Postoperative Middle Cerebral Artery Peak Systolic Velocity Changes Confirm Physiological Principles of the Sequential Laser Technique for Twin-Twin Transfusion Syndrome

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Key Words

Twin-twin transfusion syndrome • Sequential laser surgery • Middle cerebral artery Doppler • Fetal anemia • Operative fetoscopy

Abstract

Introduction: Treatment of the twin-twin transfusion syndrome (TTTS) via sequential selective laser photocoagulation of communicating vessels (SQLPCV) mandates ablation of donor-to-recipient arteriovenous anastomoses first. It is hypothesized that SQLPCV facilitates intraoperative transfusion to the donor, thereby minimizing donor hypovolemia and anemia. We sought to determine if postoperative changes in fetal middle cerebral artery-peak systolic velocities (MCA-PSV) support this hypothesis. **Materials and Methods:** Patients undergoing preferential SQLPCV for TTTS had MCA-PSV measured 1 day before surgery and on postoperative day 1 (POD-1). Fetal anemia was defined as an MCA-PSV ≥ 1.5 multiples of the median (MoM). Exclusions included: POD-1 demise, missing MCA-PSV data, or gestational age < 18 weeks. **Results:** Study criteria were met by 139 patients. Mean MCA-PSV in recipients increased from 0.97 to 1.15 MoM postoperatively ($p < 0.0001$). Donor mean MCA-PSV remained stable at 1.00 MoM preoperatively and 0.98 MoM

postoperatively ($p = 0.272$). Nine fetuses, 6 donors and 3 recipients, had preoperative anemia; SQLPCV was not attempted in the 3 anemic recipients. Postoperatively, the proportion of donors with anemia remained stable (increase 3.6%, $p = 0.419$), and the proportion of recipients with anemia increased (increase 12.2%, $p = 0.009$). **Discussion:** Our findings confirm the presumed physiological basis for the SQLPCV treatment of TTTS. Copyright © 2010 S. Karger AG, Basel

Introduction

The twin-twin transfusion syndrome (TTTS) affects approximately 10% of all monochorionic twin gestations, and is a result of placental vascular communications that lead to an unbalanced transfer of blood from the donor fetus to the recipient fetus [1]. Left untreated, TTTS has a high mortality rate [2].

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Currently, the standard treatment for TTTS involves selective laser photocoagulation of communicating vessels (SLPCV) via operative fetoscopy [3]. Using this technique, vascular communications between the donor and recipient fetuses are identified and ablated. The sequence in which ablation of the particular anastomoses occurs varies according to the placental vascular anatomy, but usually follows the order of their identification. The end result of SLPCV is complete separation of the circulatory systems, creating a functionally dichorionic placenta from a previously monochorionic one.

Sequential selective laser photocoagulation of communicating vessels (SQLPCV), a modification of the standard SLPCV technique, was described by Quintero et al. [4] in 2007 and requires that arteriovenous anastomoses (AV) from the donor to the recipient (AVDR) are photocoagulated first, followed by AVs from the recipient to the donor (AVRD), and finally followed by arterio-arterial anastomoses (AA) and veno-venous anastomoses (VV). The SQLPCV technique is believed to allow for a net intraoperative transfer of blood from the recipient to the donor fetus, thus minimizing hypovolemia and anemia in the donor [4, 5]. SQLPCV has shown higher donor twin and dual twin survival rates when compared to the standard SLPCV technique in observational trials [4–6].

Doppler velocimetry of the fetal middle cerebral artery peak systolic velocity (MCA-PSV) allows for an indirect assessment of the presence of moderate to severe fetal anemia [7]. Since SQLPCV is thought to result in a beneficial ‘intraoperative transfusion’ toward the donor fetus [4], the aim of our study was to determine if postoperative changes in the MCA-PSV in the donor and recipient fetuses support this hypothesis.

