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Sedation Prior to Intubation at Birth in Infants with Congenital Diaphragmatic Hernia: An International Survey on Current Practices

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Keywords
Sedation · Intubation · Congenital diaphragmatic hernia · Survey · Delivery room

Abstract

Introduction: Infants with congenital diaphragmatic hernia (CDH) are commonly intubated immediately after birth. Consensus on whether to provide sedation prior to intubation in the delivery room is lacking, although avoidance of stress is especially important in this population with high risk of pulmonary hypertension. We aimed at obtaining an overview of local pharmacological interventions and at providing guidance on delivery room management. ***Methods:*** An electronic survey was sent to international clinicians in referral centres for prenatal and postnatally diagnosed infants with CDH. This survey addressed demographic information, use of sedation and/or muscle relaxant prior to intubation, and use of pain scales in the delivery room. ***Results:*** We received 93 relevant responses from 59 centres. Most centres were from Europe (n = 33, 56%), followed by North America (n = 16, 27%), Asia (n = 6, 10%), Australia (n = 2, 3%), and South America (n = 2, 3%). A total of 19% (11/59) of the centres routinely provided sedation prior to intubation in the delivery room, with midazolam and fentanyl being most often used. Methods of administration varied for all medications provided. Only 5 of 11 centres using sedation reported an adequate sedative effect prior to intubation. Muscle relaxants prior to intubation were used in 12% (7/59) of the centres, although not always in combination with sedation. ***Conclusion:*** This international survey shows a substantial variation in sedation practices in the delivery room and scarce use of both sedative agents and muscle relaxants prior to intubation of CDH infants. We provide guidance on developing protocols for pre-intubation medication in this population.

Introduction

Congenital diaphragmatic hernia (CDH) is a rare condition characterised by incomplete closure of the diaphragm and herniation of abdominal organs into the foetal chest. After birth, many of those infants will experience respiratory insufficiency, often in combination with pulmonary hypertension. To avoid hypoxia and

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consequently worsening of the cardiorespiratory state, they often require respiratory support in the delivery room. As non-invasive ventilation strategies are not used due to concerns about bowel distension, intubation is often performed within the first minutes after birth [1].

The timeframe for administering medication prior to endotracheal intubation is limited given the relative urgency of providing invasive respiratory support; as such, sedation is often given after securing the airway. However, awake intubation induces stress and pain, reflected by physiological responses such as bradycardia, hypoxia, and a rise in systemic arterial blood pressure and intracranial pressure [2, 3]. Neonatal exposure to stress also affects long-term outcomes in experimental studies, warranting adequate pain treatment in newborns [4]. Pre-intubation sedation decreases the pain score, attenuates the negative physiological responses to intubation, minimises the risk of airway injury, and reduces the number of attempts till and time to successful intubation [2]. These are desirable outcomes in infants with CDH, as stress – including hypoxia – is an important trigger for pulmonary hypertension and endotracheal intubation is often challenging due to tracheal deviation.

The availability of guidelines on pre-intubation sedation in infants with CDH is limited: the CDH EURO Consortium guideline recommends to avoid neuromuscular blockade and to provide pre-intubation medication but acknowledges that this is not always possible; the Canadian guideline recommends combining sedation with neuromuscular blockade in mechanically ventilated infants, although not specifically in the delivery room; the American guideline does not address delivery room management [5–7]. Furthermore, research considering methods of administration other than intravenous (IV) administration, such as intranasal (IN), intramuscular (IM), umbilical vein (UV), is lacking, although these methods could have a shorter time to action. In combination with a lack of consensus, this likely translates into a substantial variation in local practices hampering assessment of the optimal sedation strategy. In this study, we collected information on local practices in an international survey, aiming at defining future research directions and providing guidance on sedation prior to delivery room intubation in infants with CDH.

