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Original Article

Neuraxial anesthesia in ex utero intrapartum therapy for parturients with fetal congenital diaphragmatic hernia: a prospective observational study

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ABSTRACT

Background: Congenital diaphragmatic hernia (CDH) is characterized by defects in the fetal diaphragm and thoracic herniation of the abdominal viscera. The ex utero intrapartum treatment (EXIT) procedure is used to establish the fetal airway while on placental support. These EXIT procedures are commonly performed under general anesthesia, which increases maternal bleeding and the risk of insufficient placental perfusion subsequently. This study investigated the feasibility of performing neuraxial anesthesia for the EXIT procedure for fetal congenital diaphragmatic hernia to improve outcomes.

Methods: Parturients with fetal CDH who underwent an EXIT procedure between January 2019 and May 2021 in our institution were recruited. Variables evaluated included gestational age, surgical time, intra-operative blood loss, peri-operative hemoglobin, maternal complications, fetal lung-to-head ratio, time on placental bypass, and postnatal outcome.

Results: Twenty-two cases were included. All procedures were performed under neuraxial anesthesia. The median gestational age at the time of the EXIT procedure was 37 weeks. The median estimated blood loss was 200 mL. There was no report of an adverse maternal event. The placental bypass time was 142.9 ± 72.6 s, and access to the airway was successfully established within the bypass time. Twenty-one neonates reached an Apgar score of 9 at 5 min. In the first two hours after birth, the average pH of neonatal peripheral arterial blood was 7.35 ± 0.07 (n = 19), and lactate level 1.85 ± 0.71 mmol/L (n = 19).

Conclusions: In the EXIT procedure to establish an airway for fetal CDH, neuraxial anesthesia proved a feasible technique for maternal anesthesia.

Introduction

Congenital diaphragmatic hernia (CDH) is a congenital defect in the fetal diaphragm that can cause herniation of abdominal viscera into the thorax. The resulting pulmonary hypoplasia and pulmonary hypertension are primary determinants of neonatal mortality.[1] Surgical repair of CDH after birth is the primary treatment for these patients.[1,2] In fetal CDH, early endotracheal intubation is indicated, and bag-valve-mask ventilation should be strictly avoided.[3] The ex utero intrapartum treatment (EXIT) procedure involves partial delivery of the fetus during a cesarean delivery, allowing the fetal airway to be secured while fetal oxygenation is maintained by placental perfusion.[4]

General anesthesia (GA) has been the main anesthetic technique used.[5] Inhalational anesthetic agents at high concentration are often used to provide uterine relaxation. The use of intravenous agents in EXIT, including propofol and remifentanil, is also reported.[6–8] However, GA with extensive uterine relaxation increases the risk of maternal hemorrhage, ventricular systolic dysfunction and fetal bradycardia.[4,9,10]

In fetal CDH, an EXIT procedure aims to establish an airway.[9,11] The time on placental bypass is relatively short and predictable, indicating the suitability of neuraxial anesthesia, which has been reported occasionally.[12–15] This study aimed to explore the outcomes after neuraxial anesthesia in a case series of parturients with fetal CDH. The main outcomes were the safe placental bypass time, maternal adverse

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events, neonate Apgar scores, and neonatal arterial blood gas analysis two hours after birth.

Methods

The study was approved by the Ethics Committee of Peking Union Medical College Hospital (S-K1739). We employed a prospective longitudinal design. Parturients with fetal CDH scheduled for the EXIT procedure in our institution were recruited from January 2019 to May 2021. Written consent was obtained from all subjects.

