Multi-Centre Prospective Cohort Study of Diaphragmatic Defect Phenotype and Repair in Neonates with Congenital Diaphragmatic Hernia: “The Defect Study”

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Study Protocol

Introduction

Congenital diaphragmatic hernia (CDH) occurs in 2.3/10,000 live births in Europe(1). Currently neonatal survival is around 65% in expert centres, the majority of those who succumb doing so due to pulmonary hypertension and respiratory insufficiency(2). It is hoped that novel antenatal therapies such as Fetal Endoscopic Tracheal Occlusion (FETO) will improve survival (3,4). Of patients treated in utero, the majority (75%) require a patch postnatally to close the defect (5,6). The reported postnatal patch rate is 23% in the population covered by the CDH registry(7).

The rapidly expanding rib cage of the infant, particularly within the first two years of life, challenges the diaphragmatic repair(8). Re-herniation occurs with both primary closure (4%) and patch closure (27%) (6). The CDH working group report an early (in-hospital) recurrence rate of 2.3% which was associated with larger defect size and surgical approach(9). Patch rate varies greatly between centres and some advocate liberal patch use (54%) contributing to a low re-herniation rate (5.4%) (10). Primary repair has been traditionally preferred but there is suggestion that tension free repair may reduce previously cited complications. Using the patch as a cone or dome with an overlapping border has also been suggested to reduce early recurrence(11,12). Other complications are more frequent in children following patch closure compared to primary repair such as bowel obstruction (12 vs. 6%), scoliosis (10 vs. 0%), chest wall deformities (14 vs. 6%) and gastro-oesophageal reflux(6,13).

There have been attempts to standardise intra-operative reporting on defect size. The CDH Study Group (2008) suggested the A, B, C, D method (Figure 1) of reporting defect size(14). However, a post mortem study with a prospective limb suggested that the nature of the defect is more complex than an absolute grading system (15). Ackerman et al (2007) reviewed 53 autopsy records of children with CDHs; only 67% fitted the classical posterior lateral category (15). Further to this, they prospectively studied 41 patients undergoing repair of a diaphragmatic defect; 34 of these described as posterior lateral by the surgeon. However, defects showed considerable variability in location, size and presence of diaphragmatic tissue along the chest wall when a diagrammatic visual reporting form was used(15).

Multiple working groups have published guidelines for physiological parameters related to timing of surgery and outcomes; there remains huge variability between centres (2,16–19). Parameters relate mainly to arterial BP, preductal saturations, PaCO₂, lactate and urine output. A study by the British Association of Paediatric Surgeons Congenital Anomalies Surveillance System (BAPS-CASS) group...
reported on postnatal use of vasodilators and inotropes, demonstrating that they predict mortality at one year in their cohort(20). Moreover, the CDH Study Group have already demonstrated that defect size is the greatest predictor of overall morbidity, length of hospital stay and duration of ventilation(21). A description of current practice will provide contemporaneous information around the timing and modality of surgery and the use of selected parameters that might act as a proxy for defect size.

In the United Kingdom (UK), the BAPS-CASS study reported use of a patch as proxy for defect size; this study was designed prior to CDH Study Group grading recommendations (April 2009)(20). They reported higher rates of chylothorax when synthetic patches were used(20). Currently, there is no consensus on the patch material to use or the best shape of patch. The majority of centres use Gore-Tex® (expanded polytetrafluoroethylene (PTFE), W.L Gore and associates, Arizona, USA), alternatives such as Permacol™ (Medtronic, Minneapolis, MN, USA) cross-linked acellular porcine dermal collagen (22), AlloDerm® (BioHorizons, Birmingham, AL, USA) non-cross-linked acellular human cadaveric dermis(23) and Surgisis® (SIS, Cook Biotech Inc, IN, USA) porcine small intestinal submucosa(24) have been reported. BAPS-CASS did not report on variables involved in diaphragmatic closure (i.e. suture type) or technique such as use of a dome at the time of closure(20). They were also unable to comment on the impact of minimally invasive repair due to low numbers.

To our knowledge, there are no prospective international collaborations that objectively describe defect size intra-operatively and combine this with the decision to patch (technique and material). Furthermore, we aim to provide information on current practice on timing of surgery.
Primary Aim

1. To objectively describe diaphragmatic defects at the time of neonatal CDH repair in UK, New Zealand and Irish centres over two years
2. To describe the diaphragmatic repair methods used for neonatally repaired congenital diaphragmatic hernias
3. To describe the observed pre-operative physiological parameters related to timing of surgery and their relationship to intraoperative defect size

Secondary Aim

1. To report complications requiring operative management, particularly recurrence rate, at 12 months following repair
Methods and Analysis

We will establish an international, multi-centre prospective cohort service evaluation with data collection from specialist children’s surgical care providers (collaborators). We will invite all centres undertaking neonatal surgery in UK (n=24), Republic of Ireland (n=1) and New Zealand (n=4) to enter patients over a 24-month period, with a 12-month follow-up period.

Pilot study

A national three-centre feasibility pilot was carried out to inform the wider study(25). Twelve patients were included over a 4-month period. Data collection variables (n=47) were refined, and poorly reported variables were studied to improve data quality and completeness. Intra-operative reporting was encouraged with development and refinement of a data collection sheet (Appendix 1).

Patient selection

We will include all live born infants, diagnosed either antenatally or postnatally with CDH, undergoing defect closure. We would exclude patients who die prior to a primary repair, present beyond the neonatal period i.e. >44 weeks corrected gestational age, present with eventration or congenital hiatal hernia.