Methods

This study was initiated by the Erasmus MC, Rotterdam, The Netherlands. Data were collected using an online survey developed in LimeSurvey (LimeSurvey GmbH, Hamburg, Germany). The validity of the content was ensured by pre-testing the survey by neonatologists working at the neonatal intensive care unit in the Erasmus MC and the Leiden University Medical Center. Based on their feedback, the survey was revised. The survey was distributed during the International Congenital Diaphragmatic Hernia Symposium in Glasgow (2022), via existing networks (i.e., ERNICA and CDH EURO) and via email. We aimed at collecting data on routine practices in as many centres as possible. The survey was accessible from April 2022 to August 2022. The topics addressed are demographic information, routine use of pre-intubation sedation and muscle relaxant in infants with CDH, reasons for premedication use, types of medication and methods of administering, use of pain scales in the delivery room, and ideas on how to improve the current intubation protocol for CDH infants. Supplementary material A (for all online suppl. material, see www.karger.com/doi/10.1159/000530573) provides the full-text survey questions. Responses from centres that are not involved in postnatal management of infants with CDH were excluded. In case of multiple responses from the same centre, the responses were combined to one response per centre. In case of major discrepancies between responses, we asked the respondents for clarification. Descriptive statistics are used to depict the results from the survey and data are presented as numbers (percentages).

Results

Demographic Information

Of 147 responses, 54 were excluded due to either no answers at all or no answers on the questions about sedation. The remaining 93 responses came from respondents working in 59 different centres. Those responses coming from respondents working in the *same centre* were combined into one response per centre, leaving the responses from 59 centres in 23 countries. Most centres were from Europe (55.9%, $n = 33$), followed by North America (27.1%, $n = 16$), Asia (10.2%, $n = 6$), Australia (3.4%, $n = 2$), and South America (3.4%, $n = 2$). The caseload of CDH cases per year was <5 in 16.9% ($n = 10$), 5–10 in 32.2% ($n = 19$), 10–15 in 23.7% ($n = 14$), and >15 in 27.1% ($n = 16$).

Premedication in the Delivery Room in Infants with CDH

Pre-intubation *sedation* in infants with CDH was routinely provided in 11 centres (18.6%) and not provided in 48 centres (81.4%). Table 1 depicts the routine premedication and whether premedication resulted in an adequate sedative effect prior to intubation. The centre using IV ketamine reported the use of IM ketamine in case no IV access could be established. Only in five of eleven centres in which pre-intubation sedation was provided, an adequate sedative effect was observed prior to performing intubation. Seven of eleven centres reported a second choice of premedication: fentanyl IV/IN ($n = 2$), midazolam UV/IV ($n = 2$), ketamine UV ($n = 1$), morphine UV ($n = 1$), and propofol IV ($n = 1$).

Table 1. Reported routine pre-intubation analgo-sedatives in infants with CDH

	First choice sedatives	Sedative effect prior to intubation[a]	Second choice sedatives
Centre 1	Fentanyl IV/UV	No	
Centre 2	Midazolam IN	Not known	
Centre 3	Fentanyl IV/UV	Yes	Midazolam UV
Centre 4	Ketamine IM	Yes	
Centre 5	Fentanyl UV	No	Ketamine UV
Centre 6	Fentanyl IV	Yes	Midazolam IV
Centre 7	Midazolam IV	Not known	Fentanyl IV
Centre 8	Midazolam UV	No	Morphine UV
Centre 9	Ketamine IV/IM	Yes	Propofol IV
Centre 10	Morphine IV	Not known	
Centre 11	Midazolam IN	Yes	Fentanyl IN

IM, intramuscular; IN, intranasal; IV, intravenous; UV, umbilical vein. [a]Sedative effects prior to intubation as observed by respondents.

Reported reasons to use pre-intubation sedation were prevention of stress and/or pain ($n = 7$) and facilitation of intubation ($n = 6$). The most frequent reason not to use sedation was to avoid a delay in intubation ($n = 30$). Other reasons were the lack of an available protocol for the use of sedation ($n = 6$), no need to sedate the infant, especially in non-vigorous infants with severe pulmonary hypoplasia ($n = 2$), and the risk of suppressing spontaneous breathing ($n = 4$). Many centres not providing pre-intubation sedation stated the need to improve current management. Possible suggestions were implementing video registration, performing stabilisation with an intact umbilical cord, and considering alternative methods of administration, such as IN/IM/UV.