A multidisciplinary team including anesthesiologists, obstetricians, pediatricians, pediatric surgeons, and operating room nursing teams were involved in management. Before the surgery, an interdisciplinary consultation was held to optimize the operation and anesthetic plan for each case. All patients received neuraxial anesthesia comprising either combined spinal-epidural (CSE) anesthesia or epidural anesthesia alone, according to the preference of the attending anesthesiologist. In cases of CSE anesthesia, 0.75% hyperbaric bupivacaine (diluted with 5% dextrose) 10 to 15 mg was injected at a rate of approximately 0.2 mL/s. If epidural anesthesia alone was used, a combination of 0.5% ropivacaine and 1% lidocaine 10 to 15 mL was given through the epidural catheter after a test dose of 1% lidocaine 3 mL. The dermatomal level was verified by loss of sensation to cold, aiming to achieve and maintain T4-T6. A phenylephrine infusion was titrated to keep the maternal blood pressure within 20% of the baseline. After hysterotomy, the head and one shoulder of the fetus were partially delivered, and the fetus was placed face up. The oropharyngeal area was suctioned to improve the visual field. The fetus was intubated by an anesthesiologist using a sterile videolaryngoscope, without adjunctive anesthetic or opioid. Appropriate tracheal tube placement was confirmed by an end-tidal carbon dioxide detector and fetal chest auscultation. Once the fetal airway was secured, the rest of the fetal body was delivered, and the umbilical cord was clamped. A bolus of 10 IU oxytocin was given intravenously, followed by a continuous infusion of another 10 IU. The newborn was assessed and resuscitated by pediatricians in the same operating room's incubator. Finally, the neonate was transferred to a specialised pediatric hospital for surgical repair of the hernia.

Demographic information and clinical data were recorded in the electronic anesthetic record and medical record during the treatment and follow-up. An experienced sonographer assessed the severity of the diaphragmatic hernia between 22 and 32 weeks' gestational age, and the lung-to-head ratio (LHR) and the observed-to-expected ratio were documented. Adverse maternal events included postpartum hemorrhage (defined as >1000 mL), significant intra-operative hypotension, and placental abruption. The amniotic fluid was collected by a separated suction device. If the blood loss was <200 mL, most of the blood was collected in the suction. Then, the estimated blood loss was calculated from the blood volume collected by suction minus the volume of irrigating saline. If the blood loss was >200 mL, we estimated blood loss by adding the blood volume collected by the suction to that from weighing the surgical sponges before subtracting the volume of irrigation saline and the dry weight of sponges. Finally, the volume was rounded to the nearest 10 mL. Placental bypass time was defined as the time from partial delivery of the fetus to successful intubation and umbilical cord clamping. The neonate Apgar scores at 1 and 5 min were recorded. The arterial blood gas was sampled from the neonatal umbilical artery or a peripheral artery two hours after birth. Descriptive statistics were used to summarize the data. Normally distributed data are presented as mean ($\pm$SD); otherwise, median (range) is reported.

Results

Twenty-two parturients with fetal CDH underwent EXIT procedures in our institution between January 2019 and May 2021. All patients received neuraxial anesthesia and none required conversion to GA.

The maternal characteristics, intra-operative management, and outcomes are presented in Table 1. No adverse maternal event occurred. The length of hospital stay was slightly longer than that of other cesarean delivery patients, usually three days. There was a slight reduction in hemoglobin concentration postoperatively but no need for transfusion.

The placental bypass time and fetal outcomes are summarized in Table 2. The time on placental support was 142.9 $\pm$ 72.6 s, with a longest bypass time of 5 min and a shortest of 40 s. One neonate received emergency extracorporeal membrane oxygenation because pulmonary oxygenation could not be secured by mechanical ventilation. For the other 21 neonates, the Apgar score at 1 min was 8.3 $\pm$ 0.7. The items of the Apgar test that subtracted from the score were impaired muscle tone, skin colour, and endotracheal intubation. At 5 min, these 21 neonates all reached an Apgar score of 9. Neonatal arterial blood gas analyses 2 h after birth were performed in 19 cases (Table 2). The neonates were transferred to a specialised pediatric hospital for surgical repair once their vital signs had stabilized.

