What is the impact of placental tissue damage after laser surgery for twin-twin transfusion syndrome? A secondary analysis of the Solomon trial

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Placenta 52 (2017) 71–76

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

What is the impact of placental tissue damage after laser surgery for twin-twin transfusion syndrome? A secondary analysis of the Solomon trial

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ARTICLE INFO

Article history:
Received 29 September 2016
Received in revised form
23 February 2017
Accepted 24 February 2017

Keywords:
Twin-twin transfusion syndrome
Laser therapy
Tissue damage
Image analysis
Placenta

ABSTRACT

Background: The introduction of the Solomon technique for the treatment of twin-twin transfusion syndrome (TTTS) increased placental exposure to laser energy. This study aims to identify the impact of power and energy used in laser treatment on placental tissue and pregnancy outcome.
Methods: Pictures of all dye-injected placentas since the start of the Solomon trial were analyzed. Placental damage was scored using a grading system including visual scar depth and affected proportion of the vascular equator. Parameters analyzed included laser power and total energy, gestational age (GA) at laser, GA at birth, laser-to-delivery interval and preterm prelabor rupture of membranes (PPROM).
Results: We included 122 cases in the analysis. More placental damage occurred more often in the Solomon group (42%) compared to the selective group (15%) ($p < 0.001$). In multivariate analysis, more placental damage was associated with higher laser energy (regression coefficient B 0.002) but not with higher power setting (regression coefficient B −0.442). More damage was associated with earlier GA at birth (regression coefficient B −0.167), higher incidence of PPROM <32 weeks (regression coefficient B 0.003) and a shorter laser-to-delivery interval (regression coefficient B −0.168).
Conclusions: Placental damage is positively associated with more laser energy but negatively associated with higher power setting. More placental damage was associated with a lower GA at birth, shorter laser-to-delivery interval and higher PPROM rate. Whether these results should lead to a change in surgical technique requires more research, both further ex-vivo experiments on human placentas and clinical studies.

1. Introduction

Monochorionic (MC) twin pregnancies are high-risk pregnancies, often (10%) complicated by twin-twin transfusion syndrome (TTTS). Untreated, this condition is associated with approximately 90% perinatal mortality and severe morbidity [1–3]. Survival rates increase significantly after treatment with fetoscopic laser therapy up to 88% for at least one twin and 62% for survival of both twins, in experienced centers [4].

In 2008, the Solomon technique was introduced as an adaptation of the selective fetoscopic laser coagulation technique for the treatment of TTTS complicated MC pregnancies [5]. The rationale behind the Solomon technique is to eliminate even the smallest anastomoses by coagulating a line between the visible anastomoses, thereby avoiding residual anastomoses leading to recurrence of TTTS or occurrence of post-laser twin anemia polycythemia sequence (TAPS). We concluded that the Solomon technique significantly reduces the incidences of recurrent TTTS and post-laser TAPS [5].

A possible drawback of the Solomon technique is a larger surface area of the placenta being exposed to laser energy, compared to the selective laser coagulation technique (Fig. 1). Animal studies

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http://dx.doi.org/10.1016/j.placenta.2017.02.023
0143-4004/

suggest that superficial coagulation, in time, may lead to functional loss of the entire underlying cotyledon [6]. Little research has been conducted on the impact of laser energy and laser power setting (wattage) on the human placental tissue. Emery et al. described the effect of Solomon laser treatment after pathological analysis on a human placenta. They concluded that solomonization leads to devitalization of the chorionic plate with shallow devitalization of the underlying villi [7].

A worldwide expert survey showed significant variation in laser power settings between centers [8]. Furthermore, it showed that the Solomon technique is gaining popularity. We therefore consider it important to investigate the impact of laser power and laser energy on placental tissue. Laser power is defined as the output wattage of the laser device that can be set by the operator. The total amount of laser energy (joule) used during a procedure is calculated automatically by the laser device and is the result of laser power and the laser time. This study aims to identify the impact of the level of laser power and the amount of energy used in laser treatment on placental tissue and pregnancy outcome.

2. Methods

2.1. Data source

For this study, all cases from the Leiden University Medical Center included in the Solomon Trial [5] were used, as well as all cases treated in our national referral center after the Solomon study was concluded.

