Neonatal Endosurgical Congenital Diaphragmatic Hernia Repair

A Systematic Review and Meta-Analysis

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Objective: To compare outcomes of open and endosurgical neonatal congenital diaphragmatic hernia (CDH) repairs.

Background: Historically a surgical emergency, neonatal CDH repair is now deferred pending stabilization of characteristically labile cardiopulmonary physiology. Usually accomplished via laparotomy, surgical repair may acutely worsen lung function; conversely, by reducing the visceral hernia, surgery might improve it. Theoretically, endosurgical repair could minimize deleterious effects of surgery while garnering benefits from decompressing the CDH lung. As endosurgical repair gains popularity, it is important to investigate whether or not minimally-invasive neonatal CDH repair has benefits.

Methods: We searched Medline, Embase, and Cochrane Trials databases for studies comparing open with endosurgical CDH repair. Non-neonatal series and reports without comparison groups were excluded. References from papers and conference proceedings were also hand searched. Meta-analysis used a fixed effects model and was reported in accordance with PRISMA.

Results: We included 3 studies (1 unpublished; none randomized); all compared thoracoscopic and open CDH repair and together described 143 patients. All studies had limitations, including use of historical controls. Demographics, CDH sidedness, APGAR and associated anomaly prevalence were similar between groups. For endosurgical repair, recurrence was higher (RR: 3.2 [1.1, 9.3], $P = 0.03$) and operative time longer (WMD 50 minutes [32, 69], $P < 0.00001$). Survival and patch usage were not different between open and endosurgical groups.

Conclusions: Neonatal thoracoscopic CDH repair has greater recurrence rates and operative times but similar survival and patch usage compared with open surgery. A prospective registry for all such cases would guide development of trials (Stage 2b; IDEAL recommendations).

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The Bochdalek-type of congenital diaphragmatic hernia (CDH) is a birth defect comprising a posterolateral diaphragmatic defect, intrathoracic herniation of abdominal viscera, and varying degrees of pulmonary hypoplasia. Population-based studies have shown the prevalence of CDH to be between 1 in 2600 and 1 in 3700 live births.[1,2] Despite advances in neonatal intensive care, this condition retains a mortality rate of almost 50% and survivors have considerable long-term morbidity.[1,3–5] Much of the acute mortality is a consequence of pulmonary hypoplasia and persistent pulmonary hypertension.[6,7] Managing lung hypoplasia and its physiological consequences has therefore become central to clinical CDH research. In prenatal attempts to ameliorate pulmonary hypoplasia, pediatric surgeons have trialled fetal interventions including correction of the diaphragmatic defect in utero and fetoscopic endoluminal tracheal occlusion (FETO).[8–10] Postnatally, emergency open CDH repair was used to try to decompress the hypoplastic lung and address the characteristic respiratory failure.[11] Conversely, concerns that acute surgery may worsen both pulmonary function and physiological stability led to surgeons delaying surgery in favor of prior medical stabilization.[12] This uncertainty prompted trials to compare urgent with delayed open surgical repair of CDH. These small and hence underpowered studies failed to show a difference in survival between the 2 approaches.[13,14] Common practice is now to delay open CDH repair to allow prior stabilization of labile perinatal physiology.[15] However, it remains possible that there are survival differences between acute and delayed surgery cohorts.[16] Moreover the advent of minimally-invasive surgery (MIS) raises the possibility that earlier endosurgical CDH repair may reap some of the putative gains (decompressing the hypoplastic lung) with less of the adverse physiological sequelae associated with open surgery.

Traditionally, open surgical CDH repair has been accomplished via thoracic or abdominal approaches (Fig. 1A).[17] Laparotomy has been argued to be advantageous compared with thoracotomy for CDH repair: the former allows mobilization of the posterior rim of the diaphragmatic defect to facilitate closure; laparotomy also allows easy management of midgut rotational anomalies if required[18]; neonatal thoracotomy is associated with later musculoskeletal deformity.[19] Subcostal laparotomy is now the most commonly used mode of access (91% of cases in one study).[15] However, studies have yielded conflicting results regarding the physiological and, in particular, respiratory sequelae of open CDH repair. Major et al reported that lung volume, pulmonary mechanics, and oxygenation are all improved when early CDH repair is performed in a lamb model.[20] However, Sakai et al found that respiratory compliance was reduced following open surgical repair and when this reduction was >50%, the outcome was universally fatal.[21] Furthermore, open CDH repair via laparotomy may be associated with early problems such as requirement for prosthetic patch abdominoplasty and later complications including adhesive bowel obstruction.[22,23] Hence while laparotomy for neonatal CDH repair can be seen as a "gold-standard," concerns persist over its optimum timing as well as its acute and late effects.