Discussion

We present the data from 22 EXIT procedures for fetal CDH performed with neuraxial anesthesia at our institution. In this study, neu-

Table 1
Maternal characteristics and outcomes (n = 22)

Variable	Value
Pre-operative characteristics	
Maternal age (y)	30.4 ± 4.1
Weight (kg)	73.6 ± 11.6
Height (cm)	161.2 ± 6.4
Gestational age (weeks)*	37 (37–37)
Nulliparous, n	14/22
Intra-operative management	
Surgical time (min)	73.4 ± 14.6
Intra-operative input volume (mL)	1955 ± 320.3
Estimated blood loss	200 (200–265.2)
Urine output	227.3 ± 118.2.1
Phenylephrine infusion (μg/kg/min)	0.20 ± 0.11
Total dose of phenylephrine (mg)	0.71 (0.50–1.29)
Maternal outcome	
Length of stay (days)	5.6 ± 1.3
Pre-operative Hb (g/L)	112.2 ± 12.3
Postoperative Hb (g/L)	104.5 ± 12.6
Blood transfusion, n	0/22
Placental abruption, n	0/22

Values are presented as mean ± SD, median (range), or n (%).
* Gestational age at the time of the procedure.

Table 2
Fetal characteristics and outcomes

Variable	Value
Fetal characteristics (n = 22)	
Left diaphragm hernia, n	19/22
LHR	2.32 ± 0.78
o/e LHR (%)	65.2 ± 17.2
Placental bypass time (s)	142.9 ± 72.6
Apgar score and neonatal ABG	
Apgar score at 1 min	8.3 ± 0.7
Apgar score at 5 min	9 (9–9)
pH	7.35 ± 0.07
PaO_2 (mmHg)	107.1 (69.3–154)
$PaCO_2$ (mmHg)	36.9 ± 8.0
Lactate (mmol/L)	1.85 ± 0.71

* Values are presented as the mean ± SD, median (range), or n (%).
LHR: lung-to-head ratio. o/e LHR: observed-to-expected lung-to-head ratio. ABG: arterial blood gas.

raxial anesthesia provided adequate surgical conditions for the procedure, and there were no reports of maternal or fetal adverse events. The process was also well tolerated by the women and their infants.

Although some suggest that tracheal intubation is not mandatory in cases that are diagnosed antenatally as being mild,[16] with the infant's respiratory effort the risks of further insufflation of the abdominal cavity and subsequent aspiration increase.[17] In our experience, further herniation after birth is one of the primary causes of poor prognosis after surgical repair. Further, with pulmonary dysplasia and contraindication to bag-mask ventilation, the neonate is at risk of hypoxia without an endotracheal tube. Thus, early intubation and positive pressure ventilation can protect the airway and avoid further herniation. Additionally, it has been found that performing an EXIT procedure to establish the airway and commencing resuscitation on placental bypass improves the outcome of infants with CDH.[18]

The key feature of the EXIT procedure is the partial delivery of the fetus and maintenance of placental circulation by uterine relaxation. The most popular way to provide extensive uterine relaxation has been by the use of high concentrations of anesthetic gases or inhaled anesthesia combined with propofol and remifentanil.[4] Although GA provides effective uterine relaxation, it brings a high incidence of maternal adverse events, the primary one being postpartum hemorrhage. An estimated blood loss of >1000 ml has been reported.[9] In parturients, postpartum haemorrhage increases the risk of hypotension and the need for blood transfusion. As for the fetus, excessive hemorrhage might impair placental perfusion, increase the incidence of placental abruption, and increase the risk of intubation after umbilical cord clamping.[5]

Another way to maintain uterine relaxation is the administration of intravenous nitroglycerin. There have been some reports of EXIT procedures performed under CSE anesthesia.[12–15] In these cases, intravenous nitroglycerin was used to maintain uterine relaxation and prevent placental abruption during the procedure. Theoretically, the uterine relaxation from nitroglycerin can be resolved quickly after discontinuation, and its hypotensive effect corrected by vasopressors. However, there is still a potential risk of protracted uterine atony and profound hypotension, which can lead to maternal hemorrhage and hypotension, and insufficient placental support.[19,20] In EXIT procedures done under neuraxial anesthesia and intravenous nitroglycerin, the estimated blood loss has ranged from 800 mL to 1200 mL. However, some procedures were because of various other fetal congenital malformations that require a longer bypass time, which may have contributed to greater maternal blood loss.

