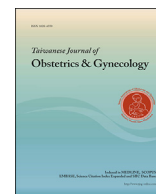


Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Outcome of twin–twin transfusion syndrome treated by laser therapy in Taiwan's single center: Role of Quintero staging system



Yao-Lung Chang^{*}, An-Shine Chao, Shuenn-Dyh Chang, Peter CC. Hsieh, Sheng-Yuan Su, Kuan-Ju Chen, Po-Jen Cheng, Tzu-Hao Wang

Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Tao-Yuan, Taiwan

ARTICLE INFO

Article history:
Accepted 4 May 2015

Keywords:
fetoscope
Quintero stage
twin–twin transfusion syndrome

ABSTRACT

Objective: To evaluate the outcome of twin–twin transfusion syndrome (TTTS) treated by fetoscopic laser therapy (FLT) stratified by Quintero staging.

Materials and Methods: A total of 100 TTTS cases treated by FLT, from October 2005 to August 2014, were included in this study. Cases were divided into first and second half periods to evaluate the learning effect-related outcomes, and logistic regression was applied to determine the independent factors in predicting the perinatal outcomes.

Results: The total fetal survival rate was 68.5%, two fetal survival rate was 55%, and at least one fetal survival rate was 82%. High Quintero stage (Stages III and IV) and small gestational age at delivery were two independent factors predicting lower two fetal survivals. Gestational age at delivery was the only independent factor predicting at least one survival. The odds ratios of high Quintero stage predicting lower two fetal survivals were 11.3 ($p < 0.001$) and 4.8 ($p = 0.043$) in the first and second periods, respectively.

Conclusion: High Quintero stage and small gestational age at delivery were associated with low two survival rate in TTTS treated by FLT; after gaining experience with FLT, the effect of high Quintero stage on lower two survival rate would decrease.

Copyright © 2016, Taiwan Association of Obstetrics & Gynecology. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Twin–twin transfusion syndrome (TTTS) complicates approximately one in five of all monochorionic, diamniotic twin pregnancies [1]. Since the first randomized trial on interventions for TTTS was published [2], it has been recognized that first-line treatment for all stages of TTTS diagnosed before 26 weeks is fetoscopic laser therapy (FLT).

The Quintero staging system initially was developed to categorically describe the ultrasound findings but not for the purpose of predicting the outcomes in cases treated by FLT [3]. One review article concluded that Quintero staging does not provide information about prognosis in cases treated by FLT [4]. However, a prospective series including 200 cases [5] and another, the largest ever

series to date, which included 682 consecutive cases of TTTS treated by FLT, both found that Quintero staging would correlate with perinatal outcomes [6]; the former study discovered that with advancing stage there occurred a gradual decline in survival rates [5], and the latter study found the worst outcome in Stage III cases [6]. Recently, a newly built center also reported that the outcomes of TTTS cases treated by FLT corresponded with Quintero staging, the worst being Quintero stage IV [7]. So there were both heavy case load [5,6] and less case load [7] centers that found correlations between perinatal outcomes and Quintero staging system in cases of TTTS after FLT.

We had previously reported our outcomes of TTTS treated by FLT for the first 44 cases and concluded that as more experience was gained on these cases, the more the two fetal survival rate improved [8]. In the present study, in order to further explore the role of Quintero staging system in TTTS treated by FLT and to demonstrate whether its categorical staging system suffices to predict the perinatal outcomes, we expand to showcase our first 100 consecutive cases, taking into account the effect of

^{*} Corresponding author. Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Linkou Medical Center, 5, Fu-Shin Street, Kweishan, Tao-yuan 333, Taiwan.

E-mail address: j12054@cgmh.org.tw (Y.-L. Chang).

experience buildup and comparing the outcomes between the first and second batches of 50 cases stratified by the Quintero staging system.

