Title

Medical Interventions to Reverse Pulmonary Hypoplasia in the Animal Model of Congenital Diaphragmatic Hernia: A Systematic Review

Research Team

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Background

Congenital diaphragmatic hernia (CDH) is a relatively common condition of the fetus occurring in 1 in 2500 live births[1]. The diaphragmatic defect results in herniation of the viscera during the embryonic phase of pulmonary development, competing for space in the thorax with the growing lungs. Affected lungs demonstrate pulmonary hypoplasia (PH) with fewer distal airways, reduced size and number of alveoli with thickened alveolar walls and an increased volume of interstitial tissue[2][3]. Over 60% of CDH cases are diagnosed by the second trimester of pregnancy on screening ultrasound[4] of which some are eligible for fetal therapy. Fetal Endoscopic Tracheal Occlusion (FETO) involving placement of a balloon to occlude the fetal trachea, prevents egress of lung fluid, leading to increased pulmonary stretch[5]. This increases airway branching morphogenesis and promotes pulmonary vasculature maturation [6][7][8]. The definitive conclusion on whether FETO improves survival is awaited from the multi-center randomized control trial TOTAL (tracheal occlusion to accelerate lung growth)[9]. Regardless, FETO carries significant risks including pre-term rupture of membranes (47.1%) with delivery before 34 weeks in 30.9% or before 32 weeks in 17.1%. Other complications include chorio-amnionitis (2.4%) and neonatal mortality and tracheal morbidity due to difficulties with balloon removal (4.8%). With survival reaching 50% at best ultimately new treatments need to be pioneered[7].

Postnatal outcome can be predicted by the severity of antenatal PH which leads to respiratory insufficiency in the neonate [10]. Persistent pulmonary hypertension of the newborn (PPHN) is a second major factor determining outcome that lacks adequate treatment[11]. This is due to a combination of pre-natal pulmonary vascular hypoplasia with vascular remodeling and altered pulmonary artery responsiveness to various vaso-active
mediators in the CDH lung[12][13][14][15]. These unresolved factors have resulted in an unacceptable mortality rate despite in utero referral to a high volume center offering standardized neonatal care [16].

There are several well-established animal models of CDH whose lung development mimics the pulmonary hypoplasia seen in the human condition[17]. This review will focus on those models which have been most widely investigated in pre-natal intervention, namely the nitrofen (NF) rat, the rabbit and sheep. The herbicide NF if given by gastric gavage at a specific gestational age in pregnant rats induces diaphragmatic hernia in up to 50% of fetuses[18]. This model has the advantage that there is a resulting independent lung and diaphragmatic defect in the embryological stage of lung development mimicking the “dual-hit” seen in humans[19]. The creation of a diaphragmatic defect in the rabbit and lamb is most commonly during the pseudoglandular stage of lung development[20][17]. Although pulmonary hypoplasia is directly secondary to the surgical defect, rabbits and sheep have the advantage that their lung development is more similar to humans; unlike in rats where they alveolize prior to birth[21][22][23].The aim of this systematic review is to identify published pre-clinical research on the medical treatment of PH in the setting of congenital diaphragmatic hernia.
METHODS

This systematic review is structured in line with the previous guidance provided in the PRISMA statement (Preferred Reporting Items for Systematic reviews and Meta-analyses)[24].

Literature search

A complete computerized literature search will be conducted using MEDLINE (Pubmed), Embase and the Web of Science including all studies from the earliest date to August 2014. The electronic search strategy will include both Medical Subject Headings (MeSH) and keywords. Mendeley will be used to eliminate duplicate reports. Reference lists and topic-related reviews will be checked manually to identify further relevant papers.

Inclusion and exclusion criteria

Studies taking place in animal models of CDH undergoing antenatal treatment to reverse pulmonary hypoplasia preferably with a confirmed diaphragmatic defect will be included. In case of missing information, corresponding authors will be contacted and asked to provide additional data. Outcomes measures will include reporting of lung to body weight ratio (LBWR), formal airway morphometry or an alternative method of airway morphology (radial alveolar count (RAC)). Studies which report only vascular morphometry will be excluded. Control groups will be documented. Letters, in vitro studies, review articles and abstracts are excluded.

Selection of Studies
Study titles and abstracts will be screened by one author (MPE) to identify the relevant articles. Foreign language articles were included. Relevant articles will then be independently reviewed by two authors (MPE/ FMR) according to the inclusion criteria, quality assessment and risk of bias. Disagreements between the reviewers will be resolved by discussion with the third author (JD). The Kappa between the first 2 authors and then with the third author will be calculated. In case of overlapping studies, only the largest and most complete data set will be included.

**Quality Appraisal**

Study quality and risk of bias will be assessed using a quality checklist developed by the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) group ([www.camarades.info](http://www.camarades.info))[25].

**Data Extraction**

A pre-designed form will be used for independent data extraction by two authors (MPE/FMR). Data extracted included information on the authors, the animal species and gestational day (GD) of diaphragmatic hernia induction with information on the type, GD, route and duration of treatment noted. Outcome measures will be recorded as noted in inclusion criteria.
References