Minimally invasive surgery (MIS) has been argued to reduce the trauma and physiological disturbance of surgery.[24] It has also been suggested that MIS can ameliorate postoperative pain, improve outcomes and enhance cosmesis.[25] Silen reported the first minimally invasive repair of a Bochdalek-type CDH in 1995.[26] However, this was undertaken thoracoscopically in an adolescent patient expected to be free of the cardinal physiological lability encountered in newborn CDH. MIS for the newborn infant has evolved over a period of more than 15 years facilitated by technological improvements in instrumentation and optics as well as better understanding

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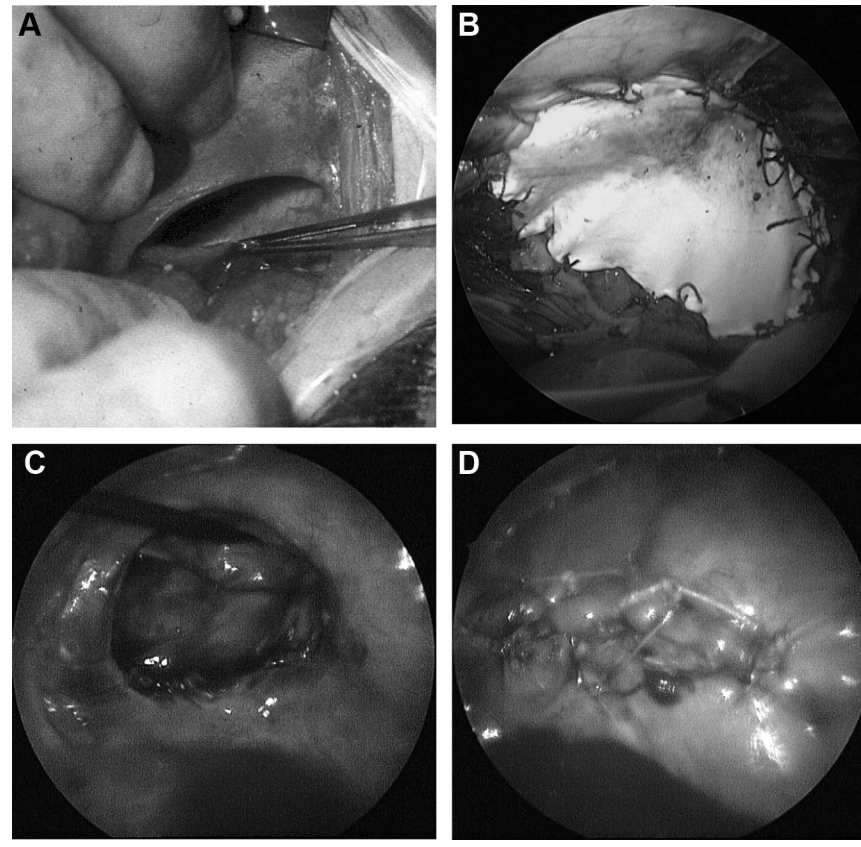

FIGURE 1. (A) Mobilization of the posterior rim of the diaphragmatic defect (held in forceps) seen from below as part of laparotomy for CDH repair (courtesy of PD Losty); (B) Laparoscopic patch repair of infant right-sided CDH (courtesy of EC Jesudason); Thoracoscopic view of left-sided neonatal CDH before (C); and after (D) repair (courtesy of EC Jesudason).

of the physiological effects of surgery in the newborn.[27] Neonates undergoing surgery are vulnerable to hypothermia and acidosis: concerns have been raised that the CO_2 insufflation for MIS may exacerbate both.[28] Newborns with CDH have a restricted ability to excrete CO_2 via their hypoplastic lungs and this may render them particularly vulnerable to acidosis during CO_2 insufflation. Similarly CO_2 insufflation into thorax and abdomen raises the intracavity pressures (and may cool the patient). Anesthetists caring for CDH newborns may respond to these 2 issues by raising minute volumes and airway pressures, respectively. Given the catastrophic effects of barotrauma on the hypoplastic lung, both of these ventilatory responses to CO_2 insufflation may potentially be harmful.[29,30] Pediatric surgeons have therefore moved with some trepidation towards MIS for the repair of neonatal CDH.

In 1998, Rothenberg described his experience with MIS in infants and this included 2 laparoscopic repairs of Bochdalek-type CDH.[31] Subsequent reports of endosurgical CDH repair in the newborn have been dominated by thoracoscopic rather than laparoscopic approaches (Fig. 1B–D).[32–41] Some of these authors expressed concerns about hypercapnea, acidosis, and frequent conversions to open surgery: they have advocated restricting endosurgical CDH repair to selected cases.[34,35] However, other surgeons have argued that MIS is applicable to the majority of CDH newborns with potential for swifter recovery and reduced postoperative pain.[39,41]

CDH is a common birth defect in neonatology and pediatric surgical practice. In the context of persistently high morbidity and mortality, varied pre- and postnatal surgical strategies have been tried with limited success. To different degrees these strategies have been evaluated via registry databases, small trials and systematic review. MIS approaches to neonatal CDH repair are emerging across the wider pediatric surgical community. We have therefore asked whether MIS approaches to neonatal CDH repair are associated with changes in survival, CDH recurrence risk, operative time, and/or prosthetic patch usage. To address these questions, we have performed a systematic review and meta-analysis of studies that compares survival, CDH recurrence risk, operative time and prosthetic patch usage between CDH neonates whose repair was approached by MIS and those where it was undertaken by open surgery.