Materials and methods

This study was approved by the local Institutional Review Board of the Chang Gung Medical Foundation, Taiwan (103-7714B). The diagnosis of TTTS is based on the Quintero staging system, and the staging system was also used to survey the outcomes [3]. High Quintero stage was defined as Stages III and IV, and low stage consisted of Stages I and II. After the diagnosis of TTTS, treatment options including serial amnioreduction, laser therapy, or expectant management, were offered to the patients. If laser therapy was chosen, surgery was performed in the operating room under regional (either epidural or spinal) or local anesthesia. Routine prophylaxis with uterine relaxants (indomethacin, 50 mg suppository, 1 hour before sending the patient to the operating room; or in the case of anaphylaxis to indomethacin, nifedipine was given via the oral route) and antibiotics (cefazolin, 2 g, intravenously; immediately prior to skin incision) were administered in all cases. The procedure was performed with a 2-mm 0° fetoscope (Storz 26008 AA; Karl Storz GmbH, Tuttlingen, Germany) or a 30° fetoscope (Storz 26008 BUA; Karl Storz GmbH) mainly for anterior placenta. The placental anastomoses were selectively coagulated with 15–30 W Nd–YAG laser continuing beams, according to the diameter of the targeted vessel. After completing the photocoagulation, amniotic fluid was drained in order to decrease the maximum vertical pocket of the recipient to < 8 cm. The abdominal wound was closed with sterile strips. Patients with a cervical length of < 2.0 cm detected prior to the operation were placed on cervical cerclage after laser therapy.

At least one fetal survival and two fetal survival rates were calculated when the babies live > 30 days after delivery. The total survival rate was calculated based on the total number of fetuses (200 in this study).

Statistical analysis was conducted with SPSS software (version 11.0 for Window; SPSS Inc., Chicago, IL, USA). Qualitative data were compared using χ^2 test or Fisher's exact test as appropriate. Continuous variables were tested for normality. Logistic regression test was applied to determine the independent factors predicting fetal survival. A probability value of < 0.05 was considered statistically significant.

Results

From October 2005 to August 2014, FLT was performed in 100 second-trimester TTTS cases. All surgeries were performed by one of the authors (Y.L.C.). Table 1 displays the relevant information from these cases. The median gestational age at the time of surgery was 20.6 weeks (range, 17–25 weeks). The placenta was anterior or predominantly anterior in 40 (40%) cases. The mean gestational age at delivery was 31.2 weeks. The total fetal survival rate was 68.5% (137/200), two fetal survival rate was 55%, and at least one fetal survival rate was 82%.

Outcomes based on the Quintero staging system are listed in Table 2. Of the total number of patients, 18% were categorized as Stage I, 29% as Stage II, 40% as Stage III, and 13% as Stage IV. The two fetal survival and total survival rates were significantly different when comparison was drawn within the four stages of TTTS ($p < 0.0001$ and $p < 0.001$, respectively); however, there was no significant difference in at least one survival rate among the four stages of TTTS ($p = 0.285$). Compared with low Quintero stage cases (Stages I and II), high Quintero stage cases (Stages III and IV)

Table 1

Outcomes of 100 cases of twin–twin transfusion syndrome after fetoscopic laser therapy.

Overall survival (200 fetuses)	68.5
Double survival	55.0
At least 1 survival	82.0
Gestational age of operation (wk)	20.6 ± 2.7
Gestational age of delivery (wk)	31.2 ± 5.8
Operation delivery interval (d)	74 ± 44
PROM within 3 wk after operation	7.0
Donor birth weight (g)	1654
Recipient birth weight (g)	1873
Donor survival	69.0
Recipient survival	70.0
Reverse TTTS, n (%)	2 (2)
Persistent TTTS	2 (2)
Twin anemia polycythemia sequence (TAPS)	2 (2)

Data are presented as %, n (%), or mean ± standard deviation, unless otherwise indicated.

PROM = premature rupture of membrane; TTTS = twin–twin transfusion syndrome.

showed lower total survival (54.7% vs. 84.0%, respectively; $p < 0.001$) and two fetal survival rates (34.0% vs. 78.8%, respectively; $p < 0.001$; Figure 1).

