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Fetoscopic Laser Photocoagulation for the Treatment of Twin-Twin Transfusion Syndrome in Monochorionic Twin Pregnancies

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Abstract: Fetoscopic laser surgery for severe twin-twin transfusion syndrome (TTTS) has become the optimal treatment choice since the release of the Eurofetus randomized clinical trial. These techniques have been adopted throughout the globe, and many institutions have instituted or will soon institute fetoscopic laser surgery procedures; however, laser surgery has a steep learning curve because of the following: challenging placental location, complex and unexpected communicating anastomoses, residual anastomoses after surgery, or discolored amniotic fluid. We have been performing laser surgery since 2002 in Japan; to date, we have compiled a series of 170 cases. Our data indicates a 78% of overall survival with 5% neonatal morbidity, 63% of survival of both twins, and 93% survival of at least one twin. The recurrent TTTS rate was 1% and the residual vessel rate was 3%.

To improve the learning curve of laser surgery, the employment of various techniques is recommended to achieve a successful surgical outcome: (1) Mapping: before laser ablation, a very thorough mapping of vascular anastomoses should be done, and should be repeated after ablation; (2) Sequential order: obliteration of arterio-venous anastomoses from donor to recipient should be done first to avoid donor hypotension and/or anemia; (3) Trocar (cannula) assisted technique: Trocar assisted technique: Using gentle indent the trocar to the placenta by withdrawing the scope shortly, then anastomoses could be ablated easily; (4) Line method: to avoid residual anastomoses, the laser should draw a virtual line at the hemodynamic equator; The operator must be careful not to miss small anastomoses.

These techniques can help achieve a successful outcome for fetoscopic laser surgery and improve the outcome for cases of severe TTTS.

Keywords: Twin-twin transfusion syndrome, fetoscopy, laser, amnioreduction, and ultrasonography.

INTRODUCTION

Fetoscopic laser surgery for severe twin-twin transfusion syndrome (TTTS) has been conducted since the early 1990s in US and Europe. After the conclusion of Eurofetus randomized clinical trial [1], fetoscopic laser surgery has become the standard and optimal treatment for the condition. Recently, these techniques have been implemented throughout the globe; many institutions have instituted or will soon institute the performance of fetoscopic laser surgery. As with many new procedures, fetoscopic laser surgery has a steep learning curve for a variety of reasons (i.e., challenging placental location, complex and unexpected communicating anastomoses, dividing membrane lifting, residual anastomoses after surgery, or discolored amniotic fluid. In Japan, we have been performing laser surgery since 2002 and five laser centers employ the same protocols. To date, more than 500 TTTS cases, including 170 cases at our institution, were performed by laser surgery. In this article, we introduce and review the new technical tips to improve the achievement of successful outcome for laser surgery and indicate our data of perinatal outcome and complication of fetoscopic laser surgery for severe TTTS.

PATHOPHYSIOLOGY AND DIAGNOSIS OF TTTS

Because of the vascular anastomoses between the fetuses, monochorionic twin pregnancies have a high-risk profile compared with dichorionic twin pregnancies. TTTS is one of the major complications resulting from vascular communications and their imbalanced blood distribution, involving about 5 - 10 % of monochorionic twin. TTTS can be characterized by an imbalanced blood distribution: a net flow from one fetus (the donor twin) to the other (the recipient twin) through placental communicating vessels. The donor twin is characterized by a hypodynamic status, manifested by hypovolemia, hypotension, oliguria, oligohydramnios, fetal growth restriction, and renal failure. These processes ultimately result in fetal demise. In contrast, the recipient twin is characterized by a hyperdynamic status, hypervolemia, hypertension, polyuria, polyhydramnios, heart failure, and hydrops fetalis; thus, it often also results in a fetal demise. The prognosis for severe early onset TTTS is dismal, with perinatal mortality rates of up to 90 % if untreated.

