Fetoscopic Laser Therapy for Twin-Twin Transfusion Syndrome

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Abstract Ever since the first randomized, controlled trial revealed that fetoscopic laser photocoagulation achieved better outcomes than serial amnio-drainage for all stages of twin-twin transfusion syndrome (TTTS) before 26 weeks, many centers have launched their fetoscopic laser therapy program for TTTS. Initially the nonselective method of laser therapy was applied, using the dividing membrane as a landmark to coagulate the placenta vessels, but currently selective methods (selective laser photocoagulation of communicating vessels (SLPCV), sequential SLPCV, and Solomon technique) have evolved to become the mainstream laser treatment modalities. Nevertheless, the nonselective method still has a role in difficult operations. Over the years, with regard to the prognoses of TTTS treated by laser, the attention has gradually shifted from survival rate to the neurological outcomes. The incidence of severe neurodevelopmental delay remains considerably high in survivors of TTTS treated by FLP, which some reports cited ranging from 6 % to 18 %; learning curve effect exists, affecting both the survival rate and neurological outcomes of TTTS treated by laser. Because more, yet smaller and less-experienced, centers are being set up worldwide, the purpose of this manuscript is to review the basic knowledge and update information about the laser therapy for TTTS.

Keywords Twin-twin transfusion syndrome · Fetoscopic laser therapy · Selective laser photocoagulation of communicating vessels · Laser therapy · Solomon technique · High-risk gestation · Prenatal medicine

Introduction

Twin-twin transfusion syndrome (TTTS) plays a significant role in increasing perinatal mortality and morbidity in monochorionic twin pregnancy [1]. It complicates approximately 1 in 5 of all monochorionic, diamniotic twin pregnancies [2]. The perinatal mortality rate of TTTS is approximately 70 %, and even in the survivors, the severe neurological deficit is high if untreated [3]. Traditionally, serial amnioreduction and laser therapy are the two most effective treatment methods for TTTS [4]. Since the first randomized trial on interventions for TTTS was published [5], it has been recognized that first-line treatment for all stages of TTTS diagnosed before 26 weeks is fetoscopic laser therapy (FLT). The pioneer to develop the basic technique of such a surgery is De Lia et al. His group performed the first laser treatment in 1988 [6]. Then, Ville et al. reported their preliminary experience using the dividing membrane as the landmark and all vessels crossing the dividing membrane were to be coagulated, a technique we call nonselective [7]. Currently, many centers use the selective method of laser therapy, which was designed by Quintero et al. as “selective laser photocoagulation of communicating vessels” (SLPCV) [8]. SLPCV selectively coagulated the communicating vessels and preserved the noncommunicating vessels even though they crossed the dividing membrane. Sequential SLPCV and the Solomon technique were later reported to show benefits of improving the donor twin outcomes and decreasing recurrent TTTS after FLT [9, 10]. This review manuscript mainly discusses the updated information relating to the techniques and prognosis of FLT for TTTS.

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Pathophysiology of TTTS

Upon the availability of FLT, the outcomes of TTTS after treatment are improved, but much of the pathophysiological basis of TTTS remains elusive [6, 8, 11•, 12•]. Inter-twin placental anastomoses are the pathophysiological basis and essential element for the onset of TTTS. Nevertheless, the risk of having TTTS stands at only approximately 15–20 % of all the monochorionic twins that invariably have inter-twin placenta vessel anastomoses.

Although a hypothesis yet to be proven, some suspect TTTS is caused by excess of unidirectional functional AV anastomoses with imbalanced inter-twin transfusion [7]. The result of imbalanced transfusion is one twin presenting with oligohydramnios due to hypotension and hypovolemia and another twin displaying polyhydramnios because of excessive urine production. Both fetuses of TTTS are in danger of fetal demise. Because inter-twin placental anastomosis is an essential element for TTTS, laser therapy to occlude the inter-twin anastomoses fundamentally could treat the disease by tackling its root cause.