All subjects treated between 2008 and 2014 at the Leiden University Center during the Solomon trial were eligible for this study. Inclusion criteria for laser surgery were: monochorionic pregnancy, gestational age between 13 and 28 weeks, TTTS Quintero stage 1 with severe clinical symptoms of polyhydramnios, or TTTS Quintero stage ≥2. For the analyses we extracted data on laser treatment specifics (including laser power, laser time and total energy usage), clinical outcome parameters and postpartum color-dye injected placenta pictures. Details on the color-dye procedure were previously reported [9].

2.2. Inclusion and exclusion criteria

All cases with an available placenta picture after selective or Solomon laser were included. Exclusion criteria were: missing documentation on both total energy and laser power setting, missing scale on the picture, single fetal demise and re-intervention laser therapy after the initial laser procedure. Cases with single fetal demise were excluded because placental maceration hampers color-dye injection. Cases with a re-intervention laser procedure were excluded because the visible damage could not be directly linked to either one of the laser procedures. Pictures from cases with a laser-to-delivery interval under seven days were excluded from grading, because these pictures showed no or little scarring.

2.3. Scoring placental tissue damage

In the absence of a validated scoring system for placental tissue damage, we developed one (Table 1) based on validated scar scales [10,11]. The amount of damage of each grade was measured in millimeters length and expressed as percentages of the total lasered line in Solomon cases, or lasered sections in selective cases of the placenta. In pictures that had a missing scale but showed an umbilical cord clamp, the clamp was used to gauge the scale. Measurements were performed using ImageJ 1.47v software (ImageJ, National Institutes of Health, Bethesda, Maryland, USA). Placental tissue damage was defined as the summed up value of grade 2 and 3 tissue damage. These two categories most likely cover the damage that is considered to be more severe than intended with laser coagulation. Two observers (SdV and JA) assessed all pictures independently and blinded from outcome, patient and procedural parameters. Inter-observer variability was assessed calculating the intraclass correlation coefficient. In cases with an inter-observer scoring difference of >5% of the tissue damage score, the case was discussed by the observers until consensus was achieved. We used the mean value of the tissue damage scores of both observers combined for analyses.

2.4. Analysis

The influence of laser power and laser energy on placental tissue damage was analyzed. Further analyses were conducted to determine the relation of placental tissue damage, laser power and laser energy to various outcome parameters. These included gestational age (GA) at birth, laser-to-delivery interval and preterm prelabor rupture of membranes (PPROM) before 32 weeks' gestation.