The main purpose of the EXIT procedure for CDH is to establish an airway for neonatal resuscitation. Since fetal airway malformation had been precluded in the prenatal evaluation, the procedure was not expected to be lengthy. In our series, the average time on placental support was only 143 s, which supports the suitability of neuraxial anesthesia without extra uterine relaxants. With careful manipulation, most of the fetal body remained in the uterus, so intra-uterine tension could be maintained to prevent placental abruption. Under this circumstance, we have demonstrated that neuraxial anesthesia can provide a safe placental bypass time of up to 5 min. Under neuraxial anesthesia conditions, uterine tone can be quickly restored using oxytocin after the clamping of the umbilical cord. The average blood loss from our EXIT procedure was approximately 200 mL, and there was no significant reduction in postoperative hemoglobin concentration. Additionally, neuraxial anesthesia avoided the risks of failed intubation and aspiration that have been associated with GA in obstetric patients.

The effect of anesthesia on neonatal outcome should also be considered. During the EXIT procedure, insufficient placental perfusion increases the risk of neonatal acidosis and hypoxemia.[21] A high concentration of inhalational anesthetic increases the risk of fetal bradycardia. In a group of neonates receiving EXIT procedures to secure the airway under GA, the umbilical cord pH was 7.12, and the plasma lactate concentration 3.8 mmol/L at 30 min after delivery.[18] In our series, neuraxial anesthesia was associated with satisfactory outcomes of neonates with CDH. Because the intubation was completed quickly, no fetus was exposed to a general anesthetic drug or opioid. The 5 min Apgar score of all 21 neonates reached 9/10 after tracheal intubation and bradycardia was not present. In addition, without deep GA or additional uterine relaxant, the maternal blood pressure was easily maintained by titration of phenylephrine, thus avoiding insufficient placental perfusion. The average pH of neonatal arterial blood of 7.35 and lactate of 1.85 mmol/L in the first two hours after birth indicated satisfactory organ perfusion and ventilation.[16]

Although we have demonstrated the feasibility and potential advantages of neuraxial anesthesia when performing EXIT procedures for parturients with fetal CDH, the indications supporting choice of this anesthetic modality should be carefully considered. First, all the procedures were performed during late pregnancy in the absence of fetal airway abnormalities in the prenatal assessment. If a longer placental bypass time is anticipated during the procedure, this anesthetic modality may not be suitable. Second, EXIT procedures need the cooperation of a multidisciplinary team and we believe experienced gynecologists, anesthesiologists, and pediatricians are crucial. Third, CSE anesthesia and epidural anesthesia do not provide fetal sedation or anesthesia. Once the airway has been secured, fetal anesthesia can be achieved with an intramuscular injection of ketamine, opioid, and neuromuscular blocking drugs, as needed.

In summary, we describe the use of neuraxial anesthesia in 22 women presenting with fetal CDH requiring an EXIT procedure to establish a neonatal airway. Neuraxial anesthesia appears to be a safe means of maternal anesthesia to provide appropriate conditions for the procedure, and improve the outcome of parturients and neonates in this setting.

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Declaration of interests

The authors have no declarations to make.

