REVIEW ARTICLE

Foetal endoscopic tracheal occlusion for severe congenital diaphragmatic hernia — a systemic review and meta-analysis of randomized controlled trials

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Abstract

To evaluate and analyze the effect of foetal endocsopic tracheal occlusion (FETO) therapy on survival rates of neonatal with congenital diaphragmatic hernia and maternal complications.

We performed a systemic review and meta-analysis of three randomized controlled trials (RCTs). The combined data on neonatal survival rates, length of gestational age and rates of premature rupture of membrane from these studies were retrieved and analysed.

Pooled data of these three RCTs revealed that FETO provided neonates with severe congenital diaphragmatic hernia a significantly higher survival rate: 27/48 VS 12/52. The odds ratio was 5.95 (95% CI: 2.11 - 16.79, p<0.0008). The gestational age (week) of FETO group was shorter than postnatal standard therapy group. The mean difference was -3.43 (95% CI: -6.82 - -0.04, p<0.05). FETO group also had a significantly greater rate of premature rupture of membranes than control group with the odds ratio of 3.35 (95% CI: 2.11 - 16.79, p<0.0008)

Foetal endoscopic tracheal occlusion improved neonatal survival rate but also increased major maternal complications including preterm delivery and premature rupture of membranes.

Keywords: Foetal endocsopic tracheal occlusion, Congenital diaphragmatic hernia, Survival, Maternal complications.

Introduction

Congenital diaphragmatic hernia (CDH) can now be diagnosed accurately with ultrasound examination during mid-gestation. Foetuses with poor prognostic factors including low lung-to-head ratio and liver herniation had high mortality and morbidity rates despite recent advances in neonatal critical care and surgical techniques.[1-3]

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As pulmonary hypoplasia was the key problem for the pathophysiological and pathological changes for neonates with CDH, measures had been taken to improve lung growth among these foetuses. Earlier attempts using open hysterotomy had been given up due to high rates of neonatal mortality and maternal complications.[4,5] Foetal endocsopic tracheal occlusion (FETO) was then introduced to promote foetal lung growth in uterus by occluding the trachea of foetuses during mid-gestation. Both animal and human studies showed improved lung development and neonatal survival rates.[6-14] But different maternal and neonatal outcome had been reported by these clinical trials and it is necessary to compare and evaluate these clinical data.

In this systemic review and meta-analysis, we attempted to evaluate and analyze the effect of FETO therapy on neonatal survival and maternal complications. The combined data on neonatal survival rates, length of gestational age and rates of premature rupture of membrane was retrieved from randomized controlled studies.

Methods

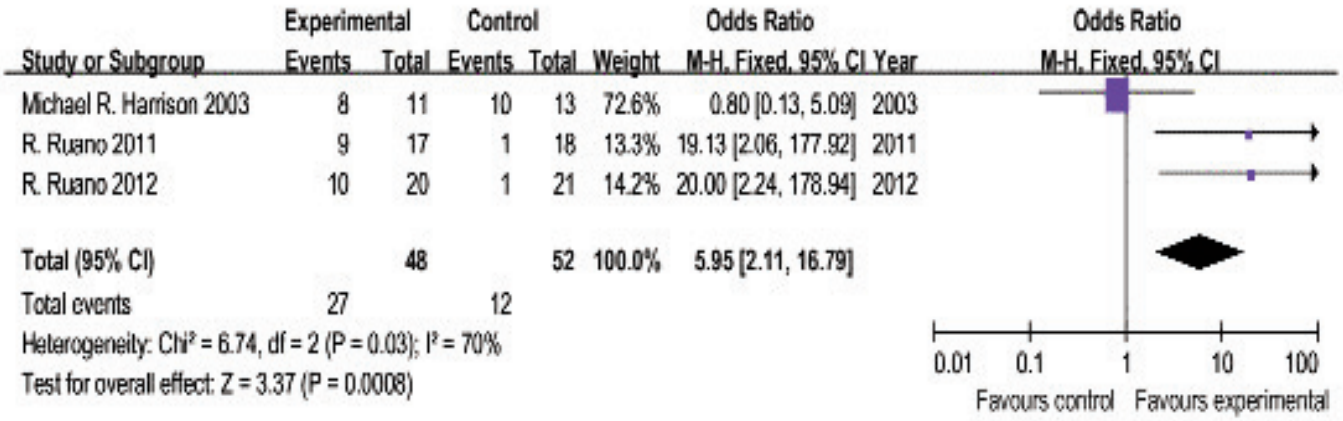
Inclusion Criteria of Trials

We included clinical trials that met all the following criteria for analysis: (1) The study was a prospective randomized controlled trial (RCT). (2) The study was designed to compare FETO with postnatal standard care for their respective maternal and neonatal outcomes. (3) Criteria for patient selection and prenatal interventional methods were described in the trial. (4) The following outcome measurements were all or partially reported: gestational age at delivery, rates of premature rupture of the membrane and neonatal survival rates.