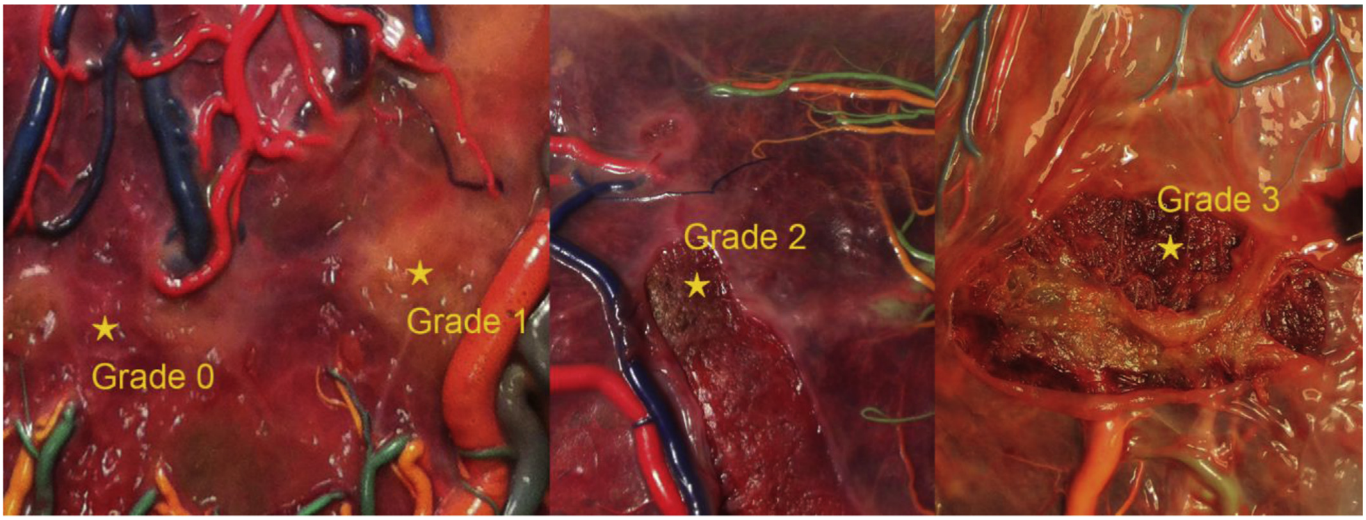
2.5. Statistical analysis

Analyses were conducted using SPSS Statistics (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Analysis for risk factors, visual placental tissue damage, laser power and laser energy, influencing either the gestational age at birth, laser-to-delivery interval and PPROM under 32 weeks gestation was conducted using univariate and multivariate regression methods. Normality of all variables was asessed prior to moddeling. The potential risk factors for each of the three outcomes were studied in a univariate regression model. The multivariate regression model included all factors that showed

Fig. 1. Left: selective laser coagulation (★ marks the laser spots). Right: Solomon laser coagulation (| marks the laser line).

Table 1
Placental damage grading system with median damage scored per category and technique. Proportion expressed in percentages of total vascular equator. Mann-Whitney *U* test. The numbers in the pictures correspond with the damage grading category.

Category	Definition	Selective Technique	Solomon Technique	P-value
		Median % (range)	Median % (range)	
Grade 0	No visible signs of laser coagulation	70,1 (13–94)	3,4 (0–89)	**<0.001**
Grade 1	Membranes intact, white/brownish	15,1 (0–58)	46,2 (0–98)	**<0.001**
Grade 2	Membranes perforated, red	4,6 (0–31)	19,0 (0–87)	**<0.001**
Grade 3	Underlying tissue damaged, irregular surface	7,5 (0–59)	13,0 (0–100)	**0.021**
Grade 2 + 3	Grade 2 and 3 combined	15,1 (0–59)	41,8 (0–100)	**<0.001**



significant association in the univariate analysis. Results are expressed as regression coefficients (B) with 95% confidence intervals (95%CI). Numerical variables with a normal distribution were expressed in mean (SD) and variables with a skewed distribution were expressed in median (range). Group differences were compared using the Mann–Whitney *U* test, the independent Student's t-test or the one-way ANOVA, as appropriate. A p-value of <0.05 was considered statistically significant.

3. Results

3.1. Selected cases

A total of 159 placenta pictures, documented after selective (n = 44 (28%)) or Solomon (n = 115 (72%)) laser coagulation, were available for this study. Included selective laser cases were treated between March 2008–June 2012 and included Solomon cases between January 2008–January 2014. Four cases were excluded because of single fetal demise with partial placental maceration, and three because a second laser procedure was performed. No pictures of double demise cases were available. Data on both laser power setting and total energy was missing in 17 cases, all in the Solomon group. Another 10 cases were excluded due to missing scale or inadequate quality of the picture. Finally, three pictures were excluded from grading because of a laser-to-delivery interval within 7 days. These cases were lasered at 25 + 3, 22 + 0 and 25 + 5 weeks GA and could not be scored due to insufficient visual placental scarring. In total, 122 placenta pictures were included in this study, 44 (36%) after selective laser and 78 (64%) after Solomon laser.

3.2. Case characteristics

The mean GA at laser was 20 (±3) weeks and mean GA at birth was 32 (±5) weeks (Table 2). Seven cases were lasered after 26 weeks' gestation, with a maximum GA at laser of 28 + 4 weeks. The placenta was localized posterior in 57% of the cases. Most lasers were performed for TTTS with Quintero stage 3 (49%). One of the cases involved a dichorionic triplet pregnancy, with a monochorionic component. Two placentas were lasered for the treatment of TAPS. The Nd:YAG laser (Dornier Fibertom 5100) was replaced by a diode laser (Dornier Medilas D Multibeam) in May 2013 due to regular replacement of equipment. Thirteen of the 78 Solomon cases in this study were lasered using the diode laser, generally with lower power levels compared to the Nd:YAG laser, in sub analyses laser type had no effect on the outcome of this study. All case characteristics and procedural parameters are shown in Table 2.