METHODS

The systematic review and meta-analysis was reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[42]

Information Sources and Search Technique

MEDLINE (1950 to present), Embase (1980 to present) and Cochrane Controlled Trials Register databases were searched using the keywords 'diaphragmatic hernia AND thoracoscopic,' 'diaphragmatic hernia AND laparoscopic,' and 'diaphragmatic hernia AND minimally-invasive.' Relevant conference proceedings were also searched for abstracts of appropriate studies. Finally, citations of relevant full text reports were hand-searched for any additional studies. Duplicate studies were excluded at this point. The date of the last electronic search was 1st October 2009.

Eligibility Criteria and Study Selection

Studies were eligible for inclusion in the review and meta-analysis if they directly compared open and endosurgical CDH repair in the newborn infant and included outcome data regarding survival, CDH recurrence, prosthetic patch use, and operative time. Studies were excluded if they reported cases that were operated on outside of the neonatal period or did not provide sufficient demo-

graphic or outcome data (despite contacting the authors with an additional data request). There were no language or publication date exclusion criteria (beyond those constraints inherent in the databases themselves). Two independent reviewers reviewed all studies in abstract form. Exclusions were only made at this point if it was absolutely clear that the above criteria were met. Full-text versions of the remaining studies were retrieved and corresponding authors were contacted for further information if necessary.

Data Collection

Data were extracted from the original study report or obtained directly from the corresponding author. The following demographic data was sought for each group: proportion of male sex, proportion with left-sided CDH, mean birth weight, mean gestational age, APGAR score at 1 minute, proportion requiring ECMO, and proportion with significant associated anomalies. The average duration of follow-up for each group was also noted.

The primary outcome measure was survival to discharge from hospital. The secondary outcome measures were: CDH recurrence rate, proportion undergoing prosthetic patching, and operative time. The number of cases in the endosurgical treatment group that required conversion to an open operation was also recorded.

Data Analysis

An intention to treat analysis was used, with cases converted to open surgery being retained in the endosurgical group. Demographic data was compared between open and endosurgical groups in each study. Categorical data was analyzed with Fisher exact test, normally distributed data with a Student t test and nonparametric data with the Mann-Whitney U test. $P \leq 0.05$ was regarded as significant.

Data meta-analysis was carried out using Review Manager (RevMan) Version 5.0 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). Weighted treatment effect was calculated using the fixed effects model. Treatment effect sizes were calculated and presented as relative risk (RR) for dichotomous variables and weighted mean difference (WMD) for continuous variables; along with 95% confidence intervals in each case. Statistical heterogeneity was assessed using a χ^2 test and the I^2 statistic used to assess the impact of heterogeneity on the meta-analysis.

RESULTS

Study Selection

The electronic search identified a total of 292 studies. Exclusions were made as detailed in the flow chart (Fig. 2). Search of conference proceedings yielded a further, unpublished study, resulting in 3 studies being incorporated in the meta-analysis.[39,41,43]

Study Characteristics and Risk of Bias

No randomized controlled trials were found. The 3 included studies compare series of neonatal thoracoscopic and open CDH repairs performed at the same institutions.[39,41,43] All are limited by their methodology, primarily due to the control (open surgery) groups being historical; there is therefore significant risk of case selection and performance bias. Gourlay et al selected a historical control group of comparable size to match features of those in their thoracoscopic group: therefore they required that included controls had no associated congenital cardiac anomaly, no preoperative ECMO, and were similar to the thoracoscopic group for 2 preoperative ventilatory parameters.[41] The studies from Cho et al and Giacomello et al did not actively match the control (open surgical repair) group to the thoracoscopic group.[39,43] The 3 studies include a total of 143 patients and data from all of these were included in the meta-analysis. The decision to exclude other studies was straightforward (eg, non-neonatal series, no control group reported, isolated case reports). Given the small number of eligible studies we have not performed a funnel plot to screen for publication bias.[44]

Analysis of Demographic Data

Analyzing the demographic data in each study, there were no statistically significant differences in proportion of male sex, mean birth weight, proportion of left sided CDH, or proportion of cases with significant associated anomalies between open and endosurgical groups. There were no significant differences in APGAR score at 1 minute or mean gestational age between groups in 2 of the studies, but this data was not available from Giacomello et al.[43] In the study by Cho et al, there was a higher ECMO requirement in the open surgery group (8/28 [29%] vs. 2/29 [6.9%] $P = 0.04$).[39] The duration of follow-up was longer in the open surgery group of all 3 studies.

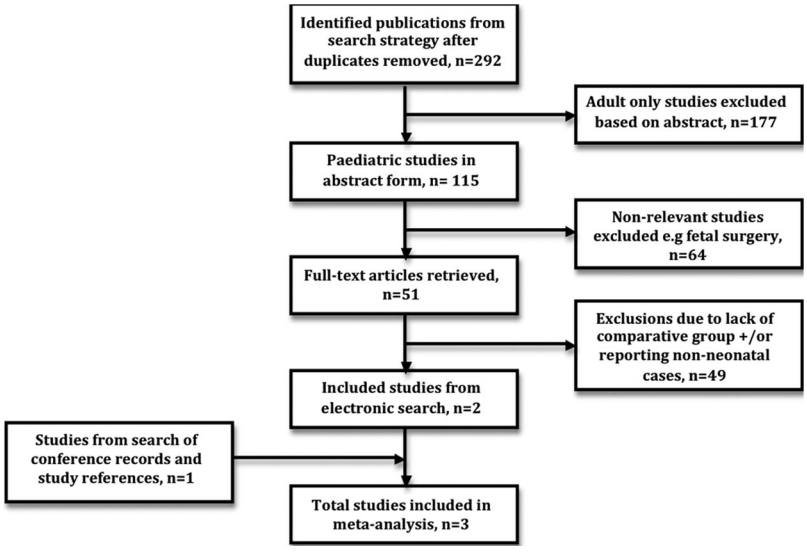

FIGURE 2. Flow chart demonstrating the process of study selection.

