Asian Journal of Surgery (2017) 40, 1–5

Available online at www.sciencedirect.com

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journal homepage: www.e-asianjournalsurgery.com

ORIGINAL ARTICLE

Analysis of risk factors of long-term complications in congenital diaphragmatic hernia: A single institution's experience

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Received 17 December 2014; received in revised form 11 February 2015; accepted 17 February 2015
Available online 1 May 2015

KEYWORDS
congenital diaphragmatic hernia;
gentle ventilation;
long-term complications;
morbidities;
short-term complications

Summary *Objective:* To establish better management practices to reduce morbidities in survivors with congenital diaphragmatic hernia (CDH).
Methods: Of 60 patients treated for CDH at our institution between 1991 and 2011, 49 patients without severe anomalies were retrospectively reviewed.
Results: Since 2004, gentle ventilation (GV) has been the main treatment for CDH. Patients were divided into the following two groups: the non-GV group ($n = 29$) who were treated before GV treatment was implemented, and the GV group ($n = 20$). The overall survival rate was 62.1% (18/29) and 95% (19/20) in the non-GV and GV groups, respectively ($p = 0.016$). Despite the high survival rate, the incidence of long-term complications in survivors was still high (14/19, 73.7%) in the GV group. In the GV group, liver-up ($p = 0.106$) and the need for patch repair ($p = 0.257$) tended to be associated with the development of long-term complications, but did not reach statistical significance. The presence of perioperative complications was associated with the development of long-term complications ($p = 0.045$) in the GV group.
Conclusion: Patients who developed short-term complications seemed to be at risk of long-term complications. Therefore, to minimize long-term morbidities in CDH survivors, the prevention of short-term complications might be important.

Conflicts of interest: The authors declare no conflicts of interest associated with this manuscript.

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http://dx.doi.org/10.1016/j.asjsur.2015.02.005

1. Introduction

Congenital diaphragmatic hernia (CDH) is one of the most challenging anomalies faced by pediatric surgeons and neonatologists. Recently, especially over the past 2 decades, many innovative techniques, including high-frequency oscillation (HFO), inhaled nitric oxide, extracorporeal membrane oxygenation, and gentle ventilation (GV), have been introduced as suitable options for CDH treatment.[1–5] In addition, prenatal diagnosis has also contributed to improvement in the outcome of CDH.[2,3] Currently, reports from a number of highly qualified centers show remarkable improvement in the survival rates, reported to be as high as 80%.[1,5,6] By contrast, in follow-up studies of infants with CDH, many complications, such as pulmonary damage, cardiovascular diseases, gastrointestinal diseases, failure to thrive, neurocognitive defects, and musculoskeletal abnormalities, have been described.[7–12] With improved management of infants with CDH, there has been an increase in morbidities among long-term survivors. Thus, we must now concentrate not only on the survival of infants with CDH but also on morbidities in surviving patients. Although some reports have addressed the issue of long-term outcomes for CDH survivors,[7–11,13–16] the variations in patient populations, management, and length of follow up make it difficult to draw firm conclusions about the quality of life of these patients. The aim of this study is to show the long-term functional impact of CDH repair on the survivors in a single-institution cohort of newborns over a 20-year period.

2. Methods

A retrospective chart review was conducted on isolated prenatally diagnosed CDH patients born during the period between 1991 and 2011. Inclusion criteria were the presence of a CDH without associated life-threatening or chromosomal anomalies. From 2004 to the present, a combination of GV and a delayed operation was the main treatment after birth. GV was performed based on the protocol presented by one of the study authors.[4] The patient was intubated just after birth. The initial settings of HFO were as follows: frequency, 15 Hz; mean airway pressure, 15 cmH_2O; stroke volume, 15 mL; and inspired O_2 fraction (FiO_2), 1.0. The pre-SpO_2 (saturation of peripheral oxygen) was maintained at $>$90% and the pre-$PaCO_2$ (pressure of arterial carbon dioxide) was maintained at $<$65 mmHg. In addition, the pre-PaO_2 (pressure of arterial oxygen) was maintained above 60 mmHg, if possible.

Liver position was determined at the time of surgery. A systematic review was conducted including the following data: gestational age at diagnosis, position of the liver, postnatal treatment, need for patch repair, duration of ventilation, perioperative complications, long-term complications, and survival. Liver position is considered to be "up" if any portion of the liver is in the chest above the normal level of the diaphragm, and "down" if it is completely within the abdomen. Major morbidities at discharge included the need for respiratory support (supplemental oxygen, mechanical ventilation, and tracheostomy), nutritional support (tube feeding and parenteral nutrition), or circulatory support (use of vasodilators).