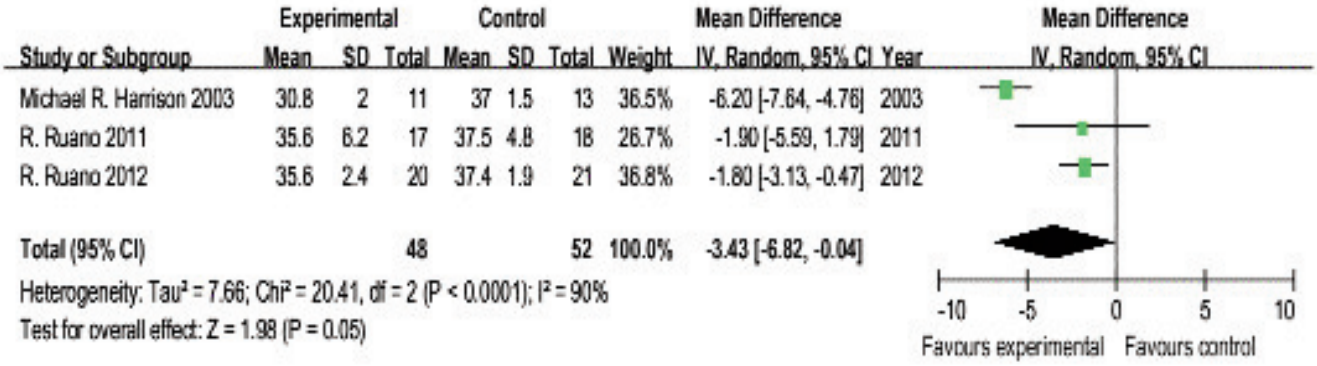
Search Strategy and Data Extraction

We searched MEDLINE (1966 to July 2012), EMBASE (1980 to July 2012), and the Cochrane Controlled Trials Register with restriction to English-language literature. The following subject heading or keywords were applied in our search: congenital diaphragmatic hernia, foetal endoscopic tracheal occlusion, foetal therapy and pulmonary or lung development. In addition, reference lists of relevant

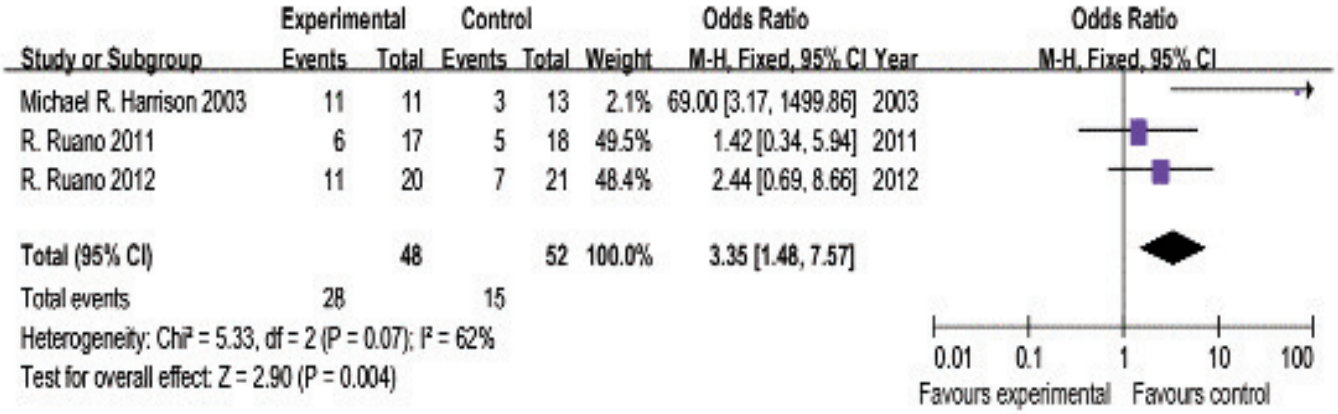
Neonatal Survival



Gestational Age



Premature Rupture of Membranes (PROM)



textbooks, review articles and abstracts of scientific meetings were also searched. Two authors independently developed an electronic database search strategy to identify studies that met the eligibility criteria. Initial searches yielded a total of 121 potentially relevant studies. After screening the abstracts of these preliminary results, we excluded 98 of them that were not related to foetal therapy for CDH. We read through the full texts of the remaining articles, 19 of them were excluded as they were narrative reviews or case reports, providing insufficient numerical results or were not controlled clinical trials. Four of the trials met the inclusion criteria. We assessed studies from the same medical center and same time period to carefully evaluate the possible overlap of cases. Three of them were finally included in our meta-analysis.

Statistical Analysis

Review Manager 5.0 created by the Cochrane Collaboration for meta-analysis (http://www.cochrane.org) was used to analyze the statistics. Heterogeneity between studies was assessed using Cochrane's Q statistic to determine whether a fixed ($p>0.1$) or random ($p<0.1$) effect model should be used. In this article, we used the random model.

For continuous (gestational age) and dichotomous (premature rupture of the membrane and neonatal survival) outcomes were expressed as mean differences (MD) and pooled odds ratio (OR) respectively with 95% confidence intervals (CI). Statistical significance was assessed by the Z test for overall effect and the pooled data would be considered statistically significant if $p<0.05$ level.

