Author’s response to reviews

Title: Effects and outcomes of septostomy in twin-to-twin transfusion syndrome after fetoscopic laser therapy

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Stephanie Springer (Reviewer 1): In this retrospective study the authors evaluated the outcome of 159 monochorionic twin pregnancies with severe twin-to-twin transfusion syndrome after accidental septostomy during fetoscopic laser therapy. Until now there are not so many publications dealing with this topic. Therefore, further publications would be of general interest.

The work has been revised and proof read by a native speaker. Additional statistical analyses have been added and recommendations incorporated. The revisions are well done.

I still recommend some minor revisions

1. Use either one or two decimal places after the comma. Round off the decimal places correctly.
Answer: thanks, we had corrected it accordingly.

2. If you specify frequencies, either always enter numbers in parenthesis, or never.
Answer: thanks, we had corrected it accordingly.

3. It is called odds ratio not odd ratios. Please correct this throughout the whole work.
Answer: thanks, we had corrected it accordingly.
4. I suggest calling the probability value just p-value.

Answer: thanks, we had corrected it accordingly.

5. Minor linguistic deficits should be revised. Expression of some phrases is deficient and need some improvement
   a. Page 7, Row 58
   b. Page 11, Row 39
   c. Page 13, Row 9, Row 12

Answer: thanks, we had corrected it accordingly.

6. In the results you first use mean and standard deviation to describe the gestational age at operation and delivery and later you perform the Mann-Whitney U Test and use the median (min,max) in the tables. Please change the mean into median.

Answer: thanks, we had corrected it accordingly.

7. Table 1: Please unify the table. Sometimes you set the percent sign next to the numbers and sometimes at the beginning. In the line under the table you write frequency (%) and in the table you describe it as percentage (frequencies).

Answer: thanks, we had corrected it accordingly.

8. Table 3: Results for neonatal cerebral image anomaly and the second variable are missing.

Ans: since we choose the forward condition mode for predicting poor perinatal outcomes, severe Quintero stage was not a significant factor for predicting Neonatal cerebral image anomaly. So we add “not significant” in the table 3. Thanks for comment.

David Alan Ellwood (Reviewer 2): Thanks for allowing me to review your interesting manuscript. Your data are clearly presented and the conclusions are very well stated. I agree that you have demonstrated that cases in which laser ablation has resulted in septostomy appear to have worse outcomes than those which dont. and I also agree with your conclusions arguing against septostomy as a form of treatment.

My main question for you is whether or not the data you have presented have caused your team to change its practice in relation to methods, or if you have any recommendations for the readers about any form of management post-laser which might reduce the risk of an adverse outcome in such cases? Cord entanglement will always be a challenge but a number of the cases also
resulted in extremely preterm birth and I am curious as to any suggestions you might have about prevention?

Ans: Thanks for comments, we had added “Since postlaser septostomy is associated with poorer fetal outcomes, careful selection of trocar site insertion for TTTS laser therapy is imperative to prevent septostomy during trocar insertion. Gentle to manipulation of the scope and laser fiber during operation is crucial to prevent mechanical trauma to the intertwin membrane. There were no differences in the incidence of cord entanglement and fetal survival rate in TTTS patients with postlaser septostomy managed with outpatient or inpatient surveillance. However, the gestational age at delivery was even earlier in cases with in patient management. [1] So the optimal management method for TTTS with postlaser septostomy is still unclear. ” Into discussion section

Could you also give some more information about the way in which treatment for TTTS is organised in Taiwan? Is there a single centre that manages all cases for a region or are there multiple operators working from many different sites? This kind of information would also be useful to understand the context in which this case series has arisen. For example, what proportion of the total TTS cases from Taiwan does this number represent?

Answer: Thanks for comment. We had added “For about 23.7 million populations, there are currently two laser therapy centers for TTTS in Taiwan. We are the largest center and had more than 95% of cases. All laser operations for TTTS were performed by a single operator (YL Chang). To the method section.

Finally, are you able to comment on any factors that seem to be associated with septostomy on this series? Was there any clear connection with more complicated procedures, in terms of time (duration) of the procedure, access to the placenta, maternal BMI etc.? Given that this is a series from one operator has there been evidence of a 'learning curve' Are cases of septostomy seen less commonly in the later years of the series?

Answer: I personally recognized mainly anterior placenta is a risk factor for septostomy in TTTS post laser therapy, but our data do not make a statistic significant (p= 0.18. 5/42 vs 7/118, mainly anterior placenta vs not, respectively) .

In total 159 cases, total 7 (8.75%) cases in the first 80 cases with septostomy and 5 (6.32%) in the remaining 79 cases, it look like with a bit of improvement with more experience but was also not significant in statistics due to small case number.

Maria Delius, MD, MPH (Reviewer 3): Dear authors, thank you very much for this well presented data.

I just wold like to have discussed one thing - why was laser treatment done in Quintero stage I?
Regarding the same risk of septostomy over all Quintero stages - as you reported - I have missed a discussion about indications for last therapy in early Quintero stages regarding the risks of laser procedure.

You could add that to the discussion.

Answer: thanks for comments, we had add “Fetoscopic laser therapy is recognized as the first line therapy for stage II to IV TTTS diagnosed before 26 weeks of gestation[3], and with some debate, for stage I TTTS[4]. The survival rate for stage I TTTS was 94.4 % for at least one twin, and 77.7% for both twins. [18]The incidences of postlaser septostomy were not significantly different between different Quintero stages in our series. The North American Fetal Therapy Network reported that 60.0% of stage I TTTS managed conservatively progressed, and only fetoscopic laser surgery, but not amnioreduction, was protective against double fetal loss or very preterm delivery before 26 + 0 weeks[4]. Therefore, offering laser therapy to stage I TTTS patients before gestational age of 26 weeks, though with risks like postlaser septostomy, as demonstrated by our series, is reasonable. ” into the discussion section.