Materials and Methods

We performed a retrospective study of all patients undergoing laser therapy for the treatment of TTTS between March 2006 and July 2009 at the University of Southern California, Los Angeles, Calif., USA. This study used data which were collected prospectively as part of an ongoing evaluation of patient outcomes with laser therapy. At initial assessment, all patients underwent a complete ultrasonographic examination, and the diagnosis of TTTS was made if the maximum vertical pocket measured ≤ 2 cm in the donor’s sac and ≥ 8 cm in the recipient’s sac. All patients were diagnosed and staged using the Quintero staging system [8]. Patients were offered laser therapy if they were diagnosed with TTTS between 16 and 26 weeks’ gestation. In addition to being offered laser therapy, patients were also counseled regarding alternative management options including expectant management, pregnancy termination, amnioreduction, and umbilical cord occlusion of

the more gravely ill twin. Informed, written consent was obtained from the women choosing laser therapy.

SQLPCV was attempted in all patients in this cohort using surgical techniques described in detail previously [5]. Cases in which the sequential technique was successfully achieved were labeled as the SQLPCV group. Cases in which the sequential process could not be completed for technical reasons were labeled as SLPCV. The entire cohort, labeled preferential SQLPCV, was included in our analysis since an intention-to-treat analytical model was employed.

An exception to the above categorization of patients was made for the rare cases in which fetal anemia was suspected in the recipient fetus, as this technique could lead to a further loss in blood volume in the already compromised recipient twin. For these patients, a reversed SQLPCV (R-SQLPCV) technique was performed. The R-SQLPCV technique requires ablation of all AVRDs, followed by AVDRs. Using this sequence for photocoagulation would in theory lead to a net intraoperative transfer of blood toward the anemic fetus, in this case the recipient. Patients undergoing R-SQLPCV were included in the SLPCV group for analytical purposes.

MCA-PSV was performed 1 day prior to surgery and on postoperative day 1 (POD-1). The MCA was identified by color or power Doppler ultrasonography. An image of the fetal head was obtained in the plane of the biparietal diameter and the transducer was angled at one end towards the base of the brain until the MCA was visualized along the greater wing of the sphenoid bone. The angle of insonation between the ultrasound beam and the vessel was $<10^\circ$. Pulsed Doppler parameters were generated automatically from three or more consecutive waveforms. We utilized the reference ranges for MCA-PSV measurements established for uncomplicated monochorionic diamniotic twins by Klaritsch et al. [9], and excluded patients <18 weeks’ gestation because normative MCA-PSV values for earlier gestational ages were not reported in that study. Moderate to severe fetal anemia was defined as a MCA-PSV of ≥ 1.5 multiples of the median (MoM) for that given gestational age (GA) as defined by Mari et al. [7].

Patients were excluded from analysis if there was a POD-1 demise of either or both twins, if there were missing MCA-PSV data, or if GA was <18 weeks. The Wilcoxon signed-rank test and the McNemar test were used to analyze paired continuous and categorical data respectively. Means are reported $\pm$ SD. The study was approved by the Institutional Review Board at the Health Sciences Campus of the University of Southern California.

Results

During the 3-year study period, 174 consecutive patients with TTTS were treated with laser photocoagulation. No patient with TTTS underwent umbilical cord occlusion in this cohort. Of the 174 patients, 18 patients were excluded from analysis due to a POD-1 demise of either twin (12 cases) or of both twins (6 cases). In addition, 16 patients were excluded from analysis due to a GA of <18 weeks, and 1 was excluded due to missing MCA-

Fig. 1. Pre- and postoperative normative values of MCA-PSV for donor and recipient fetuses.

Fig. 2. Pre- and postoperative proportions of gestations with anemia as identified by MCA-PSV normative values >1.5 MoM.