For the phenotype of polyhydramnios and oligohydramnios in TTTS, renin-angiotensin system may come into play, too. The rennin activity had been shown to upregulate in donor and downregulate in recipient kidneys [13, 14]. Because the donor suffers from chronic renal hypoperfusion, so initially it may be beneficial for adaptation to hypovolemia. Later it may further decrease the urine production and eventually lead to oligoria and oligohydramnios, and aggravate growth restriction.

Diagnosis of TTTS

After Dr. Quintero set the prenatal diagnosis criteria [15], then the diagnosis of TTTS has been based on prenatal ultrasound. But detailed ultrasound scan of the fetal structure of TTTS would be hampered by oligohydramnios in the donor twin and the frequent movement of the recipient twin. Because TTTS is linked to monochorionic (MC) placentation, early diagnosis of chorionicity is crucial. MC placenta in early ultrasound (before gestational age of approximately 15 weeks) is best identified by presence of the “T” sign, which refers to the appearance of the thin inter-twin membrane as it takes off from the placenta at a 90-degree angle. TTTS typically develops at between 15 and 26 weeks of gestation and is defined prenatally as possessing the following features [15]:

1. Polyhydramnios, ≥ 8 cm of maximum vertical pocket (MVP) in the recipient twin,
2. Oligohydramnios, MVP of ≤ 2 cm in the donor twin.
3. MC placenta

MVPs of 2 cm and 8 cm represent the 5th and 95th percentiles for amniotic fluid measurements, respectively, whereas the presence of both is used to define stage I TTTS

[16]. But some favor using the criteria of polyhydramnios as at least 8.0 cm at or before 20 weeks of gestation or 10.0 cm after 20 weeks of gestation [5].

Staging of TTTS

The widely used staging system for TTTS is Quintero staging system, [15] which spans a range from mild disease (stage I) with isolated discordant amniotic fluid volume to severe disease with demise of one or both twins (stage V).

- Stage I: The bladder of the donor twin is visible, and Doppler studies are still normal.
- Stage II: The bladder of the donor twin is not visible (during the length of the examination, usually 1 hour), but Doppler studies are not critically abnormal.
- Stage III: Doppler studies are critically abnormal in either twin and are characterized by presence of absent or reverse end-diastolic velocity in the umbilical artery, reverse flow in the ductus venosus, or pulsatile umbilical venous flow.
- Stage IV: Ascites, pericardial or pleural effusion, scalp edema, or overt hydrops are present.
- Stage V: Demise of one or both fetuses.

Usually the stage V is seldom applied for clinical use, since demise of one twin in TTTS means resolution of this disease regardless of the complication of agonal transfusion. The stage III can be categorized as either donor or recipient, and if with critical Doppler but visible donor bladder within 30 minutes then it can be called atypical stage III. Occasionally, patients may show intermittent absence or reverse of end-diastolic velocity in umbilical artery Doppler (UA-AREDV). In these cases, the patient is staged as having positive diastolic flow. And usually intermittent UA-AREDV is associated with large artery to artery anastomosis. If UA-AREDV is detected only closer to the fetus, but with normal UA Doppler near the placenta umbilical cord, the UA Doppler is recognized as normal.

There is no problem reaching a diagnosis or consensus for UA-RAEDV and reverse of A wave of ductus venosus. However, the pulsation of umbilical veins may be somewhat subjective. To establish a standardization reference, Dr. Quintero further defined the pulsation of UV as displaying a UV resistant index greater than 15 % [17].

The Quintero staging has two major principles: first, considering the pregnancy as a whole, rather than using individual risk factors for each twin; second, using categorical variables to stage the syndrome [18]. Currently, Quintero staging system for TTTS is still the most widely accepted staging system though it failed to provide the information about prognosis in cases treated by fetoscopic surgery [19].