TTTS is defined prenatally by ultrasonography as: a monochorionic diamniotic twin pregnancy; polyuric polyhydramnios in the recipient twin (maximum vertical pocket > 8 cm, and large distended bladder) with oliguric oligohydram-

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nios in the donor twin (maximum vertical pocket < 2 cm and collapsed or non-visible bladder) simultaneously; and no signs of abnormality due to poly- or oligo-hydramnios. Once the diagnosis of TTTS is made, the severity is classified by Quintero's stage [2] from I to V. Stage III TTTS is sub-classified into two sub-groups defined by whether the donor bladder is visible or non-visible. Sub-classification of Stage III [2, 3] is defined as follows: Stage III classical (Doppler studies are critically abnormal in either twin and the bladder of the donor is not visible); and Stage III atypical (Doppler studies are critically abnormal in either twin and the bladder of the donor is still visible).

METHODS AND SUBJECTS

Concept of Fetoscopic Laser Surgery for TTTS

Fetoscopic laser surgery of communicating vessels for severe TTTS consists of a few basic principles: in as much as imbalanced blood distribution due to placental vascular anastomoses are thought to be the main cause of TTTS, laser ablation of communicating vessels can eliminate the cause of TTTS; and all anastomoses (AV (arterio-venous), AA (arterio-arterial), VV (veno-venous anastomoses)) can be visualized and ablated by a fetoscopic procedure.

Preparation for Fetoscopic Laser Surgery

Essentially, before attempting the procedure, operators should be knowledgeable of the complex pathophysiology of TTTS and other TTTS-related events such as twin anemia polycythemia sequence (TAPS), acute feto-fetal hemorrhage after single fetal demise, selective intrauterine growth restriction (sIUGR) in monochorionic twin, and twin reversed arterial perfusion (TRAP) sequence. Ultrasound assessment should be conducted and the echocardiographic features of TTTS must be evaluated. The donor twin is characterized by a hypovolemic status of the placenta and circulatory insufficiency. Fetal growth restriction and umbilical arterial Doppler abnormalities are common ultrasound features. Doppler examination reveals a decrease in the end-diastolic velocity of the umbilical artery, especially the absence or reverse end-diastolic velocity in Stage III or IV. Decreased peak systolic velocities of the descending aorta are also common. Coarctation of the aorta in the donor or smaller fetus in a monochorionic twin pregnancy has been reported and, based on the hemodynamic theory, decreased blood flow into the donor or smaller twin might increase the risk of a coarctation of the aorta [4]. Most recipient fetuses develop cardiac dysfunction complicated by cardiomegaly, tricuspid and mitral valve regurgitation, ventricular hypertrophy, increased reverse flow in the inferior vena cava, and pulmonary stenosis; they also develop reverse flow of the ductus venosus and pulsatile flow in the umbilical vein [5, 6]. Typically, mild cardiomegaly and increased reverse flow in the inferior vena cava occurs first; moreover, right ventricle compromise occurs earlier than left ventricle compromise. Congestive heart failure and hydrops fetalis in the recipient may originate from chronic volume and pressure overload of the right ventricle. These conditions lead to cardiomegaly and atrio-ventricular valve regurgitation. Occasionally, some cases of a severely affected recipient can develop into acquired pulmonary stenosis/atresia with an intact ventricular septum [5, 7].

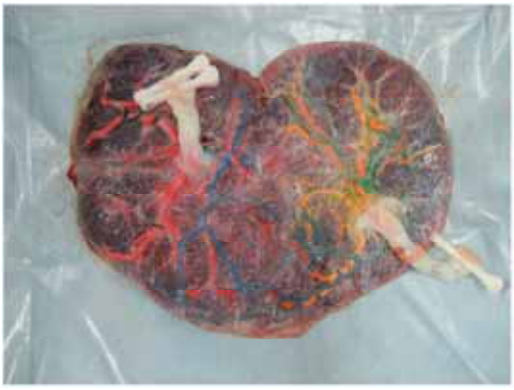

Fig. (1). Placental Dye Injection Examination of Monochorionic Placenta after Delivery
Color dye was injected into artery (blue or green) and vein (red or yellow).