Table 1. Features of preoperatively anemic recipients

Anemic recipient	Quintero stage	GA at surgery	R-SQLPCV	Preoperative MCA-PSV, MoM	Postoperative MCA-PSV, MoM	GA at delivery	Recipient 30-day survival
1	2	22 0/7	yes	1.90	1.54	22 1/7	no
2	1	23 0/7	yes	1.59	1.38	30 5/7	yes
3	4	20 3/7	yes	1.62	1.59	27 6/7	yes

PSV data. After exclusions, 139 patients remained for analysis. SQLPCV was achieved in 91 of the 139 cases (65.5%).

Of the 139 study patients, 20 (14.4%) were Quintero stage I, 27 (19.4%) were stage II, 77 (55.4%) were stage III, and 15 (10.8%) were stage IV. When the entire cohort of 174 patients was examined, the 28-day survival of at least 1 fetus was 92.5% and the 28-day dual twin survivorship was 70.7%. After exclusions, these survival rates in the remaining 139 study patients were 96.4 and 80%, respectively.

The donor and recipient pre- and postoperative MCA-PSV were analyzed in the 139 study patients. The mean $\pm$ SD MCA-PSV in the donors remained stable, and was measured at 1.00 ± 0.27 MoM preoperatively and 0.98 ± 0.32 MoM postoperatively, with the mean difference -0.01 ± 0.30 MoM (median -0.04 , range -0.87 to $+1.07$) ($p = 0.272$). The mean MCA-PSV in the recipients increased from 0.97 ± 0.24 MoM preoperatively to 1.15 ± 0.34 MoM postoperatively, with the mean difference $+0.18 \pm 0.36$ MoM (median 0.13 , range -0.40 to $+1.40$) ($p < 0.0001$) (fig. 1). Similar results were obtained in the 91 cases who were strictly SQLPCV (data not shown).

Nine fetuses had preoperative anemia, of which 6 (4.3%) were donors and 3 (2.6%) were recipients. R-SQLPCV was performed in the latter 3 cases to avoid worsening of the suspected fetal anemia in the recipient twins. In each of these 3 cases the recipient's MCA-PSV MoM decreased postoperatively: (1) 1.90 to 1.54 MoM, (2) 1.59 to 1.38 MoM, and (3) 1.62 to 1.59 MoM (table 1). No change was detected in the proportion of donor fetuses with anemia postoperatively [n (%) increased from 6 (4.3%) to 11 (7.9%), $p = 0.419$], whereas the proportion of recipient fetuses with anemia did increase [n (%) increased from 3 (2.2%) to 20 (14.4%), $p = 0.009$] (fig. 2).

Discussion

Previous observational studies have suggested that treatment of TTTS via the SQLPCV surgical technique is associated with improved donor fetus survival, and thus increased dual twin survival [4, 5]. It has been speculated that the SQLPCV technique improves outcomes in the donor fetus by providing both an anatomical and physiological treatment of TTTS [4]. This technique provides

an anatomical treatment of TTTS by the complete separation of the circulatory systems of the donor and recipient fetuses; the end result of SQLPCV is the same as that achieved when employing the standard SLPCV technique. The additional potential advantage of the SQLPCV technique lies in its temporal approach, whereby AVDRs are photocoagulated prior to AVRDRs. This sequence theoretically allows for a net intraoperative transfer of blood from the recipient to the donor fetus, which may facilitate donor twin hemodynamic stability [10]. In this study, the relative changes in the postoperative MCA-PSV measurements appear to support this contention. The stability in the donor's MCA-PSV suggests that there was no worsening of fetal anemia in the donor fetus after SQLPCV. While the donor MCA-PSV values remained stable, the recipient values did increase. These findings appear to provide evidence for the presumed underlying physiological mechanism of the SQLPCV technique.

