ANAESTHESIOLOGIC AND SURGICAL PERSPECTIVES OF PATIENTS BORN WITH ESOPHAGEAL ATRESIA

The knife cuts both ways

Camille E van Hoorn

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Het mes snijdt aan twee kanten

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General Introduction

Esophageal atresia is a rare congenital malformation of the esophagus in which the proximal part of the esophagus is not connected to the distal part and the stomach. It affects around one in every 4000 births.[1] At present, the reported in-hospital mortality rate of infants born with esophageal atresia is 5-9%, with the deaths mainly related to prematurity and associated comorbidities.[2,3] As improvements in care have led to less mortality, the long-term morbidity is increasingly of concern in this patient population. Besides physical morbidity, impairment of the neurodevelopment may occur. In the first months of life, the brain is developing rapidly and is therefore extra vulnerable to both internal and external stimuli.[4] Therefore, the long-term neurodevelopment after the intensive treatment of esophageal atresia in the neonatal period is at risk.

Various stimuli could affect the development of the brain, such as stress, surgery, anesthetics, artificial ventilation and infection, all influenced by the critical illness of these patients. A previous study from our group reported neurodevelopmental problems in patients who had undergone neonatal surgery – including children with esophageal atresia.[5]

Since esophageal atresia has direct effects on the function of the gastrointestinal and respiratory tracts, most long-term outcome research is focused on the gastro-intestinal and respiratory development.[6,7] However, the long-term outcome of this patient population goes beyond the problems directly caused by the congenital anatomical malformation itself. Research suggests that a part of the children born with esophageal atresia suffer long-term neurodevelopmental impairments.[8] Causes of these neurodevelopmental impairments are unknown. The anatomical malformation itself does not lead to long-term neurodevelopmental impairments, but the impairments may be caused by concomitant factors. It is thought that the outcome is influenced by multiple factors of the interventions required to not only solve the anatomical malformation, but also co-morbidities or their treatment. During hospitalization in the first weeks after birth, the neonate suffers critical illness, defined as illness of the neonate requiring admission to an intensive care unit for organ support. Major surgery, such as the lengthy surgery for correction of the esophageal atresia itself during the first days of life, can lead to critical illness. Factors that could influence the long-term outcome include acute problems during the perioperative phase, such as metabolical and immunological changes and the repeated and/or lengthy exposure to surgery and anesthetics. Perioperative changes in metabolic status as well as altered hemodynamics are potential risk factors for neurologic impairment on the long term, including factors such as hypercapnia, hypocapnia, hyperoxia, hypoxia, hypertension and hypotension.

Hemodynamic stability is of great importance for the neonate in view of the organ perfusion. A systemic blood pressure within its limits for cerebral autoregulation is crucial for protection of the brain. The arterial blood pressure is connected to cerebral auto-

regulation, which regulates cerebral perfusion pressures. However, the consequences of derangements in the cerebral blood flow on the long-term outcome are not known. Premature infants showed alterations in the brain on MRI-scans direct postoperatively.[9] It is yet unknown which specific factors are of critical importance for a normal neurodevelopmental outcome in surgical neonates.

Also, the anesthetics isoflurane and sevoflurane affect the cerebral autoregulation through direct effects on the vessels in the brain and modulating the endogenous regulatory mechanisms of the cerebral autoregulation.[10] The effects of changes in the autoregulation on the long-term neurodevelopment are unknown.

Each and any of the factors mentioned above could negatively impact the neurodevelopment of these neonates. Much research has been performed to investigate the occurrence of long-term neurodevelopmental impairments after neonatal surgery and neonatal critical illness.

Anesthetics themselves may affect the neurodevelopment of the surgical neonate. The U.S. Food and Drug Administration has recognized that anesthetics can be neurotoxic, and published a warning in December 2016.[11]

[12-14-2016] The U.S. Food and Drug Administration (FDA) is warning that repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains.

More than 1000 experimental research publications have reported direct toxic effects on the brain of virtually all clinically used anesthetics when applied in young rodents and non-human primates.[12] It is questionable whether these findings are applicable to clinical practice, since data on humans is lacking.

Anesthetic drugs are thought to be neurotoxic through binding to the NMDA-receptor and the GABA-receptor. These receptors have an active role in the survival, maturation and integration of progenitors and can therefore interfere with neurogenesis. If interference takes place, the binding to the NMDA-receptor and the GABA-receptor by the anesthetic agents can have effects on the neurodevelopmental outcome.[13] A study found that children exposed to anesthetics before 4 years of age showed long-term impaired cognition and language abilities, compared to peers who had not been exposed to anesthetics.[14] These retrospective studies may be subject to inclusion bias. However, short single periods of anesthesia in healthy children seem to be harmless.[15]

Children born with esophageal atresia may be at particular risk for neurotoxic effects of anesthetics in view of the long exposure to anesthetics during primary esophageal atresia repair shortly after birth. The primary surgery, in combination with successive

diagnostic and surgical procedures related to esophageal atresia (e.g., dilatation of anastomotic stricture) and/or associated comorbidities including tracheomalacia, can lead to accumulation of risks on long-term impairment due to repeated exposure.

Conclusive results on all facets of neurobehavioral development after repeated and/or lengthy exposure to general anesthetic are lacking. A study of our group investigating long-term development at ages 5 and 8 years old in children born with esophageal atresia has shown associations between the length of anesthetic exposure and impaired long-term outcome.[5] However, long-term follow-up studies are very likely biased since many events in a child's life can influence the long-term outcome. Therefore, it is hard to state whether the anesthetics are the cause of the impairments found in follow-up at ages 5 years or 8 years old.

If the hypothesis about the neurotoxicity of the traditionally used anesthetics is true, it is imperative to find a suitable alternative. A proposed alternative is dexmedetomidine. Studies have shown that dexmedetomidine is a favorable drug for sedation in the ICU and for procedural sedation.[16,17] Most importantly, it has been suggested, based on experimental research, that dexmedetomidine has a neuroprotective profile. Moreover, use of dexmedetomidine lessens the need for opioids, is associated with fewer cases of emergency delirium, and does not cause short-term problems such as postoperative agitation.[18]

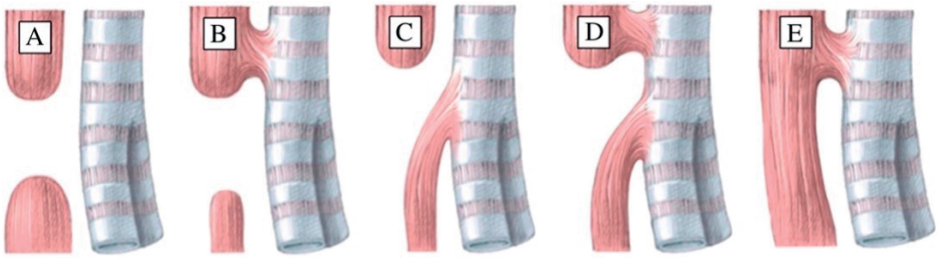
However, as of yet, no results have been published regarding the long-term safety of this drug in children and/or adults. Therefore, it is important to investigate the long-term neurodevelopmental effects of the use of dexmedetomidine in critically ill patients and young children.

ESOPHAGEAL ATRESIA

A tracheo-esophageal fistula (TEF) is present in over 80% of all children with esophageal atresia.[19] Various types of esophageal atresia are distinguished, classified according to the Gross classification, which takes into account the absence or presence of a TEF. Type A (4.9% of all cases) and type B (5.7%) present as a long-gap atresia.[20] The most common type, type C (82.1%), presents as esophageal atresia with a distal TEF. Type D (0.8%) presents as esophageal atresia with both a proximal and a distal TEF. Type E (6.5%) presents with a TEF only, without esophageal atresia, and is mostly diagnosed later in life.[21]

Esophageal atresia can be part of various malformation associations, such as the VACTERL association (vertebral defects, anorectal malformation, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities)[22] in 10% of cases, and the CHARGE syndrome (coloboma, heart defects, atresia of the choanae, retarda-

Figure 1 Types of esophageal atresia according to the Gross classification[20]



tion of mental and/or physical development, genital hypoplasia, and ear abnormalities) in 1% of cases.[23] Apart from malformation associations, esophageal atresia can co-occur with a syndrome: trisomy 18 is found in 6% of cases, and trisomy 21 in 1-3%.[1,24,25] The majority of children with esophageal atresia are not diagnosed with genetic syndromes or anomalies.

Esophageal atresia is diagnosed prenatally only around one quarter of cases in the Netherlands (26.6% (95%CI 18.7 – 36.4%)).[25] The prenatal diagnosis is based on direct and indirect ultrasound signs. Polyhydramnion can be a sign of gastrointestinal obstruction, and thus of esophageal atresia. Polyhydramnion combined with a small or absent stomach increases the positive predictive value for esophageal atresia.[26] Yet, these signs are not specific to esophageal atresia alone, but could also indicate other congenital anomalies, e.g., intestinal atresia. Therefore, the majority of children are diagnosed with esophageal atresia postnatally. Postnatal symptoms include excessive oropharyngeal secretion of saliva, sometimes presenting with respiratory distress. Feeding problems is one of the most prominent symptoms, because the milk cannot pass through the esophagus towards the stomach – leading to coughing, choking, vomiting and difficulty breathing. Furthermore, passing a nasogastric tube is impossible.

Esophageal atresia demands postnatal surgical intervention to connect both ends of the esophagus to establish normal continuity and to close the tracheo-esophageal fistula in types C and D. Generally, this surgery is performed within the first three days after birth, to enable the infant to stop regurgitation to the lungs, to swallow saliva, and to start enteral feeding. The primary repair is a delicate procedure for both the surgeon and the anesthesiologists, who need to closely collaborate to gain optimal surgical workspace while maintaining optimal respiratory and cardiovascular function. Both aspects are hampered by the infant's small size and the anatomical position of the esophagus, located posterior to the trachea. The right lung has to be compressed to gain access to the esophagus.

In many cases, the primary repair is often not the only intervention. Complications such leakage of the anastomosis (up to 20%) or stricture of the anastomosis (up to 58%)

can occur,[27] and comorbidities are seen in over half of the children.[25,28,29] These are mainly cardiac, gastrointestinal, genitourinary, musculoskeletal and respiratory comorbidities, sometimes part of VACTERL association. These complications and comorbidities are part of the reason why multiple surgeries and/or interventions may be needed following the primary repair.[30-32] Symptomatic tracheomalacia affects 16-33% of all children with esophageal atresia.[33] There is weakness of the trachea, leading to widening of the posterior wall of the trachea, resulting in reducing the lumen of the trachea. Symptoms of tracheomalacia due to tracheal collapse occur during coughing, crying and feeding. The collapse of the airway can lead to what is known as a life-threatening brief resolved unexplained event (BRUE).[34]

SURGICAL AND ANESTHESIOLOGIC CHALLENGES

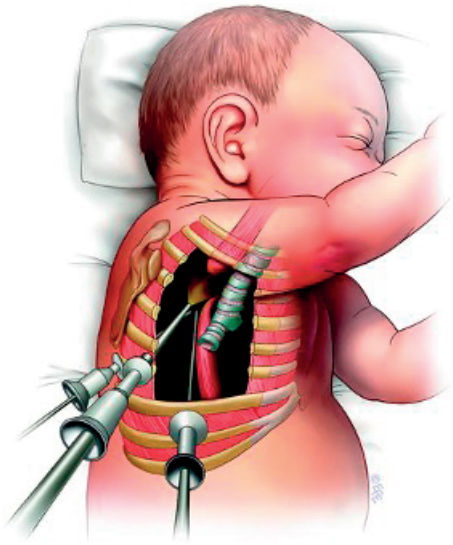
During primary repair of esophageal atresia, the surgeon makes an end-to-end anastomosis of the upper and lower parts of the esophagus and closes the tracheo-esophageal fistula. The surgical procedure is preferably preceded by a tracheobronchoscopy to inspect the trachea and bronchus and to locate the fistula or fistulae.

Endotracheal intubation carries great risk in the presence of a tracheo-esophageal fistula.[35] Preferably, the endotracheal tube is positioned beyond the distal tracheo-esophageal fistula to avoid insufflation of gas into the stomach, which carries the risk of gastric distension, which in turn may compromise respiratory and cardiac function.

Two surgical approaches are available to perform the primary repair: open and thoracoscopic approach.

Open surgical approach: The infant is placed in the left lateral decubitus position, with a small roll underneath the pectoral region to tilt the chest, which enlarges the intercostal space on the infant's right side. An incision is made 1 cm below the inferior tip of the right scapula, following the angle of the scapula. An incision is made in the fourth intercostal space, before spreading the ribs. Thereafter, using blunt dissection, parietal pleura is stripped away from the ribs and intercostal muscles to expose the posterior aspect

Figure 2 Thoracoscopic approach[36]



of the extrapleural mediastinum. The lung will be manually manipulated to create a work field.

Primary thoracoscopic approach: The infant is placed in the left lateral prone decubitus position, with a small roll underneath the pectoral region tilt the chest, which enlarges the intercostal space on the infant's right side. Cannulas are positioned as shown in Figure 2.[36] To decompress the lung, CO_2 insufflation is applied at a pressure of 4-5 mmHg and flow of 0.1 L/min though the telescope cannula.[37,38]

Due to the anatomical position of the esophagus, compression of the surrounding structures – e.g., the trachea and the superior vena cava – cannot always be avoided, thus affecting the circulatory, respiratory and metabolic status of the patient. During the open procedure, the surgeon will manually manipulate the lung to create workspace.[39] When the infant is placed in the left lateral position, adequate ventilation of the lower left lung is hampered by thorax compression and the cushion/roll below the thoracic cavity, whereas ventilation in the upper right long is hampered by compression of the lung by the surgeon (in case of open approach) and/or CO_2 insufflation (in case of thoracoscopic approach).

In thoracoscopic surgery, the aim of insufflation of CO_2 into the thoracic space is deflation of the right lung to create workspace. All proceedings, including CO_2 insufflation, require close collaboration between the surgeon and anesthesiologist, to prevent too much obstruction of the respiratory system by the applied pressure.

In both surgical approaches, metabolic derangements frequently occur, caused by CO_2 insufflation, compression of the left underlying lung and right lung by the surgeon, obstruction of the tracheal tube, or compression of the vena cava.[10] CO_2 insufflation will contribute to increased partial pressure carbon dioxide ($PaCO_2$) due to absorption of the CO_2, thereby possibly lowering the pH and creating an acidotic state. Good communication between the surgeon and the anesthesiologist is important to maintain an acceptable $PaCO_2$ level. Manipulation of the lung by the surgeon leads to respiratory and metabolic changes and affects the hemodynamics, which requires compensation by anesthesiologic intervention.

Both surgical approaches will cause reduced gas exchange, with consequently hypoxia and hypercapnia due to ventilation of mainly the left lung. Hypoxia can be resolved by providing more oxygen. Hypercapnia, however, is more difficult to reinstate and requires an increased PEEP and minute volume ventilation, which can preferably be attained by increasing the ventilation rate (up to 60 /min), while maintaining workspace for the surgeon.

Selective intubation of the left lung is not used in neonates. Generally, neonates are endotracheally intubated with selective lung compression by the surgeon. During sur-

gery, the anesthesiologist must be aware of changes in airway pressures, tidal volumes and end-tidal CO_2, which can be the result of compression by the surgeon, dislocation of the tube, or kinking of the trachea or bronchi in order to improve surgical workspace. Additionally, the superior vena cava could be compressed, leading to decreased cardiac output with consequently hypotension.

In the Erasmus MC - Sophia Children's Hospital Rotterdam, children born with severe congenital anatomical anomalies are included in a structured follow-up program since 1999. All patients born with esophageal atresia are eligible for inclusion in this program and the participants' neurodevelopment is regularly tested. Both cognitive and motor function are tested at 6 months, 12 months, 18 months, 30 months and at 5, 8, 12 and 17 years of age.[5,40] The aim of this follow-up program is to study the long-term effects of neonatal surgery and neonatal critical illness. Results of this program showed neurodevelopmental deficits in various patient populations. However, the causes of these neurodevelopmental deficits are unknown. The effects of the early postnatal period, perioperative period and the childhood on the neurodevelopment have yet to be found.

The aim of this thesis is to study the potential perioperative risk factors for long-term neurodevelopmental impairment in critical ill surgical neonates, using children born with esophageal atresia as a model. These are relatively healthy newborns who apart from the anatomical malformation of the esophagus suffer great perioperative metabolic and hemodynamic derangements.

OUTLINE OF THIS THESIS

As discussed above, critically ill surgical neonates may suffer long-term neurodevelopmental deficits. Children born with esophageal atresia are generally healthy children besides their anatomical malformation. Therefore, this patient population is a suitable model to research the influence of potential perioperative risk factors on the long-term neurodevelopmental outcome of critically-ill surgical neonates.

Various metabolic derangements can occur during ICU stay and the primary esophageal atresia repair surgery. Whether these derangements occur in both open surgical approach and thoracoscopic surgical approach has not been evaluated in bigger cohorts of children with esophageal atresia. For this study, we closely analyzed perioperative data retrospectively. Chapter 2 presents an overview of the perioperative metabolic derangements and the events during this perioperative period. The aim of this study is to answer the following questions:

- What metabolic derangements do children with esophageal atresia encounter during the perioperative period?
- What differences in perioperative events can be found between open surgical approach and thoracoscopic surgical approach?

As we looked for metabolic derangements in Chapter 2, we consequently had to look into the effects of anesthetic drugs on the long-term outcome as well. After the FDA had issued a warning about the neurotoxicity of exposure to anesthetics, the search for non-neurotoxic alternatives intensified. Dexmedetomidine has been suggested as a suitable alternative. Chapter 3 presents a systematic review on the short-term and long-term neurobehavioral effects of anesthesia with dexmedetomidine in young animals and young humans. In this systematic review, we aimed to answer the following questions:

- Is there evidence found by histological and neurobehavioral research to support the hypothesis that dexmedetomidine is a suitable non-neurotoxic alternative to the traditional anesthetics?
- Does dexmedetomidine have beneficial effects to the cellular injuries caused by traditional anesthetics?

In addition to the systematic review on dexmedetomidine in Chapter 3, we would like to learn to what extent dexmedetomidine is used off-label in pediatric anesthesiologic care. Therefore, we developed a questionnaire and distributed this among pediatric anesthesiologists in Europe, the United States, the United Kingdom, Ireland, New Zealand and Australia. The results of this survey study are discussed in Chapter 4. The aims of this study were finding answers to the following questions:

- To what amount do pediatric anesthesiologists use dexmedetomidine in pediatric anesthesiologic care?
- How are anesthesiologists trained to use dexmedetomidine in pediatric care, what are the most encountered side-effects and what are the reasons not to use dexmedetomidine?

As we aimed to study perioperative derangements in critical ill surgical neonates, we used children born with esophageal atresia as a model. These children are relatively healthy, apart from the esophageal atresia itself, but undergo major surgery within the first few days of life. This surgery is followed by various other surgeries and interventions, exposing them to a variety of risk factors for impaired neurodevelopmental outcome on the long term.

All children born with esophageal atresia type C undergo major surgery for primary repair of the esophageal atresia and the tracheo-esophageal fistula during the first days

of life. In addition, they undergo multiple surgeries and procedures for complications and co-morbidities, which could all affect the long-term neurodevelopmental outcome. To gain insight into the number of surgeries and procedures they undergo besides this primary repair, and to study the effects of these on the long-term neurodevelopment, we analyzed data of all surgeries and procedures requiring general anesthesia during the first years of life of children born with esophageal atresia. The results of this study are presented in Chapter 5. The aims of this study were finding answers to the following questions:

- Which surgeries and procedures requiring anesthesia do children with esophageal atresia undergo following the primary esophageal atresia repair?
- Which comorbidities do children with esophageal atresia have, and which part of the surgeries and procedures is due to these comorbidities?

Perioperative events, such as metabolic derangements, may affect the long-term motor outcome of children born with esophageal atresia. In Chapter 6 we studied the associations between perioperative events and the long-term motor outcome of children born with esophageal atresia. Motor outcome was assessed at the age of 5 years. This study aims to answer the following questions:

- Do children with esophageal atresia show motor outcome impairments at the age of 5 years?
- Which associations can be found between the perioperative events and the long-term motor outcome?

Various conclusions can be drawn from published research regarding the long-term outcome of children born with esophageal atresia. Conclusions are drawn from various testing methods, such as questionnaires filled out by parents and patients, clinical tests and psychological assessments. Chapter 7 presents a systematic review of studies in which the neurodevelopmental outcome on the long term was tested my means of validated tests. The aims of this study were to answer the following questions:

- What is the neurodevelopmental outcome of children born with esophageal atresia on the long term?
- Which factors are associated with the long-term outcome of children born with esophageal atresia?

The previous chapters discuss perioperative events. Events happening in the brain during the perioperative phase can be evaluated using neuromonitoring, which is more widespread used to observe changes in the brain during ICU admissions and surgeries. Chapter 8 provides an overview of the available neuromonitoring techniques for the surgical newborn. The aims of this study were:

- To evaluate methods of monitoring the brain that might be valuable in perioperative care of the surgical neonate
- To clarify risk factors that result in perioperative changes and how this might be evaluated

Finally, in Chapter 9, the results of our research are placed in a broader perspective, and we discuss our findings. Aims for future research are described, and suggestions for improvement of the care of children born with esophageal atresia are presented.

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2

Perioperative management of esophageal atresia/tracheo-esophageal fistula: an analysis of data of 101 consecutive patients

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ABSTRACT

Background: The perioperative management of esophageal atresia/tracheo-esophageal fistula by open or thoracoscopic approach can be complicated by metabolic derangements. Little is known, however, about the severity of derangements of vital and metabolic parameters in the perioperative period.

Aim: The aim of this study is to describe the perioperative courses of vital and metabolic parameters in 101 consecutive neonates undergoing surgical repair of esophageal atresia type C.

Method: In a retrospective cohort study, we extracted all data from the electronic anesthetic and medical charts of patients who underwent esophageal atresia type C repair within 30 days of life (2007- 2017). We distinguished three types of surgery: primary open, primary thoracoscopic, and primary thoracoscopic surgery converted to open surgery. Descriptive analysis was applied.

Results: The charts of 117 patients were reviewed: data of 101 were included. The perioperative anesthetic management was not standardized; various methods and medications were used for anesthesia induction and maintenance.
Intraoperative blood gas analysis data of 72 patients were available and showed derangements regardless of type of surgery. The median pH-value decreased to 7.21 [IQR 7.14-7.30] and a pH-value below 7.20 was found in 29 patients; in 4 cases below 7.0, with the lowest value 6.83. The median $PaCO_2$ reached an upper level of 7.5kPa [IQR 5.8-9.2]; in 13 cases above 10.0kPa, with a peak value of 25.8kPa. These high $PaCO_2$ levels fluctuated with lowest measured $PaCO_2$ of median 5.6 [IQR 4.5-6.6], with the lowest value 2.8kPa. The median PaO_2 level reached an upper level of 16.9kPa [IQR 11.8-25.7], in 22 cases above 20.0kPa, with a peak value of 50.0kPa. These high levels fluctuated with lowest measured PaO_2 levels of median 8.3kPa [IQR 6.73-10.5]; the lowest PaO_2 value was 4.7kPa.

Conclusions: Open and thoracoscopic correction of esophageal atresia were associated with periods of severe metabolic derangements. These events need to be taken into account for the evaluation of esophageal atresia (surgical) care and in evaluations of short- and long-term outcomes.

INTRODUCTION

Surgical repair of esophageal atresia (EA) is a challenging procedure which requires close collaboration between the surgical and anesthetic teams. Factors such as prematurity, low birth weight, respiratory problems and associated morbidities, in particular cardiac anomalies, increase the complexity of the procedure.[1,2] The presence of a tracheo-esophageal fistula (TEF) – found in the majority of cases – carries the risk of insufflating the stomach, instigating high intra-abdominal pressures and impeding ventilation.

The EA/TEF repair can be done with either a traditional open or a thoracoscopic approach.[3] The success and progress of the surgery, in particular of the thoracoscopic surgical approach, hinge on effective cooperation between surgeon and anesthesiologists because of the interference of (mostly) the right-sided lung in the working area, which compels adaptation in ventilation.[4] The arguments on the preferred surgical approach mostly relate to the perioperative severity of metabolic derangements, which are largely influenced by the anesthetic (ventilation) technique. Little is known, however, on the relation between type of the surgical approach and this severity. Only one study on this topic has been published so far.[5] This was a randomized (pilot) study comparing a primary thoracoscopic and an open surgical repair in 10 patients with congenital diaphragmatic hernia and 10 patients with EA/TEF. The thoracoscopic approach appeared to be associated with more profound and more prolonged hypercapnia and acidosis than open surgery. Thoracoscopic management is preferred in some hospitals because it provides better visualization of the surgical field, and is associated with less surgical damage and better long-term outcome with expected lower risk of scoliosis.[6] As reported EA survival rates have increased to more than 90% nowadays [7,8], leading to a shift of attention towards possible long-term morbidities.[9] Previous research on developmental outcome after EA/TEF repair showed normal to impaired motor- and mental development. The impairment was associated with the total anesthesia time.[10] Any interrelationships between intraoperative events, type of surgical approach – thoracoscopic or open – and (developmental) outcomes have not yet been elucidated. Comorbidities, intraoperative events like duration of surgery, the occurrence of hypercapnia (and its effect on cerebral autoregulation), acidosis, hypertension, postoperative complications (such as recurrence of the TEF, esophageal stricture formation and gastro-esophageal reflux) may negatively affect the short- and long-term clinical outcomes.[11-15] It is also not known what surgical technique is associated with the best outcome.[12,16]

In this paper we describe the perioperative courses of vital parameters and metabolic derangements as well as the short-term outcome in relation to the type of surgical approach in 101 consecutive neonates undergoing esophageal atresia type C repair.

METHODS

In this retrospective cohort study we made use of the electronic Anesthetic Information Management System (AIMS; Anesthesia Manager, PICIS Clinical Solutions S.A., Barcelona, Spain), Patient Data Management System dedicated to ICU (PDMS, ChipSoft, Amsterdam, The Netherlands), and medical charts (on paper until 2012 and electronically from 2012 onwards) to identify patients who underwent correction of EA/TEF between January 2007- December 2017 at the Erasmus MC-Sophia Children's Hospital, Rotterdam. All pre-, intra- and postoperative data of these patients were gathered as well as annual follow-up data on major health changes and mortality. Data was gathered during the scheduled follow-up at regular intervals (minimum once per year with the surgeon in our hospital) until the age of 18 years old. Data on mortality rates up to and including April 2019 were included. Inclusion criteria were EA type C (as classified by Gross) and surgical correction within the first 30 days of life. Patients with EA types A, B, D and E were excluded to ensure optimal homogeneity of the data.[17]

Cardiac malformations were classified as minor or major according to Hoffman.[18] Prematurity was defined as born before 37 weeks postconceptional age.

Standard preoperative care at the intensive care unit following the protocol of the Dutch Association of Pediatric Surgery consisted of (physical) examination for VACTERL association and syndromes, genetics, thoracic- and abdominal x-rays and echographic cardiac examination.[19]

During the study period, a thoracoscopic procedure was generally the preferred surgical approach to achieve continuity of the esophagus and closure of the fistula. The surgeon, anesthesiologist and the neonatologist/intensivist together decided on the type of surgical approach if the neonate had any clinically relevant cardiac or respiratory morbidities. Conversion from thoracoscopic to open surgery was based on either surgical and/or anesthesia related problems.

In 2012, pediatric surgeons and anesthesiologists of the Erasmus MC-Sophia Children's Hospital had issued a recommendation to convert thoracoscopic to open procedure if the pH was below 7.0 (independent of the duration of acidosis).