Additionally, the operator should be trained to identify and characterize the vascular anastomoses of the monochorionic placenta. Placental dye injection examination [8, 9] of the monochorionic placenta should be an important step before attempting laser surgery (Fig. **1**). All vessels on the placental surface can be precisely differentiated by fetoscopic inspection; arteries principally cross over veins and the color of arteries is dark blue due to deoxygenated blood, whereas veins appear bright red due to oxygenated blood from the placenta. AA and VV anastomoses are directly linked artery-to-artery or vein-to-vein, and have no terminal ends. While AV anastomosis is not anatomical anastomosis itself, the artery (feeding artery) comes from a fetus to cotyledon, and goes to the other fetus as drainage vein. It is called an AV anastomosis. Occasionally, three vessels or four vessels cotyledons are seen, in which three or four types of different vessels are in to same cotyledon. AA anastomoses are theoretically complex and bidirectional transfusion depends on the location of the hemodynamic equator and branch of artery. This mechanism can provide AA anastomoses as functional AV behavior for both directions [10].

Setting and Performance of Fetoscopic Laser Surgery (Procedural Steps)

Epidural anesthesia or local anesthesia with maternal conscious sedation can be chosen for fetoscopic laser surgery. In our first 36 cases, general anesthesia was chosen; this option was similar to that of other institutions in the early period of fetoscopic laser surgery because immobility of the fetuses especially in the recipient fetus; however, after operator skills improved, epidural or local anesthesia were chosen because they were less invasive for the mother and could decrease maternal complications [11].

After adequate anesthesia was achieved, a 3.8 mm trocar (Richard Wolf, Vernon Hills, IL) was inserted into the recipient amniotic sac with ultrasonographic guidance (Fig. **2**). Appropriate fetoscopes (i.e. Richard Wolf angled-view endoscope, 2.8 mm diameter, 30 cm length; 25 degree (RW-8930.402), 30 degree (RW-8930.422), 70 degree (RW-8660.412), operative 12 degree with working channel for 5 Fr instruments (RW-8746.401); and a 2 mm diameter, 26 cm, 0 degree rigid telescope (K26008AA, Karl Storz, Tuttlingen, Germany) with sheath (K11630KH)) were selected

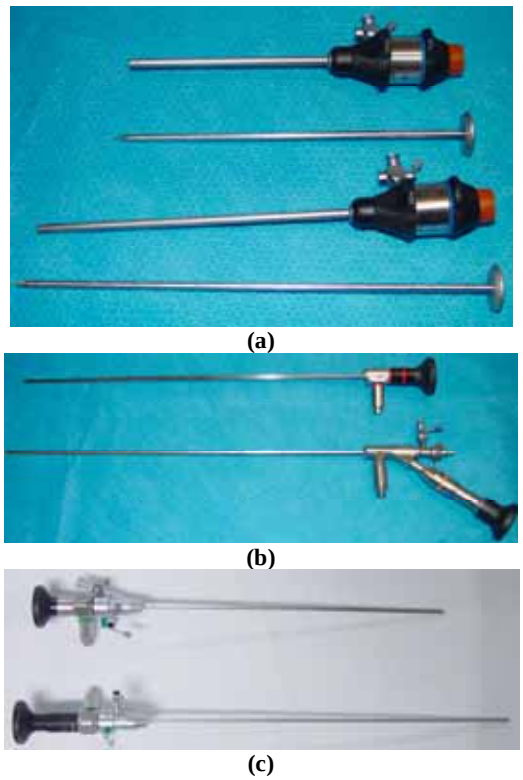

Fig. (2). Instruments for fetoscopic laser surgery
(**a**) 3.8-mm Trocar
(**b**) Diagnostic (0, 25, 30, 70 degree) and operative (12 degree with 5 Fr. channel for operating devices) fetoscope by Richard Wolf
(**c**) 3-mm fetoscope with sheeth by Karl Storz

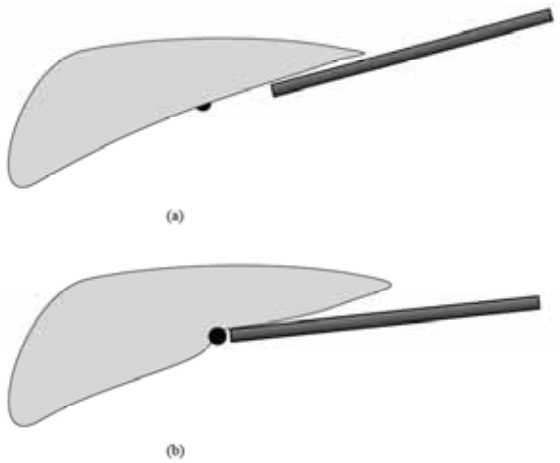

Fig. (3). Trocar assisted technique
Gentle indent the rigid trocar to the placenta by withdrawing the scope within the trocar a short distence. Angle of fetoscope and target vessel is tangential. After trocar assisted technique, pushing the trocar close to the target vessel, angle will be adequate to ablate the vessels as perpendicular.

