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Fetal heart rate changes associated with sequential selective laser surgery for twin-twin transfusion syndrome

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Objective: To investigate perioperative changes in fetal heart rate (FHR) associated with sequential vs standard selective laser photocoagulation of communicating vessels for the treatment of twin-twin transfusion syndrome (TTTS).

Study Design: Women with TTTS were treated with the intent of using the sequential procedure. Those who failed this treatment were categorized as having undergone the standard procedure. Pre- and postoperative FHR of donor and recipient fetuses were analyzed.

Result: Of 98 women, 35 received the standard technique. A postoperative drop in the mean donor FHR was observed in gestations receiving the standard laser, but not in those receiving the sequential technique. In multivariable models that included operative and gestational characteristics, the use of the sequential treatment was associated with improved stability of the FHR of the donor twin.

Conclusion: The stability in donor FHR following sequential laser ablation when compared with the standard technique is consistent with improved donor hemodynamics.
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Keywords: sequential laser therapy; monochorionic twins; bradycardia; anastomoses

Introduction

Twin-twin transfusion syndrome (TTTS) occurs in approximately 10% of monochorionic twins and is attributed to shared vascular communications in the placenta, resulting in a net transfer of blood from the donor to the recipient twin.[1] The standard surgical treatment for TTTS, termed as selective laser photocoagulation of communicating vessels (SLPCV), fetoscopically identifies and ablates the vascular anastomoses.[2] Recently, a modification of this technique was described by Quintero *et al*.[3] and is referred to as sequential selective laser photocoagulation of communicating vessels (SQLPCV). In this experimental technique, arteriovenous anastomoses from the donor to the recipient (AVDR) are lasered first, followed by the arteriovenous anastomoses from the recipient to the donor (AVRD).[3]

In theory, sequential interruption of communicating vessels allows for an advantageous intraoperative transfusion of blood from the hypervolemic recipient twin to the hypovolemic donor twin. This in turn may prevent the donor twin from becoming increasingly hypovolemic and hypotensive, which may account for the improved donor twin survival using the SQLPCV technique.[3] The sequential approach by Quintero has been supported by a computer simulation conducted by Van Gemert *et al*.[4] An inter-twin transfusion of 25 ml was simulated at 21 weeks' gestation resulting in a loss of 64% of the donor twin's blood volume when the non-sequential approach was used. In contrast, when the sequential approach was used, the donor twin's blood volume was preserved and there was a 50% loss of the recipient twin's blood volume. These computer simulation findings suggest that the intraoperative transfusion that occurs during SQLPCV surgery may benefit a hypovolemic donor fetus.

The fetal heart rate (FHR) response to various physiologic perturbations has been the subject of much animal research. When fetal sheep experience severe hypotension, a drop in heart rate occurs.[5,6] This reflexive bradycardia also occurs in response to hemorrhage.[7,8] According to Brace and Cheung,[7] a blood volume loss of 13–30% was sufficient to initiate a bradycardic reaction, whereas a more rapid 32% loss in blood volume resulted in cessation of heart rate and death. The physiological mechanisms behind this reflexive bradycardia remain unclear.

Given the hypothesis that SQLPCV may be associated with decreased intraoperative donor twin blood loss as compared with SLPCV,[3,4] which in turn may be reflected by heart rate changes,[5–8] we set out to determine whether the type of laser surgical treatment, sequential vs standard, was associated with a postoperative drop in heart rate among donor fetuses.

Methods

The study population consisted of all patients who underwent laser treatment for TTTS at our institution from March 2006 through

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March 2008. The diagnosis of TTTS was made through ultrasound examination in monochorionic diamniotic multiples by showing both a maximum vertical pocket $\geqslant$8 cm in one sac and an maximum vertical pocket $\leqslant$2 cm in the other sac. Disease severity was classified according to the Quintero staging system.[9] All patients who were diagnosed with TTTS between 16 and 26 weeks of gestation were offered laser surgery. Triplet pregnancies and patients with a short cervix were not excluded from participation.

In all laser surgeries, maternal anesthesia was provided through local anesthesia with intravenous conscious sedation. A 3.8 mm trocar was inserted into the sac of the recipient under direct ultrasound guidance. Next, a 3.3 mm diagnostic endoscope (Richard Wolf Inc., Vernon Hills, IL, USA) was used to map the entire placental vascular equator. All vascular communications were then identified and labeled as an AVDR, an AVRD, or as superficial anastomoses such as arterio-arterial or veno-venous. After placental vascular mapping was completed, the vascular communications were photocoagulated using Nd:Yag laser energy at 20–40 W delivered into the amniotic cavity by 600 μ quartz non-contact fibers through the operating channel of the endoscope (Richard Wolf Inc.). During usage of the SQLPCV technique, the anastomoses were ablated in the following sequence: arteriovenous from donor to recipient, arteriovenous from recipient to donor, superficial arterio-arterial, and superficial veno-venous anastomoses.[3] At the end of the surgery, amniotic fluid was removed until the maximum vertical pocket in the recipient's sac measured approximately 8 cm or less.