Consecutive patients will be identified primarily by the local lead collaborator (registrar or resident) in each centre on a weekly basis. Monthly reporting of patient inclusions or eligibility will be prompted by the lead study team (JB, SO).

Data collection

Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools(26,27). REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources. A REDCap number will be assigned to each patient at the local center (held in the local hospital server) and patient information (non-identifiable) will be entered into the application’s data collection form(28–30). Data collected will include demographics (sex, gestational age (GA) at delivery, birth weight, observed to expected lung to head ratio (O/E LHR %), fetal intervention, day of life at repair), peri-operative data (use of inotropes and extracorporeal
membrane oxygenation (ECMO), defect size, ipsilateral hemithorax measurement and defect repair technique) and post-operative data (days and type of ventilatory support, length of stay, early complications and management). Reporting of defect size will be reported in line with international recommendations and a data collection form (Appendix 1) will aid intraoperative reporting(14,15).

The hand-drawn defect diagram can be uploaded to the REDCap database. One year follow-up data will be requested to identify medium term complications.

Statistical analysis

The GA, Observed/Expected Lung Head Ratio (%) at 20 weeks, lung volume (on fetal Magnetic Resonance Imaging) and weight at birth will be described as median and interquartile range (IQR). Frequency of use of inotropes, and ECMO will be described numerically (%) as categorical variables. Location of diaphragmatic defect, CDH Study Group grade of defect, laterality, liver position, surgical approach and material used for patch will be described as categorical variables.

The area of the defect will be calculated using $a \times b \times \pi$ where $a$ is half of the sagittal measurement and $b$ is half of the coronal measurement. This approximation of area will be displayed as a histogram and described as median, IQR and range. The use of a patch will be compared with area of defect using univariate logistic regression analysis. Measuring the affected hemithorax will give an estimation of percentage loss of diaphragmatic tissue. This will be compared to the hand-drawn defect (data collection form) from REDCap. The early and late complications seen in these patients will be described. Univariate logistic regression analysis will be performed to assess for the association between measured pre-operative and peri-operative variables and any occurring complications. Those with a suggestion of strong association ($p<0.05$) will be entered into a multi-variate regression analysis. Variables will be removed sequentially, starting with the variable with the lowest probability of association to assess for statistical changes in the multivariate model. We do note that this study is not powered to look at this association, but the identification of important variables may help to inform future research.

Sample size calculation

Projected numbers (Table 1) were calculated on the UK (2017), Ireland (2019) and New Zealand (2016) live birth rate (Table 1)(31,32). EUROCAT data was used to predict CDH births with survival predicted at 65% (1,2). Patch rate was taken from the UK BAPS-CASS Study (n=52 patches; n=182 patients) (20).
Therefore, we would expect to include n=261 patients, 77 with patch repair to describe between 10-20 recurrences(5).

**Ethics and dissemination**

This study is proposed as a service evaluation as suggested by the Health Research Authority (HRA) decision making tool(33). Intra-operative measurement of diaphragmatic defects is routinely used in many centres to assess the size of a patch needed. HRA guidance states that service evaluation is “designed and conducted solely to define or judge current care” and “measures current service without reference to a standard”. Therefore, service evaluation does not require “research ethics committee review”. The study will be registered as service evaluation at participating centres(33).

The results will be submitted for presentation at international forums (The British Association of Paediatric Surgeons (BAPS), European Association of Paediatric Surgeons (EUPSA) and National Research Collaborative meeting (UK)). We would aim to publish in a peer-reviewed journal namely the Journal of Pediatric Surgery. Patient support groups (namely CDH-UK) are supportive of the study and provide a potential platform for dissemination of results to patients and families affected by CDH(34).
Table 1: Sample size calculation based on the UK (2017), Ireland (2019) and New Zealand (2016) live birth rate

<table>
<thead>
<tr>
<th>Country</th>
<th>Live Births</th>
<th>Over 24-months (number of patients)</th>
<th>CDH Births</th>
<th>CDH Survivors</th>
<th>Repair</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Primary</td>
<td>Patch</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>755,066</td>
<td>346</td>
<td>225</td>
<td>160</td>
<td>65</td>
</tr>
<tr>
<td>Ireland</td>
<td>61,016</td>
<td>28</td>
<td>18</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>NZ</td>
<td>59,430</td>
<td>27</td>
<td>18</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>401</td>
<td>261</td>
<td>184</td>
<td>77</td>
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References


22. Mitchell IC, Garcia NM, Barber R, Ahmad N, Hicks BA, Fischer AC. Permacol: a potential


34. CDH UK – CDH UK consists of families, friends and medical professionals affected by Congenital Diaphragmatic Hernia [Internet]. [cited 2021 Nov 9]. Available from: https://cdhuk.org.uk/
Data Collection Form

Patient Initials ............................
Date of Surgery ....../....../......

Diaphragmatic Measurements

i. Defect Size before repair (2 longest axis)
   a. Before dissection .......................(AP)x.................(ML) cm
   b. After dissection .......................(AP)x.................(ML) cm

ii. Affected hemidiaphragm size:
    .........................(AP)x.............................(ML) cm

CDH study group classification (circle relevant)

Please transfer all anonymized data onto the redcap form: XXX
Thank-you! ***** team

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Defect drawing: Please upload to your Redcap form

Please transfer all anonymized data onto the Redcap form: XXX
Thank-you! ***** team

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