Anesthetic management during the study period included standard monitoring (saturation, non-invasive blood pressure measurements, ECG, $EtCO_2$) and preferably inserting an arterial line for invasive blood pressure monitoring (considered mandatory for thoracoscopic approach) and arterial blood gas analyses. Placement of the arterial line – either preductal or postductal – had not been recorded. A central venous line was placed only on indication. Capillary, arterial and/or venous blood gas analyses were standardly performed pre- and post-operatively but not standardly during anesthesia. In the data analysis, we did not distinguish between arterial-drawn, capillary-drawn or

venous-drawn blood samples since for pH and pCO2 measurements, capillary-drawn and venous-drawn blood are clinically acceptable alternatives for arterial-drawn blood.[20,21]

Acidosis was defined as pH<7.35; severe acidosis as pH<7.20; hypercapnia as $PaCO_2$ >6.40 kPa (Erasmus MC-Sophia reference value); hypocapnia as $PaCO_2$ <4.7 kPa (Erasmus MC-Sophia reference value); hypoxemia as peripheral saturation ≤90% or PaO_2<5.4kPa; severe hypoxia as peripheral saturation <80%; and hyperoxia as PaO2>12.4kPa.[22,23] Hypotension and hypertension were defined respectively as measurement below the 2SD and above the 2SD range, calculated per patient based on weight and sex according to recently developed reference ranges.[24]

Unavailable data are referred to as unknown/missing. Due to the retrospective nature of this study we cannot distinguish between non-registered data (unknown) and missing data.

Statistics

For the evaluation of surgical techniques and their anesthetic management, the cohort was divided into three groups: primary open surgery (POS), primary thoracoscopic surgery (PTS) and converted thoracoscopic to open surgery (COS). Univariate regression analysis and multivariable regression analysis (stepwise backward) was performed exploratory, post-hoc to determine the association between the most severe metabolic derangement in pH (lowest pH) and perioperative factors (preoperative intubation, weight at surgery, duration of surgery, gestational age, gender, surgical technique, minor and major cardiac anomalies). The perioperative anesthetic management and pre-, intra- and postoperative variables are presented as frequencies and percentages for categorical variables and median with interquartile range [IQR] for continuous variables. Statistical analysis was performed with a statistical analysis program (SPSS 24.0 for Windows, SPSS, Inc, Chicago, IL, USA).

RESULTS

Patient characteristics

From January 2007 to December 2017, a hundred and seventeen neonates had undergone surgery for EA/TEF in our hospital. After exclusion of EA type A (n=5), B (n=1), D (n=1) and E (n=8), 102 neonates with EA type C remained. One of those (referred from abroad) had surgery at the age of 68 days and was excluded. Thus, we included data of 101 neonates. Sixty-three percent were boys; 38% were born premature (Table 1). Patients in the POS group had lower birth weights and lower gestational ages than those in the PTS group. Surgery was performed at a median of 2 (0 – 9) days after birth (Table 1).

Table 1. Patient characteristics

	Total n=101	POS n=34	PTS n=56	COS n=11
Male	63 (63%)	21 (62%)	36 (64%)	7 (64%)
Birth weight	2805 [2169 – 3185]	2240 [1640-3071]	2900 [2530-3240]	2910 [2456-3345]
Gest. Age	37.9 [36.3 – 39.6]	36.6 [33.8 – 38.4]	38.3 [37.0 – 40.0]	38.0 [36.9 – 39.9]
Premature	38 (38%)	17 (50%)	16 (29%)	5 (45%)
Preoperative oxygen	38 (38%)	10 (29%)	22 (39%)	6 (55%)
Preoperative intubation	15 (15%)	13 (38%)	1 (2%)	1 (9%)

Numbers are presented as n (%) or median [interquartile range]

Minor cardiac malformations had been diagnosed in 63 patients; major cardiac malformations in 5 patients, of whom only 1 had a cyanotic cardiac malformation (Supplementary Table 1). Preoperative pulmonary abnormalities confirmed by chest X-ray had been found in 41 patients (41%) (Supplementary Table 1).

The surgical approach for primary EA/TEF repair was POS in 34 patients, PTS in 56 and COS in 11 patients. Reasons for COS were insufficient overview of the surgical site (n=3); respiratory and/or hemodynamic problems that could not be corrected (n=4); failure to insert an arterial line (n=1); too long gap for thoracoscopic anastomosis (n=2, anastomosis successful after conversion); and a preoperatively unidentified right descending aortic artery (n=1, anastomosis successful after conversion). Surgical procedures for additional congenital abnormalities performed during the same surgical session included gastrostomy (3 POS), colostomy (4 POS, 1 PTS, 1 COS), duodenostomy (1 PTS) and colostomy + duodenostomy (1 COS).

Ten patients underwent a second operation related to the initial EA/TEF repair (excluding esophageal stricture dilatations) within 1 year: delayed planned primary end-to-end anastomosis due to a long gap (n=4); recurrent fistula (n=4); and fundoplication (n=2). For these patients, only the data on the initial surgery was included in this study. Prior to surgery, 38 patients had received non-invasive oxygen supplementation and 15 patients had been mechanically ventilated because of respiratory insufficiency (Table 1). Several preoperative blood gas analysis results differed between groups (Table 2).

Intraoperative Phase

For the induction of anesthesia in the 86 patients intubated in the OR (15 patients were already intubated at the ICU), thiopental (n=17), propofol (n=35), sevoflurane (n=30) and unknown/missing (n=4) were used. Muscle relaxation was provided with cisatracurium (n=66), rocuronium (n=8), suxamethonium (n=4) and unknown/missing (n=8). Pain medication consisted of fentanyl (n=61), sufentanil (n=18), remifentanil (n=5) and unknown/missing (n=2). Preoperative tracheoscopy was performed in 42 patients using rigid and/or flexible scopes. The induction time (from arrival at the OR until the incision) was longest for the COS group (75 minutes), followed by the PTS (60 minutes) and

Table 2. Blood gas analysis results

	POS	PTS	COS
Preoperative	n=32	n=54	n=10
Saturation	89 [81-96]	94 [87-98]	89 [83-95]
pH	7.31 [7.26-7.34]	7.34 [7.31-7.39]	7.35 [7.31-7.36]
PaO_2	7.80 [5.75-9.33]	11.2 [7.15-16.6]	6.20 [5.40-10.1]
$PaCO_2$	6.15 [5.73-7.13]	6.30 [5.30-6.95]	5.85 [4.98-6.03]
Intraoperative	n=23	n=39	n=9
Saturation	87 [77-92]	85 [81-89]	84 [69-91]
pH	7.25 [7.17-7.37]	7.28 [7.21-7.35]	7.24 [7.14-7.42]
PaO_2	11.1 [7.5-15.4]	10.5 [8.1-15.2]	8.9 [7.6-15.2]
$PaCO_2$	6.0 [5.0-8.5]	6.4 [5.0-7.2]	5.7 [4.0-9.3]
Postoperative	n=34	n=46	n=11
Saturation	96 [92-99]	98 [92-99]	97 [85-98]
pH	7.32 [7.23-7.41]	7.38 [7.30-7.46]	7.36 [7.31-7.42]
PaO_2	9.4 [7.6-15.0]	11.9 [8.9-19.0]	16.8 [8.8-25.8]
$PaCO_2$	5.2 [4.2-6.8]	4.7 [3.9-6.4]	5.1 [3.8-5.6]

N= number of patients, Median [IQR] of saturation (%), pH, PaO_2 (kPa) and $PaCO_2$ (kPa). Preoperative: last blood gas sample before surgery; Intraoperative: lowest saturation measured; Intraoperative; first pH, PaO_2 and $PaCO_2$ measured; Postoperative; first blood gas sample postoperative.
Preoperative number of patients with blood bas analysis: POS: arterial 14, venous 1, capillary 18, missing 1. PTS: arterial 20, venous 0, capillary 34, missing 2. COS: arterial 10, venous 0, capillary 7, missing 1.
Intraoperative number of patients with blood bas analysis: POS: arterial 23, venous 0, capillary 0, missing 11. PTS: arterial 38, venous 0, capillary 1, missing 17. COS: arterial 9, venous 0, capillary 0, missing 2.
Postoperative number of patients with blood bas analysis: POS: arterial 26, venous 0, capillary 8, missing 0. PTS: arterial 43, venous 0, capillary 13, missing 0. COS: arterial 11, venous 0, capillary 0, missing 0.
The asterisk (*) represents the sole intraoperative capillary blood gas analysis. All other measured blood gas values are from arterial blood gas samples.

POS groups (31 minutes). In the COS group, the mean time from start of thoracoscopic surgery to conversion to open surgery was 51 minutes. The total surgical time for the COS group was 189 minutes; for the POS group 116 minutes; and for the PTS group 152 minutes (Table 3).

Preoperative blood gas analysis was done with either capillary (n=59), arterial (n=37) or venous (n=1) blood samples. Intraoperative blood gas analysis was done with either capillary (n=1) or arterial (n=71) blood samples. Intraoperative blood gas analysis results of the 72 patients with intraoperative blood gas measurements were registered in AIMS. The number of analyses was highest in the COS group (median of 4), followed by 2 in the PTS group and 1 in the POS group. Postoperative blood gas analysis was done in all patients, either with capillary (n=21) or arterial (n=80) blood samples.

The mean peak non-invasive blood pressure in the COS group was higher than that in the POS group (Figures 1, 2). The mean invasive blood pressure was highest in the COS group. In total 22 patients had one or more hypertensive events and 14 patients had one

Table 3. Anesthetic and perioperative care management

	Total n=101	POS n=34	PTS n=56	COS n=11
Induction anesthesia				
Inhalation (sevoflurane)	30	14 (41%)	13 (23%)	3 (27%)
Intravenous propofol	35	6 (18%)	23 (41%)	6 (55%)
Intravenous thiopental	17	1 (3%)	15 (27%)	1 (9%)
Intubation				
Oral	23	7 (21%)	14 (25%)	2 (18%)
Nasal	57	16 (47%)	33 (59%)	8 (73%)
Tracheoscopy				
Rigid	18	7 (21%)	6 (11%)	5 (46%)
Flexible	6	6 (18%)	0	0
Combination	17	6 (18%)	8 (14%)	3 (27%)
Duration of induction		31 [17-49]	60 [31-75]	75 [51-92]
Duration of surgery		116 [95-154]	152 [124-180]	189 [141-244]
Postoperative ICU stay		12.5 [6-47]	5.0 [3-12]	13.0 [10-19]
Postoperative hospital stay		29.5 [14-84]	14.5 [10-27]	21.0 [13-31]
Postoperative intubation days		2 [1-4]	1 [1-1]	2 [2-3]
Days to oral feeding		8.0 [5-20]	5.0 [3-8]	11.0 [4-18]

Not all information is known in all patients, induction of anesthesia when performed at NICU is not reported.

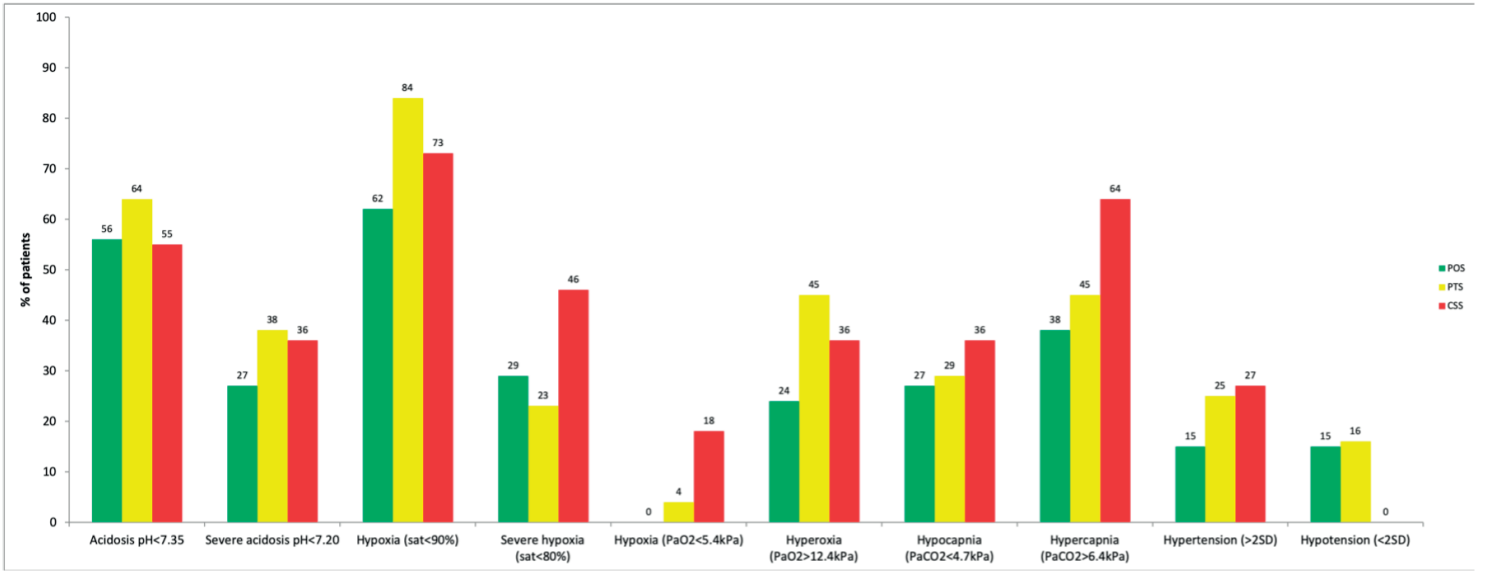
or more hypotensive events (Figures 1, 2). In total 44 patients had received inotropics and vasoactive drugs. Fluid loss (including blood and urine) during the operation was not reported.

None of the patients had been subjected to one-lung ventilation. Eighty-five patients had been placed in the left lateral position (n=85); three in the right lateral position; and for 13 patients the position was missing. The peak ventilation pressures were comparable across all groups (median 6, IQR 5-8), with a highest pressure of 20.0 cmH_2O in all groups. The median highest pressure overall was 24 (IQR 20-28). The highest pressure in the COS group was 47 cmH_2O; 44 cmH_2O in the PTS group; and 36 cmH_2O in the POS group.

Hypoxemic events (peripheral saturation <90%) had been recorded for 75 of the 101 patients, which were severe (sat <80%) in 28 patients. An O_2 saturation below 50% had been recorded for two patients (1 PTS, 1 COS); the lowest value was 42%. measured in the COS group. Blood gas analysis showed hypoxemia in 7 patients. The lowest PaO_2 of 4.70 kPa was measured in the COS group. Hyperoxia was found in 53 patients, with highest PaO_2 of 50.0 kPa in the PTS group, followed by 39.0 kPa in the POS group (Figure 1).

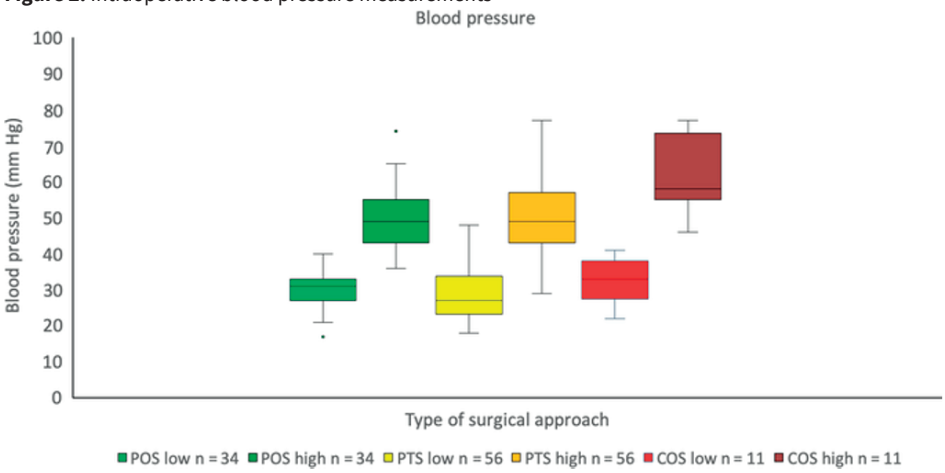
Hypocapnic episodes had been reported for 28 patients, with the lowest $PaCO_2$ of 2.8 kPa in the PTS group (Table 2). Hypercapnic episodes had been reported for 46 patients; the highest $PaCO_2$ was 25.8 kPa in the PTS group (Figure 3A). The first measured pH

Figure 1. Overview of main measured parameters



This figure shows the incidence of measured values across all surgical approaches.
Bars represent percentage of measures values per group. Numbers above bars represent absolute number of patients.

Figure 2. Intraoperative blood pressure measurements



This figure shows the lowest and highest intraoperative mean blood pressure (mmHg, mean, 95% CI) presented per surgical approach. In case of missing invasive blood pressure measurement, non-invasive blood pressure measurement was used.

value in the POS group was lower than that in the PTS group (Table 2). Intraoperatively, acidosis (pH<7.35) was found in 62 patients; severe acidosis (pH<7.20) in 33 patients, of whom three (2 PTS, 1 POS) had a pH value ≤7.0, with the lowest minimum pH 6.83 in the PTS group (Figure 3B). The pH values ≤7.0 necessitated breaks from surgery to recover metabolic balances (n=1), clearing of the tube (sputum plug, n=1) and conversion to open surgery (n=1).

The lowest intraoperative pH was associated with longer duration of the surgery, preoperative intubation and male sex in both univariate and multivariable regression analysis. Type of surgery was not associated with lowest intraoperative pH (Table 4).

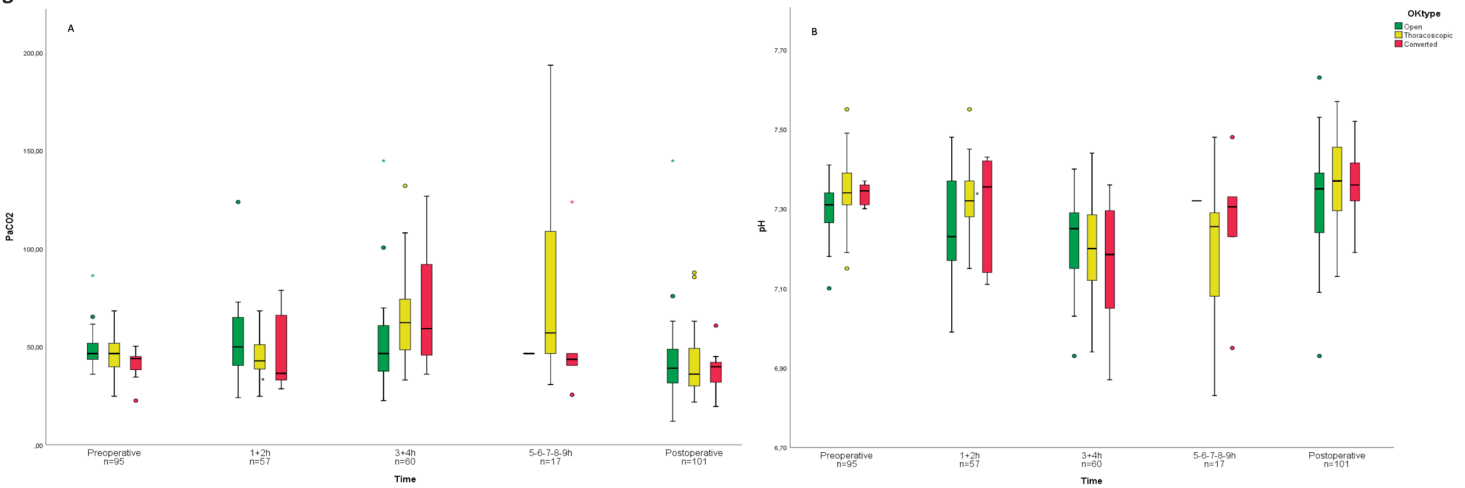
In the period 2007-2012 (before the new recommendation), fewer intraoperative blood gas analyses per patient per surgery had been performed than in the period 2012-2017 (after the new recommendation, median 1 and 3, resp.). Mean blood gas values did not differ between these periods; the only difference between these periods was a higher incidence of hypoxemic events (saturation <90%) in the POS group after 2012.

Postoperative management

Postoperatively, all patients had been admitted to the pediatric intensive care unit (PICU). Here, patients in the PTS group were extubated within a median of 1 day, those in the POS and COS groups within a median of 2 days. Postoperative blood gas analysis results were available for all patients; it appeared that pH, PaO_2 and $PaCO_2$ values had normalized in most patients (Table 2).

The total postoperative ICU stay was median 9 days [IQR 4-18]; the total hospital stay was median 18 days [IQR 11-33]. Time to start of oral feeding was median 6 days [IQR

Figure 3.



3A- Pre-, intra- and postoperative PaCO2 measurements

Highest measured $PaCO_2$ in blood gas analysis (median, IQR) preoperative, intraoperative and postoperative.

3B- Pre-, intra- and postoperative pH measurements

Lowest measured pH in blood gas analysis (median, IQR) preoperative, intraoperative stages and postoperative.

This figure (3A and 3B) shows the measured values through time: preoperative, intraoperative (per subcategory) and postoperative. It shows acceptable preoperative metabolic values, but derangements increase with length of the procedure. Postoperative values are comparable to preoperative figures.

Preoperative number of patients with blood bas analysis: POS: arterial 14, venous 1, capillary 18, missing 1. PTS: arterial 20, venous 0, capillary 34, missing 2. COS: arterial 10, venous 0, capillary 7, missing 1.

Intraoperative number of patients with blood bas analysis: POS: arterial 23, venous 0, capillary 0, missing 11. PTS: arterial 38, venous 0, capillary 1, missing 17. COS: arterial 9, venous 0, capillary 0, missing 2.

Postoperative number of patients with blood bas analysis: POS: arterial 26, venous 0, capillary 8, missing 0. PTS: arterial 43, venous 0, capillary 13, missing 0. COS: arterial 11, venous 0, capillary 0, missing 0.

The asterisk (*) represents the sole intraoperative capillary blood gas analysis. All other measured blood gas values are from arterial blood gas samples.

4-13]; time to extubation was 1 day [IQR 1-2] (Table 3). The overall mortality was 4% (POS n=0, PTS n=1, COS n=3). None of the patients died in the OR or within 24 hours after surgery. Two patients died during postoperative hospital stay: one in the COS group due to sepsis 14 days postoperatively and one in the PTS group following respiratory failure due to severe edema after cardiac arrest and systemic inflammatory response syndrome 57 days postoperatively. Two patients died after discharge from the hospital, one from refractory epilepsy due to sinus thrombosis, intracerebral hemorrhages and infarctions (COS group, 71 days postoperative) and one from serious cerebral complications related to sepsis (COS group, 225 days postoperative).

Clinically diagnosed postoperative complications during hospitalization had been reported in 50 patients. These included: anastomotic leakage (n=18; 3 POS, 12 PTS, 3 COS); pneumothorax (n=20; all managed with chest tube); respiratory failure (n=9); atelectasis (n=12); infection (n=7); severe acidosis (n=3); recurrent fistula (n=3); and kidney problems (n=2). Various patients had multiple complications (mainly pneumothorax due to an anastomotic leakage in 16 patients) (Supplementary Figure 1).

Table 4. Univariate and multivariable regression analysis of factors associated with lowest intraoperative pH

	Univariate		**Multivariable**	
Variable	**Beta**	**95% CI**	**Beta**	**95% CI**
Preoperative intubation	-0.107	-0.183 ; -0.032	-0.079	-0.144 ; -0.014
Weight at surgery	0.000	-0.037 ; 0.036	-0.006	-0.063 ; 0.050
Surgical approach	-0.017	-0.069 ; 0.036	-0.001	-0.057 ; 0.055
Duration of the surgery	-0.001	-0.002 ; 0.000	-0.001	-0.002 ; 0.000
Gestational age	0.004	-0.012 ; 0.019	0.002	-0.006 ; 0.011
Gender	0.080	0.024 ; 0.137	0.083	0.031 ; 0.134
Minor cardiac	-0.044	-0.107 ; 0.018	-0.047	-0.100 ; 0.005
Major cardiac	0.012	-0.102 ; 0.126	0.012	-0.099 ; 0.123

DISCUSSION

We report on the pre-, intra- and postoperative anesthetic management in neonates undergoing type C EA repair and the acute physiological consequences in relation to the type of surgical approach – thoracoscopic, open and thoracoscopic converted to open surgery. The hemodynamic status of most patients was stable during the operation, but many suffered from episodes of acidosis, hypercapnia and hyperoxia, the incidences of which were positively associated with longer duration of the procedure. The severities of metabolic disturbances did not differ between the different surgical approaches. Although a study has suggested that an open surgical approach leads to fewer acidosis, hypercapnia and ventilator problems than does a thoracoscopic approach,[3] we found

no difference in the occurrence of intraoperative metabolic derangements between both approaches. Therefore, we cannot assert which of the two surgical approaches is superior in this respect.

Sixty-nine percent of the patients had minor and/or major cardiac abnormalities and 41% had pulmonary abnormalities, which percentages correspond with previous reports.[25-28] Theoretically, cardiac malformations could have a large influence on the perioperative course. However, as only 5 patients had major cardiac abnormalities, of whom 1 had a cyanotic malformation (see supplementary data), and regression analyses did not show major effects of minor and major cardiac malformations on outcome (Table 4), we judged it valid to keep their data in the analyses.

More patients were intubated preoperatively in the POS group (38%) than in the PTS group (2%). It seems that preoperative intubation is an important determining factor for primary open surgical approach (Supplementary Table 1). The univariate and multivariable regression analyses showed associations between lowest intraoperative pH and preoperative intubation and surgery time (Table 4). The clinical preoperative parameters in the PTS group were better than those in the POS group, which might have influenced the postoperative recovery (fewer ventilation days, ICU days, hospital days) in the PTS group. The duration of induction of anesthesia was the longest in the COS group. The duration of the surgical intervention in the PTS group was longer than that in the POS group, as found by others.[29,30] The high occurrence of episodes of acidosis in the present study confirms the findings of Zani et al.[14]

There still is no general consensus on a preferred surgical technique (open vs. thoracoscopic procedure).[5,31] The medical and surgical management of EA repair are decided in light of comorbidities, type of EA/TEF, experience of the surgeon, distance between the two ends of the esophagus, surgical and anesthesiologist preference and local hospital practice.[2,32] Therefore, the perioperative anesthetic management of EA/TEF in the Erasmus MC-Sophia Children's Hospital was not standardized, which caused a wide variation in care.

Independent of the surgical technique used, periods of severe intraoperative acidosis, hypercapnia, hypocapnia, hyperoxia and hypoxemia, mostly independent of hypo-and hypertension, occurred in the patients this study. The hypercapnia and acidosis found in this study are most likely caused by compression of the lung (POS and PTS) and absorption of insufflated CO2 (PTS).[5,14,33,34] Hypercapnia should be avoided or solved by compensatory increase of the ventilation rate.

The influences of metabolic derangements on the long-term neurodevelopmental outcome in humans are unknown, but preclinical animal research has shown a negative association of metabolic derangements with long-term neurodevelopmental outcome.[5,10,13,14,35-38] We suggest that non-invasive intraoperative neuromonitoring could be beneficial for optimal registration of brain oxygenation and perfusion during EA repair.

Patients in the PTS group had shorter lengths of stay in the ICU and the hospital than patients in both other groups, in line with previous studies.[30,39] Patients in the COS group, however, had more complications than those in the PTS group. Recurrent fistula were only found in the PTS group. Time to postoperative extubation was longer for the POS group, in line with other studies evaluating this aspect.[40,41] Various explanations have been suggested for this phenomenon; for example, collapse of the lung caused by uniform CO2 insufflation, resulting in elimination of retraction trauma and the need of a bigger incision for open surgical approach.[40,41] Unfortunately, during the period of surveillance, intraoperative neuromonitoring and/or routine postoperative ultrasound/MRI and EEGs to detect intraventricular hemorrhage and/or seizures had not been performed. Stolwijk at al suggested that this extra monitoring would be beneficial in this patient population.[42]

One of the greatest strengths of this study is the high number of patients included. Since EA is a rare congenital anomaly, most studies regarding EA include small numbers of patients. The 101 patients included in this study give a better representation of all EA patients and their perioperative periods. Several limitations of the study need to be addressed. First, the indication for thoracoscopic surgery might have introduced bias in the findings. Smaller patients with more severe comorbidities were preferably treated with an open procedure, and these characteristics might have influenced the postoperative risk of complications. Second, in the 10-year period covered in this study, changes may have been made in the surgical decision making. Also, the learning curve might have affected the outcome of these patients in time: shorter surgery time and fewer complications are to be expected.[43] Regarding the compliance with the recommendation made in 2012, 15 patients reached a pH < 7.20 but were not converted to an open procedure. Thus, the compliance with the recommendation is low and is not likely to have introduced an important bias. Furthermore, in the data retrieved from AIMS it can be difficult to differentiate patients' actual vital state and artifacts, especially in non-normal values.[44] The storage resolution in AIMS in Erasmus MC was limited and the vital parameters were recorded only every five minutes, so that outliers may have been missed. Fourth, the anesthetic management varied largely with the attending anesthesiologist's preference. Intra-arterial blood pressure measurements and standard interval for blood gas analysis were not standard of care. Therefore, intraoperative (arterial) blood gas results at regular intervals were not available and we were obliged to use all types of blood gas samples interchangeably to evaluate metabolic derangements.