After dividing 100 cases into first and second half periods, we found that in both periods the total and two fetal survival rates were all lower in high Quintero stage groups (Figures 2A and 2B). Logistic regression analysis was performed to evaluate the impact on at least one and two fetal survival rates from among the parameters of gestational age at operation and delivery, whether high Quintero stage, whether anterior placenta, and whether PROM (premature rupture of membrane) within 3 weeks of operation (Table 3). The results indicated that gestational age at delivery and whether with high Quintero stage were the two independent factors that predicted two fetal survivals; high Quintero stage decreased [odds ratio (OR), 6.89; $p = 0.001$] and advanced gestational age at delivery (OR, 1.288; $p < 0.001$) increased the two fetal survival rate. However, only gestational age at delivery could predict at least one survival rate (OR, 2.42; $p < 0.001$), with more advanced gestation at delivery demonstrating at least one fetal survival rate.

In order to evaluate the effect of increasing experience in FLT on the fetal outcomes, logistic regression analysis meant to predict two fetal and at least one fetal survival rates was again applied, but separately to the first and second half period cases, and the results were compared. Likewise, in both half periods, high Quintero stage and small gestational age at delivery were two independent factors that predicted lower than two fetal survivals; however, the OR of high Quintero stage to decrease the chance of two fetal survivals was shown to drop from 11.4 in the first period to 4.8 in the second period.

Intraoperative complications were noted in three cases (3%): one was bleeding resulting from laceration of a placental vessel during laser therapy, but after laser coagulation of the upstream of the lacerated vessels, the bleeding ceased and the surgery was completed, resulting in two live babies delivered at gestational age of 29 weeks; the other two cases were found with bleeding from the trocar site but both stopped bleeding after about 10 minutes of compression.

Discussion

Our case series demonstrated stage-related perinatal outcomes in TTTS treated by FLT. The cases with high Quintero stage would

Table 2
Patients' characteristic and prognosis according to Quintero staging.

	Stage I (N = 18)	Stage I (N = 29)	Stage III (N = 40)	Stage IV (N = 13)	p
GA of operation	21.3 ± 2.4	20.6 ± 2.7	20.2 ± 2.7	21.3 ± 3.3	0.52
GA of delivery	33.7 ± 4.7	32.4 ± 5.8	29.7 ± 5.6	30.2 ± 6.6	0.048 (Stage I > Stage III)
At least one survival	94.4 (17)	86.2 (25)	75 (30)	76.9 (10)	0.285
Two survival	77.7 (14)	79.3 (23)	32.5 (13)	38.5 (5)	<0.001
Total survival	86.1 (31/36)	82.8 (48/58)	53.8 (43/80)	57.7 (15/26)	<0.001
Interval (d)	88.4 ± 29.4	82.8 ± 49.0	66.2 ± 41.3	64.0 ± 55.2	0.189

Data are presented as % (n), % (n/N), or mean ± standard deviation.

