between the subgroups for double twin survival. Figure 3b shows a forest plot with the results for single twin survival. Survival of both twins improved significantly ($p = 0.0001$) over the course of the introduction of new or modified techniques to the detriment of survival of only one twin ($p = 0.01$). Overall a gradual improvement in survival of at least one twin was seen for the newer techniques ($p = 0.004$).

Complications

Reports on post-treatment complications after laser therapy were not readily available in all studies. Only 12 (33%) of the included studies reported data on PPRM. Definitions ranged from '<37 weeks gestation' to 'within 7 days after fetoscopy', making comparison of these results impossible [13, 27, 29, 31, 32, 35, 36, 38, 39, 42, 46, 47].

Discussion

In this review of all published series reporting on outcomes after fetoscopic laser treatment for TTTS, we found a significant improvement in survival of both twins and at least one twin over the past 25 years. This study also shows a significant improvement in survival of both twins with the more recently developed laser techniques.

In 1990, De Lia et al. [3] published the first results of fetoscopic laser therapy as an alternative for serial amnioreduction for the treatment of TTTS. Since then the technique has undergone a variety of modifications.

The shown improvement in survival is likely multifactorial and potentially affected by different forms of bias. There are several important hypotheses to explain the improvement in perinatal survival after laser treatment in time. First of all, adaptations in laser technique such as indicated above are likely to affect survival, however the only way to demonstrate this true effect is to perform a randomized controlled trial adequately powered for perinatal survival.

Secondly, an important factor affecting treatment results is the learning curve effect. In principle, novice surgeons are assumed to perform surgery less safely and efficiently than more experienced colleagues. A learning curve represents the improvement of both the operators, from experience and practice, and, equally as important, the performance of the entire team at managing pregnancies with TTTS. Better teamwork, multidisciplinary discussion with colleagues from the neonatology department (including international audits), stimulation, controllability and continuity may have been beneficial factors [57].

Furthermore, since laser therapy has been accepted as the preferred treatment option, knowledge and aware-

Fig. 3. b Forest plot showing single twin survival rates subdivided by the laser technique used.

(For second part of figure 3b see next page.)

ness in remote centers not offering this highly specialized treatment has grown. Increased awareness may have resulted in improved timely referral and a decreasing number of cases with advanced disease and poor outcomes.

With the acceptance of laser surgery as the best treatment thus far, over the years increasing number of centers started to offer this procedure. Since TTTS is rare and both the surgical procedure as well as careful selection of cases and optimal timing of treatment is complex, con-

centration of care in specialized maternal-fetal medicine centers has been advocated. With the most recent survival rates as a benchmark, (real-time) monitoring and quality control are essential to prevent a more widespread use of this technique, at least temporarily, from leading to less favorable outcome due to learning curve effects and small numbers.

The finding that newer techniques have better perinatal survival results could be attributable to a true improve-

ment in the technique. However this effect could be positively affected by the fact that new techniques are, in general, introduced and adopted sooner by the more experienced therapists after completion of their learning curve and thus likely perform better. Another important factor influencing this improved survival is based on case selection in series comparing two techniques, which was evident in some studies on the sequential laser technique [60].

With this study we hope to set a benchmark level which established and starting centers can compare their individual results with. Regular structural reflection on one's own practice is essential to prevent late detection of sub-optimal performance. If less favorable outcomes are noticed, a quality cycle including further education, supervision of practice and improvement of learning environment should be initiated. We encourage starting up centers as well as established centers to share their performance for peer review and to publish their series in order to keep updating the benchmark for other centers [61].

Unfortunately, data on post-treatment complications such as TAPS, recurrent TTTS or PPROM were often not available in the reported studies or lacked uniform definitions. Iatrogenic PPROM is generally assumed to be one of the most important causes of premature delivery after laser therapy [6]. To gain better insight into the important complications of laser treatment, it is crucial that we use

systematic methods of reporting. Incidences are low and knowledge is largely based on small series. In order to conduct systematic reviews in these areas, definitions need to be uniform when it comes to perinatal survival (e.g. alive at 28 days after birth), PPROM (e.g. before 32 weeks gestation), TAPS and recurrent TTTS.

This study has some important limitations. Our findings could be influenced by publication bias. Centers that are still in their learning curve, or otherwise have less favorable results, might be hesitant to publish their series when they underperform compared to the published series of established centers. Also, the data may reflect selection bias. Less experienced centers may only treat less difficult cases and refer difficult cases to experienced centers, resulting in better survival in their centers and decreased survival in the latter.

The past decades have also shown significant improvements regarding (early) neonatal care resulting in overall better outcomes after preterm birth [62–64]. The effect of the above-mentioned factors are very difficult to quantify and should be taken into account when interpreting the results of this study.

Another limitation is the inclusion of series that have a large time span of data collection. This might have decreased the differences in survival over time when later series include the learning curve phase of the center.

Evaluation of technical or other adaptations of surgical techniques using historic controls is hampered by bias caused by increasing experience over time, the learning curve effect and improved neonatal care. The value of meta-analysis is highly dependent on the quality of the included studies. Most of the introduced techniques and adaptations have not been evaluated in randomized controlled trials. Comparison of survival outcomes of different techniques based on data from non-comparative observational studies is potentially hampered by high inter-study heterogeneity, as found in this study. Due to the nature of the data, statistical correction is impossible. Interpretation of the results should be done with caution and can only be used to generate hypotheses.

The treatment of TTTS yielded a fair improvement in perinatal survival with the introduction of laser surgery over two decades ago. This review shows a significant increase in perinatal survival since then. Combining all published series, as a benchmark, perinatal survival of at least one twin after laser therapy can be achieved in 81–88% of pregnancies and survival of both twins in 52–54% of pregnancies. The median GA at delivery in these series was 32.4 weeks. Nevertheless, we believe that significant improvement opportunities prevail and we see challenges in improving instrumentation and technology for the treatment of TTTS to increase survival of both twins and, almost equally important, in prolonging pregnancies beyond 34 weeks gestation. Survival and short-term neonatal morbidity should not be the only goals. The ultimate goal should be ‘disease-free survival’ and focus on reducing the rate of neurodevelopmental impairment. We sug-

gest institutions to focus on long-term pediatric neurodevelopmental outcomes. Follow-up into childhood is indispensable to determine outcome in terms of motor, cognitive and behavioral development [65].

Fetoscopic laser treatment is often hindered by technical difficulties such as reduced visibility due to stained amniotic fluid or poor accessibility of some anastomoses due to placenta location or the position of fetal parts on the vascular equator [66]. Possibly, such limitations may affect the outcome results of the treatment. Technological innovations may aid us to overcome these limitations and help us improve our outcomes. Remarkably, technological innovations in instrumentation and equipment, common in the field of laparoscopic surgery, appear to be virtually absent in the fetoscopic treatment of TTTS. The equipment used 25 years ago is almost identical to what we use today. A lack of interest from commercial companies paired with complicated licensing issues for use in pregnancy may play a role.

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Disclosure Statement

None of the authors have any conflict of interest.

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