Original Works

New Protocol for the Treatment of Neonates Diagnosed with Congenital Diaphragmatic Hernia within 24 Hours Old

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Abstract: Purpose: This study evaluated our new protocol for the treatment of neonates diagnosed with congenital diaphragmatic hernia (CDH) within 24 hours old.

Materials and Methods: Thirty-four consecutive neonates diagnosed with CDH within 24 hours old that were referred to our institution between 1997 and 2007 were included in this study. The cases were divided into two groups based on different treatment protocols. Group 1, 15 patients treated between 1997 and 2002; group 2, 19 patients treated between 2003 and 2007. In the latter group, a new protocol consisting of preoperative stabilization via gentle ventilation and administration of preoperative steroids, diuretics and routine surfactant was introduced to prevent lung injury and to manage cardiopulmonary complications. The survival rate and the postoperative intubation period (POIP) were then compared between the two groups.

Results: The overall survival rate significantly increased from 53% (8/15) in group 1 to 89% (17/19) in group 2 (p<0.05). The average POIP was shortened from 39.3 days (14 to 70 days) in group 1 to 5.3 days (1 to 15 days) in group 2 (p<0.01).

Conclusion: Our new protocol consisting of preoperative stabilization and administration of steroids, diuretics and surfactant could remarkably improve survival rates in neonates with CDH.

Key Words: Congenital diaphragmatic hernia, Gentle ventilation, Steroid, Surfactant.

Introduction

Congenital diaphragmatic hernia (CDH), especially in neonates within 24 hours old, remains a
defiant challenge for pediatric surgeons. High peak inspiratory pressure (PIP) in conjunction with alkalinization using hyperventilation appears to be the main cause of pulmonary damage in cases of pulmonary compromise, thus it has been postulated that in many cases this protocol may do more harm than good, giving rise to the utilization of gentle ventilation to limit iatrogenic lung injury with evidence of encouraging survival rates. The long-term morbidity of surviving patients has also been unclear, and is therefore now becoming an issue of interest. It is known that the period for mechanical ventilation support should be minimized to avoid iatrogenic lung injury. There is a report showing that avoiding muscle paralysis allows the infant’s own respiratory bellows to contribute to minute ventilation without compromising with functional residual capacity. Some studies also suggest that early steroid therapy combined with surfactant administration increases survival without the risks of chronic lung disease in high-risk, low birth weight infants with respiratory distress syndrome.

In 2003, we abandoned alkalinization by hyperventilation with muscle paralysis and developed a new protocol consisting of adjuvant medical management with steroid therapy and D-mannitol continuous infusion to minimize lung injury and postoperative morbidity. In this study, we evaluated how useful our protocol was for the improvement of survival and for shortening the postoperative tracheal intubation period in neonates less than 24 hours old with CDH.

**Patients and Methods**

Thirty-four consecutive neonates diagnosed with CDH prenatally or those that became symptomatic within the first 6 hours of life and were referred to Children’s Research Hospital, Kyoto Prefectural University of Medicine between January 1997 and September 2007 were included in this study, regardless of complicating anomalies, degree of pulmonary hypoplasia or medical status upon arrival. The patients were divided into two groups based on differences in the treatment protocol. Fifteen patients between 1997 to 2002 were placed in group 1, and 19 patients between 2003 and 2007 were placed in group 2. Prenatal diagnosis was established in 67% (10/15) and 74% (14/19) in groups 1 and 2, respectively. Cases of diaphragmatic agenesis comprised 2/15 (13%) and 5/19 (24%), respectively.

In group 1, treatment consisted of paralysis by muscle relaxants and alkalinization via hyperventilation for pulmonary hypertension treatment. Ventilator mode settings were started with intermittent mandatory ventilation (IMV) to maintain the PaO$_2$ above physiologic levels and PaCO$_2$ around 30 cm H$_2$O. Surgery was performed within the first 24 hours of life in the first 4 patients. Surgery in all others in group 1 was delayed from 2 to several days. Pending surgical intervention, alkalinization through hyperventilation was continued. During this period, for patients that did not stabilize, the ventilator mode was changed to high frequency oscillation ventilation (HFOV) mode. If patients showed further decline or persistent instability, inhalation of nitric oxide (iNO) with IMV ventilator mode changes were introduced. Extracorporeal membranous oxygenation (ECMO) in conjunction with iNO and 100% oxygen was reserved only for life-threatening instability defined as declining preductal oxygen saturation below 80% refractory to ventilator manipulation.