GA = gestational age (weeks); interval = interval from operation to delivery

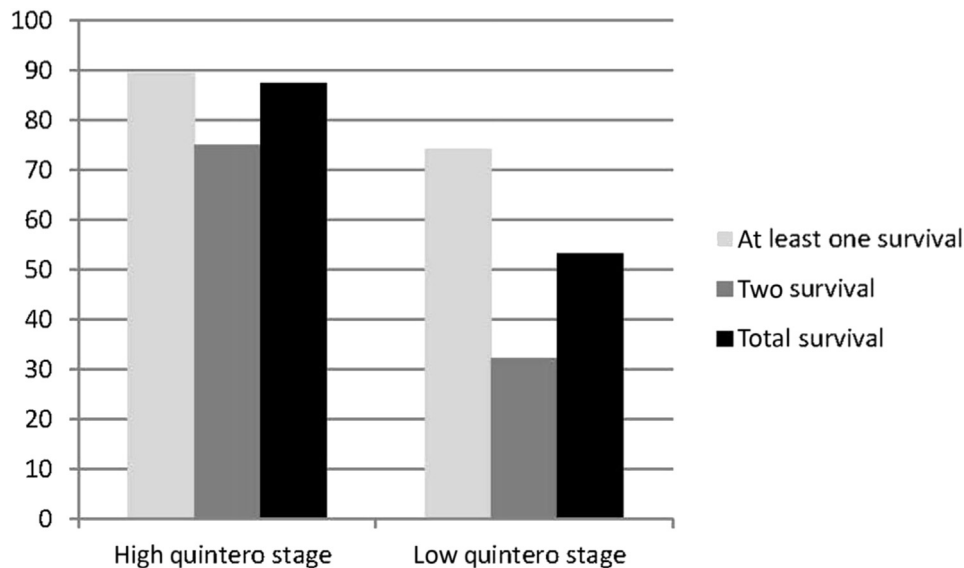


Figure 1. The at least one, two, and total fetal survival rates of 100 consecutive cases of TTTS after FLT. Data are expressed as %. There was no difference in at least one survival (89.4% vs. 75.8%, respectively; $p = 0.116$), but there was a significant difference in two fetal survival (78.7% vs. 34.0%, respectively; $p < 0.001$) and total survival rate (84.0% vs. 50.0%, respectively; $p < 0.001$) between TTTS with high and low Quintero stages. Low Quintero stage: Stages I and II; high Quintero stage: Stages III and IV. FLT = fetoscopic laser therapy; TTTS = twin–twin transfusion syndrome.

have lower two fetal survival rate and total survival rate. After dividing the cases into first and second half 50 cases, the same results were observed in each half of patients as opposed to the whole group of patients across both periods. After logistic regression analysis to go through all the cases, high Quintero stage and small gestational age at delivery were found to be the two independent factors that could predict low two fetal survival rate. But when the same analysis is performed separately on the first and second half period of patients, the negative impact on the two fetal survival rate from high Quintero stage was less significant in the second half period than in the first half period. Previously, we reported the outcomes of our first 44 cases of TTTS treated by FLT where the two fetal survival rate was found to be better in the last 22 cases than in the first 22 cases [8]. After accumulating experience from 100 cases, although the two fetal survival rate appeared higher in the second batch of 50 cases (at 60%) versus the first batch of 50 cases (at 50%), the difference did not reach statistical significance ($p = 0.315$). But by using logistic regression analysis in this study, we found that increasing experience with FLT would decrease the negative impact of high Quintero stage on fetal survival.

In the largest case series reported by Chmait et al [6], the two fetal survival rate in Stages III and IV TTTS after FLT could reach up

to 58.5% and 68.3% [6], respectively. In comparison, our data yielded 32.5% and 38.5% two fetal survival rate for Stages III and IV cases, respectively. So, there is still room for improvement on the outcomes in our center, mainly in cases with high Quintero stages. Furthermore, the difference in fetal survival between the two series reflects our findings in this study, in that buildup in experience would diminish the negative effect of high Quintero stage on the two fetal survivals in TTTS after FLT. Moreover, the learning curve effect in FLT for TTTS mainly exists in two fetal survivals, especially in high Quintero stage cases. A study conducting follow-up on the development outcomes of surviving twins with TTTS after FLT at preschool age discovered that there was a significant trend for worse outcome with higher Quintero stage [9]. So Quintero staging may not only serve as a predictor prior to FLT for fetal survival but also after FLT to foretell the development outcomes.

In conclusion, high Quintero stages found prior to the operation and a young gestational age at delivery after the operation were two independent factors that predicted lower two fetal survivals in patients with TTTS treated by FLT. Increasing experience in FLT could diminish the negative role played by high Quintero stage in achieving two fetal survival in cases of TTTS treated by FLT.