3.3. Grading

The 122 pictures were scored using the tissue damage grading system. The mean proportion of damage, expressed as the percentage of the total vascular equator for each grade is shown in Table 1 for both selective and Solomon cases. Placental tissue damage was found more frequently in the Solomon group (42%) compared to the selective group (15%) ($p < 0.001$). Inter observer variability in defining grade 2 and 3 damage was good with an intraclass correlation of 0.997 (95%CI 0.995–0.998). In 5 cases we found an inter-observer grading difference of >5%, these cases were discussed by both observers blinded from procedural and outcome parameters until consensus was reached.

3.4. Associations with placental damage

Analysis of factors associated with grade 2 and 3 placental tissue damage is shown in Table 3. Since gestational age at laser was

Table 2
Baseline characteristics.

	All cases (n = 122)	Selective Technique (n = 44)	Solomon Technique (n = 78)	P-value
Case Characteristics				
Quintero stage				
Stage 1	15 (12)	7 (16)	8 (10)	0.762
Stage 2	38 (31)	12 (27)	26 (33)	
Stage 3	60 (49)	23 (52)	37 (47)	
Stage 4	6 (5)	2 (5)	4 (5)	
Placenta localization				
Anterior	48 (39)	17 (39)	31 (40)	0.375
Posterior	69 (57)	27 (61)	42 (54)	
Lateral	4 (3)	0 (0)	4 (5)	
Anterior and posterior	1 (1)	0 (0)	1 (1)	
Laser type				
YAG	109 (89)	44 (100)	65 (83)	0.004*
Diode	13 (11)	NA	13 (17)	
GA at laser	142 (±22)	141 (±20)	143 (±23)	0.633
GA at birth	229 (±23)	228 (±26)	229 (±21)	0.775
Pregnancy prolongation	86 (±30)	87 (±29)	86 (±31)	0.900
Procedural Parameters				
Fetoscopy time (min)	28 (±11)	23 (±9)	30 (±11)	0.004
Maximum power setting (watt)	53 (±15)	55 (±12)	53 (±16)	0.477
YAG	55 (±14)	55 (±12)	56 (±15)	0.665
Diode	36 (±14)	NA	36 (±14)	NA
Total laser energy (joule)	5668 (673–32300)	2704 (673–20500)	7171 (797–32300)	<0.001*
YAG	5998 (673–32300)	2704 (673–20500)	8070 (2285–32300)	<0.001*
Diode	4175 (797–14924)	NA	4175 (797–14924)	NA
Amount anastomoses	6 (2–23)	6 (2–19)	6 (2–23)	0.841

All categorical values are expressed as N(%). All numerical values are expressed as mean (SD) or median (range). GA laser, GA birth and Pregnancy prolongation are reported in number of days. Pregnancy prolongation is defined as the number of days of pregnancy prolongation after laser therapy until the delivery.

strongly correlated with laser power (Pearson correlation 0.468; $p < 0.001$), laser energy (Spearman correlation 0.297; $p < 0.001$) and the laser-to-delivery interval (Spearman correlation −0.635; $p < 0.001$), multivariate analyses were performed. Multivariate analysis showed that laser energy ($p < 0.01$) was positively associated and that laser power ($p = 0.027$) was negatively associated with more placental damage (grade 2 and 3 damage combined). The amount of grade 2 and 3 placental damage negatively affected the GA at birth as shown in Table 4 ($p = 0.020$). Table 4 also shows that less grade 2 and 3 placental damage ($p = 0.020$) and a lower GA at laser ($p < 0.01$) were both associated with a longer laser-to-delivery interval in multivariate analysis. This finding was the same for PPROM <32 weeks' gestation. More grade 2 and 3 damage ($p = 0.031$) and a lower GA at laser ($p = 0.029$) were associated with a higher rate of early PPROM as shown in Table 4.

