Author's response to reviews

**Title:** Survival of outborns with congenital diaphragmatic hernia: the role of protective ventilation, early presentation and transport distance: a retrospective cohort study

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**Author's response to reviews:** see over
Dear Editor of BMC/Attn. Mrs Catherine Olino,

We have addressed all the comments raised by our reviewers and we provide you with a cover letter giving a point-by-point response to the concerns. We incorporate some of the changes requested by reviewer in our revised manuscript.

Also this manuscript now fully conforms to the journal style and our files are correctly formatted.

With best wishes,

Toby Weingarten, MD
Responses to reviewer No 1

Reviewer's report:

Query: The paper is well written and the analysis seems sound. However, I have doubts whether the results are actually an advance above earlier published results. Factors unique to this manuscript is lack of air transport for transporting sick neonates from distances up to 280 kilometers and lack of ECMO rescue in the tertiary center.

Response: We present comprehensive management of patients with CDH between two Epochs characterized with different approach to treatment of these sick neonates. Large distance transport is an important addition to the literature, and interesting consideration when considering outcomes is that our reported outcomes reflect neonates transported via ground ambulance and almost uniquely hand bagged ventilated. While adult and pediatric ECMO exist in Croatia in last several years, neonatal ECMO does not. Just to put into perspective, at Mayo Clinic, Rochester, MN, USA, ECMO was introduced 2001, and was unavailable before that date. Therefore, our report reflects outcomes which in many aspects were not much different comparing to the most medically advanced countries, with ECMO capabilities and state of the art transports.

Query: Minor essential revisions: Figure 2 not clear. Is the Y axis "actual survival" of patients who fell into POS high, moderate and low in the two epochs.

Response: We have clarified this issue in the legend of the figure. This figure shows the percentage of patients who were discharged alive from the hospital. X and Y axes were now relabelled for clarification.
Responses to reviewer No 2

Query: The authors state that since all subjects were outborn “Patient transfers were accomplished by ground ambulance and ventilation during transfer was assisted via hand-held, self-inflating bags or conventional ventilator integrated in transport incubator”. This is a very important issue that can significantly affect pulmonary outcomes.

Response: Agree entirely with this reviewer. We added a paragraph in introductory part of our Results section to further delineate the type of transport employed.

Query: Providing IPPV with a self-inflating bag without the benefit of PEEP can cause significant lung injury in a patient with an already hypoplastic lung that can be enough to impact the subsequent pulmonary outcome compared to ventilation with a conventional ventilator that is able to provide both PIP and PEEP. This could be true for both locally or remotely born infants since even a few breaths without PEEP may be enough to set off important cascades leading to lung injury. Are the authors able to tease out which infants received what type of support enroute top the referral center? If so could these likely affect the outcomes noted?

Response: The majority of transports were done with self-inflating bags. The information regarding number of neonates transported with ventilator vs hand-held bag is now provided in results, and from these numbers is clear that our outcomes almost universally reflect outcomes of neonates with CDH transported to major medical center via ground ambulance, sometimes from remote areas of the country, and on hand-held self-inflating bag ventilation. Because of this almost uniform type of transport ventilation, making any inference whether this had any impact on outcome is not possible.

Query: The authors stated that “Epoch I. Neonates were sedated, paralyzed, and ventilated with IMV to achieve respiratory alkalosis and postductal oxyhemoglobin saturation above 90% to ameliorate pulmonary hypertension. This strategy often required high PIP, respiratory rates and oxygen concentrations. In Epoch II, neonates received protective ventilation aimed to minimize volutrauma with the use of minimal pressure and volume settings and inspired oxygen concentration to achieve acceptable pre ductal oxygenation saturations (# 85%) while permitting hypercapnia (# 65 mm Hg)”. Are there any ventilator parameter data used in the 2 study periods e.g. mean PIP, mean airway pressure or the amount of PEEP used? In Epoch II when synchronized and volume targeted ventilation became available are there any data regarding what tidal volumes were used?
Response: The following paragraph was added to the manuscript (of note, although study was not prospective to precisely provide respiratory parameter, practice during Epoch II was protocolized and these parameters are outlined in our revised paragraph as follows:

“Epoch I. Neonates were sedated, paralyzed, and ventilated with intermittent mandatory ventilation (IMV) to achieve respiratory alkalosis and postductal oxyhemoglobin saturation above 90% to ameliorate pulmonary hypertension. This strategy often required higher peak inspiratory pressures (PIP), respiratory rates and oxygen concentrations. In those with available records of PIP, the values were between 30 and 40 cmH₂O. In Epoch II, neonates received protective ventilation aimed to minimize volutrauma with the use of minimal pressure and volume settings and inspired oxygen concentration to achieve acceptable preductal oxygenation saturations (≥ 85%) while permitting hypercapnia (≤ 65 mm Hg). Only two modes of ventilation were used: assist-control plus volume limit setting mode (A/C + VL) and pressure support ventilation with volume guarantee mode (PSV + VG). Both modes fully supported synchronized ventilation aided by controlled “demand flow” circuitry which synchronizes inspiratory gas delivery close to the breathing pattern of the neonate. Ventilatory settings were set per protocol. In the A/C + VL mode the tidal volume limit was 6 mL/kg, PEEP of 2-3 cm H₂O, PIP ≤ 25 cmH₂O, and the backup respiratory rate 40 per min. If respiratory acidosis (obtained from preductal capillary blood) was present (pH<7.25, PcCO₂>65 mmHg), ventilatory settings were changed by increasing PIP by 2 cmH₂O (until maximum PIP of 25 cmH₂O was achieved). In patients ventilated with PSV + VG mode the mean VG used was 4.0 mL/kg (range 2.6-5.5 mL/kg), PEEP 3.8 (range 2.5-5) cm H₂O, PIP ≤ 25 cmH₂O, and backup respiratory rate 40/min. If severe respiratory acidosis was present, VG was increased to a maximum 5.5 mL/kg exceeding the PIP limit if needed. With this strategy sedation and muscle paralysis were infrequently used and only in newborns with patient-ventilator asynchrony. High frequency oscillation ventilation (HFOV) was a rescue treatment for neonates who continued to have hypoxia and hypercarbia (PcCO₂>65 mmHg) despite optimization of either ventilatory mode.”

Query: There appears to be a better survival rate and better pH on admission among the remote transfers compared to the local transfers although this does not reach statistical significance. Are there any data regarding how the local and remote babies were provided respiratory support during transport? i.e. who was “hand bagged” and who was transported using a transport ventilator? For instance were the transport ventilators reserved for the remote transfers and the local transfers provided hand ventilation? If so this may produce more lung injury among the “hand-bagged” infants accounting for their lower pH and survival.

Response: Now we provide the numbers of patients who were ventilated by self-inflating bag vs mechanical ventilator. We added the following paragraph in Results:

“All neonatal transfers to our medical center were accomplished by ground ambulance. Ventilation during transfer was accomplished via hand-held self-inflating bags for all neonates in Epoch I, and for the majority of neonates in Epoch II. In Epoch II, 9 neonates, 1 local and 8
remote [3 died] transfers, received ventilation through a pressure controlled ventilator integrated in transport incubator.”

Therefore almost the entire patient population was transferred with hand heal self-inflating bags, therefore it is not possible to make any analysis between this majority and few who had incubator integrated mechanical ventilation—and it is not possible to elicit difference in outcome in relationship to transport ventilation i.e. whether the use of bag hand held ventilation might have had contributed to lung injury.

Query: In table 2 the authors provided data for the first admission blood gas among study subjects which was more likely a reflection of the interventions before arrival at the referral hospital. Are there any data about subsequent blood gases “during” the hospital stay to allow a comparison of the efficacy of the management strategies in the 2 epochs?

Response: The aim of our study was to examine the role of admission blood gases in predicting survival. Although subsequent blood gas data were available these data were not obtained at consistent intervals for all patients. We quantified these data by recording the best and worst observed values over the first 24 hours after admission. However, not all patients survived 24 hours and as expected those who did not survive to hospital discharge had worse blood gases over the first 24 hours. Since we were primarily interested in the survival and all patients have admission blood gases, we opted to use only admission values.

MINOR ESSENTIAL REVISIONS:

Table 3, reported the mean hours between delivery and surgery to be 24.5 vs. 29 in Epoch I and II, respectively. This is an incredibly short period of time to take the patients to surgery since there is evidence to show that waiting for the pulmonary vascular resistance to decrease before surgery does affect outcome. I understand that this is a retrospective data collection, but the authors should address this in the discussion.

Response: We report what was the practice pattern at the time these surgeries were performed. This reviewer is right, as an opinion was created that the timing of surgical repair should be shifted from emergent repair to a policy of stabilization using a variety of ventilatory strategies prior to operation. However, a recent Cochrane analysis showed that there is no clear evidence which favors delayed (when stabilized) as compared to immediate (within 24 hours of birth) timing of surgical repair of CDH. This reference has been added to the footnote of the Table 3.