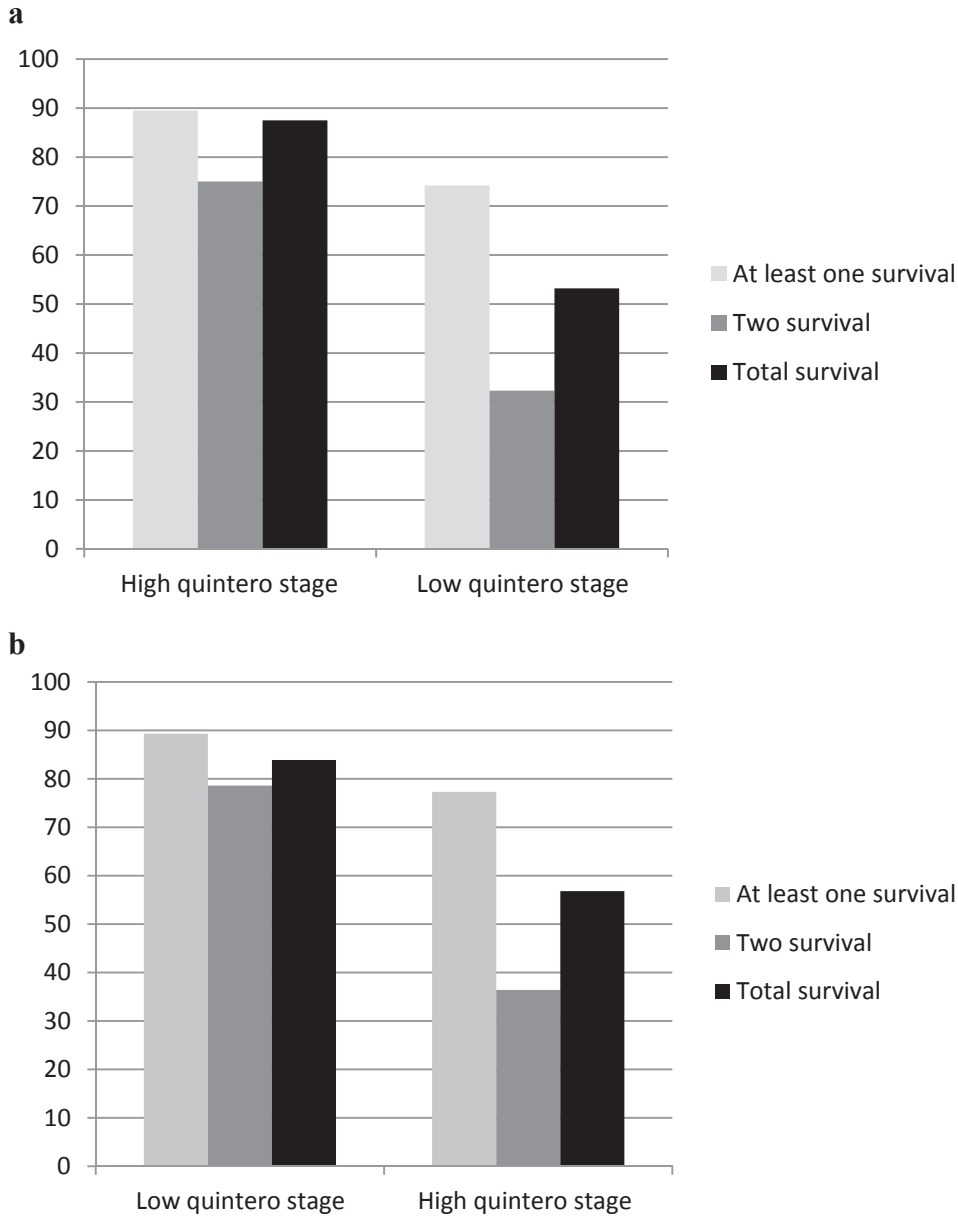


Figure 2. (A) The at least one, two, and total survival rates of the first 50 cases of TTS after FLT. Data are expressed as percentage (%). There was no difference in at least one survival (89.5% vs. 74.2%, respectively; $p = 0.173$), but there was a significant difference in two fetal survival (78.9% vs. 32.3%, respectively; $p = 0.003$) and total survival rate (84.2% vs. 53.2%, respectively; $p = 0.002$) between TTS with high and low Quintero stages. (Low Quintero stage: Stages I and II; high Quintero stage: Stages III and IV.) (B) The at least one, two, and total survival rates of the second 50 cases of TTS after FLT. Data are expressed as %. There was no difference in at least one survival (89.3% vs. 77.3%, respectively; $p = 0.277$), but there was a significant difference in two fetal survival (78.6% vs. 36.4%, respectively; $p = 0.002$) and total survival rate (83.9% vs. 54.3%, respectively; $p = 0.003$) between TTS with high and low Quintero stages. Low Quintero stage: Stages I and II; high Quintero stage: Stages III and IV. FLT = fetoscopic laser therapy; TTS = twin–twin transfusion syndrome.

Table 3

Factors predicting two fetal survivals and at least one fetal survival rates of TTS after FLT in all 100 cases, first 50 cases, and second 50 cases.^a

	Factors	High Quintero stage	Gestational age at delivery
Whole 100 cases	2 survival	7.18* (<0.001)	1.29* (<0.001)
	At least 1 survival	2.27 (0.52)	2.44* (0.001)
First half 50 cases	2 survival	11.3* (0.005)	1.33* (0.002)
	At least 1 survival	3.83 (0.50)	2.12* (0.011)
Second half 50 cases	2 survival	4.8* (0.043)	1.30* (0.001)
	At least 1 survival	1.41 (0.86)	3.72* (0.046)

* $p < 0.05$.

Data are expressed as odds ratio (p value)

^a High Quintero stage was defined as Stages III and IV. High Quintero stage decreased and advanced gestational age increased the two fetal survival rate in all 100 cases.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