Analysis of Outcome Data

Results from the individual studies for the primary and secondary outcome measures are included in forest plots (Fig. 3). Meta-analysis reveals that recurrence was higher (RR: 3.21 [1.11, 9.29], $P = 0.03$) and operative time was longer (WMD: 50.38 minutes [31.79, 68.97], $P < 0.00001$) in the endosurgical group. There was no statistically significant difference in survival to discharge (RR of death: 0.33 [0.10, 1.13], $P = 0.08$) or prosthetic patch usage (RR: 1.01 [0.67, 1.50] $P = 0.98$). The assessments of data heterogeneity and its impact on the meta-analysis (χ^2 test and I^2 statistic, respectively) are included in the forest plots (Fig. 3).

There were 6 (14.3%) conversions to open surgery in the endosurgical groups of 2 of the studies.[39,43] The rate of conversion was significantly higher in studies by Giacomello et al versus Cho et al (5/13 [38%] vs. 1/29 [3.4%] $P = 0.0074$).[39,43] The remaining study describes one case of thoracoscopic repair requiring conversion to open surgery, but this was not included in the overall comparative study and the authors only report outcome data on successful thoracoscopic repairs.[41] This issue affects our analysis in terms of intention to treat, but this effect is reportedly limited to only the one case.

DISCUSSION

This meta-analysis illustrates that thoracoscopic neonatal CDH repair is currently associated with higher CDH recurrence risk and longer operative times compared with open CDH repair. Mortality and rate of prosthetic patch repair following open and thoracoscopic surgery appears similar. However, these findings need to be considered in the context of the methodological limitations of the studies available for inclusion; for each outcome measure, we will discuss the potential for bias and other confounding factors.

We restricted our study to neonatal CDH repair because it is in this newborn population that labile cardiopulmonary physiology predominates and threatens survival; hence it is this group where choice of surgical approach may have greatest impact on mortality. Endosurgical CDH repair is a relatively new technique. Failure to report poorer outcomes from preliminary experiences may adversely influence our meta-analysis: screening for such publication bias using funnel plot asymmetry is however inappropriate given the paucity of eligible studies.[44] None of the incorporated studies were prospective, double-blind randomized controlled trials (RCTs). Lack of blinding renders the studies' findings vulnerable to selection bias (eg, undertaking standard open surgery in perceived high-risk cases). Use of even recent historical control groups allows the