SQLPCV was attempted in all patients. The group of patients categorized as having SLPCV failed SQLPCV at some point during the surgery when the sequential process could not be continued because of technical reasons. The reasons for the non-sequential procedure not being performed included the following: the AVDR was identified and occluded after initial mapping and laser ablation of the other anastomoses (13), placental factors (6), amniotic fluid was discolored (6), donor position (8), prior septostomy (1), and patient discomfort (1). Each case was categorized as having SQLPCV vs SLPCV immediately after the surgery.

FHR from both the donor and the recipient were obtained in the operating room through sonogram. The preoperative heart rates were measured 1 to 2 min before the insertion of the trocar and postoperative heart rates were measured 1 to 2 min after the trocar was removed. The heart rates were grouped according to lasering technique, SQLPCV vs SLPCV. Heart rates were further divided as having occurred pre- or postoperatively, and by donor or recipient fetus. A single case that experienced preoperative fetal bradyarrhythmia was excluded from the statistical analysis.

The data were analyzed using SAS (v. 9.1, Cary, NC, USA). All categorical data were analyzed through χ^2 test with Yates correction. Continuous data were compared using the Kruskal–Wallis test. Linear regression models were built for the drop in donor and recipient heart rates with a backwards procedure using the following variables: sequential procedure, number of AVDR, number of AVRD, number of arterio-arterial, number of veno-venous, Quintero Stage 3 or 4 vs Stage 1 or 2, gestational age at the time of surgery (weeks), duration of operation (10 min increments), and interaction terms representing the use of the sequential procedure and the number of AVDR and AVRD. A *P*-value of <0.05 was considered statistically significant. The study was approved by the Institutional Review Board at Health Sciences Campus of University of Southern California, Los Angeles, California.

Results

During the study period, 99 women with TTTS underwent laser surgery. One patient was eliminated from the study because of preoperative fetal bradycardia. Of the remaining 98 patients, the mean gestational age at time of laser surgery was 20.9 $\pm$ 2.4 weeks (median 21.0, range 16.1–26.7 weeks). SQLPCV was achieved in 63 cases (64%). Overall, 72.4% of the gestations were in Quintero Stage 3 or 4; this proportion did not vary by surgical procedure. Operative time was significantly shorter for the group of patients undergoing the sequential procedure (45.2 $\pm$ 15.2 min (median 43.0, range 20.0–103.0) vs 60.4 $\pm$ 27.4 min (median 51.0, range 23.0–128.0) ($P = 0.010$).

The mean total number of anastomoses lasered did not differ for the sequential vs the non-sequential treatment groups: 7.6 $\pm$ 3.9 (median 7.0, range 1–21) vs 7.8 $\pm$ 3.2 (median 7.0, range 3–16) ($P = 0.627$). The mean number of AVDR anastomoses was 3.7 $\pm$ 2.4 (median 3.0, range 1–14) vs 4.0 $\pm$ 2.1 (median 4.0, range 0–10) ($P = 0.339$) for these same groups, respectively.

Preoperative and postoperative heart rates of donor and recipient fetuses are shown in Table 1. Among the donor fetuses, the mean drop in heart rate for those undergoing the sequential procedure was 3.1 $\pm$ 14.7 bpm ($P = 0.097$) vs 9.3 $\pm$ 23.7 bpm ($P = 0.027$) for those undergoing the non-sequential procedure. Owing to the high degree of FHR variability, the mean FHR drop did not differ statistically between the two procedure groups ($P = 0.25$). Among the recipient fetuses, the mean drop in heart rate for those undergoing the sequential procedure was 4.3 $\pm$ 17.6 bpm ($P = 0.055$) vs 5.2 $\pm$ 9.8 bpm ($P = 0.003$) for those undergoing the non-sequential procedure. Here too, the mean FHR drop did not differ statistically between the two procedure groups ($P = 0.14$). Multivariate linear regression was performed to determine the gestational characteristics associated with the postoperative drop in FHR for both donors and recipients. Final models are shown in Tables 2 and 3. For donors, the drop in FHR was highly associated with use of the non-sequential procedure ($P<0.001$) (Table 2). Furthermore, among the donors who received the sequential procedure, the FHR drop increased with the number of AVDR anastomoses (Table 2). For recipients, neither the

Table 1 Pre- and postoperative fetal heart rates (FHR) for donor and recipient fetuses undergoing the non-sequential procedure (SLPCV) and the sequential procedure (SQLPCV)