Most of the patients included in this study had encountered periods of severe hypoxia, hyperoxia, acidosis, hypercapnia and hypocapnia intraoperatively, regardless of perioperative status and surgical approach. Checking for metabolic changes at regular time intervals during the operation, preferably with arterial blood gas analysis, is recommended.

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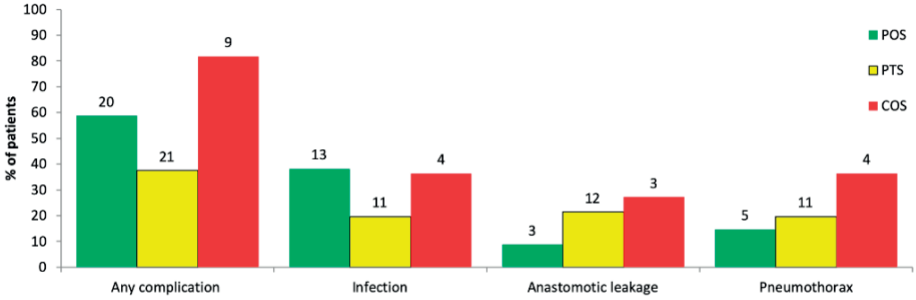
Supplementary Table 1.

Cardiovascular	**n=**	**Pulmonary**	**n=**	**Preoperative intubation?**
ASD	24	Atelectasis	14	2
VSD	11	Pneumothorax	8	
ASD+VSD	7	IRDS	5	3
Dextrocardia	5	Hypoplasia	3	2
Valve problems	5	Other pulmonary**	11	8
Pulmonary stenosis	1			
Tetralogy of Fallot	1			
Right descending aorta	1			
DORV	1			
Other cardiovascular*	12			
Chromosomal	**n=**	**Other**	**n=**	
VACTERL	6	Genitourinary	17	
Trisomy 21	3	Limb	12	
CHARGE	1	Anorectal malformation	12	
Silver Russell	1	Vertebral	9	
Pierre Robin	1	Neurological	3	
		Duodenal atresia	3	

Congenital anomalies diagnosed in the patients.
ASD atrial septal defect; VSD ventricular septal defect; DORV double outlet right ventricle; VACTERL Vertebral, Anorectal, Cardiac, TracheoEsophageal, Renal, Limb; CHARGE Coloboma, Heart disease, Atresia choanae, Retarded growth and development, Genital anomalies, Ear anomalies; IRDS Idiopathic Respiratory Distress Syndrome
* Other cardiovascular anomalies include impaired left ventricle function, absent pulmonary artery, enlarged heart, dilated right atrium and ventricle, persistent superior vena cava, overriding aorta, mesocardia
** Other non-cardiac anomalies include congenital pulmonary airway malformation, wet lung, mediastinum shift, bronchitis. All pulmonary abnormalities were confirmed by chest X-ray

Supplementary Figure 1.



3

A systematic review and narrative synthesis on the histological and neurobehavioral long term effects of dexmedetomidine

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ABSTRACT

Background: Recent experimental studies suggest that currently used anesthetics have neurotoxic effects on young animals. Clinical studies are increasingly published about the effects of anesthesia on the long term outcome, providing contradictory results. The selective alpha-2 adrenergic receptor agonist dexmedetomidine has been suggested as an alternative non-toxic sedative agent.

Aim: The aim of this systematic review is to assess the potential neuroprotective and neurobehavioral effects of dexmedetomidine in young animals and children.

Methods: Systematic searches separately for preclinical and clinical studies were performed in Medline Ovid and Embase on February 14th 2018.

Results: The initial search found preclinical (n=661) and clinical (n=240) studies. A total of 20 preclinical studies were included. None of the clinical studies met the predefined eligibility criteria.
Histologic injury by dexmedetomidine was evaluated in 11 studies, and was confirmed in three of these studies (caspase-3 activation or apoptosis). Decrease of injury caused by another anesthetic was evaluated in 16 studies and confirmed in 13 of these.
Neurobehavioral tests were performed in 7 out of the 20 studies. Of these 7 rodent studies, 3 studies tested the effects of dexmedetomidine alone on neurobehavioral outcome in animals (younger than P21). All 3 studies found no negative effect of dexmedetomidine on the outcome. In 6 studies outcome was evaluated when dexmedetomidine was administered following another anesthetic. Dexmedetomidine was found to lessen the negative effects of the anesthetic.

Conclusion: In animals, dexmedetomidine was found not to induce histologic injury and to show a beneficial effect when administered with another anesthetic. No clinical results on the long term effects in children have been identified yet.

INTRODUCTION

In December 2016 the FDA issued a warning about the use of general anesthetics and sedative drugs in young children (0-3 years of age) and pregnant women in their third trimester.[1] There is conflicting evidence that currently used anesthetics can affect children's brain development.[2-4] Dexmedetomidine, a highly selective alpha-2 adrenoceptor agonist, is a sedative with analgesic sparing properties. Therefore, it has been suggested as an alternative non-toxic sedative drug.[5] It is already clinically widely used as a sedative in adults and increasingly used in pediatric health care for sedation.[6] Due to its sedative, analgesic and anesthetic-sparing properties, dexmedetomidine can be used for anesthesia or procedural sedation. This might be advantageous in reducing the toxicity of anesthesia and minimizing concerns about adverse effects on children's brains. Still little is known, however, about the toxicity and long term effects (more than 48h after anesthesia) of dexmedetomidine in humans, especially in children.[5,7,8]

Therefore, we performed a systematic review to qualitatively summarize the available information from preclinical studies in young animals and clinical studies in children on the effects of dexmedetomidine on neurotoxicity and neurobehavioral outcome.

METHODS

We performed two systematic electronic searches in Embase and Medline Ovid, one for preclinical and one for clinical studies (appendices 1+2) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[9]

The last search in these databases was performed on February 14th 2018. Deduplication of the retrieved citations in the two databases was performed in Endnote.[10]

For preclinical studies, a broad search strategy was used, of which most important terms were: dexmedetomidine; animals; neurotoxicity; development; neuroapoptosis (full search strategy see Appendix 1). Inclusion criteria were: 1. preclinical in vivo study (young animals were alive when exposed to general anesthesia), 2. use of dexmedetomidine as general anesthetic, 3. long term outcome data reported and 4. original article or abstract. All studies in which animals suffered encompassing cerebral ischemia were excluded since we aimed to translate the conclusions of the preclinical studies to the use of dexmedetomidine in standard anesthetic care. We included only research on the effects on neonatal and young animals and excluded the research on full-grown animals (rats older than P21, sheep older than gestation days 147 and monkeys older than gestation days 165).[11]

In the search strategy for clinical studies, also a broad search was performed. Of which, most important terms were: dexmedetomidine; neurotoxicity; child; development (full

search strategy see Appendix 2). For clinical studies the following inclusion criteria were applied: 1. dexmedetomidine was administered in children, 2. dexmedetomidine was used as a general anesthetic or sedative, 3. long term outcome data of neurotoxicity and 4. original article or abstract.

Two investigators (CvH, HE) independently screened the titles and abstracts of the citations. Those not meeting inclusion criteria according to both screeners were excluded, whereas those on which the screeners disagreed were included for full text analysis. Thereafter, if available, full text studies were read independently by the same two investigators, after which their full-text selections were compared and merged. We decided to also include abstracts which present all required information relevant for this systematic review because of the limited number of studies and the fast development of the field of interest. Reviewers resolved discrepancies through discussion or, if needed, by adjudication from the third (JdG) and fourth (SH) reviewer. This resulted in the final selection of studies included in this systematic review.

The primary outcome measure for preclinical studies was the effect of dexmedetomidine on neuronal cells: neurotoxicity or lessening of toxicity caused by another anesthetic agent. This could be measured in two ways: either histological analysis of neuronal cells after exposure to dexmedetomidine (alone or with another anesthetic) in vivo or neurobehavioral tests after exposure to dexmedetomidine.

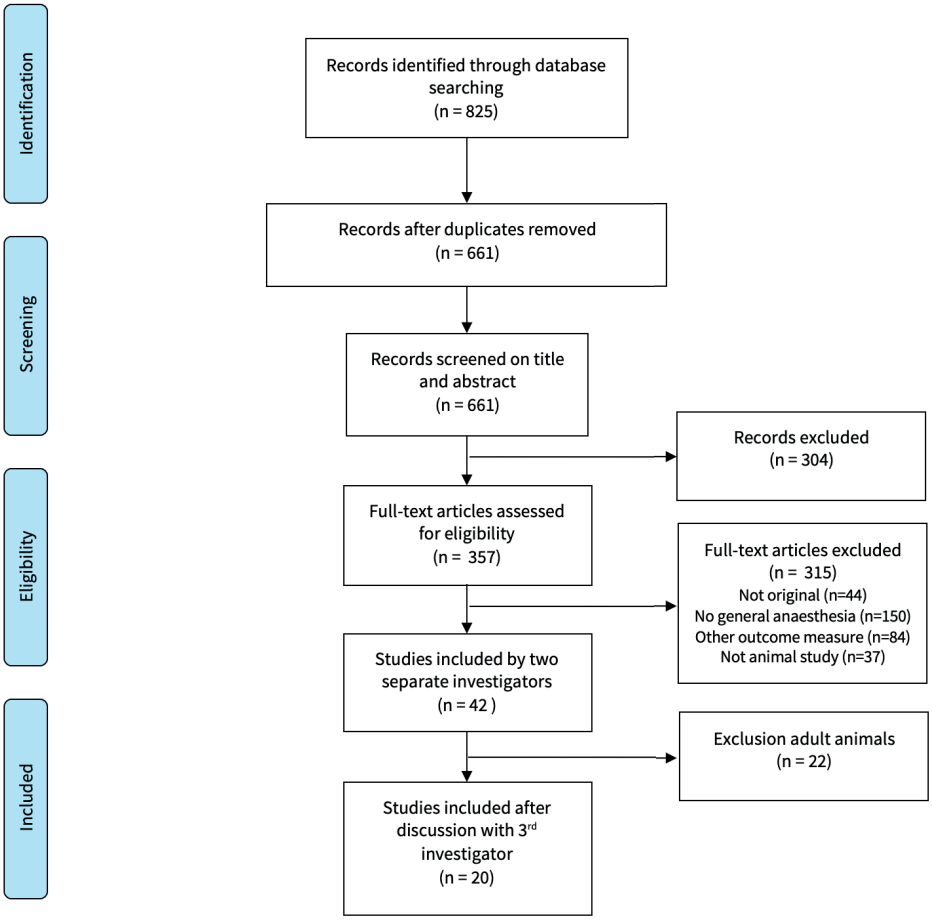
The primary outcome measure for clinical studies was children's long term neurobehavioral outcome (more than 48h after anesthesia) after administration of dexmedetomidine.

The risk of bias for each included study was established with the SYRCLE's risk of bias tool for preclinical studies.[12,13] Data of the preclinical studies were extracted on a data extraction form made by the authors (CvH, HE), including details of study population (number, animal species, age), intervention (drugs, dose, route of delivery, duration of treatment) and outcome (brain region, histological analysis, neurotoxicity, dexmedetomidine decreases toxicity caused by another anesthetic, neurobehavioral changes).

RESULTS

The search strategy for preclinical studies identified 661 studies after deduplication.[10] The initial screening of titles and abstracts excluded 304 studies; the remaining 357 studies were selected for full text screening, after which all studies in adult animals were excluded. This resulted in a final selection of 20 preclinical studies included in the systematic review (Figure 1, Table 1).[9]

Figure 1. PRISMA Flowchart selection of included preclinical studies



This figure shows an overview of the systematic search results and selection of the studies included for this systematic review. It shows the search found 661 studies, which we reduced to 20 studies included for the preclinical part of this systematic review.

For the clinical search, 240 studies were identified after deduplication, of which 212 studies were excluded after title and abstract screening. In total, 28 studies were eligible for full text analysis. This revealed that 25 studies were not original studies and that 3 studies were case reports. No study fulfilled the inclusion criteria and remained for analysis. This resulted in 0 included studies (Figure 2).[9]

The risk of bias analysis showed that allocation concealment (timing of randomization) was adequate in all studies and that all but one studies were free from selective outcome reporting (Table 1).

Random outcome assessment was reported in none of the 20 studies; blinding for performance (e.g. blinding of caregivers and researchers) was reported in 7 studies and

Table 1. Risk of bias of included studies

	Sequence generation	Baseline characteristics	Allocation concealment adequately	Random housing	Blinding (performance)	Random outcome assessment	Blinding (detection)	Incomplete outcome data	Free from selective outcome reporting
Duan 2014[17]	y	?	y	y	y	n	?	n	y
Goyagi 2016[23]	n	?	?	?	?	n	?	y	?
Han 2013[24]	y	?	y	?	?	n	?	n	?
Ibrahim 2015[22]	y	?	y	y	y	n	y	n	y
Koo 2014[14]	y	?	y	?	?	n	y	y	y
Lee 2017[25]	y	?	y	y	y	n	y	n	y
Li, J 2016[19]	y	?	y	y	n	n	?	y	y
Li,Y 2014[16]	y	?	y	?	?	n	?	y	y
Liao 2014[26]	n	?	y	?	?	n	?	y	y
Liu 2016[18]	y	?	y	y	y	n	y	y	y
Lv 2017[20]	y	?	y	y	n	n	?	y	y
Olutoye 2015[15]	n	?	y	y	n	n	y	y	n
Pancaro 2016[32]	y	?	y	?	y	n	y	y	y
Perez 2017[27]	n	?	y	y	n	n	y	n	y
Sanders 2009[29]	n	?	y	?	n	n	y	n	y
Sanders 2010[33]	n	?	y	y	n	n	y	n	y
Su 2015[30]	n	?	y	y	n	n	?	y	y
Tachibana 2011[34]	y	?	y	y	?	n	?	y	y
Wang 2016[21]	y	?	y	y	y	n	y	y	y
Zeng 2013[31]	y	?	y	?	?	n	?	y	y

N: No; Y: Yes; ?: Not reported; Green: Low risk if bias; Red: High risk of bias

Sequence generation: Was the allocation sequence adequately generated and applied?

Baseline characteristics allocation: Were the groups similar at baseline or were they adjusted for confounders in the analysis?

Concealment adequately: Was the allocation to the different groups adequately concealed during?

Random housing: Were the animals randomly housed during the experiment?

Blinding (performance): Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?

Random outcome assessment: Were animals selected at random for outcome assessment?

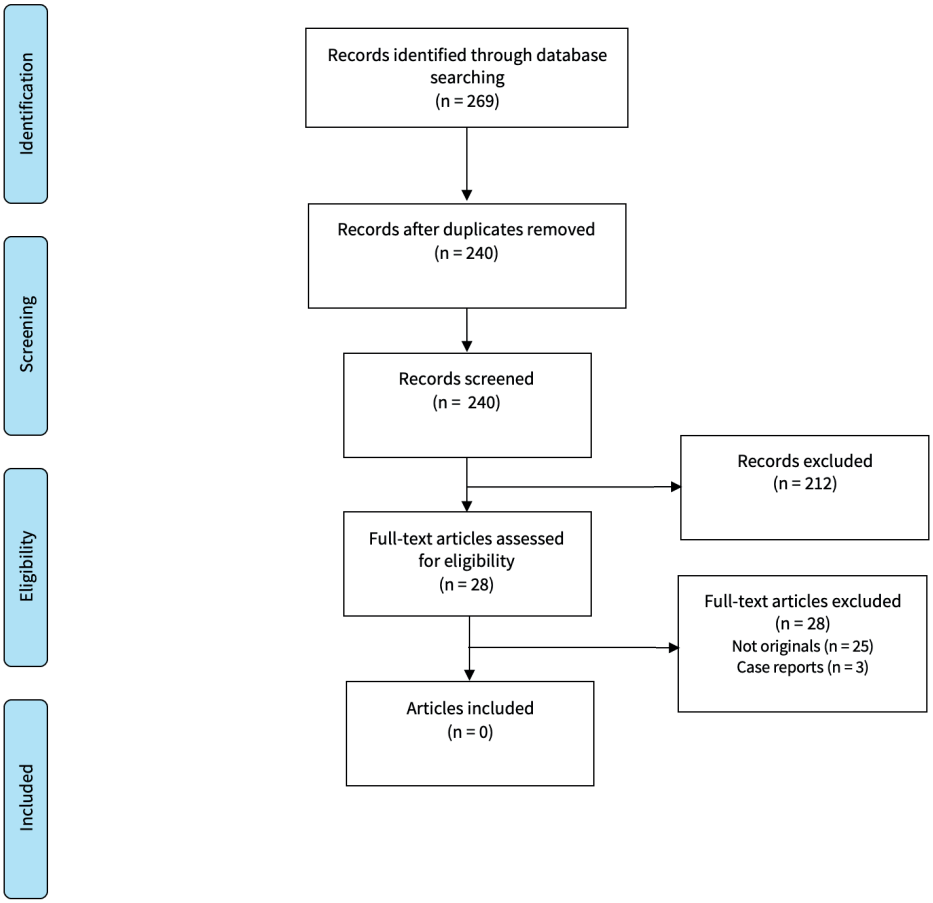
Blinding (detection): Was the outcome assessor blinded?

Incomplete outcome data: Were incomplete outcome data adequately addressed? Has dropouts been reported?

Free from selective outcome reporting: Are reports of the study free of selective outcome reporting?

Free from selective outcome reporting: Are reports of the study free of selective outcome reporting?

igure 2. PRISMA Flowchart selection of included clinical studies



This figure shows an overview of the systematic search results and selection of the studies included for this systematic review. It shows the search found 240 studies, which we reduced to 0 studies included for the clinical part of this systematic review.

blinding for detection in 10 studies. No study was completely free from risk of bias (Table 1).

Study characteristics of the 20 included preclinical studies are reported in Table 2. The sample size ranged from 9 to 102 per study and from 2 to 25 animals per group (see Table, Supplemental Digital Content 1, listing all study characteristics). Studies compared the effect of dexmedetomidine to that of another anesthetic (n=15), control (saline) (n=3) or both anesthetic and control (n=2). In 5 studies, the anesthetics were administered to the mother during pregnancy and subsequently studied in the newborn animal. In 15 studies the anesthetics were administered to young animals (P7-P21). Eighteen studies concerned rats, one study pregnant monkeys and one study pregnant ewes. Dexmedetomidine was mostly injected intraperitoneally, intramuscularly or subcutaneously. In the

Table 2. Study characteristics

Article	Study design	Single dose dex (µg/kg)	Total dose dex (µg/kg)	Additional drugs	Histologic injury by dex?	Dex decreases injury caused by other anaesthetic	Impaired function after dex	Less impairment after dex (behaviour)
Duan 2014[17]	dex+keta vs dex+con	25	75	keta: ip 75mg/kg	no	yes	-	yes
Goyagi 2016[23]	dex+sevo vs sevo+con	6.6-12.5-25	6.6-12.5-25	sevo: 3.0% 4h	-	-	-	yes
Han 2013[24]	dex+iso vs iso+con vs dex	25	75	iso: 0.75%; sevo: 1.2% 4h	-	yes	-	-
Ibrahim 2015[22]	dex+sevo vs prop+dex	3	3	sevo: 4%; prop: iv 4 mg/kg	-	no	-	-
Koo 2014[14]	dex vs con	3.0-30	39-390	keta: 20mg/kg, 20-50mg/kg/h 12h	yes	-	-	-
Lee 2017[25]	dex+sevo vs dex vs sevo	1-5-25-50-100[1]	3-15-75-150-300	sevo: 2.5% 6h	no[1]	no	-	-
Li, J 2016[19]	dex+prop vs dex+iso vs dex	2.5-5.0-10	5-10-20	prop: iv 8.0 mg/kg+1.2mg/kg/min	no	yes	-	yes
Li,Y 2014[16]	dex+iso vs iso+con vs dex	25-50-75	25-50-75	iso: 0.75% 6h	no	yes	-	-
Liao 2014[26]	dex+iso vs iso+con	25-50-75	75-150-225	iso: 0.75%	no	yes	-	-
Liu 2016[18]	dex+keta vs dex vs con	10-25-50	50-125-250	keta: ip 20 mg/kg per dose	yes	no	-	-
Lv 2017[20]	dex+prop vs con	25-50-75	25-50-75	prop: ip 100 mg/kg	-	yes	-	-
Olutoye 2015[15]	dex+iso vs iso	1	2	iso: 1.5-2.0% 2-3h+ 6h	-	yes	-	-
Pancaro 2016[32]	dex vs keta vs con	30-45	30-45	-	yes	-	-	-
Perez 2017[27]	dex+sevo vs con	1-5-10-25-50	3-15-30-75-150	sevo: 2.5% 6h	-	yes[2]	-	-
Sanders 2009[29]	dex+iso vs iso+con	1-10-25	3-30-75	iso: 0.75% 6h	no	yes	no	yes
Sanders 2010[33]	dex+iso vs iso+con	25-50-75	75-150-225	iso: 0.75% 6h	no	yes	-	-
Su 2015[30]	dex+iso vs dex+O2 vs con	10	20	iso: 1.5% 4h	no	yes	no	yes
Tachibana 2011[34]	dex vs con	5-10	5-10	-	-	-	no	-
Wang 2016[21]	dex+prop vs con	75	525	prop: ip 7 days 3x30 mg/kg/d	-	yes	-	yes
Zeng 2013[31]	dex vs dex+iso vs iso	25-50-75	25-50-75	iso: 0.75% 6h	-	yes	-	-

← **Table 2.** Study characteristics
dex; dexmedetomidine, keta; ketamine, iso; isoflurane, sevo; sevoflurane, prop; propofol, con; control. WR; Wistar rat, SD; sprague-dawley rat, CM; cynomolgus monkey, WE; Western cross ewes, ip; intraperitoneal, sc; subcutaneous, iv; intravenous, im; intramuscular, ICV; intracerebroventricular, cath; catheter, MWM; Morris Water Maze test
h; hours; d; days; w; weeks; m; months
red; toxic effect, green; nontoxic effect/amelioration
[1] Significant effects from 25 µg/kg and higher
[2] Sevo + high dose of dex leads to increased mortality (dex1:22%; dex5:55%; dex10-25: 100%)

monkey[14] and ewe[15] studies it was injected intravenously and in one other study intracerebroventricularly.[16] It was given as a single or repeated bolus with an interval varying between 1 hour and 7 days. The total dose of dexmedetomidine per animal ranged from 2 to 525 µg/kg. In 17 studies dexmedetomidine was administered in combination with another anesthetic agent, including ketamine (75 mg/kg intraperitoneal or intravenous infusion at 20 to 50 $mg \cdot kg^{-1} \cdot h^{-1}$ for a period of 12 hours)[14,17,18], propofol (intraperitoneal 30 $mg \cdot kg^{-1} \cdot d^{-1}$ for a period of 7 days to 100 mg/kg and 1.2 $mg \cdot kg^{-1} \cdot min^{-1}$ as continuous infusion for 6 hours)[19-22] and inhalation anesthetic (isoflurane 0.75%-2.0%, sevoflurane 2.5-4% up to 6 hours).[15,16,22-31]

In total, 18 studies published information about histopathological outcome and 7 studies published information about neurobehavioral outcome, of which 2 studies reported only on neurobehavioral outcome and not on histopathological outcome (Tables 2, 3 and 4). The effects of dexmedetomidine have been shown using immunohistochemistry, Terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL), Western blot, Silver Staining and transmission electron microscopy (TEM) (Table 3).

Effect of dexmedetomidine versus control on histopathological outcome

The effects of dexmedetomidine alone on caspase-3 activity were investigated in 8 studies (Table 2, 3).[14,16,18,19,25,26,29,32] Detection of caspase-3 enables to identify neurons that are undergoing apoptotic degeneration. Less (or similar to control) caspase-3 activity suggests less apoptosis[14,16,19,25,26,29] and more caspase-3 activity suggests more apoptosis after exposure to dexmedetomidine compared to control (Table 3).[18,32] Two studies showed no caspase-3 activity 6 hours after a single or repeated dose of dexmedetomidine varying between 1 and 75 µg/kg.[16,26] In contrast, 6 other studies did show caspase-3 activity after a total dose of dexmedetomidine ranging from 25 and 250 µg/kg. Of these 6 studies, 4 studies found the same amount of activity as in the control group[14,19,25,29] and 2 studies found more activity than in the control group.[18,32] Additionally, 1 study investigated synaptic cleft width using electromicroscopy; an increase in width was not shown.[30]

In total 6 studies addressed apoptosis in relation to dexmedetomidine alone.[16-18,25,30,32] In 2 studies apoptosis increased after a total dose dexmedetomidine ranging from 30 to 250 µg/kg[18,32] and apoptosis had not significantly increased in 4 studies after a total

Table 3. Histologic tests

Study	Test + protein	Result dex alone	Result dex + anesthetic
Duan 2014[17]	TUNEL	Dex = control	Less injury
Han 2013[24]	TUNEL IHC WB	No dex alone	Less injury
Ibrahim 2015[22]	IHC (caspase-3) IMF (caspase-3)	No dex alone	Not less injury
Koo 2014[14]	TUNEL TEM (activated caspase-3) SS	Dex = control Dex = control Dex = control	No dex combination
Lee 2017[25]	IHC (caspase-3) Microscopy (apoptosis)	Dex = control[1] Dex = control	Not less injury
Li 2016[19]	WB (caspase-3) IMF (caspase-3)	Dex = control Dex = control	Less injury
Li 2014[16]	TUNEL IHC (caspase-3) WB (caspase-3)	Dex = control Dex no caspase-3 activation Dex = control	Less injury
Liao 2014[26]	TUNEL WB (caspase-3)	Dex = control Dex no caspase-3 activation	Less injury
Liu 2016[18]	TUNEL (proteinase K) IHC (caspase-3) WB (cleaved caspase-3) IMF (caspase-3)	Dex > control Dex > control Dex > control Dex > control	Not less injury
Lv 2017[20]	TUNEL (proteinase K) WB (p-Akt and Akt) IMF (primary antibody) TEM	No dex alone	Less injury
Olutoye 2015[15]	IHC (anti-human/mouse caspase-3)	No dex alone	Less injury
Pancaro 2016[32]	IHC (rabbit anti-cleaved caspase-3) SS	Dex > control Dex > control	No dex combination
Perez 2017[27]	Microscope (rabbit anti-cleaved caspase-3)	No dex alone	Less injury*
Sanders 2009[29]	IHC (rabbit anti-cleaved caspase-3)	Dex = control	Less injury
Sanders 2010[33]	IHC (rabbit anti-cleaved caspase-3)	No apoptosis	Less injury
Su 2015[30]	TEM	Dex = control	Less injury
Wang 2016[21]	TUNEL WB (caspase-3)	No dex alone	Less injury
Zeng 2013[31]	TUNEL WB (?)	No dex alone	Less injury

TUNEL; Terminal deoxynucleotidyl transferase dUTP nick end labeling, IHC; immunohistochemistry, WB; Western Blot, IMF; immunofluorescence, TEM; transmission electron microscopy, SS; Silver Staining, Dex; dexmedetomidine

[1] If dex < 25 µg/kg dex = control. If dex > 25 µg/kg dex>control

* Only when low dose dex was administered in combination with another anesthetic

dexmedetomidine dose ranging from 25 to 100 µg/kg (see Table, Supplemental Digital Content 1, listing all study characteristics).[16,17,25,33]

Effect of dexmedetomidine versus other anesthetic on histopathological outcome

In total 16 studies reported on dexmedetomidine-induced decrease of injury caused by another anesthetic (Table 2). The other agent was isoflurane in 8 studies – 0.75% in 6 studies,[16,24,26,29,31,33] 1.5% in one[30] and 1.5-2.0% in one.[15] Total dexmedetomidine dose ranged from 2 to 225 µg/kg. All of these studies show a decrease of isoflurane-induced injury after dexmedetomidine. Two studies studied the effect of dexmedetomidine after sevoflurane administration for 6h at 2.5%.[25,27] Of these, one showed a decrease of injury (total dexmedetomidine dose 3 to 150 µg/kg),[27] whereas the other did not (total dexmedetomidine dose 3 to 300 µg/kg).[25]

Four studies studied the decrease of injury by dexmedetomidine after injury caused by administration of propofol at a total dose ranging from 4 to 100 $mg \cdot kg^{-1} \cdot d^{-1}$.[19-22] Total dexmedetomidine dose ranged from 3 to 525 µg/kg. Three of the 4 studies showed a decrease of injury.[19-21] The other study did not show a decrease of injury caused by dexmedetomidine (3 µg/kg) with co-administration of propofol 4 mg/kg or sevoflurane 4.0%.[22]

Two studies studied the decrease of injury by dexmedetomidine after injury caused by ketamine administration.[17,18] One showed a decrease of injury (dexmedetomidine dose 75 µg/kg, ketamine dose 75 mg/kg) caused by dexmedetomidine,[17] whereas the other study (dexmedetomidine dose max. 250 µg/kg, ketamine 20 $mg \cdot kg^{-1} \cdot dose^{-1}$) did not show a decrease of injury.[18]

Effect of dexmedetomidine on neurobehavioral outcome

In total 7 studies described neurobehavioral testing, all in rodents (Table 2).[17,19,21,23,29,30,34] Three of these studied the effect of dexmedetomidine only (total dose ranged from 3 to 75 µg/kg) on fear conditioning, Morris water maze or synaptic plasticity (Table 4).[29,30,34]

Table 4. Neurobehavioral tests

Study	Morris water maze test	Other
Duan 2014[17]	+	
Goyagi 2016[23]	+	
Li 2016[19]		Eight-arm radial maze test
Sanders 2009[29]		Fear conditioning
Su 2015[30]	+	
Tachibana 2011[34]		Synaptic plasticity
Wang 2016[21]	+	

Test performed by study is denoted by '+'.