Two other studies have provided evidence in support of the physiological basis of the SQLPCV technique. The first study by van Gemert et al. [11] analyzed the physiology underlying the SQLPCV technique via computational models. Their simulations confirmed the concept of preservation of donor fetus blood volume by demonstrating a net transfer of 25 cm³ of blood from the recipient to the donor when an AVDR was coagulated prior to an AVRDR of 1 mm inner caliber. Furthermore, they demonstrated a 64% loss of donor blood volume when the opposite coagulation sequence was employed. A second study published by Assaf et al. [10] compared pre- and postoperative donor heart rates in TTTS cases according to laser surgery technique. While a postoperative drop in the mean donor heart rate was observed in cases not receiving SQLPCV, there was no such drop noted in those that had SQLPCV. Because prior work in the sheep model has shown that fetal hypotension and hypovolemia elicit a reflexive fetal bradycardia [12], the stability in the donor heart rate after SQLPCV suggested hemodynamic stability in these fetuses.

Our rates of suspected preoperative anemia in both donor and recipient twins correspond to rates in the published literature [13]. The overall number of anemic donors remained stable, as did the MCA-PSV measurements noted in the donor twins. Specifically, the proportion of donor twins with suspected anemia, as characterized by an MCA-PSV ≥ 1.5 MoM, did not change significantly post-SQLPCV. Conversely, the overall proportion of recipients with suspected anemia did increase postoperatively from 2.6 to 14.4%. A study by Ishii et al. [14] noted even greater increases in the number of recipient

twins with an elevated MCA-PSV following fetoscopic laser photocoagulation. Specifically, 23.3% of recipients in their series had an increased MCA-PSV within 14 days of surgery while values were in the normal range in all recipient twins prior to surgery. Of note, the majority of these recipients showed normalization of their MCA-PSV within 28 days of postoperative follow-up. It has been suggested that this temporary elevation in MCA-PSV is likely a benign condition [14, 15].

In our cohort of 174 consecutive TTTS patients who underwent laser therapy, there were 3 cases (2.6%) who had an elevated MCA-PSV in the recipient fetus prior to laser therapy. This proportion of preoperative recipient anemia is consistent with that reported by Kontopoulos and Quintero [13], which involved a separate patient population. These findings are unexpected, as the recipient twin is typically susceptible to polycythemia, not anemia. Elucidating the mechanism of recipient anemia in TTTS may facilitate our understanding of the pathophysiology of this syndrome. A possible explanation for this finding is that the elevated MCA-PSV values in the recipients are simply false positive results. Regardless of the cause, employing the standard SQLPCV technique in these cases may theoretically worsen recipient fetal anemia. Thus, we suggest that the sequential procedure be performed in a reversed fashion (R-SQLPCV) if the preoperative MCA-PSVs of the recipient are ≥ 1.5 MoM. The R-SQLPCV technique mandates ablation of all AVDRs first, then all AVRDRs, followed by the superficial anastomoses.

This study had some limitations given the relatively small sample size as well as the retrospective analysis of the data. Although our data were collected in a prospective manner, this was a secondary analysis performed on data collected for the purpose of examining the overall outcomes of monochorionic diamniotic twins with TTTS when the SQLPCV technique is employed. Another limitation includes our method of assessment of fetal anemia; although the MCA-PSV is a sensitive marker for the presence of moderate to severe anemia, it is not a direct measure of fetal anemia. Such direct measures would necessitate confirmation by invasive techniques such as percutaneous umbilical blood sampling, which carries significant fetal risks. Finally, our study lacked an appropriate control group. SQLPCV was attempted in the entire cohort and was completely achieved in two-thirds of cases. To test whether the physiological principles of SQLPCV are truly valid, the MCA-PSVs of this cohort should be compared to cases who underwent R-SQLPCV. As there were only 3 cases of R-SQLPCV in this study, we had an insufficient sample size to perform this comparison.

In conclusion, this study provides supportive evidence for the physiological basis of the SQLPCV technique for the treatment of TTTS. Specifically, the preferential use of SQLPCV appeared to have prevented worsening donor anemia as evidenced by stable MCA-PSV measurements postoperatively in the donor fetus.

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