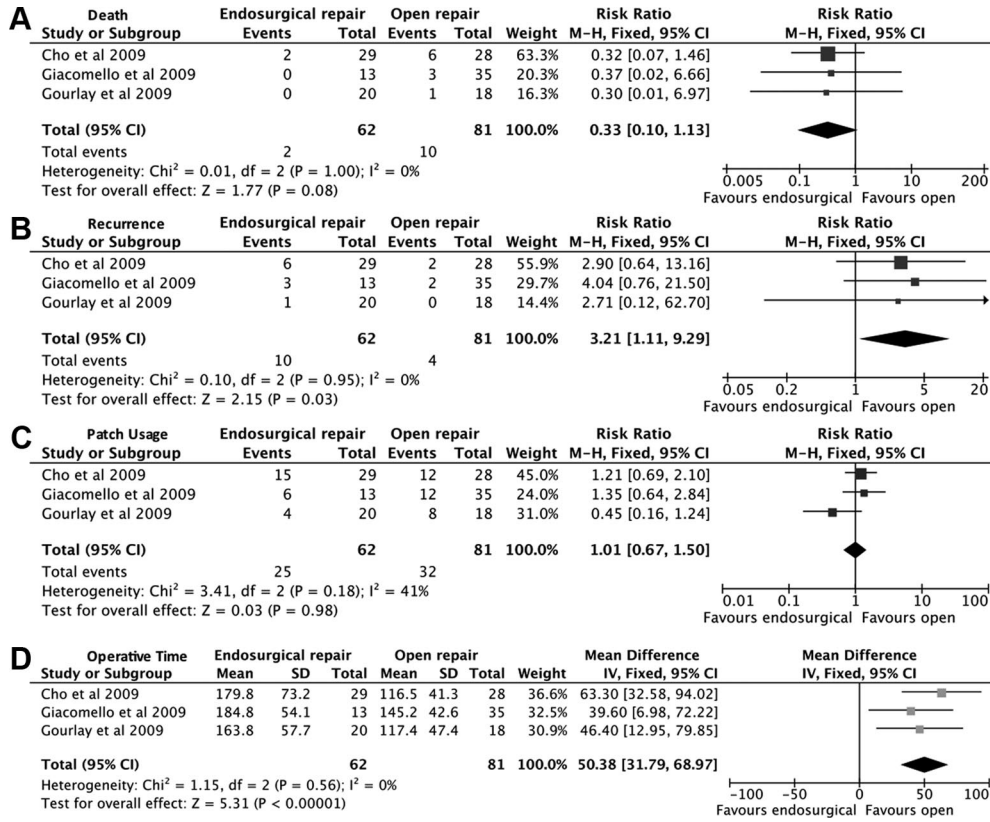

FIGURE 3. Forest plots comparing the outcome measures: (A) death, (B) CDH recurrence, (C) prosthetic patch usage, and (D) operative time, for endosurgical and open surgery groups. The plots illustrate the raw data for each study (as 2 × 2 tables for dichotomous variables and as the mean, standard deviation, and sample size for continuous variables). They give point estimates and confidence intervals for the relative risk (dichotomous variables) and weighted mean difference (continuous variable) both as blocks and lines, and as text. They illustrate the meta-analysis both as a diamond and as text. The total numbers of participants (including total number of events for dichotomous variables) in the endosurgical and open surgery groups are shown. Heterogeneity statistics (χ^2 test and I^2 statistic) are presented, percent weights given to each study, and a test for overall effect provided (along with statistical significance).

possibility for performance bias (eg, alterations in other features of CDH management to influence outcomes). Retrospective data collection may also limit the accuracy and availability of data for the studies included. All eligible studies compare thoracoscopic versus open CDH repair: we were therefore unable to compare laparoscopic CDH repair and open surgery in this meta-analysis. Among the 3 studies eligible for analysis, testing revealed minimal heterogeneity for the outcomes of survival, CDH recurrence and operative time and modest heterogeneity for prosthetic patch usage.

Survival

This meta-analysis fails to show a significant difference in survival between endosurgical and open CDH repair. However, the analyzed studies report small numbers of cases and are therefore vulnerable to type 2 error (failure to detect a real difference). It may be claimed that there is a nonsignificant trend toward higher survival rates in the thoracoscopic group. In contrast, as reviewers we would emphasize that (1) there is at present no significant difference in survival between the open and endosurgical groups and (2) vulnerability to selection and performance bias undermines claims to the contrary. For example, surgeons may have favored open surgery for higher risk, more unstable cases: in the study of Cho et al the open surgery group had higher ECMO requirement than the thoracoscopic group. Over the 3 studies, half of all postoperative deaths occurred in this single selected group.[39] Such selection bias would reduce the apparent mortality of the thoracoscopic approach. Furthermore, some authors have explicitly sought to select lower risk cases for endosurgical repair using a variety of potentially favorable criteria such as ventilatory stability and absence of pulmonary hypertension, stomach and / or liver herniation.[35,40] Future randomized trials of endosurgical CDH repair will need to resolve how best to stratify CDH cases according to risk of mortality: this may involve markers such as APGAR score, liver herniation, oxygen index and / or the CDH Study Group equation.

CDH Recurrence

Our meta-analysis estimates a 3-fold increased risk of recurrent herniation in the group undergoing thoracoscopic CDH repair. Higher recurrence risk may be an anticipated consequence of the learning curve: eg, thoracoscopic CDH repair uses skills such as intracorporeal suturing in the limited working space of the neonatal hemithorax.[45] The thoracoscopic approach may also not allow as complete mobilization of native diaphragmatic tissue (from the inferior surface of the posterior rim of the defect) compared with that achieved via subcostal laparotomy. This technical difference may therefore mean that thoracoscopically placed sutures and patches are secured to less substantial tissue. Therefore the observed difference in recurrence risk between thoracoscopic and open surgical groups has plausible technical explanations. However, there are reasons our study may even underestimate the recurrence risk. For example, the duration of follow-up is shorter for the thoracoscopic groups than the open groups in all 3 studies. Second, publication bias may mean series with high recurrence rates remain unreported. Third, as discussed above, surgeons may have selected poorer prognosis cases for open surgery; higher-risk cases have been associated with larger diaphragmatic defects[46]; if larger defects increase recurrence risk, selection bias might also be expected to underestimate the recurrence risk in the thoracoscopic surgery group. Hence, the increased recurrence risk for thoracoscopic CDH repair has both plausible surgical explanation and reasonable expectation that this risk is currently underestimated. It remains to be determined if this excess recurrence risk will reduce as surgeons progress along the learning curve and become more familiar with the technical steps involved. At the same time increased adoption of thoracoscopic CDH repair may see the overall number of endosurgical recurrences rise even as surgeons' individual recurrence rates fall. Such factors are recognized to complicate decisions on timing for trials of new techniques such as thoracoscopic CDH repair: if the new technique is trialled too early it may fail to achieve its potential and trial recruitment may be limited to unrepresentative early adopter surgeons and/or centers; however, if trials are undertaken too late, it may be difficult for participants to maintain equipoise within the study.[47] Statistical methods to monitor surgical performance have been devised that may help inform these decisions.[48,49]

