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ORIGINAL ARTICLE

Surgical complications, especially gastroesophageal reflux disease, intestinal adhesion obstruction, and diaphragmatic hernia recurrence, are major sequelae in survivors of congenital diaphragmatic hernia

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Abstract
Purpose This study aimed to characterize the surgical complications, especially gastroesophageal reflux disease (GERD), intestinal adhesion obstruction (IAO), and diaphragmatic hernia recurrence, in patients with congenital diaphragmatic hernia (CDH).
Methods Between January 1995 and December 2013, we determined the incidence of surgical complications and their predictors in CDH patients. We also examined whether the CDH repair and patch closure were associated with the incidence of IAO and the severity of adhesion.
Results Seventy-four CDH survivors were evaluated. GERD occurred in 28 patients (37.8 %) and recurred in 8 patients (10.8 %). Stomach herniation was a risk factor for GERD, and occurred in 25 patients. IAO occurred in 13 patients (17.6 %). In 240 neonatal laparotomies in the same period, the incidence of IAO was significantly higher in patients who underwent CDH repair than in patients who underwent other neonatal laparotomy ($p = 0.023$). Surgical time and intraoperative bleeding were significantly greater following CDH repair with an artificial patch compared with CDH repair with direct closure.
Conclusion Surgical complications are major sequelae in survivors of CDH repair. CDH repair and artificial patch closure were significantly associated with the incidence of IAO and the severity of adhesion.

Keywords Congenital diaphragmatic hernia · Complication · Hernia recurrence · Gastroesophageal reflux disease · Intestinal adhesion obstruction

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Introduction

Congenital diaphragmatic hernia (CDH) is a life-threatening congenital anomaly that occurs in between 1 in 2,500 to 1 in 4,000 live births. Advances in neonatal intensive care and ventilatory management have led to an improvement in the overall survival rate of CDH patients of up to 90 % in single-institution studies [1–3]. However, the improved survival of patients with CDH has also resulted in an increase in the incidences of early and late postoperative complications [4, 5]. Consequently, clinicians are now focusing on the long-term outcomes of these patients. Common disorders associated with CDH include pulmonary sequelae, neurodevelopmental deficits, chest wall and spinal deformations, hearing loss, and other abnormalities [6]. To date, however, very few studies have described the surgical complications, especially intestinal adhesion obstruction (IAO), in survivors of CDH.

The aim of this study was to describe the incidence and characteristics of surgical complications, focusing on gastroesophageal reflux disease (GERD), IAO, and diaphragmatic hernia recurrence. We also retrospectively examined the surgical data to identify possible risk factors for specific adverse surgical outcomes. Focusing on IAO after CDH repair, we compared the incidence of IAO after CDH repair with that of IAO after neonatal laparotomy. We also compared operative time and the amount of intraoperative

bleeding during ileus surgery between artificial patch repair and direct closure.

Patients and methods

Between January 1995 and December 2013, 83 patients with early symptoms of CDH were managed in Nagoya University Hospital. Seventy-four patients (89 %) survived and were included in this study. The treatment regimen comprised delayed closure, which was preceded by preoperative stabilization with high-frequency oscillatory ventilation, inhaled nitric oxide (iNO), and administration of drugs (e.g., prostaglandin) until pulmonary hypertension was attenuated. The median duration of preoperative stabilization was 4 days. All 74 patients underwent repair of the diaphragmatic defect via subcostal laparotomy. Direct closure was attempted to the best of our ability. Artificial patches (Goretex; W. L. Gore & Associates, Inc., Tokyo, Japan) were only used when it was impossible to perform a primary repair without significant tension. Twenty-four-hour esophageal pH-metry was performed just before discharge and at about 6 months old.

The following information was recorded from the patients' medical records as possible predictors: prenatal diagnosis of CDH, presence of the liver or the stomach in the thoracic cavity, iNO, use of extracorporeal membrane oxygenation (ECMO), and the method used to close the diaphragmatic defect (i.e., direct closure or use of an artificial patch). The data were analyzed to determine which of these factors were significantly associated with GERD, IAO, or hernia recurrence.

In the same period, 240 patients underwent open laparotomy to treat a variety of diseases other than CDH closure, including necrotizing enterocolitis, intestinal atresia, meconium ileus, and malrotation. We, therefore, compared the incidence and characteristics of IAO between patients who underwent CDH repair or other neonatal laparotomies. We also compared the effects of direct closure or closure with an artificial patch on complications after CDH repair.

Univariate analyses were performed using the χ^2 test or Fisher's exact test for categorical variables, and the Mann–Whitney U test for continuous variables. Values of $P < 0.05$ were considered statistically significant.

This retrospective survey was approved by the ethics committee in Nagoya University Hospital.