None reported any functional impairment caused by dexmedetomidine. Furthermore, in 6 studies dexmedetomidine (dose ranging from 3 to 525 µg/kg) decreased the negative effect on neurobehavioral outcome caused by co-administration of ketamine, sevoflurane, propofol or isoflurane.[17,19,21,23,29,30]

DISCUSSION

In a recently published review, dexmedetomidine was proposed as a suitable alternative for currently used, allegedly toxic anesthetics in children, and has been suggested to have a neuroprotective effect when co-administered with these anaesthetics.[5] In this systematic review we analyzed the results of both preclinical and clinical studies to assess whether dexmedetomidine is a suitable alternative for the allegedly neurotoxic anesthetic agents. In preclinical studies, exposure to dexmedetomidine alone had contradictory effects on caspase-3 activity by histologic examination; no differences with controls in 6 studies (total dexmedetomidine dose ranging from 3 to 300 µg/kg),[14,16,19,25,26,29] more caspase-3 activity in 3 other studies (total dexmedetomidine dose ranging from 30 to 250 µg/kg).[14,18,32] Co-administration of dexmedetomidine (total dexmedetomidine dose ranging from 3 to 525 µg/kg) decreased the negative histologic effect caused by other anesthetics in 13 studies[15-17,19-21,24,26,27,29-31,33] but the effect was not found in 3 other studies.[18,22,25] All 6 studies that report on adverse neurobehavioral outcome showed a decrease of injury when co-administration of dexmedetomidine (dose ranging from 3 to 525 µg/kg) with other anesthetics (isoflurane, sevoflurane, ketamine or propofol).[17,19,21,23,29,30] To evaluate neuronal injury, most studies focused on testing for apoptosis. Other signs of neuronal injury, such as synaptogenesis and gliogenesis were not used as markers for neuronal injury by most studies, except for one, which studied synaptic width to evaluate neuronal injury.[30]

Furthermore, our systematic search did not yield clinical studies on children's neurobehavioral outcomes after administration of dexmedetomidine as a sedative agent. Excluded were studies that evaluated acute effects after anesthesia (for example agitation and delirium), since the aim of this study was to evaluate effects on the long term (more than 48h after anesthesia) only. Although an increase in publications on dexmedetomidine administration in children for sedation, pain management and delirium management is noted, studies focusing on long term effects are not published yet.

The reviewed pre-clinical studies overall show an advantageous effect of dexmedetomidine regarding neurotoxicity. Histologically, neurons show less apoptosis after exposure to dexmedetomidine compared to exposure to other anesthetics (see results).[14,16,19,25,26,29] Most of the histologic research focuses on a basic element of toxicity: apoptosis (and the connected caspase-3 activity). Apoptosis is programmed cell death,

which can be triggered by cell damage. Cell damage can activate caspase-3 as a precursor in the pathway that leads to apoptosis.[35] Apoptosis can be marked histologically with techniques like Terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL), Silver Staining and Western Blot. Using these techniques, a few study results show brain damage induced by dexmedetomidine; caspase-3 activity was increased in animals (Sprague-Dawley rats) after exposure to dexmedetomidine.[14,18,25,32]

Out of the 18 studies that performed histological analysis, 16 addressed decrease of injury caused by another anesthetic agent. Thirteen of these found a decrease of injury, suggestive of a neuroprotective effect of dexmedetomidine. Only 1 study shows major negative effects of dexmedetomidine co-administered with another anesthetic. The mortality rate among Wistar rats in that study was not affected when either sevoflurane 2.5% or dexmedetomidine (5, 25 or 50 µg/kg) was administered alone, but a significant increase in dose-dependent mortality and neuronal cell apoptosis was seen when a total dose of dexmedetomidine ranging from 3 to 150 µg/kg was co-administered with 2.5% sevoflurane. In the surviving animals, however, co-administration of low dose dexmedetomidine (1 and 5 µg/kg) lead to a significant reduction in sevoflurane-induced apoptosis.[27] Hypothetically the increased mortality (like suggested by one study that found increased mortality) might be a sevoflurane overdose leading to too deep levels of anesthesia resulting in death.[25]

Neurobehavioral outcome in animals can be tested by learning tasks (radial maze), executive tasks (motor skills), memory (eight-arm radial maze test) and social skills (fear conditioning). Seven studies performed neurobehavioral tests, of which the Morris Water Maze test was used the most.[17,21,23,30] This test is used in rodents for assessing spatial learning and memory. Three of these studies examined whether administration of dexmedetomidine alone causes impaired outcome.[29,30,34] These studies showed that the outcome of the tests is worse after exposure to anesthetics compared to control. Six studies showed that when the rats were subsequently exposed to dexmedetomidine, performance improved, which indicates that dexmedetomidine decreases the negative effects caused by other anesthetics on the neurobehavioral outcome in all tests.[17,19,21,23,29,30]

Furthermore, overall, studies show that dexmedetomidine itself does not have a negative effect on task execution and that it ameliorates the negative effects caused by other toxic anesthetics.

Anesthetics were mostly injected intraperitoneal, because intravenous access is challenging in small animals.[36] The total dexmedetomidine dose administered varied widely between the included studies, from 3 to 525 µg/kg, in contrast to standard doses of sevoflurane (2.5%-4.0%) and isoflurane (0.75%).

The results of the preclinical studies suggest a neuroprotective profile in animals. However, although there is a logical relation between experimental and clinical studies,

not all pathophysiological mechanisms can be translated 'from bench to bed'.[37-40] For example, where sevoflurane is nephrotoxic in preclinical studies, this appears not to hold for humans.[41] On the other hand, interventions that are harmful in clinical studies may not be harmful in preclinical studies.[42-44] Preclinical studies usually examine toxicity of interventions, pathology and mechanisms of disease, whereas clinical studies focus on clinical efficacy.[45] Considering these different study objectives, differences in outcome between preclinical and clinical studies are not that unexpected. Still, only clinical studies following sufficient reliable proof from preclinical studies could give an indication of the safety of new drugs/treatments in humans.[46]

Furthermore, although an animal data on the large doses of dexmedetomidine is important and fully within concept of animal research, it may not be extrapolated to humans: in humans, dexmedetomidine is used either as a sedative or as an adjunct to other anesthetics, but never as a "sole anesthetic".

The present systematic review makes clear that the long term effects of dexmedetomidine in children are not known yet. The milestones of neurobehavioral development vary across species but the developmental progression in general is comparable. In the first weeks of life critical neurodevelopment occurs; apoptosis, synaptogenesis, gliogenesis and myelination, regardless of biological differences between species.[47]

There are some considerations regarding this review. All studies in which animals had suffered cerebral ischemia were excluded. Still, this is a large group in which dexmedetomidine is suggested to have a (neuro)protective effect.[7,48,49] The results of these studies might give more information about the effects of dexmedetomidine on the brain that could help to determine whether dexmedetomidine administration would be applicable and/or beneficial for secondary prevention after ischemic brain injury. Furthermore, studies that did not report dexmedetomidine as a general anesthetic agent were excluded. We aimed to address the effect of dexmedetomidine on the neurons in the brain, and deemed general anesthesia to be the best fit to do so. We reasoned that in other applications of anesthesia (such as local anesthesia and nerve block) the drug would possibly not reach the brain.

Importantly, the quality of the studies included in the present systematic review was intermediate. Not all studies randomly assigned the animals to the groups, which could have led to confounding. Furthermore, methodological descriptions are often poorly reported. Most important issues are the descriptions of dropouts and detailed description of the intervention (dose). Only 8 out of 20 studies reported on the mortality of the experiment (see Table, Supplemental Digital Content 1, listing all study characteristics). When studied animals are replaced after dropout without description, important outcome can be missed.

Lastly, we performed a broad search in two databases without any language limitations or exclusions due to language barriers. Still, we may have missed relevant studies,

with the concomitant risk of search bias. Furthermore, non-reporting of study results could have given rise to publication bias (not reporting certain outcomes) and/or author bias (judgement of the authors of the study).[50]

In conclusion, the overall trend of the results show a substantial variety in species, exposure paradigm and histological assessment to render conclusive results. A clear conclusion cannot be stated: 8 out of 11 studies demonstrated no histological injury by dexmedetomidine when administered by itself and 13 out of 16 studies found beneficial neuroprotective effects of dexmedetomidine co-administrated with other anesthetics.

Dexmedetomidine is currently clinically used, however, as our systematic search shows, studies are lacking about the long term neurobehavioral effects when administered in children for sedation or anesthesia. A randomized controlled trial to find out what the long term neurobehavioral effects of dexmedetomidine are in children (compared to currently used neurotoxic anesthetics), with the ultimate aim to find a safe(r) alternative to the currently used neurotoxic anesthetics in children is mandatory. Furthermore, the safety of the combination of dexmedetomidine (especially in high dose) with other anesthetics needs to be monitored meticulously.

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Supplemental Digital Content 1. Listing all study characteristics

Article	Reference	Study design	Number of animals per group	Total number of animals	Mortality rates	Type publication	Species	Age of exposure	Time of exposure	Dex route of delivery	Single dose dex (µg/kg)	Total dose dex (µg/kg)	Length of treatment	Placebo	Additional drugs administration	Time histologic test after exposure	Histologic brain region tested	Histologic caspase-3 activity by dex?	Histologic apoptotic injury by dex?	Dex ameliorates injury caused by other anesthetic	Time behavioral test after exposure	Type behavioral testing	Impaired function after dex alone	Neuroprotection (behavior)
Duan 2014	13	dex+keta vs dex+con	6	30	?	full paper	SD	P7	neonate	sc	25	75	1 dd 3 days	saline	keta: ip 75mg/kg	4d histo	hippocampus	-	no	yes	2m	MWM	-	yes
Goyagi 2016	20	dex+sevo vs sevo+con	?	35	?	abstract	rats	P7	neonate	ip	6.6-12.5-25	6.6-12.5-25	4h	saline	sevo: 3.0% 4h	?	-	-	-	-	3w	MWM	-	yes
																		-	-	-	5+6w	Fear conditioning	-	yes
																		-	-	-	6w	Spatial memory	-	yes
Han 2013	21	dex+iso vs iso+con vs dex	5	50	?	abstract	SD	P7	neonate	ip	25	75	3 times	saline	iso: 0.75%; sevo: 1.2% 4h	6h	hippocampus	-	-	yes	-	-	-	-
Ibrahim 2015	19	dex+sevo vs prop+dex	6	27	4	full paper	SD	P21	neonate	ip	3	3	150min	saline	sevo: 4%; prop: iv 4 mg/kg	150min	brain	-	-	no	-	-	-	-
Koo 2014	14	dex vs keta vs con	5	20	?	full paper	CM	intrauterine	intrauterine	iv	3.0-30	39-390	10min; 12h	-	keta: 20mg/kg, 20-50mg/kg/h 12h	up to 18h	brain	yes	-	-	-	-	-	-
Lee 2017	22	dex+sevo vs dex vs sevo	10	102	5	full paper	WR	intrauterine-P7	intrauterine	ip	1-5-25-50-100[2]	3-15-75-150-300	3 times; 2h	saline	sevo: 2.5% 6h	up to 6h	brain	no[1]	no	no	-	-	-	-
Li 2016	16	dex+prop vs dex+iso vs dex	10-15	41	?	full paper	SD	intrauterine	intrauterine	ip	2.5-5.0-10	5-10-20	2 times	saline	prop: iv 8.0 mg/kg+1.2mg/kg/min	6h	brain	no	-	yes	1-5 d	Radial Maze	-	yes
Li 2014	23	dex+iso vs iso+con vs dex	5-12	50	0	full paper	SD	P7	neonate	ip, ICV	25-50-75	25-50-75	1-3 times	saline	iso: 0.75% 6h	up to 6h	hippocampus	no	no	yes	-	-	-	-
Liao 2014	24	dex+iso vs iso+con	6	30	?	full paper	SD	P7	neonate	ip	25-50-75	75-150-225	3 times	saline, air	iso: 0.75%	after 6h	hippocampus	no	-	yes	-	-	-	-
Liu 2016	15	dex+keta vs dex vs con	6	36	0	full paper	SD	P7	neonate	ip	10-25-50	50-125-250	5 times; 6h	saline	keta: ip 20 mg/kg per dose	6h	brain	yes	yes	no	-	-	-	-
Lv 2017	17	dex+prop vs con	6	60	?	full paper	SD	P7	neonate	ip	25-50-75	25-50-75	1 time	saline	prop: ip 100 mg/kg	up to 2h	hippocampus	-	-	yes	-	-	-	-
Olutoye 2015	25	dex+iso vs iso	2-5	9	?	full paper	WE	intrauterine	intrauterine	iv	1	2	2-3h; 6h	-	iso: 1.5-2.0% 2-3h+ 6h	2w	hippocampus, cortex	-	-	yes	-	-	-	-
Pancaro 2016	31	dex vs keta vs con	6	24	0	full paper	SD	P7	neonate	sc	30-45	30-45	6 times	saline	-	24h	brain	yes	yes	-	-	-	-	-
Perez 2017	26	dex+sevo vs con	4-11	57	14	full paper	WR	P7	neonate	ip	1-5-10-25-50	3-15-30-75-150	3 times	saline	sevo: 2.5% 6h	6h	brain	-	-	yes[4]	-	-	-	-
Sanders 2009	28	dex+iso vs iso+con	6	36	0	full paper	SD	P7	neonate	ip	1-10-25	3-30-75	3 times	saline	iso: 0.75% 6h	6h	hippocampus, cortex, thalamus	no	-	yes	32d	Fear conditioning	no	yes
Sanders 2010	32	dex+iso vs iso+con	6	24	0	full paper	SD	P7	neonate	ip	25-50-75	75-150-225	3 times	saline	iso: 0.75% 6h	6h	brain	-	no	yes	-	-	-	-
Su 2015	29	dex+iso vs dex+O2 vs con	10	50	?	full paper	SD	intrauterine	intrauterine	im	10	20	2 times	saline	iso: 1.5% 4h	1 to 4 d	hippocampus	no[1]	-	yes	21d	MWM	no	yes
Tachibana 2011	33	dex vs con	4-6	27	?	full paper	WR	P7	neonate	ip	5-10	5-10	1 time	saline	-	9w	hippocampus	-	-	-	9w	Synaptic plasticity	no	-
Wang 2016	18	dex+prop vs con	25	75	?	full paper	SD	P7	neonate	ip	75	525	1dd; 7days	saline	prop: ip 7 days 3x30 mg/kg/d	?	hippocampus	-	-	yes	p29-33	MWM	-	yes
Zeng 2013	30	dex vs dex+iso vs iso	10	60	?	abstract	rats	P7	neonate	ip	25-50-75	25-50-75	6h	saline	iso: 0.75% 6h	2h	hippocampus	-	-	yes	-	-	-	-

dex; dexmedetomidine, keta; ketamine, iso; isoflurane, sevo; sevoflurane, prop; propofol, con; control, ?; not reported
WR; Wistar rat, SD; sprague-dawley rat, CM;cynomolgus monkey, WE;Western cross ewes
ip; intraperitoneal, sc; subcutaneous, iv; intravenous, im; intramuscular, ICV;intracerebroventricular, cath;catheter
keta;ketamine, iso;isoflurane, sevo;sevoflurane, prop;propofol, MWM;Morris Water Maze test
h;hours; d; days; w; weeks; m; months
red;toxic effect, green;non toxic effect/amelioration
[1] Significant effects from 25 µg/kg and higher
[2] Sevo + high dose of dex leads to increased mortality (dex1.22%, dex5.55%, dex10-25: 100%)
[3] The dose of 1 µg/kg was only applied in combination with sevoflurane
4 Histologic evaluation included only synaptic cleft width with electromicroscopy

Supplementary table 1

Article	Reference	Study design	Number of animals per group	Total number of animals	Mortality rates	Type publication	Species	Age of exposure	Time of exposure	Dex route of delivery	Single dose dex (µg/kg)	Total dose dex (µg/kg)
Duan 2014	13	dex+keta vs dex+con	6	30	?	full paper	SD	P7	neonate	sc	25	75
Goyagi 2016	20	dex+sevo vs sevo+con	?	35	?	abstract	rats	P7	neonate	ip	6.6-12.5-25	6.6-12.5-25
Han 2013	21	dex+iso vs iso+con vs dex	5	50	?	abstract	SD	P7	neonate	ip	25	75
Ibrahim 2015	19	dex+sevo vs prop+dex	6	27	4	full paper	SD	P21	neonate	ip	3	3
Koo 2014	14	dex vs keta vs con	5	20	?	full paper	CM	intrauterine	intrauterine	iv	3.0-30	39-390
Lee 2017	22	dex+sevo vs dex vs sevo	10	102	5	full paper	WR	intrauterine-P7	intrauterine	ip	1-5-25-50-100[3]	3-15-75-150-300
Li 2016	16	dex+prop vs dex+iso vs dex	10-15	41	?	full paper	SD	intrauterine	intrauterine	ip	2.5-5.0-10	5-10-20
Li 2014	23	dex+iso vs iso+con vs dex	5-12	50	0	full paper	SD	P7	neonate	ip, ICV	25-50-75	25-50-75
Liao 2014	24	dex+iso vs iso+con	6	30	?	full paper	SD	P7	neonate	ip	25-50-75	75-150-225
Liu 2016	15	dex+keta vs dex vs con	6	36	0	full paper	SD	P7	neonate	ip	10-25-50	50-125-250
Lv 2017	17	dex+prop vs con	6	60	?	full paper	SD	P7	neonate	ip	25-50-75	25-50-75
Olutoye 2015	25	dex+iso vs iso	2-5	9	?	full paper	WE	intrauterine	intrauterine	iv	1	2
Pancaro 2016	31	dex vs keta vs con	6	24	0	full paper	SD	P7	neonate	sc	30-45	30-45
Perez 2017	26	dex+sevo vs con	4-11	57	14	full paper	WR	P7	neonate	ip	1-5-10-25-50	3-15-30-75-150
Sanders 2009	28	dex+iso vs iso+con	6	36	0	full paper	SD	P7	neonate	ip	1-10-25	3-30-75
Sanders 2010	32	dex+iso vs iso+con	6	24	0	full paper	SD	P7	neonate	ip	25-50-75	75-150-225
Su 2015	29	dex+iso vs dex+O2 vs con	10	50	?	full paper	SD	intrauterine	intrauterine	im	10	20

	Length of treatment	Placebo	Additional drugs administration	Time histologic test after exposure	Histologic brain region tested	Histologic caspase-3 activity by dex?	Histologic apoptotic injury by dex?	Dex ameliorates injury caused by other anesthetic	Time behavioral test after exposure	Type behavioral testing	Impaired function after dex alone	Neuroprotection (behavior)
	1 dd 3 days	saline	keta: ip 75mg/kg	4d histo	hippocampus	-	no	yes	2m	MWM	-	yes
	4h	saline	sevo: 3.0% 4h	?	-	-	-	-	3w	MWM	-	yes
						-	-	-	5+6w	Fear conditioning	-	yes
						-	-	-	6w	Spatial memory	-	yes
	3 times	saline	iso: 0.75%; sevo: 1.2% 4h	6h	hippocampus	-	-	yes	-	-	-	-
	150min	saline	sevo: 4%; prop: iv 4 mg/kg	150min	brain	-	-	no	-	-	-	-
	10min; 12h	-	keta: 20mg/kg, 20-50mg/kg/h 12h	up to 18h	brain	yes	-	-	-	-	-	-
	3 times; 2h	saline	sevo: 2.5% 6h	up to 6h	brain	no[1]	no	no	-	-	-	-
	2 times	saline	prop: iv 8.0 mg/kg+1.2mg/kg/min	6h	brain	no	-	yes	1-5 d	Radial Maze	-	yes
	1-3 times	saline	iso: 0.75% 6h	up to 6h	hippocampus	no	no	yes	-	-	-	-
	3 times	saline, air	iso: 0.75%	after 6h	hippocampus	no	-	yes	-	-	-	-
	5 times; 6h	saline	keta: ip 20 mg/kg per dose	6h	brain	yes	yes	no	-	-	-	-
	1 time	saline	prop: ip 100 mg/kg	up to 2h	hippocampus	-	-	yes	-	-	-	-
	2-3h; 6h	-	iso: 1.5-2.0% 2-3h+ 6h	2w	hippocampus, cortex	-	-	yes	-	-	-	-
	6 times	saline	-	24h	brain	yes	yes	-	-	-	-	-
	3 times	saline	sevo: 2.5% 6h	6h	brain	-	-	yes[2]	-	-	-	-
	3 times	saline	iso: 0.75% 6h	6h	hippocampus, cortex, thalamus	no	-	yes	32d	Fear conditioning	no	yes
	3 times	saline	iso: 0.75% 6h	6h	brain	-	no	yes	-	-	-	-
	2 times	saline	iso: 1.5% 4h	1 to 4 d	hippocampus	no[4]	-	yes	21d	MWM	no	yes

Supplementary table 1 (continued)

Article	Reference	Study design	Number of animals per group	Total number of animals	Mortality rates	Type publication	Species	Age of exposure	Time of exposure	Dex route of delivery	Single dose dex (µg/kg)	Total dose dex (µg/kg)
Tachibana 2011	33	dex vs con	4-6	27	?	full paper	WR	P7	neonate	ip	5-10	5-10
Wang 2016	18	dex+prop vs con	25	75	?	full paper	SD	P7	neonate	ip	75	525
Zeng 2013	30	dex vs dex+iso vs iso	10	60	?	abstract	rats	P7	neonate	ip	25-50-75	25-50-75

	Length of treatment	Placebo	Additional drugs administration	Time histologic test after exposure	Histologic brain region tested	Histologic caspase-3 activity by dex?	Histologic apoptotic injury by dex?	Dex ameliorates injury caused by other anesthetic	Time behavioral test after exposure	Type behavioral testing	Impaired function after dex alone	Neuroprotection (behavior)
	1 time	saline	-	9w	hippocampus	-	-	-	9w	Synaptic plas-ticity	no	-
	1dd; 7days	saline	prop: ip 7 days 3x30 mg/kg/d	?	hippocampus	-	-	yes	p29-33	MWM	-	yes
	6h	saline	iso: 0.75% 6h	2h	hippocampus	-	-	yes	-	-	-	-

APPENDIX 1. SEARCH PRECLINICAL STUDIES

Embase

('dexmedetomidine'/exp OR (dexmedetomidine OR cepedex OR dexamedetomidine OR dexdomitor OR dexdor OR mpv-1440 OR mpv1440 OR precedex OR primadex OR sedadex OR sileo):ab,ti) AND ('neurotoxicity'/exp OR 'toxicity and intoxication'/de OR intoxication/de OR 'drug intoxication'/de OR 'neuroprotection'/de OR 'toxicity'/de OR 'brain toxicity'/exp OR 'drug toxicity'/de OR 'behavior change'/exp OR 'behavior disorder'/exp OR 'neuropsychology'/de OR 'memory disorder'/de OR 'cognitive defect'/de OR 'developmental toxicity'/de OR 'nervous system development'/exp OR 'developmental disorder'/de OR cognition/de OR learning/exp OR memory/exp OR 'mental capacity'/exp OR 'mental development'/exp OR 'mental performance'/exp OR 'social cognition'/exp OR 'experimental behavioral test'/exp OR 'neuropsychological test'/exp OR (neurotoxic* OR neuroprotect* OR toxic* OR intoxicat* OR (behav* NEAR/3 (change* OR test OR disorder*)) OR memor* OR neuropsycholog* OR cogniti* OR learning OR neurocogniti* OR ((development*) NEAR/3 (disorder* OR dysfunct* OR function* OR declin* OR defect* OR impair* OR improv*)) OR (maze NEAR/3 test*) OR (('nervous system' OR brain) NEAR/3 (develop*)) OR neuroapoptos* OR adhd OR (attention NEAR/3 (deficit OR hyperactiv*)) OR iq OR intelligence OR autis*):ab,ti) AND ([animals]/lim OR nonhuman/de OR (rat OR rats OR mouse OR mice OR murine OR animal* OR monkey* OR makak* OR primate* OR nonhuman):ab,ti)

Medline ovid

(Dexmedetomidine/ OR (dexmedetomidine OR cepedex OR dexamedetomidine OR dexdomitor OR dexdor OR mpv-1440 OR mpv1440 OR precedex OR primadex OR sedadex OR sileo).ab,ti.) AND (Neurotoxicity Syndromes/ OR neuroprotection/ OR toxicity.xs. OR Memory Disorders/ OR Cognitive Dysfunction/ OR nervous system/gd OR Neuropsychology/ OR Developmental Disabilities/ OR cognition/ OR Cognition Disorders/ OR learning/ OR exp memory/ OR Neuropsychological Tests/ OR (neurotoxic* OR neuroprotect* OR toxic* OR intoxicat* OR (behav* ADJ3 (change* OR test OR disorder*)) OR memor* OR neuropsycholog* OR cogniti* OR learning OR neurocogniti* OR ((development*) ADJ3 (disorder* OR dysfunct* OR function* OR declin* OR defect* OR impair* OR improv*)) OR (maze ADJ3 test*) OR ((nervous system OR brain) ADJ3 (develop*)) OR neuroapoptos* OR adhd OR (attention ADJ3 (deificit OR hyperactiv*)) OR iq OR intelligence OR autis*).ab,ti.) AND ((exp animals/ NOT humans/) OR (rat OR rats OR mouse OR mice OR murine OR animal* OR monkey* OR makak* OR primate* OR nonhuman).ab,ti.)