In group 2, gentle ventilation with adjuvant medical management was utilized instead of hyperventilation. Preductal oxygen saturation over 70% in the first 2 hours was considered acceptable as long as bradycardia or persistent metabolic acidosis was absent. Initial ventilator settings were
started on IMV mode with a respiratory rate of 40 to 60/min, peak inspiratory pressure (PIP) of 16 cm H₂O and positive end-expiratory pressure (PEEP) of 5 cm H₂O. Inspired oxygen was started at 100%. Weaning as tolerated commenced at 6 hours of life with a goal of maintaining postductal saturations above 97%. To support mean arterial pressure at or above the patient’s gestational age, total parental nutrition and crystalloid boluses (5 to 10 cc/kg) were given under close monitoring of cardiac function and volume by ultrasonography. None of the patients received muscle relaxants. Continuous sedation was provided with a fentanyl infusion of 5 to 10 μg/kg/hr. For prevention of cardiac failure, systemic and pulmonary edema, adjuvant medical management consisting of routine steroid administration (methylprednisolone, 20 mg/kg/day, during the first 3 days of management) and continuous intravenous infusion of diuretics (D-mannitol 16 mg/kg/hr, furosemide 0.2 mg/kg/hr) were initiated until stable urinary output was obtained. All patients received routine glycerin enemas to decompress intestinal contents. Surgical repair was delayed at least 2 to 3 days. If patients were unstable or required significant ventilator support, surgery was delayed further. After CDH repair, the patients were slowly weaned from mechanical ventilation and extubated to nasal continuous positive airway pressure (CPAP).

In both groups, prenatally diagnosed neonates were delivered by scheduled cesarean section so that a pediatric surgical team was prepared and available. Patients with prenatal diagnosis were born at our hospital resuscitated immediately after delivery by tracheal intubation and nasogastric decompression of the stomach. In group 2, surfactant was administered at a total dose of 4 ml/kg immediately at delivery to patients born at our hospital and was also administered to patients referred from other hospital as soon as adventitious lung sounds were heard on chest auscultation. In group 1, surfactant was administered only to 3 patients based on surgeon’s preferences. Dopamine was infused at 3 μg/kg/min through a peripherally inserted central catheter. Unnecessary handling of the infant was avoided for stress management except for glycerine enema in group 2. Primary repair was preferred if it could achieved with minimal tension, otherwise, a 0.6-mm-thick Gore-Tex patch (JGI, Tokyo) was employed for repair.

The survival rate, postoperative intubation period (POIP) and complication sequelae were compared between the 2 groups. For statistical analysis, Student t-test for the intubation period and Fisher’s exact probability test for survival rate were used. P-values less than 0.05 were considered significant.

**Results**

There were no significant difference in the degree of severity and risk factors, such as, highest A-aDO₂, major cardiac anomalies, liver in chest, and need for patch repair. The mean airway pressure (MAP) in group 2 (9.4±2.1) was significantly lower than that in group 1 (16.2±3.4).

Intratracheal surfactant administration was performed in 4 patients (27%) in group 1 and in 18 patients (95%) in group 2. In group 2, adventitious breath sounds disappeared and chest movements remarkably improved immediately after surfactant administration. However, in group 1, patients showed no clinical improvement and demonstrated a transient depression of oxygen saturation after postoperative administration. None of the patients in group 2 showed a transient depression of oxygen saturation following surfactant administration. Compared with that in group 1, the necessity for HFOV, iNO and ECMO was significantly reduced by the new protocol in group 2.
Overall survival rates were 53% (8/15) in group 1 and 89% (17/19) in group 2. Statistical analysis confirmed significant differences between the two groups. In group 1, one neonate died from cardiac complications as a consequence of aortic coarctation. The second cause of death was respiratory failure during preoperative stabilization or the postoperative period. In group 2, deaths were attributed to lethal multiple cardiac anomalies in one neonate and extreme lung hypoplasia (total lung volume of 5 g) in another. The latter neonate was also complicated with anorectal malformation. Survival rates in prenatally diagnosed patients were 50% (5/10) in group 1 and 86% (12/14) in group 2. Half of the patients in group 1 (5/10) that underwent preoperative stabilization to be followed by delayed surgery could not be sustained on mechanical ventilation and died before surgical intervention. In neonates who underwent patch repair for the diaphragmatic agenesis, survival rates were 50% (1/2) and 100% (5/5) in groups 1 and 2 respectively.