Prosthetic Patch Usage

There was no significant difference in prosthetic patch usage between open and endosurgical groups. Given the numbers of cases and number of patches used, this comparison may again be susceptible to type 2 error. Furthermore, if poorer preoperative physiology is associated both with larger diaphragmatic defects and preferential selection for open surgery, then selection bias may underestimate the need for patch placement in the thoracoscopic group.[46] As discussed above, the thoracoscopic approach may permit less complete mobilization of native diaphragmatic tissue (furled inferior to the posterior rim of the defect). Hence, for a given defect size, thoracoscopic repair may plausibly increase the risk of patch usage compared with open repair. Therefore, while we have demonstrated no significant difference in patch usage between groups, selection bias could obscure a surgically plausible increased risk in the thoracoscopic group. In contrast to the other outcomes examined, data on patch usage rates showed some heterogeneity between the included studies. Furthermore, rates of patch usage can depend on subjective assessment of need by the operating surgeon. Hence some of the observed heterogeneity may result from the influence of surgeon preference on rate of patch usage.

Operative Time

This meta-analysis indicates that thoracoscopic CDH repair takes longer to perform than open surgery for CDH (with a weighted mean difference of more than 50 minutes). This finding is consistent with other comparisons of pediatric MIS versus open surgery.[50–52] The clinical significance of increased operative time is unclear: while survival and recurrence risk appear similar between open and thoracoscopic groups, increased operative time may be viewed as undesirable in physiologically labile CDH newborns. Anticipation of longer endosurgical operations may therefore reinforce selection bias as surgeons avoid thoracoscopic surgery in CDH cases perceived to be at higher risk. Previous experience with MIS indicates that operative times (and hence, perhaps, selection bias) are likely to fall as surgeons' expertise with endosurgical CDH repair improves.[53]

Future Considerations

Innovation is a key theme in the history and development of modern surgery. The proliferation of MIS has challenged the role of several open surgical techniques.[54] However, adoption of, and evidential support for, MIS alternatives remains highly variable. Recently published IDEAL guidelines represent a consensus statement that seeks to provide a practical framework for the rigorous evaluation of surgical innovation.[47] IDEAL stages of surgical innovation progress through Idea, Development, Exploration, Assessment to Long-term study. The IDEAL initiative is a welcome and timely response to concerns about surgical innovation in the context of the modern patient safety agenda. Endosurgical CDH repair currently conforms to IDEAL Stage 2b where the new technique has been adopted by a number of surgeons but experience may still be limited. At this IDEAL stage it is recommended that data be captured systematically for every patient having the new procedure. Examples of resources that might be adapted to collect such data on thoracoscopic CDH repair range from the US Agency for Healthcare

Research and Quality (AHRQ) to the British Association of Pediatric Surgeons Congenital Anomalies Surveillance System (BAPS-CASS).[55,56] The CDH Study Group Registry is the leading disease specific international database (prospectively compiled over 14 years and including over 4000 cases); it affords important opportunities for CDH research in general and evaluation of endosurgical CDH repair in particular.[15,57] Hence a prospective international, multi-institutional research database for endosurgical CDH repair could ameliorate effects of selection, performance and publication biases and facilitate RCT development by highlighting adverse effects of the novel procedure, providing data for risk-stratification of CDH cases, improving quality of parent information and delineating the learning curve for neonatal thoracoscopic CDH repair.[47]

CONCLUSIONS

This meta-analysis of methodologically limited comparative studies indicates neonatal thoracoscopic CDH repair has increased recurrence risk and operative time compared with open repair: although survival and patch usage appear comparable, such similarities may be subject to type 2 error as well as biases. Better quality evidence is therefore required. Systematic reviews and meta-analyses frequently conclude with calls for more randomized controlled trials (RCTs). In contrast, we call for prospective, comprehensive, multi-institutional registry data on neonatal endosurgical CDH repair. IDEAL guidelines emphasize that such registry data enhances the development and design of subsequent RCTs.[47]

With its high mortality, management of CDH remains a challenge: theoretically, MIS correction of CDH could help by reducing the physiological perturbation of surgery while still alleviating any compression of the hypoplastic lung by the visceral hernia. Via registry data on endosurgical CDH repair and consequent well-designed RCTs, pediatric surgeons should test this important potential for the benefit of vulnerable CDH newborns.