Equipments of FLT for TTTS

Fetoscope

Several manufacturers have developed equipments specifically designed for fetal surgery. Currently, the experience gathered with any type of fetoscope is limited and no evidence shows that one particular brand of endoscope performs better than another [16]. Eurofoetus group had cooperated with the manufacturer of endoscopic instruments, Karl Storz, Tuttlingen, Germany, and the Karl Storz's fetoscope had gained FDA approval. So this is the only fetoscope available in Taiwan due to the government regulation. In Storz's design, the laser fiber can be curved, but at the cost of fitting in a larger sheath (3.7 mm) for anterior placenta compared with a smaller one (2.2 mm) for the posterior placenta plus a limited angle of 30 degrees. Quintero designed the fetoscope, which is like a laparoscope; the scope and sheath can be separated during operation. In this kind of design, not only can we laser the vessels through the trocar while exerting gentle pressure on the vessel to decrease blood flow during the coagulation [2], but it also can be applied to TTTS where there is an anterior placenta and the anastomoses are inaccessible with the standard technique (inaccessible anterior placentas) [17]. But with the fetoscope that the scope and cannulas cannot be separated during operation like in Storz's design, the trocar assisting technique cannot be performed. Another disadvantage of Storz's design is the limitation to change fetoscope with different angles (0 degree or 30 degree) due to the different cannulas for 0- and 30-degree scope. If a 0-degree scope was chosen initially but not all anastomoses could be coagulated, then you need to put another puncture to the uterine cavity to insert the 30-degree scope.

In our own experience, Storz's design has the advantage of using a small-diameter scope in cases with mainly posterior placenta. In cases with anterior placenta, although the design of angle scope with forward oblique 30-degree view and a deflecting mechanism for the laser fiber could fire vessels in difficult angle, nevertheless the scope and cannula was fitted together so it cannot prevent the amniotic fluid leakage from the uterus. Thus, the leakage of amniotic fluid becomes a problem if the fetoscope needs to move a larger angle to hit the vessels. The amniotic fluid leak is especially a concern when the fetoscope insertion site is at the low segment of uterus where the myometrium is thin.

Laser Machine

The working environment in FLT for TTTS is within the amniotic fluid cavity; the Nd:YAG and diode lasers are used for FLT. The diode laser has been recognized as having several advantages, both theoretical and practical, over the Nd:YAG: a more appropriate wavelength to achieve

blood vessel coagulation, a smaller size, and a significantly lower cost [2]. We tried both Nd:YAG and Diode laser in the initial period and found the efficiency of both kinds of laser comparable.

Techniques of FLT

Nonselective Method

In 1955, Ville et al. reported their preliminary experience with laser treatment for TTTS [20]. They used the dividing membrane as the landmark and all vessels crossing the dividing membrane were coagulated, a technique that we call nonselective. By this kind of method, certain non-inter-twin anastomotic vessels across the dividing membrane also could be coagulated. This would result in a smaller residual placenta perfusion than would a selective technique, but in difficult cases like an anterior placenta location, nonselective technique still can be applied.

Selective Methods

They are mainly selective laser photocoagulation of communicating vessels (SLPCV), Sequential SLPCV, and Solomon technique.

SLPCV In 1998, Quintero et al. described a surgical technique named "selective laser photocoagulation of communicating vessels" (SLPCV) [21]; SLPCV selectively coagulated the communicating vessels and preserved the noncommunicating vessels even though they crossed the dividing membrane. SLPCV compares favorably with the previous nonselective technique, resulting in a lower rate of dual fetal demise (5.6 % vs. 22 %) [22].

Sequential SLPCV Also described by Dr. Quintero, the method is to laser first the arteriovenous anastomoses from the donor to the recipient (AVDRs) (sequential SLPCV or SQLPCV; it would improve the hemodynamic status and decrease the likelihood of intrauterine fetal demise of the donor twin [9].