Overall postoperative intubation period (POIP) was 39.3±19.0 days in group 1 and 5.3±4.1 days in group 2. In group 1, POIP in prenatally diagnosed neonates was 43.8±23.1 days and 5.8±4.4 days in group 2. In neonates without prenatal diagnosis, POIP was 33±3.6 days in group 1 and 4.2±3.6 days in group 2. There was a significant decrease of POIP in group 2 compared with that in group 1. There were no negative effects associated with prenatal diagnosis in either group.

As for postoperative morbidity, gastroesophageal reflux (GER) was found in 3 of the group 2 which was diagnosed with upper GI contrast media study. All of these cases had diaphragmatic agenesis and underwent patch repair for CDH. Two of them underwent fundoplication at 8 months and 4 years of age, respectively. Symptoms in the remaining one case were not severe and the patient now remains under observation with a prescription for a proton pump inhibitor.

One patient in group 1 survived with oxygen dependence and has neurological deficits with hydrocephalus and periventricular leukomalacia caused by intraventricular hemorrhage. This patient was managed with preoperative and postoperative ECMO after failing to achieve stabilization with IMV hyperventilation, HFOV and iNO inhalation. One patient with a right diaphragmatic hernia in group 2 has survived with oxygen dependence, but there are no neurological deficits. None of the surviving neonates has shown any signs of hearing loss (Table 1).

**Discussion**

After implementing our new protocol for the management of neonates diagnosed with CDH within 24 hours old, the survival rate remarkably improved. With the exception of a neonate with lethal cardiac anomalies, all neonates in group 2 could be saved without using ECMO, regardless of whether they were born at our hospital or referred from outside. There were no negative effects of prenatal diagnosis as reported in other articles10.

In group 1, although alkalization by hyperventilation transiently appeared to be effective and succeeded for the initial periods of stability after emergent surgery, a phenomenon known as a honeymoon periods, many patients deteriorated postoperatively. Patients in group 2 never demonstrated a honeymoon phase during preoperative stabilization. While it was common for such patients to have very low oxygen saturation in the first few hours, most of the patients except for those with lethal cardiac anomalies or extreme lung hypoplasia, gradually showed improvement of oxygen saturation within 6 hours.

Regarding the ventilator mode, we abandoned HFO in group 2 because we could not control
excessive hypercapnia (more than 100 cm H₂O) in severe cases and conventional IMV mode with limited PIP and iNO inhalation was more useful for controlling excessive hypercapnia. The survival rate and POIP including cases of severe diaphragmatic agenesis should serve as conformation of the effectiveness of this strategy.

Throughout this study, the use of iNO was often necessitated during periods of oxygen saturation deterioration and uncontrolled excessive hypercapnia. However, its efficacy or reliability were frequently questionable when iNO was administered in group 1 because we found little improvement in the ongoing deterioration after the honeymoon period. All patients in group 2 managed with iNO under gentle ventilation showed remarkable improvement in oxygen saturation and in the blood CO₂ levels. This finding showed that the efficacy of iNO could be disturbed by iatrogenic lung injury from hyperventilation.

Some studies report that exogenous surfactant administration could be harmful for patients with CDH[11-13]. Those reports, however, were multi-center investigations where management and environmental variables were difficult to standardize. In our experience, adventitious breath sounds, chest movements and oxygen saturation often improved remarkably soon after surfactant administration in group 2, while such effect was not expected in group 1. Exogenous surfactant administration could be one of the most important factors in addition to the gentle ventilation strategy to prevent lung injury and promote preoperative stabilization, which should facilitate minimal PIP during ventilation and shorten the time needed for weaning from high concentration oxygen.