References

- [1] Benirschke K. The placenta in twin gestation. *Clin Obstet Gynecol* 1990;33: 18–31.
- [2] Senat MV, Deprest J, Boulvain M, Paupe A, Winer N, Ville Y. Endoscopic laser surgery versus serial amnioreduction for severe twin-to-twin transfusion syndrome. *N Engl J Med* 2004;351:136–44.
- [3] Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kruger M. Staging of twin-twin transfusion syndrome. *J Perinatol* 1999;19:550–5.
- [4] Rossi AC, D'Addario V. The efficacy of Quintero staging system to assess severity of twin–twin transfusion syndrome treated with laser therapy: a systematic review with meta-analysis. *Am J Perinatol* 2009;26:537–44.
- [5] Huber A, Diehl W, Bregenzer T, Hackeloer BJ, Hecher K. Stage-related outcome in twin–twin transfusion syndrome treated by fetoscopic laser coagulation. *Obstet Gynecol* 2006;108:333–7.
- [6] Chmait RH, Kontopoulos EV, Korst LM, Llanes A, Petisco I, Quintero RA. Stage-based outcomes of 682 consecutive cases of twin–twin transfusion syndrome treated with laser surgery: the USFetus experience. *Am J Obstet Gynecol* 2011;204. 393 e1–6.
- [7] Has R, Kalelioglu I, Corbacioglu Esmer A, Ermis H, Dural O, Dogan Y, et al. Stage-related outcome after fetoscopic laser ablation in twin-to-twin transfusion syndrome. *Fetal Diagn Ther* 2014;36:287–92.
- [8] Chang YL, Chao AS, Chang SD, Hsieh PC, Wang CN. Short-term outcomes of fetoscopic laser surgery for severe twin–twin transfusion syndrome from Taiwan single center experience: demonstration of learning curve effect on the fetal outcomes. *Taiwan J Obstet Gynecol* 2012;51:350–3.
- [9] McIntosh J, Meriki N, Joshi A, Biggs V, Welsh AW, Challis D, et al. Long term developmental outcomes of pre-school age children following laser surgery for twin-to-twin transfusion syndrome. *Early Hum Dev* 2014;90:837–42.