Solomon technique (equatorial dichorionization)

This method was proposed by Pro KH Nicolaides to reduce the residual anastomoses during laser therapy for TTTS. There was a report claiming that the technique decreases TTTS recurrence without increasing adverse outcome and improves survival compared with the selective technique [10•].

Surgical Failure of FLT for TTTS

Surgical failure usually results from patent anastomoses left after laser therapy for TTTS. The anastomoses may have been

overlooked altogether, or, as in most cases, sublasered [7]. Symptomatic surgical failure characterized by persistent TTTS, reverse TTTS and twin anemia-polythythemia sequence in TTTS treated by FLP has been reported standing at 18 % [23]. Because they may occur weeks after operation, there is a need for continuous ultrasound surveillance until delivery. Repeat FLP for surgical failure is usually difficult; amnioreduction or selective termination may serve as an alternative.

Complications of FLT

FLP has evolved as the treatment of choice in TTTS. Certainly, the procedure is not free of complications. In our series, 11.36 % of cases experienced PROM within 3 weeks, 6.5 % of mothers suffered pulmonary edema, 4.3 % of cases had uterine bleeding, and 2.2 % of case required termination due to chorioamnionitis [8].

Learning Curve of FLT

The review report by Ahmed et al. emphasized that a learning curve certainly exists, although they failed to show a significant impact of high case loads (experience) on the fetal outcomes [24]. We also found that with increasing experience using FLP for TTTS that the fetal survival rate could be improved [8].

Survival of TTTS after FLT

Overall survival of TTTS treated by FLP had been estimated to range from 45 % to 70 %, and survival of at least one twin had been reported as 60 % to 85 % or even higher according to a meta-analysis by Rossi et al [25]. In our series, for severe TTTS cases treated by FLP in Chang Gung memorial Hospital, two survival rates were at 50 % and the least survival rate was 79.5 % in the first 44 cases [8].

Neurological Outcomes in Survivors of TTTS Treated by FLP

Although the neurological outcomes of fetuses treated by FLP are better than treated by serial amniocentesis [4], the incidence of severe neurodevelopmental delay is still considerable. A recent systematic review and meta-analysis on the neurodevelopment outcomes of survivors after FLP reported an incidence of 11.1 %

with neurologic impairment; cerebral palsy (CP) was the most prevalent dysfunction [12•]. Our experience with the first 44 cases showed that the severe neurological deficit by neurological evaluation at corrected age of 1 year was 6 %, which was comparable to what had been published [11•]. Even in a newly established center starting with a small case number, the neurological outcomes of fetuses treated by FLP also could generate acceptable results as experiences gradually increase [11•].

Fetal Growth After FLT

Laser therapy can reverse the unbalanced umbilical blood flow between the two fetuses in TTTS [23, 26]. Therefore, after FLP, there was 8 % reduction in weight discordance between the two fetuses and more than half of donor fetuses with IUGR at the time of laser surgery showed subsequent in utero catch-up growth to the extent that their birth weights reached within normal range [27]. So, twin weight discordance and donor fetus IUGR appear to improve after laser therapy for TTTS [27]. However, not all the inter-twin birth weight discordance can be attributed to the effect of TTTS; some inter-twin birth weight discordance is caused by placenta share discordance, which FLP does not help to improve [28].

Conclusions

Currently, FLT is the first choice for treatment of severe TTTS with its onset before 26 weeks; the survival rate and neurological outcomes are better if compared with serial amniocentesis. The outcomes of TTTS treated by FLT would improve after a learning period and procedure-related complications would decrease as the number of cases performed increases. Selective techniques are chosen over nonselective method to coagulate the inter-twin anastomoses; as to which selective method (nonsequential, sequential, or Solomon method) produces the best effect, future large-scale studies may be required to address the issue.

Compliance with Ethics Guidelines

Conflict of Interest Yao-Lung Chang and Shuenn-Dyh Chang declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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