APPENDIX 2. SEARCH CLINICAL STUDIES

Embase

('dexmedetomidine'/exp OR (dexmedetomidine OR cepedex OR dexamedetomidine OR dexdomitor OR dexdor OR mpv-1440 OR mpv1440 OR precedex OR primadex OR sedadex OR sileo):ab,ti) AND ('neurotoxicity'/exp OR 'toxicity and intoxication'/de OR intoxication/de OR 'drug intoxication'/de OR 'neuroprotection'/de OR 'toxicity'/de OR 'brain toxicity'/exp OR 'drug toxicity'/de OR 'behavior change'/exp OR 'behavior disorder'/exp OR 'neuropsychology'/de OR 'memory disorder'/de OR 'cognitive defect'/de OR 'developmental toxicity'/de OR 'nervous system development'/exp OR 'developmental disorder'/de OR cognition/de OR learning/exp OR memory/exp OR 'mental capacity'/exp OR 'mental development'/exp OR 'mental performance'/exp OR 'social cognition'/exp OR 'experimental behavioral test'/exp OR 'neuropsychological test'/exp OR (neurotoxic* OR neuroprotect* OR toxic* OR intoxicat* OR (behav* NEAR/3 (change* OR test OR disorder*)) OR memor* OR neuropsycholog* OR cogniti* OR learning OR neurocogniti* OR ((development*) NEAR/3 (disorder* OR dysfunct* OR function* OR declin* OR defect* OR impair* OR improv*)) OR (maze NEAR/3 test*) OR (('nervous system' OR brain) NEAR/3 (develop*)) OR neuroapoptos* OR adhd OR (attention NEAR/3 (deficit OR hyperactiv*)) OR iq OR intelligence OR autis*):ab,ti) AND (child/exp OR adolescent/exp OR adolescence/exp OR pediatrics/exp OR childhood/exp OR 'child development'/de OR 'child growth'/de OR 'child health'/de OR 'child health care'/exp OR 'child care'/exp OR 'childhood disease'/exp OR 'pediatric ward'/de OR 'pediatric hospital'/de OR (adolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*):ab,ti) AND ('anesthesia'/exp OR 'anesthetic agent'/de OR (anesthe* OR anaesthe*):ab,ti) NOT ([animals]/lim NOT [humans]/lim)

Medline Ovid

(Dexmedetomidine/ OR (dexmedetomidine OR cepedex OR dexamedetomidine OR dexdomitor OR dexdor OR mpv-1440 OR mpv1440 OR precedex OR primadex OR sedadex OR sileo).ab,ti.) AND (Neurotoxicity Syndromes/ OR neuroprotection/ OR toxicity.xs. OR Memory Disorders/ OR Cognitive Dysfunction/ OR nervous system/gd OR Neuropsychology/ OR Developmental Disabilities/ OR cognition/ OR Cognition Disorders/ OR learning/ OR exp memory/ OR Neuropsychological Tests/ OR (neurotoxic* OR neuroprotect* OR toxic* OR intoxicat* OR (behav* ADJ3 (change* OR test OR disorder*)) OR memor* OR neuropsycholog* OR cogniti* OR learning OR neurocogniti* OR ((development*) ADJ3 (disorder* OR dysfunct* OR function* OR declin* OR defect* OR impair* OR improv*)) OR

(maze ADJ3 test*) OR ((nervous system OR brain) ADJ3 (develop*)) OR neuroapoptos* OR adhd OR (attention ADJ3 (deificit OR hyperactiv*)) OR iq OR intelligence OR autis*).ab,ti.) AND (exp Child/ OR exp Infant/ OR exp Adolescent/ OR exp "Child Behavior"/ OR exp "Parent Child Relations"/ OR exp "Pediatrics"/ OR "Child Nutrition Sciences"/ OR "Infant nutritional physiological phenomena"/ OR exp "Child Welfare"/ OR "Child Development"/ OR exp "Child Health Services"/ OR exp "Child Care"/ OR "Child Rearing"/ OR exp "Child development Disorders, Pervasive"/ OR "Child Psychiatry"/ OR "Child Psychology"/ OR "Hospitals, Pediatric"/ OR exp "Intensive Care Units, Pediatric"/ OR (adolescen* OR infan* OR newborn* OR (new ADJ born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under ADJ1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*).ab,ti.) AND (exp anesthesia/ OR anesthetics/ OR (anesthe* OR anaesthe*).ab,ti.) NOT (exp animals/ NOT humans/)

4

Off-label use of dexmedetomidine in paediatric anaesthesiology: an international survey of 791 (paediatric) anaesthesiologists

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ABSTRACT

Purpose: The purpose of this international study was to investigate prescribing practices of dexmedetomidine by paediatric anaesthesiologists.

Methods: We performed an online survey on the prescription rate of dexmedetomidine, route of administration and dosage, adverse drug reactions, education on the drug and overall experience. Members of specialist paediatric anaesthesia societies of Europe (ESPA), New Zealand and Australia (SPANZA), Great Britain and Ireland (APAGBI) and the United States (SPA) were consulted. Responses were collected in July and August 2019.

Results: Data from 791 responders (17% of 5171 invitees) were included in the analyses. Dexmedetomidine was prescribed by 70% of the respondents (ESPA 53%;SPANZA 69%;APAGBI 34% and SPA 96%), mostly for procedural sedation (68%), premedication (46%) and/or ICU sedation (46%). Seventy-three percent had access to local or national protocols, although lack of education was the main reason cited by 26% of the respondents not to prescribe dexmedetomidine. The main difference in dexmedetomidine use concerned the age of patients (SPA primarily <1 year, others primarily >1 year). Dosage varied widely ranging from 0.2–5 $ug*kg^{-1}$ for nasal premedication, 0.2–8 $ug*kg^{-1}$ for nasal procedural sedation and 0–4 $ug*kg^{-1}$ intravenously as adjuvant for anesthesia. Only ESPA members (61%) had noted an adverse drug reaction, namely bradycardia.

Conclusion: The majority of anaesthesiologists use dexmedetomidine in paediatrics for premedication, procedural sedation, ICU sedation and anaesthesia, despite the off-label use and sparse evidence. The large intercontinental differences in prescribing dexmedetomidine call for consensus and worldwide education on the optimal use in paediatric practice.

INTRODUCTION

Dexmedetomidine is increasingly used in children for premedication, sedation in the intensive care unit (ICU), procedural sedation, and anaesthesia, but also to prevent postoperative agitation, nausea and vomiting.[1,2] Dexmedetomidine is an alpha-2 adrenoceptor agonist that provides adequate sedation with facilitated arousal and analgesia without respiratory depression. Dexmedetomidine offers advantages over traditional anaesthetics for its hemodynamic stability, sedative properties and multimodal pain management.[3,4] Its colourless and odourless properties make it suitable for paediatric intranasal administration as premedication. Furthermore, dexmedetomidine ameliorates separation anxiety in children.[5,6]

Despite the lack of evidence and off-label use of dexmedetomidine for anaesthesia in patients younger than 18 years of age, the worldwide use of dexmedetomidine for paediatric anaesthesia is still increasing.[7,8] Experimental research has shown that dexmedetomidine may have a neuroprotective effect when co-administered with other anaesthetic medications.[9,10] However, evidence is lacking from clinical studies and randomized controlled trials on the short- and long-term effects of dexmedetomidine use in children undergoing general anaesthesia or receiving prolonged dexmedetomidine infusions. Multiple ongoing studies in children investigate the relationship between dexmedetomidine-based general anaesthesia and long-term neurodevelopmental outcomes.[4,11]

Furthermore, dosing protocols for children have not yet been published, and an international consensus on the use of dexmedetomidine in paediatrics is missing.[12-16] Incorrect application could lead to yet unknown adverse long-term effects. Therefore, overexposure to the drug should be avoided.

We postulated that dexmedetomidine is frequently used in paediatric anaesthesia without a structured implementation procedure including, for example, education and protocols, which leads to large application differences. We performed a survey of international paediatric anaesthesia specialist societies in order to gather information on the use of dexmedetomidine in children by paediatric anaesthesiologists worldwide and identify areas of future need for safe and effective use of dexmedetomidine in children.

METHODS

We performed an online survey on the use of dexmedetomidine in paediatric anaesthesiology, starting July 16th 2019 and with closing date August 16th, 2019. The target response rate was 25%.

Survey respondents were recruited from the following societies for paediatric anaesthesiologists: European Society for Paediatric Anaesthesiology (ESPA), Society for Paediatric Anaesthesia in New Zealand and Australia (SPANZA), Association of Paediatric Anaesthetists of Great Britain and Ireland (APAGBI), and Society for Paediatric Anesthesia (SPA). The boards of these societies were invited to distribute a survey, described below, amongst their members via an e-mail with a link to the survey. ESPA, APAGBI and SPA sent an e-mail with the link to the survey to all members. SPANZA mentioned the survey and link in a newsletter. ESPA and SPANZA sent a reminder one month later. APAGBI and SPA have email usage protocols for survey distribution in place, which do not provide for reminders.

Survey

Experts in the field of paediatric anaesthesia developed a 16-question survey to collect information on the use of dexmedetomidine in paediatric anaesthesiology care. The items addressed whether the respondent regularly prescribes dexmedetomidine to children, perceived barriers for the use of dexmedetomidine in practice, in what setting dexmedetomidine was used, the availability of a local protocol, how the respondent had been educated on dexmedetomidine in paediatrics, and clinical experiences with the drug, such as adverse events (survey in Supplementary Data).

The survey was designed to be completed anonymously within 10 minutes by every anonymous participant. It was delivered through Limesurvey (Limesurvey GmbH, Hamburg, Germany) secure web application for building and managing online surveys and databases.[17] The survey was tested among paediatric anaesthesiologists at the Erasmus MC-Sophia Children's Hospital Rotterdam. Following this test, some of the questions were adjusted for improvement.

Analysis

The survey data were exported from Limesurvey to Microsoft Excel Version 16.32 (Microsoft Corporation, Redmond, Washington, USA) and SPSS Statistics Version 24 (IBM Corporation, Armonk, NY, USA) to perform descriptive statistical analysis. SPSS was used to compare the groups and summarize the data. Due to the explorative nature of the study, no comparative statistics were performed.

Incomplete responses with at least 40% completion were still included for analysis. The numbers of respondents per question were determined in order to provide accurate response rates per question.

Responses of respondents who had not stated the country of practice were excluded from analysis because these responses could not be assigned to a societal group.

Questions asked regarding experience with adverse drug reactions were not specified as to whether these reactions were experienced once or that these were experienced more frequently.

RESULTS

In total 5171 society members received an invitation (Fig. 1). The number of anaesthesiologists who were members of multiple societies was unknown. Sixty respondents were excluded because the country of practice was missing. The overall response was 17% and varied from 35% (SPANZA) to 10% (SPA) among the various societies (Table 1). Seventy-five incomplete surveys were included for analysis. No incomplete surveys were excluded due to >40% completion of the survey. Respondents who did not answer a specific question were left out of consideration regarding this question, as reflected in the Tables 1, 3 and 4. Across all societies, most respondents worked in a tertiary hospital as a full-time paediatric anaesthesiologist (693/791, 88%). Respondents had practised as a physician for a median duration of 12 years [IQR 6-21].

Almost all (96%) SPA respondents used dexmedetomidine in paediatric practice (310/322,), versus 69% of SPANZA respondents. ESPA respondents and APAGBI respondents did not use dexmedetomidine as often: 53% and 34%, respectively (Table 1).

Figure 1. Distribution and response diagram of the survey

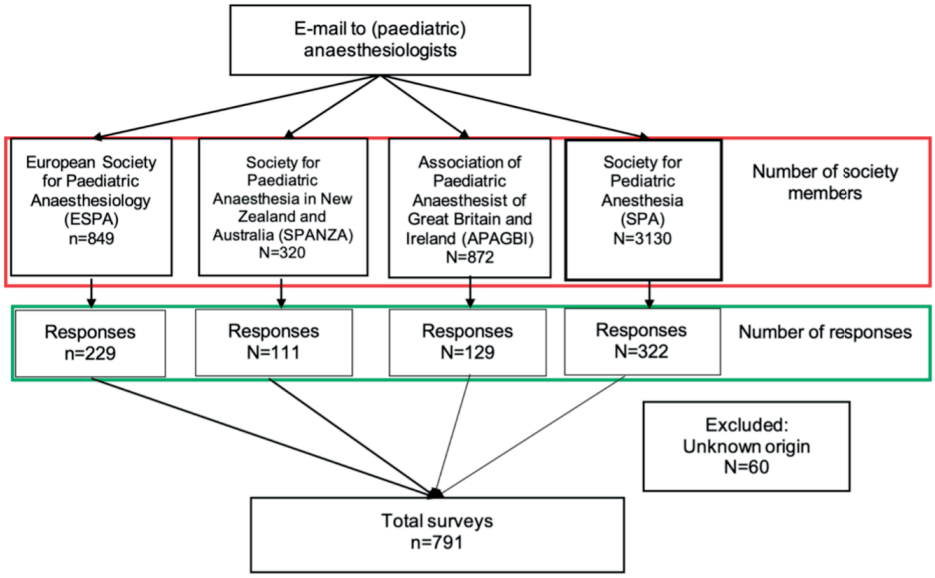


Table 1. Baseline characteristics of all respondents

	Total		**ESPA**		**SPANZA**		**APAGBI**		**SPA**	
Member		5171		849		320		872		3130
Response rate	791	15.3%	229	27.0%	111	34.7%	129	14.8%	322	10.3%
Do you use dexmedetomidine in paediatric anaesthesiology?										
Yes	552	69.8%	121	52.8%	77	69.4%	44	34.1%	310	96.3%
No	206	26.0%	90	39.3%	32	28.8%	80	62.0%	4	1.2%
Missing	33	4.2%	18	7.9%	2	1.8%	5	3.9%	8	2.5%
Total	791	100.0%	229	100.0%	111	100.0%	129	100.0%	322	100.0%
What type of hospital do you work at?										
Tertiary	558	70.5%	152	66.4%	91	82.0%	93	72.1%	222	68.9%
Paediatric	116	14.7%	22	9.6%	4	3.6%	13	10.1%	77	23.9%
Secondary	87	11.0%	38	16.6%	12	10.8%	18	14.0%	19	5.9%
Primary	21	2.7%	10	4.4%	4	3.6%	4	3.1%	3	0.9%
Missing	9	1.1%	7	3.1%	0	0.0%	1	0.8%	1	0.3%
Total	791	100.0%	229	100.0%	111	100.0%	129	100.0%	322	100.0%
What percentage of your work includes paediatric anaesthesiology?										
10%	44	5.6%	23	10.0%	8	7.2%	8	6.2%	5	1.6%
25%	74	9.4%	25	10.9%	14	12.6%	11	8.5%	24	7.5%
50%	88	11.1%	37	16.2%	11	9.9%	5	3.9%	35	10.9%
75%	169	21.4%	45	19.7%	41	36.9%	40	31.0%	43	13.4%
100%	402	50.8%	90	39.3%	36	32.4%	63	48.8%	213	66.1%
Missing	14	1.8%	9	3.9%	1	0.9%	2	1.6%	2	0.6%
Total	791	100.0%	229	100.0%	111	100.0%	129	100.0%	322	100.0%
What type of anaesthesiologist are you?										
Paediatric	693	87.6%	182	79.5%	97	87.4%	112	86.8%	302	93.8%
Ped training	29	3.7%	11	4.8%	5	4.5%	5	3.9%	8	2.5%
General	43	5.4%	23	10.0%	8	7.2%	7	5.4%	5	1.6%
Resident	7	0.9%	3	1.3%	0	0.0%	1	0.8%	3	0.9%
Missing	19	2.4%	10	4.4%	1	0.9%	4	3.1%	4	1.2%
Total	791	100.0%	229	100.0%	111	100.0%	129	100.0%	322	100.0%

Respondents who use dexmedetomidine

Overall, seventy percent of the respondents used dexmedetomidine in paediatric practice. A protocol was not available for members of ESPA (57/121, 47%) and SPANZA (33/77, 43%), whereas nearly all SPA members (285/310, 92%) had access to a protocol, as well as the majority of the APAGBI members (27/44, 61%). The drug was used for children of all ages: SPA members used dexmedetomidine mainly in patients younger than 1 year of age, whereas all other respondents used dexmedetomidine mainly in patients older than 1 year of age. Overall, dexmedetomidine was mostly used for procedural sedation

(375/552, 68%), as reported by ESPA respondents (78/121, 65%) and SPA respondents (253/310, 82%). The main indication for members of SPANZA (62/77, 81%) and members of APAGBI (30/44, 68%) was premedication.

Broad ranges of dosages were reported for the use of dexmedetomidine for different applications (Table 2). For premedication, the most frequently used dose was 2.0 ug/kg intranasal bolus administration. For procedural sedation, intensive care sedation, anaesthesia and postoperative analgesia an intravenous infusion was the most frequently used route of administration. Dosages for intravenous administration differed widely (Table 2). Oral and intramuscular administration were reported as well.

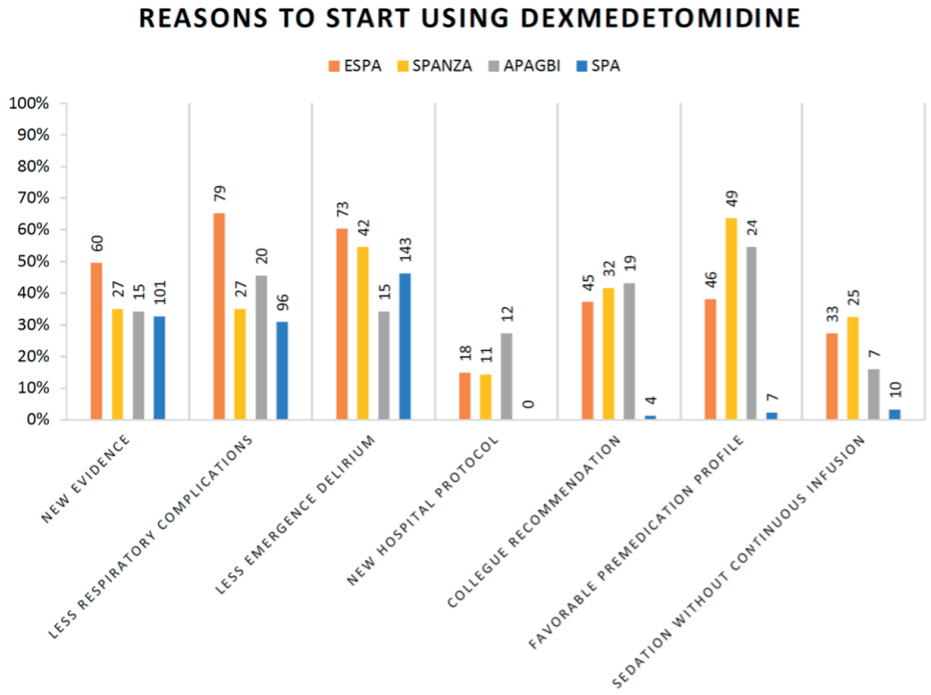
Table 2. Dexmedetomidine dosages reported by respondents (median with interquartile ranges, minimum and maximum dose)

Setting	Bolus min ug*kg^{-1}	Bolus max ug*kg^{-1}	IV min mg*kg/h^{-1}	IV max mg*kg/h^{-1}
Premedication (nasal)	2.00 [1.00-2.00]	2.00 [2.00-3.00]	1.50 [0.50-4.00]	2.50 [1.00-4.25]
Min - max	0.00 5.00	0.20 5.00	0.25 5.00	0.50 5.00
Procedural sedation	1.00 [0.50-2.00]	1.10 [1.00-2.38]	0.50 [0.30-1.00]	1.0 [0.70-1.75]
Min - max	0.00 8.00	0.20 8.00	0.00 2.50	0.20 6.00
Intensive care sedation	1.00 [0.50-1.00]	1.0 [0.50-1.05]	0.50 [0.30-0.70]	1.0 [0.70-1.50]
Min - max	0.50 8.00	0.50 8.00	0.00 5.00	0.10 7.00
Anaesthesia	0.50 [0.50-1.00]	1.00 [0.50-1.00]	0.50 [0.30-0.70]	1.00 [0.50-1.00]
Min - max	0.00 2.00	0.00 4.00	0.00 5.00	0.03 4.00
Postoperative analgesia	0.50 [0.40-0.50]	0.50 [0.50-1.00]	0.40 [0.20-0.50]	0.50 [0.43-1.00]
Min - max	0.00 2.00	0.20 3.00	0.00 1.00	0.10 2.00
Other	0.50 [0.30-1.00]	0.85 [0.50-1.00]	0.90 [0.50-1.75]	1.0 [0.78-2.00]
Min - max	0.10 2.00	0.20 5.00	0.10 2.00	0.60 3.00

Median [IQR] and minimum and maximum (min – max) dosage administered.
Lowest and highest reported doses for bolus and continuous infusion of dexmedetomidine.
All settings, except for premedication, was mainly administered intravenously.

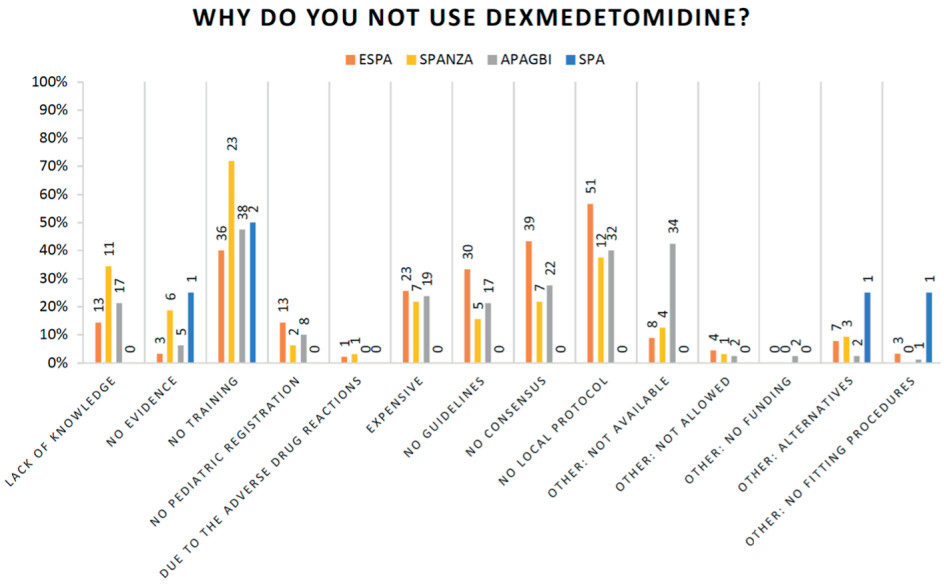
The arguments to start using dexmedetomidine in paediatric practice were fewer cases of emergence delirium compared to traditionally used anaesthetics (273/552, 50%), and fewer respiratory complications (222/552, 40%). The SPA respondents mainly reported fewer emergence delirium cases (143/310, 46%), the ESPA respondents fewer respiratory complications (79/121, 65%). The APAGBI respondents (24/44, 55%) and SPANZA respondents (49/77, 64%) mainly reported a good profile for premedication (Fig. 2). Few respondents had started using dexmedetomidine for its opioid sparing effect. Fifty-six respondents reported they had received specific training or training though a protocol. Others had individually consulted relevant literature (n=98); had discussed the application with colleagues (n=79) or had learned to use dexmedetomidine via trial and error (n=50).

Figure 2. Reasons why respondents started using dexmedetomidine



Multiple answers possible

Figure 3. Reasons why respondents do not use dexmedetomidine



Multiple answers possible

The most commonly observed adverse drug reactions were bradycardia (n=129) and nausea (n=99). However, many respondents from all societies (275/552, 50%) had not observed adverse drug reactions. Respondents from the SPA were not familiar with contraindications (286/310, 92%), but the majority of respondents from other societies (67%) were aware of contra-indications for the use of dexmedetomidine in paediatric care (Table 3).