Muscle relaxants prior to intubation were used by 7 centres (11.9%) and not used by 50 centres (84.7%). Two centres were uncertain on their institutional policy. Overall, only four centres used a combination of a sedative and muscle relaxant, and thus three centres used a muscle relaxant without sedative. The reported muscle relaxants were rocuronium (IV/UV), vecuronium (IV/UV), and atracurium (IV/IM). Reported reasons for the use of muscle relaxants were optimisation of intubation ($n = 4$), avoidance of stress ($n = 1$), prevention of thoracic rigidity caused by fentanyl ($n = 1$), and prevention of spontaneous breathing and air entry into the stomach or bowel ($n = 1$).

Pain Scales in the Delivery Room

The use of pain scales to assess the infant's level of (dis)comfort in the delivery room was limited to three hospitals. The mentioned scores are Kölner Sedierungsbogen; Neonatal Pain, Agitation and Sedation Scale (N-PASS); Premature Infant Pain Profile (PIPP); and the Children's Revised Impact of Event scale (CRIES) score.

Discussion

The actual positive effects of pre-intubation sedation have been clearly demonstrated, but our survey shows that premedication in the delivery room with either sedatives and/or muscle relaxants is very scarcely used in infants with CDH. Although many centres emphasised the need to improve current pain and stress management in this population, only 19% of the responding centres commonly use premedication, and between these centres, local practices vary widely.

The limited timespan between administering sedation and the moment of intubation inherently plays a role in premedication practices, with intubation often being successful within 2 min after birth [8]. This translates into the need for premedication with a short time till action, which is not the case for several of the currently used medications. This emphasises the need for evidence-based protocols considering aspects such as time till and duration of action and potential adverse cardiorespiratory effects.

Apart from the choice of medication, another important consideration is the method of administration. IV administration will usually have the quickest effect but establishing IV access prior to intubation can be challenging and it can induce neonatal stress. An alternative could be using the umbilical cord to administer medication; however, this might not be preferable when the infant is stabilised with an intact cord – an intervention that is currently under investigation in two randomised trials [9, 10]. On the other