Regarding the use of steroid, there are some reports saying that early steroid administration increases survival without risking chronic lung disease in high-risk, low birth weight infants with respiratory distress syndrome[610]. Barr also reported that the use of dexamethasone was associated with significant improvement in oxygen saturation as well as rapid weaning from mechanical ventilation[14]. To minimize lung injury, the administration of steroid was introduced in all group 2 patients, and we speculate that this strategy could have contributed to the shortening of POIP in group
2 patients, although contribution of this factor could not be isolated in this analysis.

In the management of neonates with CDH, fluid balance and fluid overload are common challenges that often quickly complicate already delicate situations. By introducing continuous D-mannitol infusion during preoperative stabilization, the fluid balance could quickly be manipulated and no colloid infusion was necessary to stabilize circulatory difficulties in group 2 patients.

For patients in group 1 who received ECMO therapy for preoperative cardiopulmonary deterioration and/or refractive oxygen saturation, efforts were almost always futile. This implies that the effectiveness of ECMO is problematic in circumstances of ongoing deterioration following the honeymoon phase after pursuing a hyperventilation strategy for respiratory management. Certainly, the early use of ECMO combined with gentle ventilation is a potential therapeutic approach that should be investigated as previously reported5, specifically for severe cases with compounding risk factors. However, caution must be exercised as there are technical difficulties, medical complications, and implicit dangers in the use of ECMO6,17. All patients in group 2 were managed without ECMO and their survival attained in this series was 89%, which included 2 patients with lethal anomalies that did not survive long enough to receive surgical intervention. All of the 5 patients who underwent patch repair survived without neurological morbidity. Wilson et al.5 reported that the survival of patients with patch repair was 36%; a considerable difference from the outcomes for group 2 in this study.

Regarding the postoperative GER, as Su et al.18 described, fragile crura of the left diaphragm, especially in those with diaphragmatic agenesis, could be the main cause of GER. Our data concurs with this theory. From this perspective, there is a possibility that more severe cases were saved in group 2 compared with those in group 1. In other words, such severe cases in group 1 might have died during preoperative stabilization.

In conclusion, our new protocol for the treatment of neonates diagnosed with CDH within 24 hours old showed a remarkably high survival rate, minimal postoperative tracheal intubation period and minimal need for ECMO.

References

8 ) Kolobow T, Moretti MP, Fumagalli R, Mascheroni D, Prato P, Chen V, Joris M. Severe impairment in lung function induced by high peak airway pressure during
生後24時間以内発症の先天性横隔膜ヘルニアに対する我々の新しい治療法

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【目的】生後24時間以内発症の先天性横隔膜ヘルニアに対する我々の新しい治療方法の有効性について検討した。
【対象と方法】1997年から2007年までの間に治療した生後24時間以内発症の先天性横隔膜ヘルニア34例を対象とした。それらを治療方法の違いにより1997年から2002年までの15症例（グループ1）と2003年から2007年までの19症例（グループ2）の2グループに分けた。後者は肺損傷予防および循環動態を安定させるために、新しい治療方法として術後術後の呼吸管理においてはできるだけ吸気圧を低く設定し、肺水腫予防を目的としたステロイド投与、マンニトールを主体とした利尿剤の持続的投与、および陽圧換気による肺損傷予防目的の術前気管内サーファクタント投与を導入した。2群間の生存率、術後挿管期間を比較検討した。
【結果】生存率はそれぞれ53％および89％であり、グループ2で著明な改善を認めた（p<0.05）。術後挿管期間ではそれぞれ39.3日および5.3日とグループ2で著明な術後挿管期間の短縮を認めた（p<0.01）。
【結論】我々の新しい治療法の導入により、生後24時間以内発症の先天性横隔膜ヘルニアの治療成績は著明に改善した。

キーワード：先天性横隔膜ヘルニア，低圧換気，ステロイド，サーファクタント。（特別掲載）