Table 3. Responses of respondents who use dexmedetomidine

	Total		**ESPA**		**SPANZA**		**APAGBI**		**SPA**	
	552		**121**		**77**		**44**		**310**	
Is there a protocol available in your centre?										
Yes. a protocol is available	402	72.8%	57	47.1%	33	42.9%	27	61.4%	285	91.9%
No. no protocol is available	102	18.5%	47	38.8%	37	48.1%	11	25.0%	7	2.3%
Missing	48	8.7%	17	14.0%	7	9.1%	6	13.6%	18	5.8%
Total	**552**	**100.0%**	**121**	**100.0%**	**77**	**100.0%**	**44**	**100.0%**	**310**	**100.0%**
In what age categories do you use dexmedetomidine?*										
- 0-3 months old	363	65.8%	50	41.3%	23	29.9%	6	13.6%	284	91.6%
- 3 months to 1 year	404	73.2%	76	62.8%	37	48.1%	17	38.6%	274	88.4%
- 1 to 4 years	330	59.8%	100	82.6%	63	81.8%	34	77.3%	133	42.9%
- 4 to 6 years	291	52.7%	102	84.3%	73	94.8%	38	86.4%	78	25.2%
- 6 to 12 years	388	70.3%	87	71.9%	70	90.9%	35	79.5%	196	63.2%
- older than 12 years	256	46.4%	75	62.0%	63	81.8%	33	75.0%	85	27.4%
For what purposes do you use dexmedetomidine?*										
For premedication	255	46.2%	57	47.1%	62	80.5%	30	68.2%	106	34.2%
For procedural sedation	375	67.9%	78	64.5%	34	44.2%	10	22.7%	253	81.6%
For IC sedation	251	45.5%	65	53.7%	17	22.1%	10	22.7%	159	51.3%
For anaesthesia	93	16.8%	31	25.6%	40	51.9%	13	29.5%	9	2.9%
For postoperative analgesia	178	32.2%	27	22.3%	11	14.3%	6	13.6%	134	43.2%
What adverse drug reactions have you experienced?[a]										
Hypotension	78	14.1%	46	38.0%	19	24.7%	6	13.6%	7	2.3%
Hypertension	20	3.6%	16	13.2%	1	1.3%	1	2.3%	2	0.6%
Bradycardia	129	23.4%	74	61.2%	29	37.7%	11	25.0%	15	4.8%
Hypoxia	55	10.0%	2	1.7%	0	0.0%	0	0.0%	53	17.1%
Apnoea	9	1.6%	6	5.0%	1	1.3%	1	2.3%	1	0.3%
Nausea	99	17.9%	0	0.0%	0	0.0%	0	0.0%	99	31.9%
Emergence delirium	16	2.9%	13	10.7%	3	3.9%	0	0.0%	0	0.0%
None	275	49.8%	27	22.3%	36	46.8%	22	50.0%	190	61.3%
Are you familiar with any contraindications for the use of dexmedetomidine?										
Yes. I am familiar with contraindications	170	30.8%	88	72.7%	52	67.5%	23	52.3%	7	2.3%
No. I am not familiar with contraindications	350	63.4%	25	20.7%	22	28.6%	17	38.6%	286	92.3%
Missing	32	5.8%	8	6.6%	3	3.9%	4	9.1%	17	5.5%
Total	**552**	**100.0%**	**33**	**100.0%**	**25**	**100.0%**	**21**	**100.0%**	303	100.0%
How would you rate your experience with dexmedetomidine? Median [IQR]										
			8 [7-9]		8 [7-8]		8 [7-8]	10 [9-10]		

[a]multiple answers possible

Table 4. Responses of respondents who do not use dexmedetomidine

	Total 206		**ESPA 90**		**SPANZA 32**		**APAGBI 80**		**SPA 4**	
Are you trained in the use of dexmedetomidine?										
Yes	23	11.2%	8	8.9%	4	12.5%	9	11.3%	2	50.0%
No	182	88.3%	81	90.0%	28	87.5%	71	88.8%	2	50.0%
Missing	1	0.5%	1	1.1%	0	0.0%	0	0.0%	0	0.0%
Total	**206**	**100.0%**	**90**	**100.0%**	**32**	**100.0%**	**80**	**100.0%**	**4**	**100.0%**
Are you familiar with dexmedetomidine?										
Yes	89	48.9%	43	53.1%	18	64.3%	26	36.6%	2	100.0%
No	90	49.5%	37	45.7%	10	35.7%	43	60.6%	0	0.0%
Missing	3	1.6%	1	1.2%	0	0.0%	2	2.8%	0	0.0%
Total	**182**	**100.0%**	**81**	**100.0%**	**28**	**100.0%**	**71**	**100.0%**	**2**	**100.0%**
Are you willing to start using dexmedetomidine?[a]										
Yes. I am willing to start using	174	84.5%	77	85.6%	29	90.6%	66	82.5%	2	50.0%
Yes: good alternative	38	21.8%	14	15.6%	8	25.0%	16	20.0%	0	0.0%
Yes: benefits of the drug	82	47.1%	31	34.4%	13	40.6%	36	45.0%	2	50.0%
Yes: literature information	4	2.3%	3	3.3%	0	0.0%	1	1.3%	0	0.0%
Yes: if recommended	3	1.7%	2	2.2%	0	0.0%	1	1.3%	0	0.0%
Yes: if more information is available	7	4.0%	3	3.3%	1	3.1%	3	3.8%	0	0.0%
Yes: other	40	23.0%	24	26.7%	7	21.9%	9	11.3%	0	0.0%
Total	**174**		**77**		**29**		**66**		**2**	**50.0%**
No. I am not willing to start using	29	14.1%	12	13.3%	3	9.4%	12	15.0%	2	50.0%
No: better alternative	7	24.1%	5	5.6%	0	0.0%	1	1.3%	1	25.0%
No: not registrated in country	4	13.8%	1	1.1%	1	3.1%	2	2.5%	0	0.0%
No: no protocols	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
No: no need	9	31.0%	3	3.3%	2	6.3%	3	3.8%	1	25.0%
No: price	1	3.4%	1	1.1%	0	0.0%	0	0.0%	0	0.0%
No: more experience needed	7	24.1%	2	2.2%	0	0.0%	5	6.3%	0	0.0%
No: other	1	3.4%	0	0.0%	0	0.0%	1	1.3%	0	0.0%
Total	**29**	**100.0%**	**12**	**98.9%**	**3**	**100.0%**	**12**	**97.5%**	**10**	**100.0%**
For what purposes would you use dexmedetomidine?[a]										
For premedication	126	72.4%	42	54.5%	26	89.7%	58	87.9%	0	0.0%
For procedural sedation	133	76.4%	65	84.4%	20	69.0%	48	72.7%	0	0.0%
For IC sedation	58	33.3%	34	44.2%	7	24.1%	17	25.8%	0	0.0%
For anaesthesia	75	43.1%	27	35.1%	11	37.9%	37	56.1%	0	0.0%
For postoperative analgesia	48	27.6%	18	23.4%	8	27.6%	22	33.3%	0	0.0%
Missing	1	0.6%	0	0.0%	0	0.0%	0	0.0%	1	50.0%
Other	8	4.6%	4	5.2%	2	6.9%	1	1.5%	1	50.0%

[a]multiple answers possible

Respondents who do not use dexmedetomidine

In total 206 of the 791 respondents (26%) did not use dexmedetomidine in paediatric care, mainly members of ESPA (90/229, 39%) and APAGBI (80/129, 62%) (Table 4). Most of them had not been educated in the use of dexmedetomidine (182/206, 88%), but were familiar with the drug (89/229, 49%). Lack of education was one of the main reasons not to use dexmedetomidine in paediatric practice (99/206, 48%). Other perceived barriers to using dexmedetomidine were the absence of local protocol (95/206, 46%), and no consensus among local staff (68/206, 33%) (Fig. 3). Furthermore, for 46 of these 206 respondents (22%) the drug was not available; mainly reported by APAGBI respondents (34/80, 43%). The majority of non-users (174/206, 85%) were willing to start using dexmedetomidine for premedication (126/174, 72%) and for procedural sedation (133/174, 76%, Table 4). The most important reasons for the willingness to start using dexmedetomidine were the benefits (82/174, 47%) and the safer alternative to the currently used drugs (38/174, 22%). Reasons for not being willing to start using dexmedetomidine (29/206, 14%) were the availability of better alternatives (7/29, 24%), no need (9/27, 31%), and need for more individual and general experience with dexmedetomidine (7/29, 24%).

DISCUSSION

This international survey revealed that despite the off-label use in children, dexmedetomidine is frequently used in paediatric anaesthesiology settings, even without the availability of national or local protocols. The main indications were premedication, procedural sedation and IC sedation. Most of the anaesthesiologists who used dexmedetomidine reported absence of adverse drug reactions, as well as awareness of contraindications for the use in paediatrics.

A prospective pilot study showed that dexmedetomidine-based anaesthesia creates satisfactory conditions for paediatric surgery.[4] Dexmedetomidine proved to be useful for various types of surgical procedures, such as airway procedures, neurosurgery, cardiac surgery and ambulatory procedures.[18] Dexmedetomidine has not been approved for use in paediatric care in any country worldwide, which would explain why structured education of paediatric anaesthesiologists on its use by manufacturers is lacking. Only 56 respondents (10%) who use dexmedetomidine had received such education. Most respondents did not have access to structured education and taught themselves by reading scientific papers, discussing with colleagues and/or were self-taught. Respondents from the SPA primarily used dexmedetomidine in patients younger than 1 year of age, whereas respondents from other societies mainly used it in patients older than 1 year of age. This discrepancy might be related to the interpretation of the 2016 FDA statement

concerning the effects of anaesthesia on the young brain; i.e., children younger than 3 years of age.[19] Shortly thereafter, a consensus statement for European anaesthesiologists concluded that there was no compelling evidence to change anaesthetic practice, but that unnecessary procedures should be avoided.[20] These conflicting statements may have had effects on the change of current practice. Since anaesthesiologists in the USA have been warned for the effects on the young brain, it is likely that they would search for a less neurotoxic alternative to the traditional anaesthetics –and use this alternative in the young patients. This may also explain why respondents who do not use dexmedetomidine are willing to start using it as an alternative to the currently used anaesthetics, as dexmedetomidine is thought not to be neurotoxic and provides satisfying sedation. Other different indications reported by the respondents from the different societies cannot be explained by the issued warnings. SPANZA and APAGBI members used dexmedetomidine mainly for premedication, whereas ESPA and SPA members used it mainly for procedural sedation. In the present survey study, the opioid-sparing effect was another reason for some anaesthesiologists to start using dexmedetomidine in paediatric practice. Administration of dexmedetomidine intraoperatively has been associated with a lesser need for postoperative analgesia and a lesser need for fentanyl intraoperatively.[21-24]

Our survey showed that dosing regimens for paediatric care differ widely. Studies describing the pharmacokinetics of dexmedetomidine indicate that children would require a higher dosage per kg bodyweight compared to adults to achieve comparable exposure, due to a larger volume of distribution in children.[25] A previous study described the off-label use of dexmedetomidine in paediatric care within the European Union (EU), indicated for ICU sedation, anaesthesia and procedural sedation.[7] In the EU, a maximum infusion rate of 1.4μg*kg^{-1}*h^{-1} is approved for adult sedation; however, a recently published study in Europe showed that infusion rates exceeding 1.4μg*kg^{-1}*h^{-1} were used in 11% of children.[7] Our study shows a similar practice: reported infusion rates ranged from 0.1 μg*kg^{-1}*h^{-1} to 3.0 μg*kg^{-1}*h^{-1}. Dosing seems to vary inter-individually, especially in paediatrics, which may largely be the result of clearance maturation with age, and consequently changing elimination half-life.[15] Furthermore, the dosing regimen depends on the route of administration. For nasal administration, a 2 μg*kg^{-1} dose was the most commonly used premedication dose in the present study. Therefore, various dosing regimens should be available for physicians to use.

Dexmedetomidine pharmacodynamics and pharmacokinetics have mainly been described in adult populations. Despite the fact that several papers have described the PK of dexmedetomidine in infants over the last years,[26-29] there still is an urgent need for well-designed studies describing the PK as well as the PD of dexmedetomidine in infants covering all age groups following intravenous and nasal administration. Given the large variability of estimated PK-parameters between paediatric and adults popula-

tions, such as the estimated volume of distribution and the clearance which changes rapidly in paediatric patients under the age of 1 year, more evidence is needed. Reported studies suggest that this inter-individual variability is substantially larger than the effect of maturation alone. The variability may be also influenced by the variety of processes involved in metabolism and excretion of inactive dexmedetomidine metabolites following glucuronidation, methylation as well as oxidation by CYP-enzymes which are renally excreted. Especially for children under one year of age, pharmacokinetics and pharmacodynamics are less known.[15]

Bradycardia and hypotension were the most frequently reported side effects of dexmedetomidine. Generally, these side effects do not require additional treatment.[15] Interestingly, only SPA respondents reported an adverse drug reaction, which was nausea. A meta-analysis has shown that dexmedetomidine prevents postoperative nausea and vomiting in children and in adults when administered during general anaesthesia.[30] The SPA respondents mostly use dexmedetomidine in patients younger than 1 year of age, and respondents from the other societies mostly in patients above 1 year of age, which might explain the difference in reported adverse drug reactions.[31]

Dexmedetomidine is not the only anaesthetic drug used off-label in paediatric anaesthesiology. Other studies have found that most drugs administered to induce and to maintain anaesthesia are off-label.[32] Our study confirmed that dexmedetomidine is used in infants, the age group with the least number of drugs licenced for use.[33] In a previous study, patients treated with off-label drugs had a significantly higher risk of adverse drug reactions.[34] As we should not expose children to unnecessary risks, it is important to investigate the pharmacokinetics and pharmacodynamics of new drugs in clinical trials in the paediatric population.[35] In the absence of trials, formal education for those prescribing and administering dexmedetomidine to children would be necessary.

Our survey revealed various barriers to the use of dexmedetomidine in paediatric practice. The main barriers were the price of dexmedetomidine, non-availability of the drug, the lack of knowledge, and the lack of education. Introduction of new drugs or adjusted use of drugs in anaesthesia rarely comes with education of the anaesthesiologists.[36] However, bed-side teaching of an anaesthesiologist with experience (local opinion leader) in use of dexmedetomidine during anaesthesia could counteract this barrier, because this is an intervention for successful implementation.[37,38] Unfortunately, our survey did not investigate the reason why the lack of training has such a negative effect on the use of dexmedetomidine, specifically. Mainly respondents from the APAGBI reported not to have access to dexmedetomidine, which explains the low use amongst APAGBI members. This might be due to the fact that dexmedetomidine has not been licensed for anaesthesia in the UK.[39,40] Another reason why respondents do not use dexmedetomidine is that they lack information about the drug. Long-term effects on the use of dexmedetomidine in children have not yet been published. Studies have fo-

cussed on the short-term effects, such as safety of administration, emergence delirium, postoperative nausea and vomiting.[41]

The use of dexmedetomidine amongst respondents from different societies clearly differed with regard to patient age categories, routes of administration, bodyweight-based dosages, dosing regimens and the availability of protocols. We argue that paediatric anaesthesiologists from different societies must learn from each others' experiences, share information, and ultimately reach consensus on the optimal dexmedetomidine therapy in paediatric anaesthesia. Consensus could be reached by evidence, expert interpretation and experience. Consequently, appropriate use of dexmedetomidine would be stimulated and lead to fewer differences in drug prescriptions amongst hospitals, and consequently improve patient safety.[42] This consensus should also include adverse drug reactions in infants and provide an option to report suspected adverse drug events for pharmacovigilance. According to the published data in 2020 in the public dashboard of FDA Adverse Events Reporting System (FAERS), currently 16% (269/1698) of the reports regarding dexmedetomidine as a suspect agent for an adverse event were found in paediatric population.[43] Of these 269 reports, 247 are classified as serious. These data support the need for close monitoring of patients, adequate pharmacovigilance, more information on the PK/PD in paediatrics and awareness of potential life-threatening events in off-label use.

We hypothesise that the unproven neurotoxicity of currently used anaesthetics reduces the need for introduction of new drugs. The lack of evidence on the advantages of dexmedetomidine does not provide a reason to change current practice by introducing a new off-label drug with unknown short-term and long-term risks.

Although we reached out to four major societies and associations for paediatric anaesthesiologists, we could not reach all paediatric anaesthesiologists because not everybody is a member of one of these societies. We probably missed a large proportion, primarily those working in Asia, Africa and South America.[44] E-mails with a link to the survey were sent out by the societies themselves, on different dates after July 16th, 2019. The closing date was the same for all societies: August 16th. The different time windows to respond to the survey could have led to response bias. We acknowledge the responder and non-responder bias for this survey, which could have influenced the results. Those who do not use dexmedetomidine in paediatrics might have been less likely to participate, since they do not have any benefits from participation in the study. The target response rate was set on 25%, based on the anaesthesiologists' heavy workload. The total number of anaesthesiologists approached could be an overestimation because some anaesthesiologists may a member of multiple societies, which could be an explanation of the low response rate. Furthermore, except for ESPA members, we do not know how many anaesthesiologists actually read the e-mailed invitation and did not respond, or how many anaesthesiologists missed the e-mail because it was relegated to

the “spam” folder. Furthermore, since physicians receive at least one survey daily, it is not likely that they participate in every survey.[45]

The majority of respondents in this survey use dexmedetomidine in paediatric anaesthesia, despite its off-label status and the lack of protocols. Dexmedetomidine provides sedation with minimal respiratory depression and quick onset mechanism. Furthermore, it quickly wears off, augments analgesia and is associated with only mild adverse drug reactions that rarely require treatment. Intercontinental sharing of experience and information would be desirable. Due to the off-label use and lack of evidence on dexmedetomidine in children, a consensus amongst experts on the use of this promising drug is decisive for the future use. Peer-reviewed protocols, dosage recommendations and teaching opportunities would be helpful in sharing the promising properties and safety of dexmedetomidine in paediatric care.

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Supplementary Table 1. Online survey questions and answers

Question	Answers
1. What country do you practise medicine at?	Albania, Algeria, Andorra, Angola, Armenia, Austria, Australia, Argentina, Azerbaijan, Belarus, Belgium, Benin, Bosnia and Herzegovina, Bolivia, Bulgaria, Burkina Faso, Burundi, Canada, Cameroon, Chad, Chile, Croatia, Colombia, Congo, Cote d'Ivoire, Cyprus, Czech Republic, Denmark, Ecuador, Egypt, Eritrea, Estonia, Ethiopia, Finland, France, French Guiana, Gabon, Gambia, Georgia, Germany, Ghana, Greece, Guinea, Guyana, Hungary, Iceland, Ireland, Israel, Italy, Kazakhstan, Kenya, Kosovo, Latvia, Libya, Liberia, Liechtenstein, Lithuania, Luxembourg, Macedonia (FYROM), Madagascar, Malta, Malawi, Mali, Morocco, Mexico, Moldova, Monaco, Montenegro, Mozambique, Netherlands, New Zealand, Niger, Nigeria, Norway, Paraguay, Peru, Poland, Portugal, Qatar, Romania, Russia, San Marino, Saudi Arabia, Serbia, Senegal, Sierra Leone, Slovakia, Slovenia, Somalia, South Africa, Spain, Sudan, Suriname, Sweden, Switzerland, Tanzania, Togo, Turkey, Uganda, Ukraine, United Kingdom (UK), Uruguay, USA, United Arabian Emirates, Vatican City, Venezuela, Zambia, Zimbabwe
2. What kind of hospital do you work at?	• Tertiary/university (paediatric) hospital
	• Paediatric hospital
	• General hospital (secondary referral)
	• General hospital (rural/primary)
	• Other
3. What amount of your (clinical) work comprises paediatric anaesthesia?	• 10%
	• 25%
	• 50%
	• 75%
	• 100%
4. Do you have a special training in paediatric anaesthesia?	• Specialized paediatric anaesthesiologist (with or without fellowship)
	• Currently in training for paediatric anaesthesiologist
	• General anaesthesiologist
	• Resident anaesthesiology
5. How many years have you been working as an anaesthesiologist (after registration)?	In years
6. Do you use dexmedetomidine in paediatric practice?	• Yes
	• No
IF NOT USING DEXMEDETOMIDINE IN PAEDIATRIC PRACTICE	
7. Are you trained in the use of dexmedetomidine in paediatric setting?	• Yes
	• No
8. Are you familiar with dexmedetomidine?	• Yes
	• No

Supplementary Table 1. Online survey questions and answers (continued)

Question	Answers
9. Why do you not use dexmedetomidine?	• Lack of knowledge about dexmedetomidine in general
	• Lack of evidence of dexmedetomidine in paediatric care
	• Lack of personal experience/no training for dexmedetomidine use in paediatric setting
	• Not registered for use in paediatric population
	• Negative side effects/Adverse events
	• Too expensive
	• No national/international guideline available for paediatric use
	• No consensus among local staff
	• No local protocol
	• Other
10. Are you willing to start working with dexmedetomidine in paediatric setting?	• Yes, because
	• No, because
11. If previous question is YES: For what purposes are you willing to use dexmedetomidine?	• Premedication (for a non-invasive procedure/ anaesthesia/etc.)
	• Procedural sedation
	• Intensive care sedation
	• General anaesthesia
	• Postoperative analgesia
	• Other
12. Are you interested in participating in a multicentre prospective study regarding use of dexmedetomidine in paediatric anaesthesia? If yes, please fill in your e-mail address	• Yes, my e-mail address is:
	• No
IF USING DEXMEDETOMIDINE IN PAEDIATRIC PRACTICE	
7. Is there a protocol available at your centre for dexmedetomidine use in paediatric setting?	• Yes
	• No
8. What age are the patients you use dexmedetomidine for?	• Neonates (age 0 - 3 months)
	• Baby (age 3 months - 1 year)
	• Toddler (age 1 - 4 years)
	• Child (age 4 - 6 years)
	• Scholar (age 6 - 12 years)
	• Teenager (age > 12 years)

Supplementary Table 1. Online survey questions and answers (continued)

Question	Answers
9. What do you use dexmedetomidine for? Please provide dose used in ug/kg for bolus and mcg/kg/hr for continuous infusion	• Premedication (ug/kg)
	• Procedural sedation (ug/kg)
	• Intensive care sedation (ug/kg)
	• Anaesthesia (ug/kg)
	• Postoperative analgesia (ug/kg)
	• Other (ug/kg)
10. What was the reason to start using dexmedetomidine in paediatric care?	• New evidence
	• No respiratory complications
	• Less emergency delirium
	• New hospital protocol
	• Colleague recommendation
	• Good profile as premedication (not irritating, no bad taste)
	• Practical use for sedation without continuous infusion
	• Other
11. How long have you been using dexmedetomidine for in paediatric setting?	• 1-6 months
	• 6-12 months
	• 1-2 years
	• >2 years
12. How were you trained in using dexmedetomidine in paediatric setting?	Open question
13. Have you experienced any clinically relevant adverse events when using dexmedetomidine?	• Hypotension
	• Hypertension
	• Bradycardia
	• Hypoxia
	• Apnoea
	• Nausea
	• Agitation/emergence delirium
	• None
	• Other
14. Are you familiar with any contraindications for the use of dexmedetomidine in paediatric setting?	• No
	• Yes, namely:
15. How would you rate your overall experience with dexmedetomidine use in paediatric care on a scale from 1 to 10?	Mean grade
16. Are you interested in participating in a multicentre prospective study regarding use of dexmedetomidine in paediatric anaesthesia? If yes, please fill in your e-mail address	• No
	• Yes, my e-mail address is:

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Primary repair of esophageal atresia is followed by multiple diagnostic and surgical procedures

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ABSTRACT

Background: Children born with esophageal atresia (EA) face comorbidities and complications often requiring surgery and anesthesia. We aimed to assess all procedures performed under general anesthesia during their first 12 years of life.

Methods: We performed a retrospective cohort study about subsequent surgeries and procedures requiring general anesthesia in children born with type C EA between January 2007 and December 2017, with follow-up to March 2019.

Results: Of 102 eligible patients, 63 were diagnosed with comorbidities, of whom 18 had VACTERL association. Follow-up time for all patients varied between 14 months and 12 years (median 7 years). The patients underwent total 637 procedures, median 4 [IQR2-7] per patient. In the first year of life, 464 procedures were performed, in the second year 69 and in the third year 29. Thirteen patients underwent no other procedures than primary EA repair. In 57 patients, 228 dilatations were performed. Other frequently performed procedures were esophagoscopy (n=52), urologic procedures (n=44) and abdominal procedures (n=33).

Conclusions: Patients with EA frequently require multiple anesthetics for a variety of procedures related to the EA, complications and comorbidities. This study can help care providers when counselling parents of a patient with an EA by giving them more insight into possible procedures they can be confronted with during childhood.

INTRODUCTION

With an incidence of 1 in 4000 births, esophageal atresia (EA) is a rare congenital anomaly in which the upper esophagus is not connected to the lower esophagus and the stomach.[1-3] It is prenatally diagnosed in 24% to 32% of the cases.[4-6] Five types of EA are distinguished on the basis of the presence or absence of a tracheo-esophageal fistula (TEF) and the length of the present esophagus.[1] The type referred to as type C is the most common type, found in approximately 85% of individuals with a TEF.

The primary EA repair is a lengthy procedure, which often requires intraoperative anesthesia for over 3 hours and postoperative sedation for several days.[7,8] Moreover, most patients face hospital admissions and procedures at a young age for the management of comorbidities and complications. For some, these comorbidities might have a bigger impact on life than the primary surgery itself, and the procedures required to manage the comorbidities might negatively affect the long-term outcome. Studies have reported developmental problems,[9] behavioral problems,[10,11] motor functional impairment and attention deficits in children after primary EA repair.[12] The long-term outcome is mainly dependent on multiple interrelated variables, however, and the etiological determinants are hard to define. Therefore, prenatal and postnatal parental counselling should address possibly relevant variables and make clear that for many the comorbidities diagnostic or therapeutic procedures under general anesthesia are required. We hypothesize that the aggregate duration of anesthesia and the number of procedures performed under anesthesia during childhood have impact on this long-term outcome as well, while a direct correlation will be hard to find. To test this hypothesis, we evaluated the aggregate duration and number of anesthesia exposures in EA patients treated in our hospital, and made a groupwise comparison of the type of primary surgery – open, thoracoscopic or converted thoracoscopic to open - performed in these patients.

METHODS

Patients

In this retrospective cohort study, we included all patients who, from 1 January 2007 up to and including 31 December 2017, underwent repair of EA/TEF type C in a tertiary, specialized referral pediatric hospital (Erasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands). Patients with EA types A, B, D and E were excluded, as well as patients not primarily cared for in our hospital. Patients and procedures under anesthesia were identified from the hospital's electronic Anesthetic Information Management System (AIMS; Anesthesia Manager, PICIS Clinical Solutions S.A., Barcelona, Spain), ICU Patient Data Management System (PDMS, ChipSoft, Amsterdam, the Netherlands), and

anesthesia charts (on paper until 2012 and electronically from 2012 onwards). Primary care was performed by our multidisciplinary team under direction of the pediatric surgical department, and all surgeries and consultations had taken place in our hospital. The end of the follow-up period for this study was March 1, 2019. All anesthetic events were supervised by a board-certified anesthesiologist with specific training in pediatric anesthesia. Anesthesia was not protocolized, sevoflurane and propofol were the most frequently used anesthetics, combined with an opioid and muscle relaxant. Neuroprotective measures such as brain monitoring were not taken. It is common practice in our hospital to combine procedures that require anesthesia, also from different specialties, where possible. Induction of anesthesia at the primary surgery encompassed various actions: intubation, insertion of an arterial line if possible, insertion of an intravenous drip, and bronchoscopy performed by an ENT doctor before the start of the surgery. In this study, the bronchoscopy before the start of primary surgery was considered part of the primary surgery, not as a separate procedure. Bronchoscopy after the first surgery was counted as a separate procedure. The end time of anesthesia of the primary surgery was defined as the moment when the patient left the operation room to be transported to the ICU, still intubated and sedated. The decision to extubate after primary EA repair was made by the surgeon and pediatric intensivist. We divided the patients into three groups: primary open surgery (POS), primary thoracoscopic surgery (PTS) and converted thoracoscopic to open surgery (COS). We did this with the aim to detect differences in numbers and length of procedures between these three groups, since there is no consensus on which surgical approach is superior to the other. We defined a surgical or diagnostic intervention requiring general anesthesia as an interventional procedure, e.g. esophagoscopy with balloon dilatation for an anastomotic stricture constitutes one interventional procedure. Additionally, general anesthesia for a diagnostic procedure is defined as diagnostic procedures, e.g. esophagoscopy without balloon dilatation. Altogether, all interventions are referred to as 'procedures' in this manuscript.

Procedures

All procedures performed during the follow-up period, including the primary EA repair, were included for analysis. All diagnostic procedures (e.g. esophagoscopy, bronchoscopy and MRI) and interventional procedures (e.g. esophageal balloon dilatation) under general anesthesia were defined as 'procedure'. Conscious sedation is not included in this study.

We distinguished three groups of procedures in this respect.

1. *Direct EA-related procedures (e.g. leakage, reflux, stenosis, etc.).*
   This group includes all procedures that are directly related to the EA. The choice for a primary thoracoscopic surgical approach or primary open surgical approach, as well

as a decision to convert from a thoracoscopic to an open surgical approach during surgery, had been made jointly by the surgeon and the anesthesiologist based on vital parameters (stability of the patient), surgical view/working space, and logistics. Other procedures included in this group are complications related to the primary repair, such as leakage of the anastomosis, stenosis of the anastomosis and gastro-esophageal reflux, which had to be resolved surgically.

2. *EA-associated comorbidity-related procedures (e.g. cardiac anomaly, vesicourethral reflux, limb malformation, etc.).*
   EA may be associated with multiple congenital comorbidities which might require interventions or surgeries. This group includes all procedures that can be directly related to a diagnosed comorbidity.
3. *Procedures for comorbidities that are not EA-related (e.g. intracerebral bleeding, etc.)*
   Apart from congenital comorbidities, patients may suffer from comorbidities not directly related to the EA, but which may require procedural or surgical treatment. These procedures are part of the burden these children face.

Data collection and definitions

We collected information on the duration of anesthesia for primary EA repair, as well as the total number and aggregate duration of repeated exposures to anesthesia during follow-up. Procedures not requiring anesthesia were left out of consideration. If during an anesthetic session both a surgery and a procedure were performed, this session was defined as one procedure.

Statistics

All data presented are descriptive data, expressed as median [interquartile range] in the tables and in the text. Differences between surgical approach groups were tested with ANOVA and with Kruskal Wallis test for variables that were not normally distributed.

Multivariable ordinal logistic regression based on a proportional odds model was performed to find association between various variables and the total number of procedures the patients underwent. The total number of procedures was categorized into groups of 1-2 procedures, 3 procedure, 4-5 procedures, 6-8 procedures and >8 procedures. The number of procedures per patient was adjusted for confounders: the time of follow-up in each patient, which was log-transformed. Included variables are: premature (yes/no), surgical approach for primary EA surgery (thoracoscopic, open or converted thoracoscopic to open), number of diagnosed comorbidities, anastomotic leakage (yes/no) and stricture dilatation within the first year of life (yes/no). The odds ratios of the ordinal logistic regression can be interpreted as the relative change in the odds, due to a change in the independent variable, that the total number of procedures is in a given category or higher.

All statistical tests were two-sided with a significance level of 0.05. All analyses were performed with the SPSS 24.0 software package (SPSS Inc., Chicago, IL).

RESULTS

In total, 117 children underwent a primary correction for EA between January 2007 and December 2017, of whom 102 had EA/TEF type C and were included in this study (Table 1). Five patients of the study group had died during the follow-up period: three of these children were treated with an open approach, died at ages 17 days, 71 days and 225 days; and two were treated with a thoracoscopic approach, died at ages 57 days and 10.5 years. Details about cause of death are presented in Supplementary Table 1. There was a male predominance (63%), and 63/102 (62%) had been born full term; most of the 102 patients were mature for gestational age (66%) (Table 1).