according to the placental and fetal location (Figs. **2, 3**). All communicating vessels were initially mapped and then ablated by neodymiu:yttrium-aluminium-garnet (Nd:YAG) laser (Surgical Laser Technology, Montgomery, PA); this was conducted via the non-contact method with fetoscopic guidance. Laser fibers were inserted into the operating channel of the fetoscope and the laser power was usually set from 15 to 40 watts for Nd:YAG (1,064 nm) laser. Re-examination and re-lasering of anastomoses with mapping was then done; subsequently, the hemodynamic equator was drawn by laser. Finally, amniodrainage was done if indicated.

Mapping System

During the procedure, placental vessel mapping helps the operator to identify and orient the direction and location the anastomoses. Before laser ablation, a very thorough mapping of vascular anastomoses must be done by the operator and navigator. Each vascular anastomosis was labeled as AV-DR, AV-RD, AA, or VV (for example, AV-DR represented an arterio-venous anastomosis from donor to recipient); the navigator records this information as figures or comments. During the laser ablation, the operator eliminates each anastomosis by referring to the mapping system. After ablation, reevaluation of all placental anastomoses should be done. Additionally, by using the mapping system before ablation, we can choose an appropriate sequence for the ablations.

This system also has the potential to reduce the incidence of residual anastomoses and recurrence of TTTS. A low incidence of residual anastomoses and recurrence of TTTS was reported by Cincotta *et al*. [12], Chmait *et al*. [13] and our series (3); all three studies employed a mapping system.

Sequential Order

To reduce the incidence of a fetal demise after laser surgery, especially a donor with absent or reversed umbilical arterial flow, Quintero *et al.* and Nakata *et al.* proposed the new technique that all anastomoses should be ablated in a specific order: first, AV-DRs; then, AV-RDs [14, 15]. In particular, the donor twin with an abnormal Doppler of the umbilical artery appears logically to be more vulnerable to an acute hemodynamic change such as hypotension or anemia. If AVRDs are obliterated first, intertwin transfusion from donor to recipient occurs; thus, the donor twin develops increased hypotension and anemia followed by fetal demise. Sequential laser ablation of anastomoses and elimination of the AVDRs prior to the AVRDs could result in improved blood pressure of the donor via an intraoperative intertwin transfusion, rescue as well as stabilization of the hemodynamics of the donor. It is currently controversial whether arterio-arterial and veno-venous anastomoses should ablated first, prior to AV anastomoses, or last; however, an AVDR first policy could reduce fetal demise after laser surgery especially in donors with abnormal Doppler [14, 15]. The US Fetus Consortium is currently undergoing a randomized control trial to compare outcomes between the standard laser approach and the sequential laser approach.

Trocar (Cannula) Assisted Techniques

Generally, an anterior placenta is the one of the most difficult settings for FLP cases. Because of the tangential angle of target vessels and fetoscope alignment, it becomes quite difficult to confirm the anastomoses and to ablate the vessels by laser. Quintero *et al.* originally proposed the technique of trocar-assisted selective laser photocoagulation [16]. Using the rigid trocar, gently indent the placenta by withdrawing the scope within the trocar a short distance. At this point, the anastomoses can be easily ablated because the

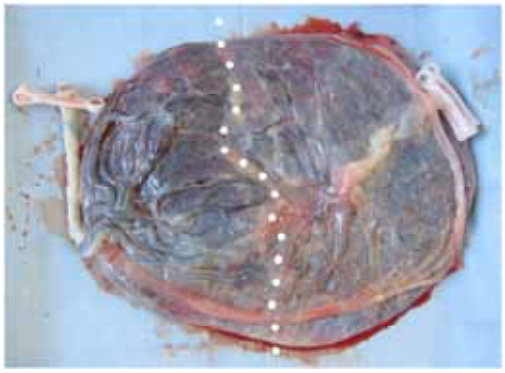

Fig. (4). Line method.
Draw the laser line along with the hemodynamic equator (dot line), creating dichorionized placenta.