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REFERENCES

1. Colvin J, Bower C, Dickinson JE, et al. Outcomes of congenital diaphragmatic hernia: a population-based study in western Australia. *Pediatrics*. 2005;116:E356–E363.
2. Gallot D, Boda C, Ughetto S, et al. Prenatal detection and outcome of congenital diaphragmatic hernia: a French registry-based study. *Ultrasound Obstet Gynecol*. 2007;29:276–283.
3. Levison J, Halliday R, Holland AJ, et al. A population-based study of congenital diaphragmatic hernia outcome in New South Wales and the Australian Capital Territory, Australia, 1992–2001. *J Pediatr Surg*. 2006;41:1049–1053.
4. Muratore CS, Kharasch V, Lund DP, et al. Pulmonary morbidity in 100 survivors of congenital diaphragmatic hernia monitored in a multidisciplinary clinic. *J Pediatr Surg*. 2001;36:133–140.
5. Stege G, Fenton A, Jaffray B. Nihilism in the 1990s: the true mortality of congenital diaphragmatic hernia. *Pediatrics*. 2003;112:532–535.
6. Smith NP, Jesudason EC, Featherstone NC, et al. Recent advances in congenital diaphragmatic hernia. *Arch Dis Child*. 2005;90:426–428.
7. van den Hout L, Sluiter I, Gischler S, et al. Can we improve outcome of congenital diaphragmatic hernia? *Pediatr Surg Int*. 2009;25:733–743.
8. Harrison MR, Adzick NS, Bullard KM, et al. Correction of congenital diaphragmatic hernia in utero VII. A prospective trial. *J Pediatr Surg*. 1997;32:1637–1642.
9. Harrison MR, Keller RL, Hawgood SB, et al. A randomized trial of fetal endoscopic tracheal occlusion for severe fetal congenital diaphragmatic hernia. *N Engl J Med*. 2003;349:1916–1924.
10. Deprest JA, Gratacos E, Nicolaides K, et al. Changing perspectives on the perinatal management of isolated congenital diaphragmatic hernia in Europe. *Clin Perinatol*. 2009;36:329–347.
11. Firor HV. Surgical emergencies in newborns and infants. *Surg Clin North Am*. 1972;52:77–98.
12. Langer JC, Filler RM, Bohn DJ, et al. Timing of surgery for congenital diaphragmatic hernia—is emergency operation necessary? *J Pediatr Surg*. 1988;23:731–734.
13. Nio M, Haase G, Kennaugh J, et al. A prospective randomized trial of delayed versus immediate repair of congenital diaphragmatic hernia. *J Pediatr Surg*. 1994;29:618–621.
14. delaHunt MN, Madden N, Scott JE, et al. Is delayed surgery really better for congenital diaphragmatic hernia? A prospective randomized clinical trial. *J Pediatr Surg*. 1996;31:1554–1556.
15. Clark RH, Hardin WD, Hirschl RB, et al. Current surgical management of congenital diaphragmatic hernia: a report from the congenital diaphragmatic hernia study group. *J Pediatr Surg*. 1998;33:1004–1007.
16. Moyer V, Moya F, Tibboel R, et al. Late versus early surgical correction for congenital diaphragmatic hernia in newborn infants. *Cochrane Database Syst Rev*. 2002:CD001695.
17. Harting MT, Lally KP. Surgical management of neonates with congenital diaphragmatic hernia. *Semin Pediatr Surg*. 2007;16:109–114.
18. Rescorla FJ, Shedd FJ, Grosfeld JL, et al. Anomalies of intestinal rotation in childhood—analysis of 447 cases. *Surgery*. 1990;108:710–716.
19. Bianchi A, Sowande O, Alizai N, et al. Aesthetics and lateral thoracotomy in the neonate. *J Pediatr Surg*. 1998;33:1798–1800.
20. Major D, Cloutier R, Fournier L, et al. Improved pulmonary function after surgical reduction of congenital diaphragmatic hernia in lambs. *J Pediatr Surg*. 1999;34:426–429.
21. Sakai H, Tamura M, Hosokawa Y, et al. Effect of surgical repair on respiratory mechanics in congenital diaphragmatic hernia. *J Pediatr*. 1987;111:432–438.
22. Dagostino JA, Bernbaum JC, Gerdes M, et al. Outcome for infants with congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation—the first year. *J Pediatr Surg*. 1995;30:10–15.
23. Schnitzer JJ, Kikiros CS, Short BL, et al. Experience with abdominal wall closure for patients with congenital diaphragmatichernia repaired on ECMO. *J Pediatr Surg*. 1995;30:19–22.
24. Glaser F, Sannwald GA, Buhr HJ, et al. General stress-response to conventional and laparoscopic cholecystectomy. *Ann Surg*. 1995;221:372–380.
25. Nelson H, Sargent D, Wieand HS, et al. A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med*. 2004;350:2050–2059.
26. Silen ML, Canvasser DA, Kurkchubasche AG, et al. Video-assisted thoracic surgical repair of a foramen of bochdalek hernia. *Ann Thorac Surg*. 1995;60:448–450.
27. Ponsky TA, Rothenberg SS. Minimally invasive surgery in infants less than 5 kg: experience of 649 cases. *Surg Endosc Other Interv Tech*. 2008;22:2214–2219.
28. Tobias J. Anesthetic considerations for laparoscopy in children. *Semin Laparosc Surg*. 1998;5:60–66.
29. Guarino N, Teramoto H, Shima H, et al. Effect of mechanical ventilation on the pulmonary expression and production of elastin in nitrofen-induced diaphragmatic hernia in rats. *J Pediatr Surg*. 2002;37:1253–1257.
30. Wung JT, Sahni R, Moffitt ST, et al. Congenital diaphragmatic hernia—survival treated with very delayed surgery, spontaneous respiration, and no chest tube. *J Pediatr Surg*. 1994;30:406–409.
31. Rothenberg SS, Chang JH, Bealer JF. Experience with minimally invasive surgery in infants. *Am J Surg*. 1998;176:654–657.
32. Holcomb GW, Ostlie DJ, Miller KA. Laparoscopic patch repair of diaphragmatic hernias with Surgisis. *J Pediatr Surg*. 2005;40:E1–E5.
33. Shah AV, Shah A. Laparoscopic approach to surgical management of congenital diaphragmatic hernia in the newborn. *J Pediatr Surg*. 2002;37:548–550.
34. Arca MJ, Barnhart DC, Lelli JL, et al. Early experience with minimally invasive repair of congenital diaphragmatic hernias: results and lessons learned. *J Pediatr Surg*. 2003;38:1563–1568.
35. Yang EY, Allmendinger N, Johnson SM, et al. Neonatal thoracoscopic repair of congenital diaphragmatic hernia: selection criteria for successful outcome. *J Pediatr Surg*. 2005;40:1369–1375.
36. Schaarschmidt K, Strauss J, Kolberg-Schwerdt A, et al. Thoracoscopic repair of congenital diaphragmatic hernia by inflation-assisted bowel reduction, in a resuscitated neonate: a better access? *Pediatr Surg Int*. 2005;21:806–808.