Results

Seventy-four newborns who were diagnosed with CDH <24 h after birth and who were alive at hospital discharge were included in this study. Their characteristics are shown in Table 1. The median birth weight was 2,760 g (range 982–4,102 g). The median follow-up of the 74 patients was 50 months (range 4–225 months). Four patients had the right side hernia. Of the 74 patients, 47 (63.5 %) were ventilated with iNO. Thirteen (17.6 %) patients were treated with ECMO and 25 (33.8 %) received artificial patch repairs. The most common surgical complications that needed another operation after CDH repair were GERD, IAO, and hernia recurrence. The numbers and timing of the operations after CDH repair are shown in Table 2. The relationships between the clinical variables and the surgical complications are shown in Table 3. Patients with their stomach located in the thoracic cavity were significantly more likely to undergo surgery for CDH recurrence and fundoplication for GERD than patients with the stomach in the correct location. Prenatal diagnosis, liver located in the thoracic cavity, iNO, use of ECMO, and patch repair method were not significantly associated with complications of CDH repair.

Reoperation for IAO was required in 13/74 (17.6 %) patients who underwent CDH repair compared with 16/240 (6.7 %) patients who underwent other neonatal laparotomies. Of these 16 patients with IAO after neonatal laparotomy, 6 had intestinal perforation, 4 had intestinal atresia, 3 underwent Ladd's operation, 1 had

Table 1 Characteristics of the infants

	n	%
Total	74	100
Males	44	59.5
Right side hernia	4	5.4
Prenatal diagnosis	60	81.1
Liver located in the thoracic cavity	29	39.2
Stomach located in the thoracic cavity	50	67.6
Inhaled nitric oxide	47	63.5
Use of ECMO	13	17.6
Patch repair	25	33.8

ECMO extracorporeal membrane oxygenation

Table 2 Surgical complications and timing of operations after CDH repair

	n (%)	Timing of subsequent operation (months)[a]
GERD	28 (37.8 %)	8 (0–83)
IAO	13 (17.6 %)	4 (1–48)
Hernia recurrence	8 (10.8 %)	2.5 (0–10)

CDH congenital diaphragmatic hernia, *GERD* gastroesophageal reflux disease, *IAO* intestinal adhesion obstruction

[a] Median (range)

Table 3 Associations between clinical variables and surgical complications after CDH repair ($n = 74$)

Variables	GERD			IAO			Hernia recurrence		
	Yes ($n = 28$)	No ($n = 56$)	p	Yes ($n = 13$)	No ($n = 61$)	p	Yes ($n = 8$)	No ($n = 66$)	p
Prenatal diagnosis	24 (86 %)	34 (74 %)	0.55	10 (77 %)	50 (82 %)	0.7	8 (100 %)	52 (79 %)	0.34
Liver located in the thoracic cavity	15 (54 %)	14 (30 %)	0.055	7 (54 %)	22 (36 %)	0.35	5 (63 %)	4 (36 %)	0.25
Stomach located in the thoracic cavity	25 (89 %)	25 (54 %)	**0.002**	9 (69 %)	41 (67 %)	>0.99	8 (100 %)	42 (64 %)	**0.048**
Inhaled nitric oxide	20 (80 %)	27 (59 %)	0.33	10 (77 %)	37 (61 %)	0.35	5 (63 %)	42 (64 %)	>0.99
Use of ECMO	4 (12 %)	9 (20 %)	0.76	3 (23 %)	10 (16 %)	0.69	3 (38 %)	10 (15 %)	0.14
Patch repair	12 (43 %)	13 (28 %)	0.22	6 (46 %)	19 (31 %)	0.34	5 (63 %)	20 (30 %)	0.11

CDH congenital diaphragmatic hernia, *GERD* gastroesophageal reflux disease, *IAO* intestinal adhesion obstruction, *ECMO* extracorporeal membrane oxygenation

Bold values are statistically significant at $p < 0.05$

Table 4 Comparative of operative time and blood loss during reoperation for IAO after CDH repair with an artificial patch, CDH repair with direct closure, or neonatal laparotomy other than CDH repair

	Operative time (min)		Blood loss relative to body weight (g/kg)	
CDH repair with direct closure	79.7 ±36.3	§	3.68 ±3.8	§
CDH with an artificial patch	199.4 ± 50.4	=	40.0 ± 48.8	=
Neonatal laparotomy other than CDH repair	125.6 ± 70.0	§	7.4 ± 10.1	§

IAO intestinal adhesion obstruction, *CDH* congenital diaphragmatic hernia

§ $p < 0.05$

retroperitoneal tumor, 1 had torsion of small intestine and 1 had gastroschisis. Median timing of these IAO operations after neonatal laparotomy was 8 months (range 1–190). The incidence of IAO was significantly greater in patients who underwent CDH repair than in patients who underwent other neonatal laparotomies ($p = 0.023$). The mean duration of the reoperation for IAO was 129.6 ± 72.9 min after CDH repair compared with 125.6 ± 70 min after other neonatal laparotomies ($p = 0.98$). The mean intraoperative blood loss during IAO reoperation relative to the patient's body weight was 18.8 ± 36.3 g/kg after CDH repair compared with 7.4 ± 10.1 g/kg after other neonatal laparotomies ($p = 0.26$). The severity of intestinal adhesion in all patients of the CDH repair was not significantly different from that in patients of other neonatal laparotomies.