Statistical analysis was performed to assess the patients' backgrounds in the non-GV and GV groups using the Wilcoxon signed-rank test and Fisher exact test. Univariate analyses were also performed for comparison of the outcomes in the non-GV and GV groups using the Wilcoxon signed-rank test and Fisher exact test. A p value <0.05 was defined as significant. The values are expressed as the mean $\pm$ standard deviation. This study design was approved by the Ethical Committee of our university.

3. Results

We retrospectively reviewed 60 neonates with CDH treated at our institution from 1991 to 2011. Of these neonates, one who became symptomatic more than 24 hours after birth, and 10 with fatal anomalies were excluded, leaving 49 patients for review in this study. The patients were divided into two groups, namely, the non-GV group ($n = 29$) who were treated before GV was implemented and the GV group ($n = 20$) who were treated after GV was implemented.

3.1. Survival

Table 1 shows the outcomes in both groups. The overall survival rate improved with GV treatment (non-GV group 62.1%, GV group 95%; $p = 0.016$). The 90-day survival rate also improved with GV treatment, but did not reach statistical significance (non-GV group 72.4%, GV group 95%; $p = 0.064$). In the non-GV group, eight patients died before 90 days of life. The causes of deaths were heart failure in four cases, severe persistent pulmonary hypertension in one case, pneumonia in one case, and diffuse intravascular coagulation in two cases. Six of these eight cases were outborn deliveries and two of them were already in a state of cardiopulmonary arrest when they arrived at our institution. Only one patient died in the GV group, due to catheter infection-related sepsis at 68 days of life after the surgery. There were three late death cases after 90 days of life in the non-GV group and are attributed to the following causes: pneumonia at 1 year of age, severe enteritis at 1 year of age, and tracheostomy trouble at 16 years of age. There were no late death cases in the GV group.

3.2. Perioperative and long-term complications

The perioperative and long-term complications in both groups are listed in Tables 2 and 3, respectively. The incidence of perioperative complications was 13/29 (44.8%) patients and 9/20 (45.0%) patients in the non-GV and GV groups, respectively. The incidence of long-term

Table 1 Outcome in study groups.

	Non-GV group	GV group	p
Overall survival	62.1 (18/29)	95.0 (19/20)	**0.016**
Survived at 90 d of birth	72.4 (21/29)	95.0 (19/20)	0.064

Values in bold indicate values with significant difference.
Data are presented as % (n).
GV = gentle ventilation.

Table 2 Perioperative complications in the study groups.

Complications	Non-GV group (n = 29)	GV group (n = 20)	p
Pneumothorax	2 (6.9)	2 (10.0)	>0.999
Pneumonia	2 (6.9)	1 (5.0)	>0.999
PPHN attack	1 (3.4)	0 (0.0)	>0.999
Pulmonary hemorrhage	1 (3.4)	0 (0.0)	>0.999
Chylothorax	0 (0.0)	2 (10.0)	0.162
Pleural effusion	0 (0.0)	1 (5.0)	0.229
Pyothorax	0 (0.0)	1 (5.0)	0.229
Others	7 (24.1)	2 (10.0)	0.277
Any complications	13 (44.8)	9 (45.0)	>0.999

Data are presented as n (%).
GV = gentle ventilation; PPHN = persistent pulmonary hypertension of the newborn.

complications was 10/21 (47.6%) patients and 14/19 (73.7%) patients in the non-GV and GV groups, respectively. Of the 13 patients who developed perioperative complications in the non-GV group, six patients died before 90 days of life and six patients suffered from long-term morbidities including three late deaths. Of the nine patients who developed perioperative complications in the GV group, one patient died before 90 days of life and eight patients suffered from long-term complications.

Details of the major morbidities of the patients at discharge are presented in Table 4. Many of them suffered from more than two major morbidities at discharge. At discharge, four patients in the non-GV group and three in the GV group needed respiratory support (tracheostomy and supplemental O_2). The number of patients discharged that required tube feeding was two in the non-GV group and five in the GV group. There were no patients discharged that required supplementation of vasodilators in the non-GV group because vasodilators were not administrated routinely during the non-GV period. Four patients were discharged with supplementation of vasodilators in the GV group. Indication for vasodilators depended on the surgeon's individual decision. Three of these four patients were not using vasodilators at the time of writing. Three of 21 survivors (14.3%) in the non-GV group were discharged with major morbidities. By contrast, six of 19 survivors (31.6%) in the GV group were discharged with major morbidities. Thus, the rates of the patients at discharge without major morbidities were 62.1% (18/29 patients) and 65.0% (13/20 patients) in the non-GV and GV groups, respectively. Of patients without major morbidities at discharge, 10/18 (55.5%) patients and 5/13 (38.5%) patients in the non-GV and GV groups, respectively, survived without developing long-term complications.