37. Liem NT, Dung LA. Thoracoscopic repair for congenital diaphragmatic hernia: lessons from 45 cases. *J Pediatr Surg*. 2006;41:1713–1715.
38. Ferreira CG, Reinberg O, Becmeur F, et al. Neonatal minimally invasive surgery for congenital diaphragmatic hernias: a multicenter study using thoracoscopy or laparoscopy. *Surg Endosc*. 2009;23:1650–1659.
39. Cho SD, Krishnaswami S, McKee JC, et al. Analysis of 29 consecutive thoracoscopic repairs of congenital diaphragmatic hernia in neonates compared to historical controls. *J Pediatr Surg*. 2009;44:80–86.
40. Kim A, Bryner B, Akay B, et al. Thoracoscopic repair of congenital diaphragmatic hernia in neonates: lessons learned. *J Laparoendosc Adv Surg Tech A*. 2009;19:575–580.
41. Gourlay DM, Cassidy LD, Sato TT, et al. Beyond feasibility: a comparison of newborns undergoing thoracoscopic and open repair of congenital diaphragmatic hernias. *J Pediatr Surg*. 2009;44:1702–1707.
42. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:6.
43. Giacomello L, Nah SA, De Coppi P, et al. Thoracoscopic repair of congenital diaphragmatic hernia: intraoperative ventilation and recurrence. In: 56th Annual Congress of the British Association of Paediatric Surgeons and 10th Annual Congress of the European Paediatric Surgeons' Association; 2009; Graz, Austria.
44. Lau J, Ioannidis JP, Terrin N, et al. Evidence based medicine—the case of the misleading funnel plot. *BMJ*. 2006;333:597–600.
45. Watson DI, Baigrie RJ, Jamieson GG. A learning curve for laparoscopic fundoplication—definable, avoidable, or a waste of time? *Ann Surg*. 1996; 224:198–203.
46. Lally KP, Lally PA, Lasky RE, et al. Defect size determines survival in infants with congenital diaphragmatic hernia. *Pediatrics*. 2007;120:E651–E657.
47. McCulloch P, Altman DG, Campbell WB, et al. Surgical innovation and evaluation 3: no surgical innovation without evaluation: the IDEAL recommendations. *Lancet*. 2009;374:1105–1112.
48. Novick R, Fox S, Stitt L, et al. Assessing the learning curve in off-pump coronary artery surgery via CUSUM failure analysis. *Ann Thorac Surg*. 2002;73:S358–S362.
49. Beiles CB, Morton AP. Cumulative sum control charts for assessing performance in arterial surgery. *ANZ J Surg*. 2004;74:146–151.
50. Hamilton BD, Gatti JM, Cartwright PC, et al. Comparison of laparoscopic versus open nephrectomy in the pediatric population. *J Urol*. 2000;163:937–939.
51. Koivusalo AI, Korpela R, Wirtavuori K, et al. A single-blinded, randomized comparison of laparoscopic versus open hernia repair in children. *Pediatrics*. 2009;123:332–337.
52. Lejus C, Delile L, Plattner V, et al. Randomized, single-blinded trial of laparoscopic versus open appendectomy in children—effects on postoperative analgesia. *Anesthesiology*. 1996;84:801–806.
53. Rothenberg SS. Experience with 220 consecutive laparoscopic Nissen fundoplications in infants and children. *J Pediatr Surg*. 1997;33:274–277.
54. Georgeson KE, Owings E. Advances in minimally invasive surgery in children. *Am J Surg*. 2000;180:362–364.
55. U.S. Department of Health & Human Services. Agency for Health Quality and Research (AHQR). Available at: http://www.ahrq.gov/. Accessed October 28, 2009.
56. Knight M, Marven SS. British Association of Paediatric Surgeons Congenital Anomalies Surveillance System (BAPS-CASS). Available at: http://www.npeu.ox.ac.uk/baps-cass. Accessed October 28, 2009.
57. Tsao K, Lally KP. The Congenital Diaphragmatic Hernia study group: a voluntary international registry. *Semin Pediatr Surg*. 2008;17:90–97.