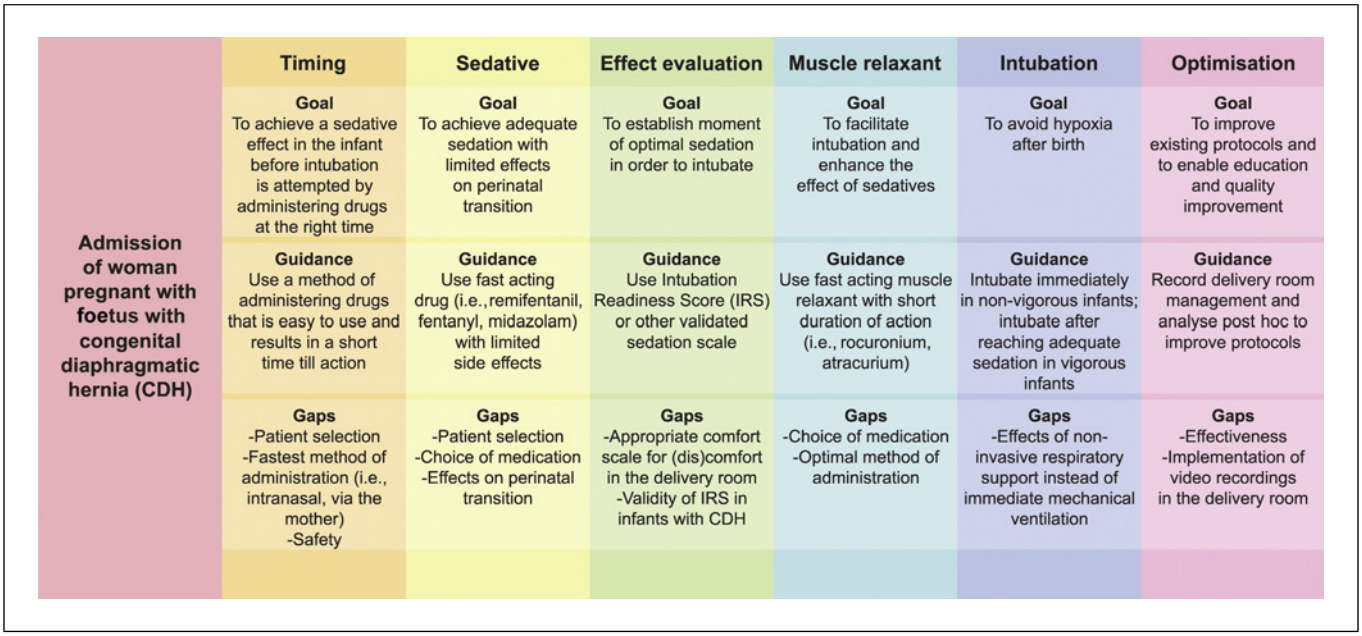

Fig. 1. Guidance on clinical practice and overview of current knowledge gaps in pre-intubation medication practices in infants with CDH.

hand, we can speculate that the advantage of infants still having the benefits of being oxygenated via the placental gas exchange might provide a larger window for administering pre-intubation sedation.

The opioid fentanyl is used by almost one-third of our respondents providing pre-intubation analgesia and potential sedation. In general, IV fentanyl has a rapid effect, i.e., within 1 min, and it exerts minimal haemodynamic side effects [11, 12]. However, one major concern is the rigid chest syndrome, especially after fast infusion, which could be treated with either naloxone or muscle relaxants [13]. The onset of action of fentanyl IN and IM is suggested to be 5–10 min and 7–8 min, respectively, reducing their applicability in the delivery room [12]. A faster alternative is remifentanil, with an onset of action of 3 min in case of IN administration and a duration of action of less than 6 min [12]. However, remifentanil is more difficult to titrate and has a high risk of chest wall rigidity [14].

Another agent reported by a third of the centres is midazolam, a benzodiazepine with effect within 2 min when administered IV and 5 min when administered IN [12]. A potential disadvantage of midazolam includes haemodynamic effects such as hypotension, decreased cardiac output, and decreased cerebral blood flow velocity [2, 15]. Responding centres tend to combine midazolam with morphine or fentanyl, but studies support a potential better effect on pain and stress when using fentanyl as compared to morphine [3, 12]. With morphine having both an unacceptable long time till action (>5–15 min) and known negative effects on neonatal haemodynamics, including hypotension and bradycardia, its use prior to urgent intubation is obsolete [16, 17].

Two centres reported using ketamine as pre-intubation sedation, and interestingly, both centres report a sedative effect of IM ketamine prior to intubation. IM ketamine has been shown to result in significantly decreased levels of pain and distress in infants and a longer duration of action when compared to IV ketamine [18]. Although IM ketamine might have a longer time till action than IV ketamine, the latter has a rapid onset of action <1 min [19]. Potential side effects of ketamine, such as hallucinations in older patients and decreases in arterial blood pressure, cannot be ruled out, but no major side effects were observed in earlier trials in neonates [19, 20].

An alternative method to reach sedation in the infant immediately after birth could potentially be to administer medication to the mother before birth of the infant. None of the responding centres are currently using this method of sedation. A potential candidate could be pethidine, an opioid often used for relief of labour pain, although it might have limited efficacy [21, 22]. Maternal sedation during labour is unwanted, and reassuringly, most studies did not show a strong sedative effect during labour [23, 24]. Other than that, pethidine can result in neonatal side effects, such as respiratory depression and a decreased alertness after birth [21].

However, these potential side effects might actually be favourable in infants with CDH as respiratory depression and decreased alertness could facilitate intubation.

Approximately one-third of the centres using pre-intubation sedation also administer muscle relaxants prior to intubation. However, some centres reported the use of muscle relaxants *without* sedation, a practice that is deemed highly questionable. The positive effects of specific sedatives are known to increase when combined with muscle relaxants, an example being fentanyl [12]. Also, a lower incidence of adverse events was reported when performing intubation after administering a combination of sedation and neuromuscular blockade rather than just sedation [25]. Muscle relaxants with a possible onset of action within minutes include agents reported in our survey, such as rocuronium (1–3 min) and vecuronium (2–3 min), but this all concerns IV administration [12]. Although rocuronium could be administered IM, its onset of action increases to 7 min [12]. With vecuronium having a slow elimination phase and thus a long duration of effect, its use in an acute setting seems limited [26].