Table 3 Long-term complications in both groups.

Complications	Non-GV (10/21)	GV (14/19)	p
Mental retardation	3 (14.3)	9 (47.4)	**0.038**
Failure to thrive	2 (9.5)	5 (26.3)	0.226
Intestinal obstruction	5 (23.8) (Operation 5)	2 (10.5) (Operation 1)	0.412
GER	2 (9.5) (Operation 2)	4 (21.1) (Operation 2)	0.398
Hearing loss	0 (0)	1 (5.2)	0.475
Chest wall deformities	2 (9.5)	2 (10.5)	>0.999
Others	3 (14.3) (Death in late term 3)	1 (5.2) (Recurrence 1)	0.607
Any morbidities	10 (47.6)	14 (73.7)	0.117

Values in bold indicate the values with significant difference.
Data are presented as n (%).
GER = gastroesophageal reflux; GV = gentle ventilation.

Table 4 Major morbidities at discharge in both groups.

Morbidities	Non-GV (n = 21)	GV (n = 19)	p
Tracheostomy	2 (9.5)	0 (0)	0.489
Supplemental O_2	2 (9.5)	3 (15.8)	0.654
Tube feeding	2 (9.5)	5 (26.3)	0.226
Vasodilators	0 (0)	4 (21.1)	**0.042**
Any morbidities	3 (14.3)	6 (31.6)	0.442

Values in bold indicate the values with significant difference.
Many patients listed were discharged with more than two morbidities.
Data are presented as n (%).
GV = gentle ventilation.

3.3. Predictors for long-term complications

Although the survival rate has improved after the administration of GV, the incidence of long-term complications has remained high. To investigate the predictors for long-term complications in the GV group, we examined the associated disease's severity and long-term complications with regard to liver position and the need for patch repair in the GV group. As demonstrated in Table 5, liver-up (p = 0.106), the need for patch repair (p = 0.257), and the existence of major morbidities at discharge (p = 0.126) tended to be associated with the development of long-term

Table 5 Incidence of long-term complications in patients with liver-up, patch repair, perioperative complications, and major morbidities at discharge in the gentle ventilation group.

	Long-term complications (+)	Long-term complications (−)	p
Liver-up	50 (7/14)	0 (0/5)	0.106
Patch repair	36 (5/14)	0 (0/5)	0.257
Major morbidities at discharge	42.9(6/14)	0 (0/5)	0.126
Perioperative complications	57 (8/14)	0 (0/5)	**0.045**

Values in bold indicate the values with significant difference.
Data are presented as % (n).

complications, but did not reach statistical significance. The presence of perioperative complications was associated with the development of long-term complications ($p = 0.045$). Of interest, all patients without the studied risk factors mentioned earlier were free from long-term complications.

The duration of mechanical ventilation indicates the disease severity especially in the perioperative period. In addition, patients with perioperative complications may need prolonged respiratory support. Therefore, we hypothesized that the duration of mechanical ventilation is predictive of long-term complications. As shown in Fig. 1, the duration of mechanical ventilation was significantly shorter in the patients without long-term complications in the GV group (6.00 ± 3.17 days and 48.9 ± 11.95 days in the patients without and with long-term complications, respectively; $p = 0.016$).

4. Discussion

As more children with severe forms of CDH survive, more cases of CDH-associated complications will occur. The increase in CDH patient survival shifts the focus to improving survivor morbidity, because CDH survivors have a high incidence of respiratory, nutritional, musculoskeletal, neurological, and gastrointestinal morbidities.[2,3,7–17] In our series, 31.6% (6/19) of patients were discharged with major morbidities (3 on supplemental O_2, 5 requiring tube feeding, and 4 received vasodilators) even after implementation of GV. In addition, the majority of patients developed long-term complications (Table 3), especially in the GV group, in which 73.7% (14/19) of the survivors suffered from long-term complications even though the survival rate improved to as high as 95% (19/20 patients).

Recently, several reports mentioned the precise incidence patterns of morbidities in CDH survivors. Okuyama et al[5] reported that the rate of growth and motor/speech retardation was 44% and 80% in intact discharge patients and nonintact discharge patients, respectively, at 1 year and 6 months of age. Rocha et al[10] reported that the rate of CDH survivors with one morbidity, two morbidities, and more than three morbidities was 15.6%, 15.3%, and 20.2%, respectively. Based on our results and these reports, significant numbers of CDH patients may live with complications, resulting in poor quality of life.[2,3,9,13,15,16] In particular, the incidence of mental retardation was significantly higher in the GV group. This is not only due to the improved survival rate but also due to a much longer and more closely monitored follow-up program started recently in our study.