Results

Characteristics of the Trials

A total of 100 patients were included in our meta-analysis of the three randomized controlled trials (Table). Two of the trials were reported by the same author and were not overlapping cases of each other as the author clearly explained this in another published work.[4] Patients with prenatal diagnosis of congenital diaphragmatic hernia received either foetal endoscopic tracheal occlusion or standard postnatal treatment. Foetuses of the FETO group received ex utero intrapartum therapy procedures (EXIT) to remove the tracheal balloon. Neonatal intensive care and surgical intervention ensued. The average gestational age at randomization and maternal ages were similar among trials. Lung-to-head ratio of the foetus ranged from 0.79 - 0.97 for patients receiving FETO. The screen for publication bias was not performed due to the small number of studies.

Neonatal and Maternal Outcomes

Our meta-analysis of combined data revealed that foetal endoscopic tracheal occlusion therapy provided neonates with severe congenital diaphragmatic hernia a significantly higher survival rate: 27/48 VS 12/52. The odds ratio was 5.95 (95% CI: 2.11 - 16.79, $p<0.0008$). The gestational age (week) of FETO group was shorter than postnatal standard therapy group. The mean difference was -3.43 (95% CI: -6.82 - -0.04, $p<0.05$). FETO group also had a significantly greater rate of premature rupture of membranes than control group with the odds ratio of 3.35 (95% CI: 1.48 - 7.57, $p<0.004$).

Discussion

The primary purpose of foetal endoscopic tracheal occlusion for severe congenital diaphragmatic hernia was to promote foetal lung development and growth thus improving neonatal survival. Maternal complications occurring during and after this intra-uterine intervention were also of clinical concern. In this way, it is important to evaluate this therapy in the perspective of evidence based medicine.

Animal studies using foetal lambs were performed to evaluate the pulmonary microstructure alterations after tracheal occlusion. Histological structures of lung including the alveolar space and pulmonary vascularity were noted to improve. But the portion of type II alveolar cells and

Table: Characteristics of studies included in the meta-analysis.

Author		Year	Country	Study Design	Number of Patients	Maternal Age	GA at randomization	LHR	Follow-up of neonatal survival
Michael R. Harrison[6]	FETO	2003	USA	RCT	11	29.5±5.6	24.5±1.6	0.97±0.14	90 days
	Control				13	28.5±5.7	25.4±1.3	0.96±0.20	
Rodrigo Ruano[8]	FETO	2010	Brazil	RCT	17	29.2±6.5	25.4±3.4	0.79±0.09	28 days
	Control				18	30.5±6.1	25.2±4.4	0.80±0.08	
Rodrigo Ruano[7]	FETO	2012	Brazil	RCT	20	29.5±6.6	25.3±3.8	0.80±0.11	6 months
	Control				21	30.3±6.4	25.5±3.5	0.79±0.10	

LHR: Lung to Heart Ratio.

surfactant amount were decreased compared to foetal lamb with diaphragmatic hernia not receiving tracheal occlusion. Pulmonary fluid retention following tracheal occlusion was considered to cause lung expansion during foetal development. But compressions from both herniated organs and tracheal occlusion might bring unfavourable pulmonary morphological changes.[12-14]

Sonographic lung-to-head has been considered to be a predictor of neonatal survival. Increased LHR was associated with increased survival probability.[2,15] One of the randomized trials also indicated that LHR of 0.9 marked a significant difference for neonatal survival rates.[6] All foetuses involved in our analysis of receiving FETO had average LHR less than 1.0 which were thus considered to be the severe CDH.

A neonatal survival advantage was found in our meta-analysis. The first published randomized controlled trial evaluating the effect of foetal endoscopic tracheal occlusion did not reveal advantage in the aspect of neonatal survival in 2003.[6] But the other two trials in recent years performed by the same medical center reported a prominently improved neonatal outcome compared with the postnatal treatment group.[7,8] Authors of the last two trials pointed that their more strict criteria of patient selection (mean lung-to-head ratio: less than 0.8 VS more than 0.9) might explain the better survival rates. This further indicated that using the lung-to-head ratio as inclusion criteria for FETO was important to predict the neonatal prognosis. A longer follow-up evaluated the pulmonary functions of some of the neonates who were randomized to receive FETO but did not show definite advantage regarding survival.[11]

As with other prenatal interventions, maternal complications were another concern. Of the three trials in our analysis, rates of premature rupture of membranes ranged from to 35.3% to 100% of FETO mothers. Average gestational ages were all less than 37 weeks. Applications of thinner surgical instruments including both trochar and fetoscope were shown to have lower obstetrical complications. As a newly introduced technique, surgical outcomes also depended partially on performer's experience and learning curve.

Conclusion

Foetal endoscopic tracheal occlusion improved neonatal survival rate but also increased major maternal complications including preterm delivery and premature rupture of membranes. Progress in surgical technique and more suitable criteria for patient selection may bring more benefits to both babies and mothers.

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