One could also argue that rescue intubation without sedation might be acceptable in non-vigorous infants, as it has been suggested that this subgroup will likely only experience the negative effects on the cardiorespiratory system without having the benefits of sedation. In vigorous infants, on the other hand, pain scales or sedation scales could aid in establishing the level of (dis)comfort in the delivery room and thus the need for premedication. The scales mentioned in our survey are, however, not validated for the assessment of either (dis)comfort in the delivery room or the effect of pre-intubation sedation [27, 28]. We suggest using the Intubation Readiness Score that could assist in establishing the optimal moment to intubate after providing sedation [28].

Our data clearly demonstrate that immediate intubation of almost all CDH infants, as dictated by most guidelines, often results in awake intubation. This potentially causes neonatal stress and pain but also negative effects on the long term, although further research would be required to evaluate differences between centres with different sedation practices. We hypothesise that a change of the standard of care interventions after birth could optimise the transition period by avoiding neonatal stress and pain. A combination of delayed cord clamping, early positioning of an oro-/nasogastric tube with continuous suctioning, and initiating non-invasive respiratory support after birth, such as high flow or continuous positive airway pressure, would provide a larger timespan to administer premedication without the problem of bowel distension. Intubation should then only be done after reaching adequate sedation and muscle relaxation. As premedication reduces the time till successful intubation, we speculate that this changed approach might not have a significant impact on the time till successful intubation. Given the lack of studies on non-invasive ventilation in infants with CDH and the current dogma of required primary intubation, we cannot provide clear recommendations on the use of this modality. We emphasise that this approach should only be used in vigorous infants with spontaneous breathing and that non-invasive respiratory support should be adjusted to the individual infant's needs.

Considering the results of our survey, including the questionable choices on pre-intubation medication and existing literature, we have created an overview with guidance on clinical practice and current knowledge gaps (Fig. 1). However, it may not be possible to address all questions by means of a randomised controlled trial given the issues performing such studies in rare diseases (slow recruitment, long trial periods, and multicentre design). Prospective data collection in international registries could be considered an alternative to overcome some of these hurdles and to inspire innovations in perinatal stabilisation.

To the best of our knowledge, this is the first study collecting data on local practices regarding pre-intubation medication in infants with CDH. We were able to collect responses from large referral centres across the world with expertise on the management of infants with CDH. Our results are probably most representative of European practices, as the majority of the respondents work in centres across Europe. Another limitation inherent to any survey research is the potential of recall bias; however, we expect that the impact will be limited as most respondents work in centres with a relatively high number of CDH cases per year. On top of that, several responses were combined as certain centres were represented by more than one respondent, providing a validation of their responses.

Conclusion

The lack of consensus on the use of sedation prior to intubation translates into variation in clinical practices in infants with CDH across the world. In fact, despite clearly described negative effects of awake intubation, premedication in infants with CDH is only used in a minority of centres. Although innovations such as delayed cord clamping could aid the perinatal transition and increase the timespan to provide sedation, further research and guidelines on both the optimal pre-intubation medication strategies and optimal sequence of interventions after birth are warranted.

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Statement of Ethics

In accordance with local guidelines of the Medical Ethical Committee of the Erasmus MC and national guidelines, ethical approval and consent were not required as this study was not based on patient data. Informed consent to participate was not directly obtained but inferred by completion of the questionnaire/participation in the interview.

Conflict of Interest Statement

The authors report no conflicts of interest.

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Authors' Contributions

E.J.J.H.-O., A.M.B., and P.L.J.D. conceptualised and designed the online survey. E.J.J.H.-O., R.K., I.K.M.R., and P.L.J.D. contributed to the analysis and interpretation of the results. E.J.J.H.-O. and A.M.B. wrote the first draft, which was critically reviewed by all authors. E.J.J.H.-O., A.M.B., G.E.v.d.B., S.H.P.S., R.K., A.B.t.P., I.K.M.R., and P.L.J.D. were all involved in the conception of this paper.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author, Dr. P.L.J. DeKoninck.

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