	Donor fetus HR	*Recipient fetus HR*
All gestations (N = 98)		
Preoperative FHR	144.6 ± 12.7,	140.0 ± 9.0
	143.0, 118.0−195.0	140.0, 122.0−164.0
Postoperative FHR	139.3 ± 15.8	135.4 ± 15.1
	141.0, 79.0−176.0	136.0, 48.0−161.0
Drop in FHR	5.3 ± 1.7	4.7 ± 15.2
	2.5, −23.0 to +85.0	2.0, −25.0 to +98.0
P-value for the drop in FHR	0.0054	0.0031
Gestations undergoing the non-sequential procedure (N = 35)		
Preoperative FHR	145.4 ± 14.6	140.5 ± 9.9
	143.0, 122.0−195.0	138.0, 126.0−164.0
Postoperative FHR	136.1 ± 18.1	135.3 ± 9.3
	136.0, 79.0−176.0	135.0, 113.0−155.0
Drop in FHR	9.3 ± 23.7	5.2 ± 9.8
	5.0, −23.0 to +85.0	2.5, −10.0 to +30.0
P-value for the drop in FHR	0.0265	0.0032
Gestations undergoing the sequential procedure (N = 63)		
Preoperative FHR	144.2 ± 11.5	139.8 ± 8.6
	144.0, 118.0−173.0	140.0, 122.0−163.0
Postoperative FHR	141.1 ± 14.2	135.4 ± 17.6
	141.0, 83.0−168.0	136.0, 48.0−161.0
Drop in FHR	3.1 ± 14.7	4.3 ± 17.6
	2.0, −22.0 to +63.0	1.0, −25.0 to +98.0
P-value for the drop in FHR	0.0968	0.0550

Table 2 Multivariable linear regression model for the postoperative drop in fetal heart rate among donor fetuses

Variable	*Parameter estimate*	*Standard error*	P-*value*
Intercept	26.65	6.53	<0.0001
Sequential treatment (Yes/No)	−30.41	7.70	0.0002
Number of AVDR anastomoses	−4.32	1.45	0.0037
Sequential treatment *Number of DR anastomoses	6.17	1.72	0.0005

$F = 5.24$ ($P = 0.0022$).

Table 3 Multivariable linear regression model for the postoperative drop in fetal heart rate among recipient fetuses

Variable	*Parameter estimate*	*Standard error*	P-*value*
Intercept	15.35	13.10	0.2445
Gestational age at the time of surgery (weeks)	−0.87	0.65	0.1808
Operative time in 10 min increments	0.15	0.07	0.0452

$F = 2.41$ ($P = 0.0957$).

procedure type nor the anastomoses number and type were associated with a drop in FHR. Rather, the recipients' postoperative FHR difference appeared to increase with gestational age and decrease with the duration of surgery, although the model itself did not have sufficient power (Table 3).

A total of 15 cases of fetal bradycardia (defined as FHR $\leqslant$120 bpm) were observed postoperatively, 7 (11.1%) of the sequential group and 8 (22.9%) of the standard group ($P = 0.15$). The occurrence of bradycardia was not associated with the number or type of anastomoses, the Quintero Stage, the gestational age at time of surgery, or the duration of surgery.

Discussion

Earlier research performed by Quintero *et al.*[3] suggested that an increase in donor twin survival may occur when using the sequential as opposed to the standard laser treatment for TTTS. The investigators hypothesized that this may be secondary to improved intraoperative donor twin hemodynamics by minimizing donor blood loss.[3] Computer simulations have supported the plausibility of this hypothesis.[4] Our pilot data suggests that sequential laser ablation is associated with increased stability of the donor's FHR. Our present observations are supportive of the hypothesis that sequential ablation may be beneficial to the donor fetus.

The physiological mechanisms resulting in these observed FHR decreases remain to be fully explored. Both hypotension and hypovolemia have been shown to trigger a reflexive bradycardic reaction in fetal sheep.[5–8] A drop in blood volume of as little as 13% in fetal sheep trigger bradycardia,[7] and such a drop was well below the estimated blood loss derived by Van Gemert *et al.*[4] in their computer simulation of donor blood loss using SLPCV, the standard laser surgery treatment of TTTS. As hypotension and hypovolemia have been hypothesized as being contributing factors to the increased risk of fetal demise, it follows that our findings of a greater donor twin FHR drop in the SLPCV group may agree with the hypotheses suggested by Quintero *et al.*[3] The potential function of hypovolemia is further supported by the highly significant correlation between FHR drop and the number of anastomoses in our multivariate linear regression model.

This observational study is focused on only one aspect of cardiovascular status, FHR, and only for the immediate operative period. The inherent variability in the FHR and changes in both donor and recipient fetuses precludes us from making any firm conclusions. Such limitations are compounded by the inability of this study design to randomly assign patients to the two procedures. Finally, FHR changes noted in the standard group may be further confounded by the inherent difficulty of cases in which the sequential technique could not be performed. Nevertheless, the observed FHR changes showed by this study support the hypothesis that the sequential procedure may improve donor fetus hemodynamics and warrants further investigation.

In summary, a postoperative drop in the mean donor FHR was observed in gestations receiving the standard laser treatment for TTTS, but not in those receiving the sequential technique, supporting the hypothesis that the sequential approach may offer a potential for achieving improved hemodynamics. Potentially, improved cardiovascular stability offered by the sequential technique may in turn lead to an improved survival for the hypovolemic donor twin. A multi-center randomized trial is being organized to compare perinatal outcomes in cases of TTTS treated by standard vs sequential SLPCV. In this setting, FHR changes can be more clearly attributed to the technique used as opposed to confounding factors associated with choosing one technique over the other. Further research on human FHR in reaction to hypovolemia and hypotension may also serve to elucidate the physiological mechanisms responsible for these observations.

Conflict of interest

The authors declare no conflict of interest.

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