Table 1. Baseline and Surgical Characteristics (n=152)

Maternal Age (Year)	30 (15 – 40)
Gestational age at surgery (weeks)	21 (16 – 25)
Location of placenta	
Anterior	77 (51%)
Posterior	75 (49%)
Quintero stage	
Stage I	18 (12%)
Stage II	27 (18%)
Stage III	84 (55%)
atypical	29
classical	55
Stage IV	23 (15%)
Complete surgery	152 (99%)
Anesthesia	
General	36 (24%)
Epidural	116 (76%)
Operation time (minutes)	60 (25 – 158)

Data are shown as median (range) or number (%)

target vessel and fetoscope are perpendicular rather than tangential (Fig. **3**).

This trocar-assisted technique has three potential benefits: (1) It allows perpendicular rather than tangential alignment of the target vessels as described above; (2) Reduction of the blood flow in large communicating vessels, which are difficult to ablate with normal laser energy; the pressure exerted by the trocar reduces the flow and allows for ablation with less laser energy; and (3) We can use this technique to avoid inadvertent injury to the fetus and dividing membrane (The fetus and membrane can move unexpectedly toward the fetoscope and laser; thus, slightly withdrawing the fetoscope within the trocar allows for safe ablation of the target vessels).

Using the trocar has another technical benefit. If we choose direct sheath centesis without the trocar, we can only use one type of fetoscope; however, we can use an appropriate fetoscope (i.e., 0 degree, 30 degree, or 70 degree for an anterior placenta. Furthermore, both Richard Wolf and Karl Storz instruments fit a 3.8 mm cannula.

Table 2. Pregnancy Outcome and Survival Rates (n=152)

Gestational Age at Delivery (Weeks)	33 (19 – 40)
Miscarriage (delivery < 22 weeks)	6 (3.9%)
Recurrent TTTS	1 (0.7%)
TAPS	2 (1.3%)
Residual anastomoses	4 (2.6%)
Over all survival (n=304)	237/304 (78%)
Neurological sequale (n=237)	13/237 (5.5%)
2 survivors	96 (63%)
1 survivor	45 (30%)
0 survivor	11 (7%)
At least 1 survivor	141 (93%)

Data are shown as median (range) or number (%)

Line Drawing Methods

To avoid residual anastomoses, a virtual line should be drawn with the laser at the hemodynamic equator, not the membrane equator (Fig. **4**). This technique is also reported as the Solomon Technique; a trial is currently ongoing to test this method in Europe (www.trialregister.nl, trial ID: NTR1245). Small anastomoses are not missed by the virtual line method. First, selective laser ablation of each vascular end of anastomotic vessels is performed; second, construct a dotted line with the laser; and finally construct as virtual line along with the laser along the hemodynamic equator.

TTTS PATIENTS

From 2002 to 2010, 152 Japanese women whose pregnancy was complicated by severe TTTS before 26 weeks gestation underwent fetoscopic laser surgery in our institution. All patients were delivered and their infants were followed-up for until at least six months of age. TTTS was diagnosed in monochorionic twin pregnancies based on standard ultrasound criteria: polyhydramnios and oligohydramnios with the deepest vertical amniotic pocket measuring at least 8.0 cm in the recipient and at most 2.0 cm in the donor. All patients met the following criteria for laser surgery: gestational age less than 26 weeks; and classification by Quintero's stage from I to IV. The laser procedure for placental communicating vessels was based on a previously reported method [3] with additional techniques described above if indicated: mapping system; sequential order of AV-DR first policy if possible; using a trocar of appropriate diameter for the fetoscope; employing trocar-assisted techniques; and laser line drawing methodology. Patient baseline and surgical characteristics are presented in Table **1**. Seventy percent of the patients were stage III (55%) and IV (15%) and 50% of the patients had an anterior placenta.