In terms of CDH repair methods, the operative time and intraoperative blood loss relative to body weight were greater in patients who received an artificial patch compared with patients who underwent direct closure or patients who underwent other neonatal laparotomies (Table 4). These results suggested that ileus operation after CDH repair with an artificial patch is a technically difficult procedure associated with increased blood loss.

Discussion

Surgical complications that require another laparotomy are thought to be common in CDH survivors, but data are limited regarding the long-term incidences of these complications and their risk factors [4, 6–9]. According to prior reports, the most common conditions that require surgical treatment after CDH repair include GERD, IAO, and diaphragmatic hernia recurrence [8–14]. In our study, we examined the relationships between CDH repair and these complications, and evaluated possible risk factors, including prenatal diagnosis, location of the liver or stomach in the thoracic cavity, iNO, use of ECMO, and the use of an artificial patch for hernia repair.

Gastroesophageal reflux disease is a well-known complication of CDH repair, and is thought to occur in 12–81 % of patients with CDH, including 38 % of patients who underwent CDH repair in our study [6]. The mechanisms responsible for GERD have not been fully clarified in CDH survivors. In our study, stomach translocation to the thoracic cavity was the only risk factor for GERD. Liver located in the thoracic cavity or patch repair was not associated with GERD. Three patients with liver herniation and two with patch repair did not have stomach herniation because they had CDH on the right. All of them did not have GERD. So in this study, liver herniation or patch repair was not significantly associated with GERD. Kieffer et al. [15] reported that the presence of an intrathoracic stomach at operation is associated with pathological GERD, and that a shortened abdominal esophagus and obtuse angle of His were implicated in the phenomenon.

Closing a large defect by approximation and direct suture under tension may place excess strain on the crus, increasing the risk of a hiatal hernia [11]. Esophageal and gastric manometry in CDH patients revealed that abnormal peristaltic contractility and propagation could predispose to GERD. Therefore, a combination of these congenital abnormalities may result in GERD after CDH repair.

Hernia recurred in eight CDH survivors (10.8 %). Recurring diaphragmatic hernias have been reported in 8–50 % of patients with CDH [8]. Therefore, a large defect that requires patch repair might increase the risk of recurrence [10]. However, in our study, only the location of the stomach in the thoracic cavity was a significant risk factor for hernia recurrence. In our patients, the hernias recurred soon after CDH repair, but they can recur several months to several years after the CDH repair. Patients may remain asymptomatic and the recurrence is often found incidentally. Therefore, the long-term risk and incidence of recurrence are still unclear.

Intestinal adhesion obstruction was one of the most common reasons for reoperation after CDH repair in our patients. IAO was reported to occur in approximately 10–20 % of CDH patients [11]. Some prior studies have described about GERD or diaphragmatic hernia recurrence, but very few studies have described IAO after CDH repair. So we performed a close examination of the cases of IAO after CDH repair. In our study, IAO was found in 13 patients (17.6 %) after CDH repair; this rate was significantly greater than that in patients who underwent other neonatal laparotomies. Other neonatal laparotomies were performed under many different causes and conditions. In this point of view, our comparative study may include any bias, but it has some informative one. In other reports, the incidence of IAO ranged from 2.2 to 6 % after neonatal laparotomies other than CDH repair [16–18]. Although comparative studies of CDH patients and patients undergoing neonatal laparotomy have not been performed, these earlier data support our findings. Several mechanisms may contribute to the increased susceptibility to IAO in CDH patients. For example, abnormal positioning of the intestine may cause intestinal kinking and increased intra-abdominal pressure may impair peristalsis [13]. Furthermore, prolonged illness and intestinal paralysis could increase the risk of intestinal adhesion and bowel obstruction.

We also showed that the mean operative time and blood loss were significantly greater in CDH patients who received an artificial patch than in CDH patients who underwent direct closure or patients who underwent other neonatal laparotomies. It was reported that patch repair significantly increased the risk of IAO in CDH patients [11]. We did not observe a similar association between IAO and CDH repair, but patch repair did increase the severity of intestinal adhesion and ileal release. Large CDH defects requiring an artificial patch for closure pose a surgical challenge, and may increase the risk of future operations, which will also be technically difficult. It is possible that intraperitoneal placement of a patch may have pathologic effects that promote tissue adhesion. Therefore, operative time and intraoperative blood loss were significantly greater in patients who received an artificial patch compared with patients who underwent direct closure. Adverse surgical outcomes were reported to be more common in patients with a large CDH defect requiring patch repair [7, 10, 19–22], and our results support the validity of this clinical condition.

In conclusion, although advances in the treatment of CDH have remarkably improved its survival rates, CDH survivors frequently develop surgical complications, including GERD, IAO, and hernia recurrence. The location of the stomach in the thoracic cavity at initial surgery was the only predictor of these complications in this study. The incidence of IAO was significantly greater after CDH repair than after other neonatal laparotomies. The operative procedure involved in the release of an IAO after CDH repair with an artificial patch is very difficult and is associated with a high risk of bleeding because of the formation of firm adhesions. Neonates are faced with a long time to experience complications associated with CDH repair. Therefore, it is vital that pediatric surgeons evaluate new strategies to reduce the risk of these surgical complications.

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