The median duration of follow-up was 7y1m [IQR 3y8m-10y]. The total number of surgical, diagnostic or interventional procedures under anesthesia was 637, median 4 [IQR 2-7] per patient (Table 2). The total number of procedures during the follow-up period was 535. Thirteen patients (13%) did not have any surgeries or interventions besides the primary EA repair. The timing of the procedures is illustrated in Supplementary figure 1.

Table 1. Baseline characteristics

	Total (n=102)	POS (n=34)	PTS (n=57)	COS (n=11)	p-value
Gender (male)	64 (63%)	21 (62%)	36 (63%)	7 (64%)	NS
Gestational age (weeks)	37.9 [36.3-39.6]	36.6 [33.8-38.4]	38.3 [37.0-40.0]	38.0 [36.9-39.9]	0.001
Weight at primary EA surgery (kg)	2.9 [2.2-3.2]	2.3 [1.8-3.1]	3.0 [2.6-3.3]	3.0 [2.5-3.4]	0.005
Age at primary EA surgery (days)	2.0 [1.0-2.3]	2.0 [1.0-3.0]	2.0 [1.5-2.0]	2.0 [1.0-3.0]	NS
Days ICU *	8 [4-17]	12.5 [6-47]	5 [3-10]	13 [10-19]	0.001
Days hospital*	18 [11-33]	29.5 [14-84]	15 [10-26]	21 [13-31]	0.002
Days to extubation*	1 [1-3]	2 [1-4]	1 [1-1]	2 [2-3]	0.005
Days to oral feeding*	6 [4-11]	8 [5-20]	5 [3-8]	11 [4-18]	0.002
Number of stricture dilatations**	3 [2-5]	3 [2-5]	2 [1-4.5]	5 [3-11]	0.026
Anastomotic leak***	22 (22%)	6 (18%)	12 (21%)	4 (36%)	NS

Data are presented as median with an interquartile range [IQR]
*after primary EA repair
** Number of stricture dilatations amongst infants who had to undergo a stricture dilatation
*** number of anastomotic leaks detected, no median [IQR]
POS: primary open surgery; PTS: primary thoracoscopic surgery; COS: converted thoracoscopic to open surgery
Strictures, recurrent fistula, anastomotic leak and pneumothorax are number of infants in each group

Table 2. Surgeries and procedures performed in all patients

Surgery/procedure	Total		POS (n=34)		PTS (n=57)		COS (n=11)		p-value
	Patients	number	patients	number	patients	number	patients	number	
Primary EA repair	102	102	33	33	58	58	11	11	NS
EA other (fistula, foreign body, tracheotomy)	11	14	4	6	6	6	1	2	NS
Esophageal stricture dilatations	57	228	21	76	28	102	7	50	0.026
Broncho*/laryngoscopy	22	35	11	22	9	11	2	2	NS
Esophagus/gastroscopy	35	61	13	23	19	35	3	3	NS
NISSEN fundoplication**	21	23	11	12	7	8	3	3	NS
Aortopexy	4	4	1	1	2	2	1	1	-
Pyloromyotomy	4	4	1	1	1	1	2	2	NS
Gastrostomy	3	3	2	3	0	0	0	0	NS
Abdominal***	17	33	9	23	6	6	2	4	NS
Urology	14	44	7	29	5	13	2	2	NS
Ears	6	9	4	4	2	4	1	1	NS
Cardiac****	8	9	5	6	3	3	0	0	NS
Hands	9	11	4	5	4	5	1	1	NS
MRI	10	14	4	7	6	7	0	0	NS
CT	2	2	1	1	1	1	0	0	-
Other (line, PAC, venflon)	19	41	7	12	10	24	2	5	NS
Total surgeries/procedures		**637**		**264**		**286**		**87**	**NS**
Median number of procedures [IQR]		**4 [2-7]**		**6 [2-11]**		**4 [2-6]**		**5 [3-13]**	**NS**
Median total duration anesthesia (hh:mm) [IQR]	7:11 [5:04 – 12:19]		7:56 [5:15 – 15:31]		6:16 [4:39 – 10:28]		8:03 [6:27 – 15:34]		NS
Median total duration surgery / procedure (hh:mm) [IQR]	5:07 [3:23 – 9:01]		5:55 [3:33 – 11:41]		4:15 [3:20 – 7:51]		6:18 [4:20 – 11:12]		NS

Anastomotic leak was found and cared for in 4 POS patients, 12 PTS patients and 3 COS patients.

* not including bronchoscopy during dilatation or during primary repair

** 1 patient in the POS group had an open procedure for NISSEN fundoplication. 1 patient in the COS group had open Nissen fundoplication, relaparotomy. All other 19 patients had a laparoscopic Nissen fundoplication.

***PTS: placement of gastric tube, gastroduodenal tube, gastric foreign body, malrotation, ileostomy, duodenal web

POS: reconstruction of peri-anal structures, ileus (2x), colostomy (2x), rectal examination under anesthesia, PSARP (4x), stoma, colon segment resection, feeding jejunostomy tube, gastric perforation, cholecystectomy, resection of the small intestine, duodenal tube, duodenal web, removal of gastric tube, jejunostomy, remove colostomy, repair of double chambered right ventricle in a patient with Fallot

COS: malrotation colon, exploratory laparotomy, pull through anorectal malformation, remove colostomy

****PTS: mitral valve, resection infundibulum, VSD

POS: ASD, clip patent ductus arteriosus, Fallot + resection infundibulum, ASD+PAPVR, resection infundibulum

Duration surgery is the time from the first incision until the last stitch.

Direct EA-related procedures

All 102 infants underwent primary EA repair, at a median age of 2 [1-2.25] days (Table 1). Thoracoscopic surgery (PTS) was initiated in 68 cases but was converted to open surgery (COS) in 11 cases. Primary open surgery (POS) was performed in 34 patients. The median [IQR] duration of anesthesia for primary EA repair with thoracoscopic approach was 3:49h [3:20-4:27h], with open approach 3:06h [2:25-3:57h], and with converted approach 4:46h [3:16-5:00h]. The anesthesia time for POS was significantly shorter than that for both PTS and COS (p=0.007). Both the induction time and surgery time were not significantly different between all three groups.

The gestational age in the POS group was lower than that in the other groups. The POS group differed on more aspects from the other groups: lower weight at the time of surgery (p=0.005) and more days in hospital (p=0.002). Both the time to extubation (p=0.005) and the time to oral feeding (p=0.002) were longer in the POS group than in the other groups.

Thirteen infants underwent primary surgery repair only (10 PTS, 2 POS, 1 COS).

One extremely premature infant (25 weeks, 750 grams) had undergone two separate surgeries prior to the primary EA repair: fistula ligation and a placement of a gastrostomy. Four others had undergone other surgeries in combination with primary EA repair: one underwent a duodenoduodenostomy; one a colostomy; one a gastrostomy and duodenostomy; and one a colostomy and duodenostomy.

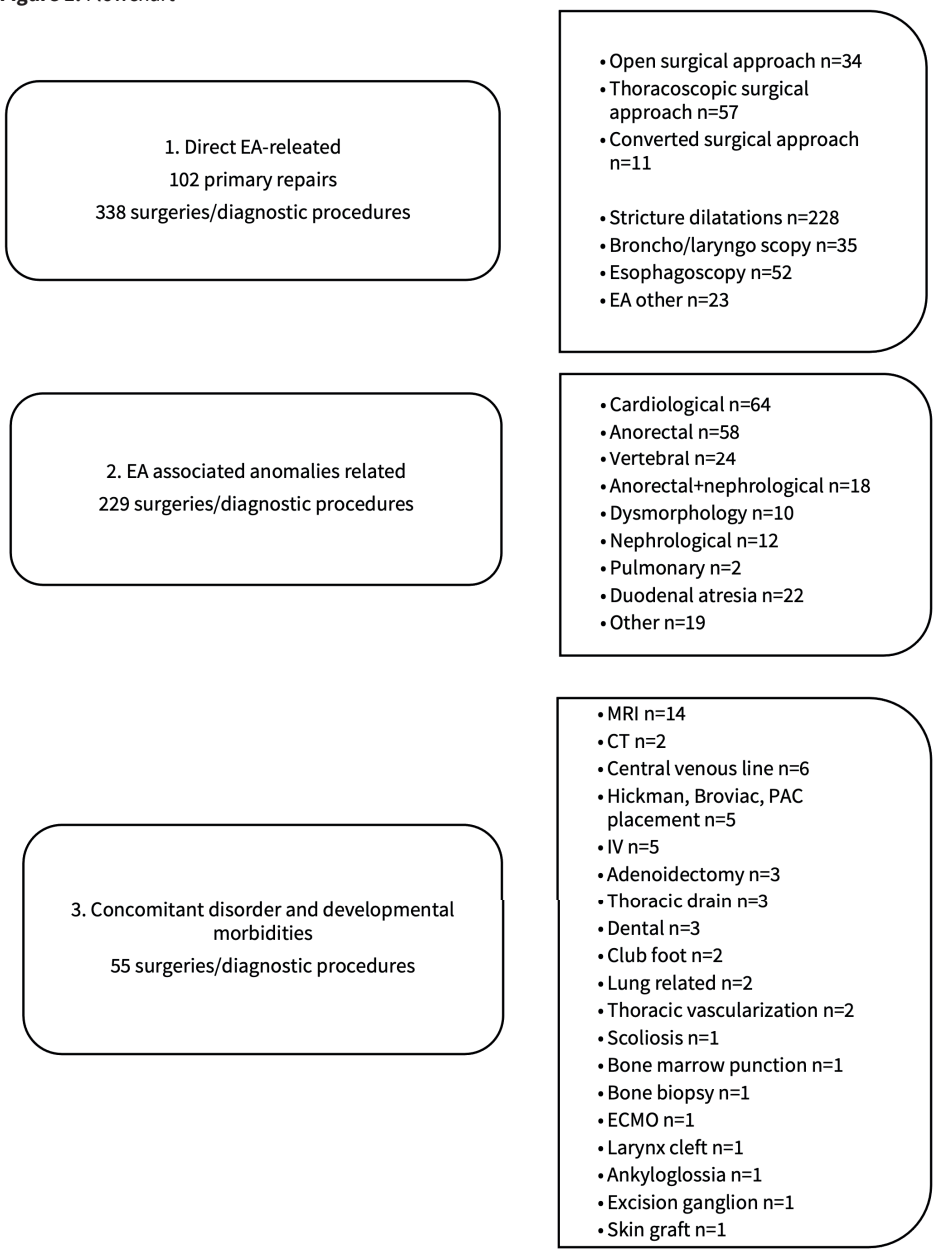
Of the 535 procedures other than primary EA repair during the entire follow-up period, 338 were EA-related: stricture dilatations, fistula repair, removal foreign body from esophagus, esophagoscopy and broncho/laryngoscopy (See Figure 1: Flowchart, and Table 2).

Esophageal stricture dilatation was performed in 57 infants, with a median of 3 [2-5] dilatations per infant. The number of dilatations per infant ranged from 1 to 19. Twenty-three of these 57 infants (40%) underwent more than three dilatations. Significantly more dilatations had been performed in infants in the COS group compared to both other groups (5 [3-11] dilatations COS vs 3 [2-5] POS and 2 [1-4.5) PTS, p=0.026).

Three infants were diagnosed with a recurrent fistula. One of them developed a second recurrent fistula. All three patients underwent a primary thoracoscopic repair. The recurrent fistulae developed several years after the primary repair. Two patients underwent thoracoscopic repair of the recurrent fistula, one was repaired via a neck incision.

Esophagoscopy/gastroscopy was performed 52 times in 32 infants after primary surgery, bronchoscopy/laryngoscopy was performed 35 times in 22 infants. Most of these procedures had been performed in the first year of life (Tables 3). The median number of broncho/laryngoscopies and esophagoscopies during follow-up was 2 [1-3].

Figure 1. Flowchart



Other EA-related procedures (n=14) were fistula repair of one re-fistula and three undetected fistulae during primary repair (n=4), tracheotomy (n=3), re-anastomosis (n=1), partial esophageal resection (n=1), delayed end to end anastomosis (n=3) and additional correction of the primary EA repair (n=2).

Tracheomalacia had been diagnosed in 55 infants by bronchoscopy or by clinical presentation; an aortopexy was performed in four of those. A Nissen fundoplication to treat gastroesophageal reflux with or without respiratory incidents was performed in 21 infants (21%). Eighteen infants underwent the Nissen fundoplication in their first year of life, two in their second year of life, and one after the age of 7 years (Table 2). Nineteen of these 21 surgeries were performed laparoscopically. In one case the surgery was combined with surgery of the colon; in another case it was performed with a laparotomy. Anastomotic leakage had been diagnosed in 22 infants, all managed by chest drainage and antibiotics. None required surgery for closure of the leak (Table 1).

EA-associated comorbidity-related procedures

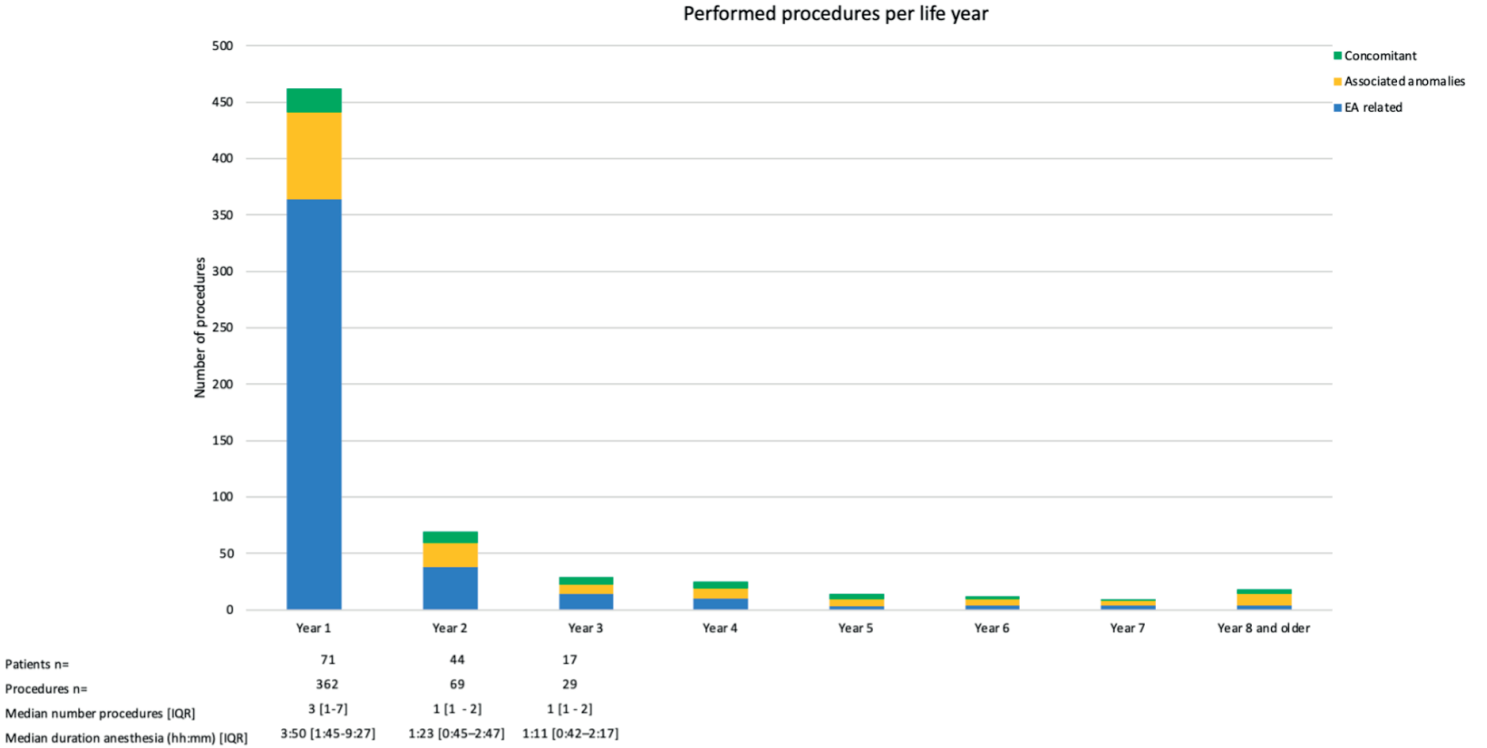
One or more comorbidities were diagnosed in over half of the infants (n=63, 62%) (Supplementary table 2). Most of the comorbidities were of cardiological, anorectal or nephrological origin. The numbers of comorbidities did not significantly differ between the three surgical groups (p= 0.33). Fifty infants (49%) required surgical or procedural interventions to manage the comorbidities (Supplementary table 2); in total 229 surgeries, median 3 [IQR 1-5] per patient (besides primary EA repair and stricture dilatations). Most of the procedures targeted cardiological problems (n=64), followed by anorectal (n=58) and vertebral anomalies (n=24) (Figure 1: Flowchart, Supplementary table 2). Other procedures for associated comorbidities were brain surgery (n=1), hypertrophy of the pylorus (n=1), choanal atresia (n=1) and cleft palate (n=1). Some infants were diagnosed with syndromes and required other procedures as well: Down syndrome (n=2), CHARGE syndrome (n=2), Silver Russell (n=1), and 47XXX (n=3).

VACTERL association (vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities) was found in 18/63 infants (29%) with comorbidities. These 18 infants underwent in total 151 procedures besides primary EA repair (151 out of 542). The median number of procedures was 6 [4-14], which is significantly higher than that in infants without VACTERL (p=0.031). Fourteen of the 18 infants underwent procedures in the first year of life besides primary EA repair, a median number of 4 [2-9].

Procedures for comorbidities that are not EA-related

Twenty-five infants received anesthesia for an MRI, CT or procedure for a comorbidity that was not EA-related. Twelve infants underwent a total of 16 MRIs or CTs for various problems, such as tethered cord, lung agenesis and nerve problems in the shoulder. Chest CT for tracheomalacia and CT for feeding problems were EA-related, other MRI and CT procedures were not directly EA-related (Supplementary table 3).

Figure 2. Procedures performed per life year



The other 39 procedures requiring anesthesia involved, for instance, insertion of an intravenous drip (n=5) or central venous line (n=6), or dental cleaning (n=3) (Figure 1, Flowchart, Supplementary table 3).

Total numbers of procedures and associations

All 637 procedures together, had a median [IQR] total anesthesia duration of 7:11h [5:04h – 12:19h], and a median [IQR] total surgery duration of 5:07h [3:23h – 9:01h] per patient (Table 2). The median [IQR] number of procedures per patient was 4 [2-7]. The number of procedures did not significantly differ between the three surgical groups (thoracoscopic, open and converted groups). Infants with VACTERL underwent significantly more procedures (median 6 [4-14], p=0.031) than other infants. Of the total number of procedures, 464 (73%) had been performed in the first year of life (including the 102 primary EA repairs) (Figure 2). The 362 procedures performed in the first year following primary EA repair concerned 71 (70%) infants, who underwent a median of 3 [IQR 1-7] procedures besides primary EA repair. In total 69 procedures had been performed in 44 infants in their second year of life, and 29 in 17 infants in their third year of life (Figure 2).

For the multivariable ordinal logistic regression analysis, no data were missing. We did not find multicollinearity of variables (VIF > 3.0). As we categorized the total number of procedures into five groups as discussed in the Methods, the number of patients per group were as follows: 1-2 procedures (n=33), 3 procedures (n=12), 4-5 procedures (n=19), 6-8 procedures (n=18) and >8 (n=20) procedures.

The odds for an increased number of procedures for the number of diagnosed comorbidities was 1.729 (OR, 95% CI 1.220 – 2.451, p=0.002). The odds for increased number of procedures when the patient underwent stricture dilatation within the first year of life was 0.029 (OR, 95% CI 0.011 – 0.079, p<0.001). Prematurity, surgical approach for primary esophageal atresia repair and anastomotic leakage did not show significant odds ratios.

DISCUSSION

We found that 90% of study population had undergone multiple procedures, and had received anesthesia not only for primary EA repair, but even more frequently for procedures to manage complications and comorbidities. These children had undergone a median of 4 procedures in the maximum of 12 years follow-up, necessitating a median anesthesia time of 7:11h. Almost three quarters of the procedures had been performed in the first year of life, and a little more than half of all procedures were related to the EA. This information can be used to counsel the parents on the expected care path and the possible burden in the child's first years of life.

Primary EA repair

Since there is no consensus on the best surgical approach for primary EA repair – open or thoracoscopic– the choice of surgical approach is determined by the patient's condition and the surgeon's preference.[13] The approach chosen might affect the individual patient's outcome. Previous studies have not been able, however, to associate the type of surgical approach with number of complications and long-term outcome.[8,14] Regarding our study population, the open approach was preferred in more unstable infants, as reflected by these infants' lower gestational age, lower weight at surgery, and longer stay in the ICU and hospital for primary EA repair. Duration of the primary EA repair in this study was comparable with that reported by others, with a median anesthesia time of 3:42h [3:09-4:27h].[15-20] The postoperative complications in our study population were mainly strictures and anastomotic leakage. Anastomotic leakage had occurred in 22 infants (22%), equally spread over all surgical groups. Of these 22 infants, none required surgical correction of the leakage. Other studies found comparable proportions of anastomotic leakage and emphasized that anastomotic leakage does not always require surgical intervention.[21,22]

Dilatations

The percentage of infants with anastomotic strictures did not differ between the three surgical groups, whereas the number of dilatations differed significantly between groups: infants in the COS group underwent more dilatations compared to the other groups. The median number of dilatations in the entire cohort was 3 – the same as reported by others.[23-26] Anastomotic strictures have been reported for 37-58% of cases, comparative to the 56% found in our study.[24,27] The higher number of dilatations in the COS group might be due to more traction on the anastomosis, thus leading to more strictures. A previous study suggested that thoracoscopic repair was associated with stricture formation.[28] Nevertheless, a systematic review and meta-analysis did not find any differences in stricture formation between the thoracoscopic and the open approach.[7,29] Both these studies did not address a converted surgery group, because infants undergoing converted surgery had been included in the open surgery group.[7,29] Risk factors for dilatations reported in the literature are prematurity, VACTERL syndrome, isolated EA, first dilatation within 1 month after primary EA repair, anastomotic tension, and anastomotic leak.[24,27] In our study, the frequency of dilatations did not differ between infants with and without VACTERL. This might be related to the small number of infants with VACTERL who underwent 1 or more dilatations.

The logistic regression analysis showed that having an anastomotic dilatation within the first year of life had an OR of 0.029 for the number of procedures. Thus, patients that underwent stricture dilatation within the first year of life are prone to undergo more procedures during their youth compared to patients who did not. This finding can be

addressed when counseling parents and show that clinical preventive studies on anastomotic strictures may be important.

Number of procedures

In this study, we found no difference between the overall number of procedures after primary open repair, primary thoracoscopic repair and converted repair. Over half of the procedures were EA-related. The literature contains no studies presenting data on the number of procedures performed in this patient population beyond the staged or primary EA repair; thus, we have no source of comparison in this respect. Infants with VACTERL underwent more surgeries (p=0.031) than infants without VACTERL. This was expected, since these infants born with EA had two additional comorbidities, possibly requiring surgery.[30,31]

Comorbidities

Generally, 70% of infants with EA type C have diagnosed comorbidities for which surgical intervention might be needed.[2,32-34] In our cohort, this percentage was 62%. The majority of comorbidities were of cardiac or anorectal nature, in line with the VACTERL association presenting in association with EA.[30] VACTERL had been diagnosed in 18/102 infants (18%) in our study, which proportion is comparable to those reported by others.[35,36]

Besides primary EA repair, comorbidities might require other surgical interventions, such as gastrostomy, colostomy or repair of a cardiac defect. Comorbidities may be diagnosed at birth but can also present later in life. For the present study, this implies that diagnosis and treatment could have taken place beyond the 12 years' follow-up period. The number of comorbidities provided in this study could therefore be an underestimation.

Our results indicate that we have to be aware that the amount of comorbidities may influence the number of procedures patients have to undergo during their childhood (OR 1.729). Parents should be well informed on this topic, in order to manage their expectations after the primary EA repair.

Long-term effects of the repeated hospitalization and anesthesia exposures

Concerns may be raised regarding the effect of anesthesia on the development of the immature brain. In the present cohort, the majority of the procedures (84%) had been performed in the first 2 years of life, when the brain largely is growing, and myelinization, white matter and grey matter increase significantly.[37] Studies on the long-term outcome of children born with EA show conflicting results. Some studies found significantly impaired long-term development compared to the reference population,[38,39] but others found the development to be normal.[40,41] The total anesthesia time has been found

negatively associated with impaired long-term outcome in EA patients.[12] This would suggest that these patients are at risk of developmental impairments as a result of the repeated anesthesia periods in the first 2 years of life. A previous study on a part of this cohort showed impaired motor function at 5 years of age in children born with esophageal atresia, which was negatively associated with the number of days of postoperative endotracheal intubation, and was positively associated with intraoperative high blood pressure.[42]

Hypoxia-ischemia, inflammation, exposure to anesthetics and stress in the period of neonatal critical illness has been suggested to be important factors for development of brain anomalies.[43] A case-control study indeed found that infants after EA repair had different brain structures at age 25.5 days compared to controls not exposed to neonatal surgery. However, their neurodevelopmental outcome scores at two years of age did not differ from the control population.[44] Long-term follow-up studies at older ages are still lacking.

The high number of procedures performed in infants with EA found in this study emphasizes that more procedures may be needed besides the primary EA repair and that lifelong management for various issues is inevitable.[45] Besides the possible negative impact of anesthesia expose on the brain development, frequent hospital admissions can have negative effects as well.[46,47] Hospital admissions may lead to anxiety and behavioral alterations, leading to multiple negative consequences presenting after the hospital admission.[48,49] The above mentioned problems may have a possible negative impact on the quality of life. An elaborate review on the health-related quality of life (HrQOL) of patients born with esophageal atresia showed that these patients experience a lower quality of life as compared to their peers.[50]

Limitations

The present clinical study retrospectively included EA infants primarily cared for at the single hospital in which the primary EA repair took place. It cannot be excluded that in some cases emergency surgeries had been performed in other hospitals. Therefore, the number of surgeries could be underestimated. We expect, however, that the effect is nihil, as all children were regularly seen in our structured follow-up program at standardized time points between 6 months and 17 years of age.[51] During these consultations, admissions and procedures in other hospitals is asked for and would have been added to the patients' file. The scope of this study was limited in terms of selection of the patient population. We only included infants with EA type C, all other types of EA were not included. Children born with other types of EA, with different morphology, could encounter yet other problems during childhood.

Implementation of findings

Data provided on the number and length of anesthesia periods and procedures in patients with EA type C can be used to inform the parents. For example, primary EA repair is most likely not the sole procedure under general anesthesia the child has to undergo.

CONCLUSIONS

To conclude, infants with esophageal atresia are prone to undergo multiple anesthesia periods and procedures beyond the primary repair operation: in the first year of life, but also at later ages. This vulnerable patient population risks impaired quality of life due to the number of hospital admissions, procedures and potential effects on the brain development.

The information provided by this study can help caregivers when counselling parents of a patient with EA by giving them more insight into procedures they can be confronted with during childhood.