RESULTS

We completed laser surgery on 99% of the patients. The median surgical time was 60 minutes; however, surgical time was counted from the insertion of the trocar to amniodrainage with the following intervening steps: fetoscopic inspection, mapping, and lasering. Tables **2** and **3** present the perinatal outcomes. The overall survival rate was 78%; 5.5% of the cases had neurological sequelae including periventricular

Table 3. Perinatal Outcome According to Quintero Stage

Stage	I n=18	II n=27	III Atypical n=29	III Classical n=55	IV n=23
2 survivors	12 (67%)	18 (67%)	13 (45%)	39 (71%)	14 (61%)
1 survivor	5 (28%)	5 (18%)	14 (48%)	12 (22%)	9 (29%)
0 survivor	1 (5%)	4 (15%)	2 (7%)	4 (7%)	0 (0%)
At least 1 survivor	17 (95%)	23 (95%)	27 (93%)	51 (93%)	23 (100%)
Overall survival	29/36 (81%)	41/54 (76%)	40/58 (67%)	90/110 (82%)	37/46 (80%)
Neurological sequale	1/29 (3.4%)	4/41 (9.8%)	3/40 (7.5%)	2/110 (1.8%)	13/237 (5.5%)

Table 4. Comparison of Perinatal Outcomes in Published Series

	Ville *et al.* 1998 n=132	Hecher *et al.* 1999 n=73	Hecher *et al.* 2000 n=200	Quintero *et al.* 2003 n=95	Senat *et al.* 2004 n=72	Huber *et al.* 2006 n=200	Middledorp *et al.* 2007 n=100	Cincotta *et al.* 2009 n=100	Sago *et al.* 2010 n=181	Chmait *et al.* 2011 n=682	Present study 2011 n=152
Median gestational age at delivery (weeks)	-	33	34	32	33	34	33	31	33	33	33
Perinatal survival (%)	55	61	-	64	56	72	70	76	76	79	78
Neurological sequale (%)	4	6	6	4	7	-	-	3	5		5
2 survivors (%)	36	42	50	44	36	60	58	66	62	72	63
1 survivor (%)	38	37	30	38	38	24	23	19	28	18	30
0 survivor (%)	26	21	20	17	26	17	19	15	10	10	7
At least 1 survivor	74	79	80	82	74	84	81	85	90	90	93

neurological sequale including periventricular leukomalasia, interaventricular hemorrhage grade III and IV and cerebral palsy

leukomalacia, intraventricular hemorrhage grade 3 and 4, and cerebral palsy. At six months after delivery: in 63% of the cases, both twins survived; in 30% of the cases, one twin survived; and in 93% of the cases at least one twin survived. The Quintero stage did not worsen in any of the survivors; however, stage III atypical, which was defined as abnormal Doppler flow with visible donor bladder, had a decreased survival rate especially in 2 survivors.

DISCUSSION

Table **4** presents the perinatal outcomes in published series including early series of pioneer operators [1, 17-20] and published data [12, 21-24] from the conclusion of the Eurofetus trial comparison to the present study. Early series reported approximately a 60% overall survival rate, a 5% neurological complication rate; and a 40% survival rate of both twins. Middledorp *et al*. [21], Cincotta *et al.* [12], Huber *et al*. [22], and Chmait *et al*. [23] describe improved perinatal outcomes: > 70% overall survival, 58-69% with two survivors and; and > 80% with at least one survivor. Hecher *et al.* and Huber *et al*. reported the data from their 400 consecutive case series divided into two groups: the first 200 [20] and last 200 [22]. As their experience increased, they reported an increasing overall survival rate, especially for cases of two survivors. In our series, the overall perinatal survival for at least six months was 78%; the neurological complication rate was 5% of neurological complications; the rate for both twins surviving was 63%; and at least one twin survived in 93% of the cases. These data appear favorable 93% of the cases. These data appear favorable and are comparable to that of the latest 200 case series of Huber *et al*. [22] We attribute our favorable results to mapping, trocar assisted techniques, selection of the appropriate fetoscope, sequential order ablation, and the laser line drawing method.

CONCLUSION

In view of our experience regarding the management of TTTS, comprehensive techniques including preparation of various new devices, selection of instruments, and advanced laser ablation techniques have contributed to the progress of fetoscopic laser surgery for TTTS in monochorionic twins.

CONFLICT OF INTEREST

None declared.

ACKNOWLEDGEMENT

None declared.

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