4. Discussion

4.1. Main findings

In this study, we evaluated the impact of gestational age of laser, laser power, laser total energy and post-partum visual placental damage after laser treatment for TTTS on pregnancy outcome. Visual tissue damage appeared to be a significant risk factor for a higher incidence of PPROM under 32 weeks' gestation and a shorter laser-to-delivery interval and a lower GA at birth. Cases with more extensively damaged placentas more often developed PPROM and had a lower GA at birth compared to cases with less placental tissue damage. Anterior placenta localization did not lead to use of more laser energy or more placental tissue damage. More laser energy used during the procedure was associated with more extensive placental damage, whereas a higher power setting was found to lead to less damage. Furthermore, we found a significant correlation between GA at laser with laser power and laser energy used.

4.2. Interpretation

The correlation of GA at laser with laser power, and total energy is most likely explained by the fact that the superficial placental vessels increase in diameter over time, and concurrently the fetal blood volume increases during pregnancy [12]. Larger vascular diameter requires more energy to achieve successful coagulation of the vessel and a higher power setting delivers this energy more rapidly. The significant association between laser power and laser-to-delivery interval in the univariate linear regression model is explained by the strong correlation of both variables with GA at laser. Higher laser power settings are used in cases with more advanced GA and these cases are associated with shorter pregnancy prolongation than cases with laser therapy at earlier GA.

With the results of this study, we speculate that higher total energy use in laser treatment for TTTS leads to significantly more placental tissue damage. Higher laser power showed the opposite effect. We hypothesize that, with a higher power setting, energy transfer is more effective and takes shorter time and less energy

Table 3
Analysis of factors contributing to grade 2 and 3 damage.

Variable	Univariate analysis B (95% CI)	SE	P	Multivariate analysis B (95% CI)	SE	P
Laser power	−0,256 (−0,596 to -0,070)	0,166	**0022**	−0,442 (−0,833 to -0,050)	0,198	**0027**
Laser energy	0,001 (0,000 - 0,002)	0,000	**<0,01**	0,002 (0,001–0,003)	0,000	**<0,01**
GA at laser	−0,106 (−0,335–0,123)	0,116	0361	−0,072 (−0,327–0,183)	0,129	0577

Values are regression coefficient B (95%CI, standard error (SE) and P. Values represented in bold script represent a significance level of p < 0.05

Table 4
Analysis of factors associated with different outcomes.

Variable	Univariate analysis B (95% CI)	SE	P	Multivariate analysis B (95% CI)	SE	P
Factors associated with gestational age at birth						
Laser power	0,045 (−0,233–0,323)	0,140	0750	−0,021 (−0,362–0,319)	0,172	0901
Laser energy	0,000 (−0,001–0,001)	0,000	0821	0,000 (−0,001–0,001)	0,000	0944
Grade 2 and 3 damage	−0,163 (−0,296 - -0,029)	0,067	**0017**	−0,167 (−0,307 - -0,026)	0,071	**0020**
GA at laser	0,093 (−0,098–0,283)	0,096	0338	0,063 (−0,158–0,284)	0,111	0563
Factors associated with the laser-to-delivery interval						
Laser power	−0,646 (−0,997 - -0,296)	0,177	**<0,01**	−0,036 (−0,388–0,315)	0,177	0838
Laser energy	−0,001 (−0,002–0,000)	0,000	0244	0,00 (−0,001–0,001)	0,000	0871
Grade 2 and 3 damage	−0,137 (−0,314 - -0,041)	0,090	0130	−0,168 (−0,306 - -0,026)	0,071	**0020**
GA at laser	−0,907 (−1098 - -0,717)	0,096	**<0,01**	−0,937 (−1161 - -0,713)	0,113	**<0,01**
Factors contributing to PPROM before 32 weeks' gestation						
Laser power	0,010 (−0,016–0,036)	0,010	0450	0,032 (−0,003–0,067)	0,018	0073
Laser energy	0,000 (0,000 - 0,000)	0,000	0457	0,000 (0,000 - 0,000)	0,000	0711
Grade 2 and 3 damage	0,015 (0,001–0,028)	0,007	**0030**	0,016 (0,001–0,030)	0,007	**0031**
GA at laser	−0,016 (−0,036–0,003)	0,010	**0049**	−0,026 (−0,05 - -0,003)	0,012	**0029**

Values are regression coefficient B (95%CI, standard error (SE) and P. Values represented in bold script represent a significance level of $p < 0.05$

than with a lower wattage. In addition, the energy is less dispersed than in a low power setting and thus leads to less collateral damage.