References

1. Puligandla PS, Skarsgard ED, Offringa M, et al. Diagnosis and management of congenital diaphragmatic hernia: a clinical practice guideline. *CMAJ*. 2018;190:E103–E112.
2. Tsao K, Johnson A. Fetal tracheal occlusion for congenital diaphragmatic hernia. *Semin Perinatol*. 2020;44:151164.
3. American Heart Association. 2005 American Heart Association (AHA) guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care (ECC) of pediatric and neonatal patients: pediatric advanced life support. *Pediatrics*. 2006;117:E1005–E1028.
4. Weber SU, Kranke P. Anesthesia for predelivery procedures: ex-utero intrapartum treatment/intrauterine transfusion/surgery of the fetus. *Curr Opin Anaesthesiol*. 2019;32:291–297.
5. Nelson O, Simpao AF, Tran KM, Lin EE. Fetal anesthesia: intrauterine therapies and immediate postnatal anesthesia for noncardiac surgical interventions. *Curr Opin Anaesthesiol*. 2020;33:368–373.
6. Garcia PJ, Olutoye OO, Ivey RT, Olutoye OA. Case scenario: anesthesia for maternal-fetal surgery: the Ex Utero Intrapartum Therapy (EXIT) procedure. *Anesthesiology*. 2011;114:1446–1452.
7. Dinges E, Heier J, Delgado C, Bollag L. Multimodal general anesthesia approach for Ex Utero Intrapartum Therapy (EXIT) procedures: two case reports. *Int J Obstet Anesth*. 2019;38:142–145.
8. Ioscovich A, Shen O, Sichel JY, Lajos Y, Orkin D, et al. Remifentanil-nitroglycerin combination as an anesthetic support for ex utero intrapartum treatment (EXIT) procedure. *J Clin Anesth*. 2011;23:142–144.
9. Kumar K, Miron C, Singh SI. Maternal anesthesia for EXIT procedure: A systematic review of literature. *J Anaesthesiol Clin Pharmacol*. 2019;35:19–24.
10. Novoa RH, Quintana W, Castillo-Urquiaga W, Ventura W. EXIT (ex utero intrapartum treatment) surgery for the management of fetal airway obstruction: A systematic review of the literature. *J Pediatr Surg*. 2020;55:1188–1195.

11. Abraham RJ, Sau A, Maxwell D. A review of the EXIT (Ex utero Intrapartum Treatment) procedure. *J Obstet Gynaecol*. 2010;30:1–5.
12. Benonis JG, Habib AS. Ex utero intrapartum treatment procedure in a patient with arthrogryposis multiplex congenita, using continuous spinal anesthesia and intravenous nitroglycerin for uterine relaxation. *Int J Obstet Anesth*. 2008;17:53–56.
13. Clark KD, Viscomi CM, Lowell J, Chien EK. Nitroglycerin for relaxation to establish a fetal airway (EXIT procedure). *Obstet Gynecol*. 2004;103:1113–1115.
14. Fink RJ, Allen TK, Habib AS. Remifentanil for fetal immobilization and analgesia during the ex utero intrapartum treatment procedure under combined spinal-epidural anesthesia. *Br J Anaesth*. 2011;106:851–855.
15. George RB, Melnick AH, Rose EC, Habib AS. Case series: Combined spinal epidural anesthesia for Cesarean delivery and ex utero intrapartum treatment procedure. *Can J Anaesth*. 2007;54:218–222.
16. Snoek KG, Reiss IK, Greenough A, et al. Standardized postnatal management of infants with congenital diaphragmatic hernia in Europe: The CDH EURO Consortium Consensus - 2015 Update. *Neonatology*. 2016;110:66–74.
17. Chatterjee D, Ing RJ, Gien J. Update on congenital diaphragmatic hernia. *Anesth Analg*. 2020;131:808–821.
18. Lefebvre C, Rakza T, Weslinck N, et al. Feasibility and safety of intact cord resuscitation in newborn infants with congenital diaphragmatic hernia (CDH). *Resuscitation*. 2017;120:20–25.
19. Mohammad S, Olutoye OA. Airway management for neonates requiring ex utero intrapartum treatment (EXIT). *Paediatr Anaesth*. 2020;30:248–256.
20. Subramanian R, Mishra P, Subramaniam R, Bansal S. Role of anesthesiologist in ex utero intrapartum treatment procedure: A case and review of anesthetic management. *J Anaesthesiol Clin Pharmacol*. 2018;34:148–154.
21. Chinnappa V, Halpern SH. The ex utero intrapartum treatment (EXIT) procedure: maternal and fetal considerations. *Can J Anaesth.*. 2007;54:171–175.