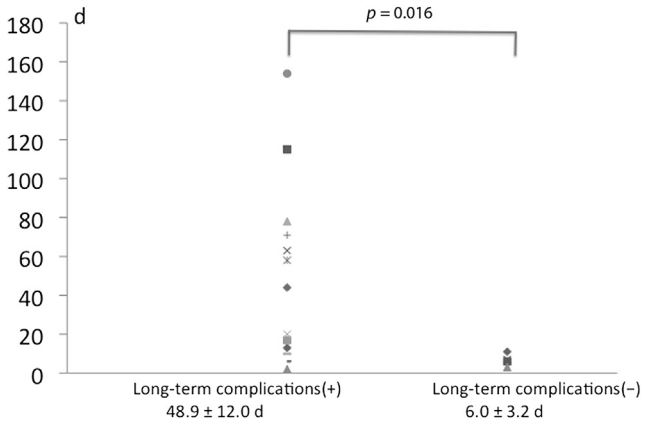

Figure 1 Duration of mechanical ventilation and long-term complications in the gentle ventilation group. Duration of mechanical ventilation was significantly shorter in patients without long-term complications.

To reduce the incidence of long-term complications, we investigated the predictors for long-term complications in the GV group. Large hernia size, patch repair, and liver herniation are reported to be significant predictors of surgical complications and long-term adverse outcomes.[11,18,19] In the present study, all the patients in the liver-up and patch repair groups had long-term complications (Table 5). The cases with liver-up ($p = 0.106$) and patch repair ($p = 0.257$) seemed to be at risk of long-term complications, but did not reach statistical significance (Table 5). From our observations, perioperative complications seem to be important risk factors for long-term complications to improve the long-term outcome of the CDH survivors. In the GV group, we evaluated the association between perioperative complications and long-term complications. Of 14 patients who developed long-term complications, eight had perioperative complications. By contrast, all five disease-free survivors experienced no perioperative complications. Patients who developed perioperative complications seemed to be at risk of long-term complications ($p = 0.045$, Table 5). Interestingly, the duration of mechanical ventilation was significantly shorter in the patients without long-term complications (Fig. 1). Not alone the severity of the disease, but also the perioperative complications may prolong the duration of mechanical ventilation. Pneumothorax, empyema, and pneumonia can especially cause prolonged intubation. Based on our result, perioperative management to prevent such complications might be a key to reducing the incidence of long-term complications. In addition, we have to pay increased attention to patients who developed perioperative complications even after discharge because they seem to be at risk of long-term complications.

In the present study, the survival rate of patients with CDH improved using the GV protocol. However, in accordance with other previous reports, the incidence of long-term morbidities was still high.[2,3,5,7–13,15,16] As the survival rate increases, we have to focus on the long-term complications. The rescuing of more severely affected patients results in more patients with severe morbidities. The more carefully we track patients, the more adverse outcomes in survivors we might find. For example, the incidence of mental retardation significantly increased in the GV group. The increase in mental retardation cases might be due to the more complete and careful follow-up system. Based on our results, besides indicated markers such as patch repair and liver herniation, the risk of long-term morbidities was high in patients with perioperative complications and delayed extubation.

After discharge from hospital, CDH survivors may have long-term sequelae such as respiratory insufficiency, gastroesophageal reflux, failure to thrive, neurodevelopmental delay, behavior problems, hearing loss,

hernia recurrence, and orthopedic deformities.[2,3,5,7–17] Underlying pulmonary hypoplasia and pulmonary hypertension cause neurodevelopmental deficits including hearing loss due to hypoxia or hypoperfusion associated with pulmonary problems.[8–13,15] In addition, surgical complications such as recurrence, small bowel obstruction, gastroesophageal reflux, and musculoskeletal problems occur in CDH survivors.[2,7–11,13,14,17] Both nutritional problems resulting in neurodevelopmental deficits and surgical complications may lead to failure to thrive.

Our study is limited by the relatively small number of the patients studied. However, to describe the long-term morbidities and to investigate risk factors for long-term complications, a single institution's study is informative because the patients were treated by the same protocol in the acute phase and followed by a unified follow-up protocol.

Based on our study, it is important to recognize that CDH survivors are unique because they are at high risk of multisystem disability. Long-term follow up by a multidisciplinary health-care team is essential to detect morbidities early and to improve the long-term outcomes for CDH survivors. Timely intervention for disabilities in growth, neurodevelopment, and hearing is only possible if they are recognized early in the follow-up process. Our data suggest that to minimize morbidities, strict follow up with closer evaluations is mandatory for patients who develop perioperative complications.

Acknowledgments

We would like to thank Mr Brian Purdue for reviewing the English used in this manuscript.

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