This study is the first to systematically evaluate and score placental damage in relation to laser power, time and total energy. Previous studies showed a relation between laser power setting and tissue damage in tissues other than placenta. Kirschbaum et al. [13] showed a significant positive correlation between laser power output and the mean cutting depth in paracardiac lung lobes of pigs. Likewise, an ex-vivo experiment on kidney models by Khoder et al. [14] showed a nearly linear increase of ablation depth with increasing laser power output. These studies were performed in an experimental setting and used interstitial laser techniques. In contrast to the laser therapy for TTTS, interstitial laser treatment is used for direct tissue destruction. Hence, tissue damage could be analyzed more precise because the effect is directly visible after treatment. With the interstitial laser technique, the transfer of energy to the tissue is direct, whereas in laser therapy for TTTS the distance between the tip of the laser fiber to the placenta highly impacts effective energy transfer [14].

Firing distance and angle are thought to be important factors influencing effective energy transfer to the tissue. These factors are difficult to control and hard to measure in vivo. Khoder et al. [14] showed a significant reduction in ablation depth with increasing tissue distance in experimental setting. A higher power setting is necessary in order to achieve tissue ablation because laser energy is lost in the distance between the laser fiber and tissue. The true influence of firing angle is unclear. Theoretically, because the vessels are localized on the placental surface, a wide range of angles should lead to comparable energy transmission onto the vessel. Future studies should provide more knowledge about the optimal distance and angle for laser therapies.

The optimal laser power setting for laser coagulation of placental vessels is unknown. A wide range of laser power setting and technique is used worldwide [8]. It is also unclear whether coagulating with a high laser power setting for a short time span would lead to different results than coagulating longer with a lower laser power. It is plausible that various settings lead to different tissue effects. Branisteau et al. addressed the effect of laser coagulation on placental tissue using an in-vivo ovine placenta model. Results showed that the tissue effects, in time, spread beyond the surface and induces complete functional elimination of the involved cotyledon [6]. The results of this study might imply that the operator should strive towards superficial coagulation of the placental tissue in order to obtain complete cotyledon elimination while avoiding the risk of complications as PPROM or early delivery.

In order to decrease the amount of energy used during a Solomon procedure for treating TTTS one could lower the laser power setting during coagulation between true anastomoses. More research on human placentas is necessary in order to confirm this, the results of this study, and to determine the optimal laser power setting.

4.3. Limitations

An important limitation in this study is the case selection of treated pregnancies with two live born children. This prevents us from drawing conclusions about the strong outcome measure of survival. Furthermore, documentation on laser power included only the maximum used setting. In most of the cases this is the predominant setting used during a procedure, however, in some cases the results might be influenced because the maximum setting was used for only a short time span.

Another limitation of this type of study is the retrospective nature, based on placenta pictures and not live tissue preventing us to use other anticipated important factors as number, type and caliber of anastomoses and placental weight. Finally, a wide range of pregnancy prolongation after laser was present in our sample. Scar tissue develops in time and therefore it is possible that cases with a short prolongation are graded differently than ones with a longer prolongation, even though perhaps the same scarring would have developed within more time.

5. Conclusion

We found a significant association between laser power and total energy used during laser treatment for TTTS and postpartum placental tissue damage. More energy leads to more damage whereas a higher power setting leads to less damage. In this study, greater tissue damage was associated with a lower GA at birth, a higher PPROM rate under 32 weeks' gestation and a shorter laser-to delivery interval. These early results of our research into detailed technical aspects of fetoscopic laser surgery should be interpreted with caution, we do not recommend changes in practice at this time. We do believe more in-depth analysis of all details of fetoscopic surgery may ultimately lead to improvements in outcome.

Disclosure

None of the authors have a conflict of interest.

Acknowledgement

This research is supported by the Dutch Technology Foundation STW (STW project number 12711), which is part of the Netherlands Organisation for Scientific Research (NWO), and which is partly funded by the Ministry of Economic Affairs.

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