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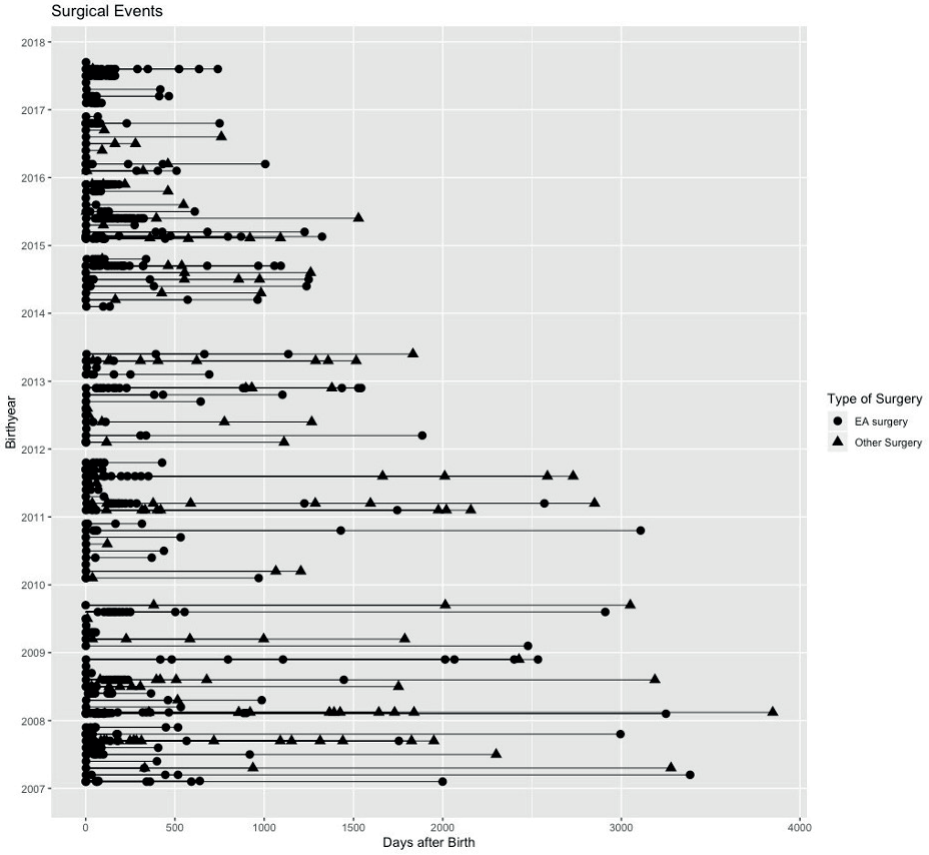
Supplementary Figure 1. Total performed procedures



All surgeries performed in all patients. Patients born January 2007 are longer included in the follow-up than patients born in December 2017. Ending date of follow-up was March 2019. All patients had primary EA surgery at median 2 days of age.

Supplementary Table 1. Information of deceased patients

Age death	Comorbidities	Complications	Surgeries	Reason death
17 days	Long-gap EA, duodenal atresia, anorectal malformation, complex cor vitium, trachea stenosis, ARM, infarct left cerebral artery, right mono kidney	Sepsis pneumothorax	Primary EA – cancelled, Tracheotomy+scopy EA+duodenoduodenostomy +stoma sigmoid, urodynamics	Multiple comorbidities and infarct left cerebral artery
57 days	Prematurity (34+4, 2500gr), Down syndrome, ASD2	Anastomotic leak, pneumothorax, mediastinitis, necrotizing enterocolitis, pulmonary hypertension	Primary EA Ileostomy	Multiorgan failure after resuscitation
71 days		Pneumothorax, anastomotic leak, mediastinitis	Primary EA, pyloromyotomy	ALTE, followed by severe cerebral injury leading to untreatable epilepsy
225 days	Severe tracheomalacia, ASD2, VSD	Pneumothorax, Sepsis	Primary EA, Bronchoscopy, Malrotation colon, Dilatation (11 times), Laparotomy, Broviac, Aortopexy, Nissen, esophagus scopy, ECMO	Ischemia after respiratory failure due to severe tracheomalacia
10.5 years	ASD2, patent ductus arteriosus, anorectal malformation, hypospadias, recto-urethral fistula, Fanconi anemia		Primary EA, Arterial line, EA, Bronchoscopy, Gastroscopy (2 times), dilatation (3 times), central venous line, catheter, urodynamics, Hickman (2 times), Fanconi anemia marrow punction, dentistry (2 times), MRI + tongue biopsy, bone biopsy	Head/neck tumor

Supplementary Table 2. Number of procedures in patients with diagnosed comorbidities

	Total number of procedures	**Diagnosed comorbidity**
Cardiac	87	ASD, VSD (n=3), tetralogy of Fallot (n=2), dextroposition of the heart, cor vitium, dilated right atrium and ventricle
Intestinal	46	Duodenal atresia (n=2)
Anorectal	111	Anorectal malformation (n=10), anterior anus (n=2)
Vertebral/ribs	64	Vertebral dysmorphology (n=6), scoliosis (n=2), extra rib
Nephro-/urological	25	Polycystic kidney (n=2), horseshoe kidney (n=2), renal agenesis (n=4), hydronephrosis (n=2), solitary kidney (n=2), hypospadias, vesicoureteral reflux
Brain	2	Hydrocephalus
Head/hands/feet	36	Syndactyly (n=4), dysmorphologies, dysplasia of the radius, oral cleft, choanal atresia
Lungs	3	Hypoplastic lung, congenital lung malformation (n=2)
Syndromes/ chromosomal disorders	50	Down syndrome (n=2), Fanconi anemia, 47XXX, Silver Russell, CHARGE (n=2), Feingold, 22q11 deletion, Pierre Robin sequence

Supplementary Table 3. Procedures for concomitant disorder or developmental morbidity

Patient	Number of procedures	MRI/CT	Other procedure
1	2	-	Adenoidectomy
2	10	MRI + tongue biopsy for tongue tumor	2 central venous line placement, adenoidectomy, bone biopsy, 2 dental cleaning, 2 Hickman placement, bone marrow puncture for Fanconi anemia
3	1	-	Dental cleaning
4	3	-	Clubfoot, tendon transfer foot, excision ganglion
5	1	Brain MRI+CT screening for cochlear implant	
6	1	Brain MRI+CT for nerve problems	
7	1	Chest CT for tracheomalacia	
8	4		Central venous line, thoracic drain, 2 IV
9	1	MRI spinal cord and brain for shoulder movement issues	
10	2	MRI + CT for scoliosis	Scoliosis
11	3	Brain MRI hydrocephalus check and brain MRI after near drowning	Drainage of the pleura
12	1		IV
13	1		Skin graft
14	1		central venous line
15	5	MRI lower spinal cord for check tethered cord	central venous line, IV, 2 PAC
16	1	CT thorax for lung agenesis and feeding issues	
17	2	MRI for tethered cord and MRI for reevaluation of tethered cord	
18	3	MRI for lung hypoplasia, MRI for vascularization and MRI for tethered cord	
19	1	MRI abdomen for liver cyst	
20	1		Correction of ankyloglossia
21	1		Pneumonectomy
22	1		Lobectomy
23	2		Drainage pneumothorax, central venous line
24	2		Correction abnormal non-cardiac thoracic vascularization, larynx cleft
25	3		Correction abnormal thoracic vascularization, Broviac placement, ECMO

6

The association of patient and procedure characteristics on impaired motor outcome in children with esophageal atresia repair

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ABSTRACT

Background: Children born with esophageal atresia experience long-term neurodevelopmental deficits, with unknown origin.

Aims: To find associations between perioperative variables during primary esophageal atresia repair and motor function at age 5 years.

Methods: This ambidirectional cohort study included children born with esophageal atresia who consecutively had been operated on in the Erasmus MC-Sophia Children's Hospital, University Medical Center Rotterdam from January 2007 through June 2013. The perioperative data of this cohort were collected retrospectively; the motor function data prospectively.

Results: After exclusion of patients with syndromal congenital diseases (n=8) and lost to follow-up (n=10), the data of 53 children were included. The mean (SD) total motor function impairment z-score at 5 years of age was -0.66 (0.99), significantly below normal (P <0.001). In multivariable linear regression analysis, number of postoperative days endotracheal intubation (B= -0.211, 95% CI: -0.389 – -0.033, p= 0.021) was negatively associated with motor outcome, whereas high blood pressure (B=0.022, 95% CI 0.001 – 0.042, p=0.038) was positively associated. Preoperative nasal oxygen supplementation versus room air (B= 0.706, 95% CI: 0.132 – 1.280, p=0.016) was positively associated with motor outcome, which we cannot explain.

Conclusions: Motor function in 5-year-old esophageal atresia patients was impaired and negatively associated with the number of postoperative days of endotracheal intubation and positively associated with high blood pressure. Prospective studies with critical perioperative monitoring and monitoring during stay at the intensive care unit are recommended.

INTRODUCTION

Thanks to improved intraoperative and perioperative intensive care, survival rates of infants born with esophageal atresia nowadays exceed 90%.[1] This major congenital malformation, which occurs in 2.43 per 10,000 live births, consists of a discontinuity of the esophagus, in over 90% of cases co-occurring with a tracheo-esophageal fistula.[2,3] Postnatal surgical intervention is needed to enable enteral feeding and to prevent respiratory complications. Primary repair involves closing the tracheo-esophageal fistula and constructing an end-to-end anastomosis of the esophagus.[2,4] As mortality rates of esophageal atresia have decreased, attention has shifted towards the survivors' long-term morbidity. Follow-up studies have mainly focused on physical impairments such as gastro-esophageal reflux, pulmonary infections and dysphagia.[1,5,6]

Neurodevelopmental outcome has been less well studied; the outcomes point at impaired cognitive performance and motor function in children born with esophageal atresia, compared to the normal population.[7-10] A previous study from our institution in children born with esophageal atresia between 1999 and 2006 found that the cumulative duration of anesthesia within the first 24 months was negatively associated with motor outcome in that cohort,[8] whereas most other studies did not examine possible causes of impaired neurodevelopment. Various perioperative factors have been suggested to contribute to impaired neurodevelopment, including comorbidities, intraoperative factors (surgical and anesthetic techniques, acidosis, hypercapnia, hypoxia, anesthetic neurotoxicity), severity of disease, postoperative factors (airway infections, growth), and fluctuations in children's respiratory, hemodynamic and metabolic status.[11,12] However, associations of specific perioperative variables, such as blood pressure, heart rate and blood pH, with long-term outcome have not been investigated thus far. In a previous study we showed severe derangement in blood pressure and pH in the operative phase during esophageal atresia surgery, and we hypothesized that these factors might be causative with impaired brain function.[13] Therefore, in the present cohort of children born between 2007 and 2013, we evaluated associations between pre-, intra- and post-operative variables with esophageal atresia patients' motor development at age 5 years.

METHODS

Participants

This prospective, single-center cohort study included consecutive patients operated on for all types of esophageal atresia from January 2007 through June 2013, in a tertiary referral specialized pediatric academic hospital (the Erasmus MC-Sophia Children's Hospital, the Netherlands). The study was authorized by the Medical Ethics Review Board

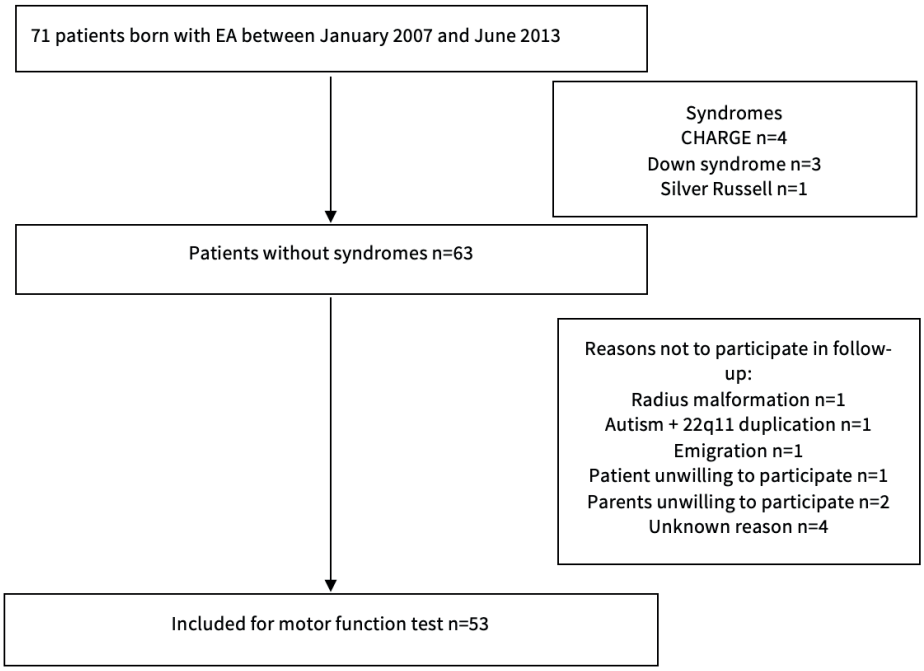
(IRB: MEC 2017-185) of Erasmus University Medical Center, Rotterdam, the Netherlands. Written consent was obtained from all participants' parents, and the study complied with the standards set by the Declaration of Helsinki. This manuscript adheres to the applicable STROBE guidelines.

Since 1999, all esophageal atresia patients are offered a standardized follow-up program with motor function assessments at 5, 8 and 12 years.[8] Electronic anesthesia records before 2007 are not available; therefore, inclusion and analysis of patients born before 2007 was not possible.

Perioperative variables

The present study is an analysis of the perioperative data of esophageal atresia patients born between 2007 and 2017 who underwent primary surgery in the Erasmus MC-Sophia Children's Hospital, and which results have been published previously.[13] Additional perioperative data in the present study were retrieved from the electronic pre-, intra- and postoperative hospital charts. All heart rate and blood pressure measurements had been stored electronically, every second for invasive measurements and every 5 minutes for non-invasive blood pressure measurements. A specific protocol for the choice of non-invasive or invasive blood pressure measurements during surgery was not available.

Figure 1. Inclusion flowchart



***This is a subgroup of patients reported previously.[13]*

Table 1. Perioperative patient characteristics**

Preoperative variables	**n=53**
Boys n (%)	33 (62)
Gestational age at birth, median [IQR], week	38.0 [36.4-39.4]
Born premature (<37 weeks)	17 (32)
Birth weight, median [IQR], kg	2.9 [2.3-3.1]
Esophageal atresia type A, n (%)	2 (4)
Esophageal atresia type C n (%)	47 (89)
Esophageal atresia type D n (%)	1 (2)
Esophageal atresia type E n (%)	3 (6)
Surgical approach	
Open surgical approach n (%)	15 (28)
Thoracoscopic surgical approach n (%)	36 (68)
Converted thoracoscopic to open n (%)	2 (4)
Minor/non hemodynamic cardiac anomaly n (%) †	33 (62)
Major cardiac anomaly n (%) ‡	2 (3.8)
Preoperative lung problems n (%) §	21 (40)
Atelectasis n (%)	9 (17)
Pneumothorax n (%)	4 (8)
Lung hypoplasia n (%)	2 (4)
IRDS n (%)	2 (4)
Other n (%)	4 (8)
Preoperative respiratory support n (%)	21 (39)
Preoperative endotracheal intubation n (%)	6 (11)
Preoperative oxygen n (%)	15 (28)
Weight at time of surgery, median [IQR], kg	3.0 [2.4-3.3]
Patients from another hospital, n (%)	6 (11%)
Intraoperative variables	
Duration of surgery, median [IQR], minutes	150 [126-191]
Highest heart rate, median [IQR], bpm	153 [140-165]
Highest MAP during surgery, median [IQR], mmHg	61 [49-72]
Lowest MAP during surgery, median [IQR], mmHg	29 [25-33]
Lowest pH, median [IQR], (n=35)	7.20 [7.09-7.29]
PaO2 [IQR] n=35	12.5 [8.15-17.0]
Highest paCO2 [IQR], n=35	8.50 [6.38-12.70]
Postoperative variables	
Time in ICU, median [IQR], days	7.0 [3-13]
Time in hospital, median [IQR], days	16.0 [11-32]
Postoperative endotracheal intubation, median [IQR], days	1.0 [1-2]
Number of esophageal dilatations, median [IQR]	0 [0-3]
Number of surgeries first 3 years, median [IQR]	3.0 [2.0-6.0]

† *Minor cardiac anomalies/cardiac anomalies without hemodynamic consequences: open foramen ovale (OFO) 7 patients; open ductus Botalli (ODB) 3 patients; OFO+ODB 13 patients; ventricular septum defect (VSD) 5 patients; pulmonary artery stenosis+atrial septum defect type 2 (ASD2)+OFO+right atrial and right ventricular dilatation 1 patient; mitral valve insufficiency+OFO+ODB 1 patient; dextroposition of the heart 1 patient; OFO+ASD2 1 patient; VSD+OFO+ODB 1 patient.*
Minor cardiac anomalies are not included in the univariable- or multivariable linear regression analysis.
‡ *Major cardiac anomalies were defined according to Hoffman. One patient with dextroposition of the heart with atrium septum defect (ASD) and open ductus (ODB). One patient with dextroposition of the heart with pulmonary veins ending in the sinus coronaries, ASD, ODB, ventricular septum defect*
§ *Diagnosed with x-thorax. Others: atelectasis+pneumothorax 1 patient; wet lung 2 patients; hyperinflation of the lung 1 patient*
***This is a subgroup of patients reported previously.*[13]

We preferred to include invasive blood pressures, but if these were not available, we included non-invasive blood pressures. Blood pressure was considered persistently low, or high, on the basis of at least a 5-minute period for invasive blood pressure measurement, or two consecutive measurements with a 5-minute interval for non-invasive blood pressure measurement. Cardiac comorbidities and anomalies at birth were classified as major and minor cardiac heart disease according to the Hoffman criteria.[14] Only major cardiac anomalies that were of clinical relevance on the child's cardiac performance and circulation were classified as cardiac abnormalities; minor cardiac anomalies were not included for statistical analysis. The described preoperatively diagnosed pulmonary problems are the problems that caused respiratory problems and had been preoperatively confirmed by X-ray. The lowest pH-value of all blood gas measurements during the anesthetic period was included in the analysis, irrespective of the method of sampling (arterial, capillary and/or venous).[15,16]

Follow-up data

The follow-up patient data had been prospectively collected within the framework of our standardized follow-up program.[11] We excluded children who could not be tested with the standardized assessment instrument as well as children with motor impairment as a result of a genetic syndrome or a congenital skeletal malformation (Figure 1).[17]

As standard of care, all children had been assessed with the Movement Assessment Battery for Children (MABC) band 1 by an experienced pediatric physical therapist.[8,11] The MABC 1 had been used until October 2012 (n=6), the MABC 2 from November 2012 onwards (n=47). The content of the two editions is the same, and both have been validated and standardized for healthy Dutch children.[18] The outcome scores of the elements of the MABC are combined in the Total Impairment Score, which was compared to age-related normative scores of Dutch children.

Statistical analysis

To combine the outcome scores of MABC 1 and 2, percentile scores based on Dutch age-specific norms were transformed into z-scores using inverse normal transformations. The z-scores were compared to the Dutch population mean (z=0) using the one sample

t-test test.[18] Normally distributed data are presented as mean (SD); continuous variables as median with interquartile range (IQR).

To investigate whether preoperative and perioperative characteristics were associated with long-term motor outcome, we defined in advance the 11 variables that we considered clinically most relevant, and included those in the univariable and multivariable regression models. These variables related to three phases:

1) preoperative phase: weight at time of surgery (kilograms), major cardiac/pulmonary problem (yes/no), mode of respiration (three categories: spontaneous breathing with room air; spontaneous breathing nasal oxygen supplementation; and preoperative endotracheal intubation);
2) operative phase: duration of surgery (min), highest intraoperative heart rate during surgery (heart rate), highest and lowest intraoperative mean arterial pressure during surgery (MAP) for a minimum duration of at least 5 minutes (mmHg), lowest intraoperative pH during surgery and duration of surgery; and
3) postoperative phase: number of postoperative endotracheal intubation days (days), intensive care unit (ICU) length of stay after surgery (days), and total number of surgeries performed in the first 3 years of life.[13]

Associations between each variable and motor outcome at 5 years of age were explored using univariable and multivariable linear regression analysis. All above-mentioned 11 variables were included in the multivariable model. Preoperative nasal oxygen supplementation and preoperative endotracheal intubation were considered categorical values, each with room air as reference value. To account for missing pH values in the operative phase, missing data were imputed using multiple imputation with fully conditional specification.[19,20] Fifty imputed data sets were created and the results of these 50 data sets were pooled using Rubin's rules.

For the multivariable linear regression analysis, multicollinearity was assessed using variance inflation factors (VIF). VIF levels lower than 3.0 were considered acceptable. The authors had selected the variables which would be included into the statistical analysis before the start of analysis.

All analyses were performed with SPSS Statistics Version 24 (IBM Corporation, Armonk, New York, USA).

RESULTS

Participants

In total 71 patients had undergone esophageal atresia repair surgery in the study period, and follow-up data were available for 53 of them. Follow-up data were missing for 18 patients because for eight patients the MABC was not a suitable test to evaluate their motor function because of associated congenital disease (CHARGE, Down and Silver Russell), and for ten patients for other reasons (radius malformation, autism, 22q11 duplication, emigration, and refusal to participate; Figure 1).

Perioperative phase

Surgery had been performed with either an open approach (n=15), a thoracoscopic (n=36) approach, or a thoracoscopic approach converted to an open approach (n=2). Most patients had esophageal atresia type C (Table 1).[4] Twenty-one patients had received preoperative respiratory support, of whom six had preoperatively been intubated (29%) and fifteen (71%) had received nasal oxygen supplementation (Table 1). Reasons for preoperative intubation are reported in supplementary Table 1. Thirty patients had a preoperatively diagnosed cardiac malformation, of which two were major cardiac anomalies that required surgery after the primary esophageal atresia repair.

Blood gas was measured in arterial blood (n=31) or capillary blood (n=2) during surgery; measurements were missing for 20 patients. Thirty-five patients had an arterial line for invasive blood pressure measurements; only non-invasive blood pressure measurements were available for 18 patients. The median for the lowest MAP was 29 mmHg (IQR 25-33); the median for the highest MAP was 61mmHg (IQR 49-72), median lowest pH was 7.20 (IQR 7.09 - 7.29; Table 1).

The main reasons for prolonged postoperative intubation (n=5) were respiratory failure and infections, leading to 5 to 8 days postoperative intubation (Supplementary Table 2). The median overall duration of intubation was 1 day; the overall length of ICU stay was 7 days (IQR 3-13) (Table 1). Reasons for ICU stay longer than the median 7 days (n=17) were infections and sepsis, pneumothorax and esophageal atresia complications such as anastomotic leakage (Supplementary Table 3). The number of surgeries in the first 3 years of life was median 3 (Table 1).

Motor outcome

The children's median age at the time of assessment with the MABC test was 5.1 (IQR 5.1-5.2) years. The z-score for the motor outcome was -0.66 (SD 0.99), which is significantly lower than the score in the age-related reference population ($p<0.001$, Figure 2). These scores indicate that 17% of our study population scored below the 5th percentile, which percentage is higher than the expected 5% from the norm scores.

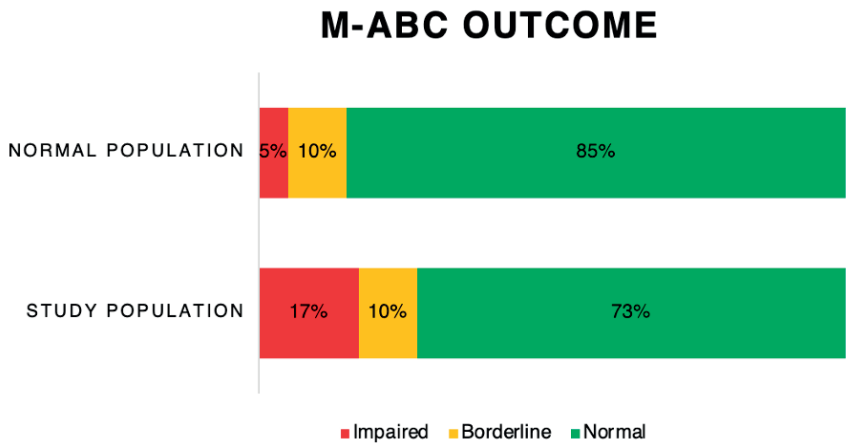


Figure 2. MABC outcome in 5-year-old children after esophageal atresia repair in the neonatal phase[14]

Table 2. Predictive factors (univariable and multivariable linear regression model)

Variable	Univariable linear regression analysis		Multivariable linear regression analysis	
	Estimated coefficient (95% CI) n=53	p-value	Estimated coefficient (95% CI) n=53	p-value
Weight at surgery (kilogram)	-0.082 (0.421 - 0.258)	0.631	0.002 (-0.344 – 0.348)	p=0.991
Mode of ventilation		0.019	-	
Room air	Reference		Reference	
Preoperative nasal oxygen supplementation (yes/no)	0.738 (0.221 - 1.254)	0.006	0.706 (0.132 – 1.280)	p=0.016
Preoperative endotracheal intubation (yes/no)	0.489 (-0.369 - 1.347)	0.257	0.553 (-0.384 – 1.489)	p=0.247
Major cardiac/Pulmonary problem (yes/no)†	-0.155 (-0.705 - 0.396)	0.576	-0.070 (-0.614 – 0.473)	p=0.799
Duration of surgery (min)	0.000 (-0.004 - 0.004)	0.924	-0.002 (-0.008 – 0.003)	p=0.432
Highest heart rate (frequency)	0.006 (-0.010 - 0.022)	0.467	0.009 (-0.007 – 0.025)	p=0.263
Highest MAP (mmHg)	0.012 (-0.008 - 0.033)	0.229	0.019 (-0.003 – 0.040)	p=0.091
Lowest MAP (mmHg)	0.003 (-0.042 - 0.047)	0.909	-0.008 (-0.051 – 0.035)	p=0.706
Intraoperative lowest pH	-1.784 (-4.337 - 0.768)	0.164	-0.317 (-2.433 – 1.799)	p=0.769
Postoperative days endotracheal intubation (days)	-0.198 (-0.356 - -0.039)	0.015	-0.173 (-0.361 – 0.015)	p=0.071
ICU LOS from surgery (days)	-0.018 (-0.032 - -0.005)	0.010	-0.004 (-0.022 – 0.014)	p=0.645
Number of surgeries first 3 years	-0.117 (-0.180 - -0.055)	<0.001	-0.075 (-0.161 – 0.011)	p=0.089

LOS: length of stay
CI: confidence interval
† Only major cardiac anomalies were included. The described preoperatively diagnosed pulmonary problems are the causes of respiratory problems and had been preoperatively confirmed by X-ray

Association of perioperative factors with motor outcome

Univariable analysis showed that the number of postoperative days with endotracheal intubation (B= -0.198, 95% CI: -0.356 - -0.039), ICU length of stay from surgery (days) (B= -0.018, 95% CI: -0.032 - -0.005), and the total number of surgeries in the first 3 years of life (B= -0.117, 95%CI -0.180 - -0.055) were negatively associated with motor outcome. Preoperative nasal oxygen supplementation, compared to room air, was positively associated with motor outcome (B= 0.824, 95% CI: 0.260 - 1.389); (Table 2).

The multivariable linear regression analysis indicated that the number of postoperative days endotracheal intubation (B= -0.211, 95% CI: -0.389 - -0.033) was negatively associated with motor outcome. A persistently high blood pressure (B=0.022, 95% CI 0.001 – 0.042) was positively associated with motor outcome. Preoperative nasal oxygen supplementation compared to room air (B= 0.706, 95% CI: 0.132 - 1.280) was positively associated with long-term motor outcome (Table 2). The multivariable analyses did not show signs of multicollinearity (all VIFs < 3.0).

DISCUSSION

This study analyzes associations between perioperative variables and long-term motor outcome of esophageal atresia patients at age 5 years, and found that motor outcome at this age was negatively associated with the duration of endotracheal intubation postoperatively, and positively associated with an episode of high blood pressure. Preoperative nasal oxygen supplementation was found to be positively associated with motor outcome compared to room air. Intraoperative factors such as heart rate, low blood pressure and pH were not associated with motor outcome at age 5 years.

There is an ongoing discussion about the possible effects of perioperative surgical and anesthesiologic events on the development of children's brain in the long term.[21] This study did not find associations between intraoperative variables and long-term motor outcome; still, various pre- and postoperative variables were associated with long-term outcome.

Up to now, few studies have investigated the long-term neurodevelopmental outcome of children born with esophageal atresia. Most of these considered somatic, medical and psychosocial development (respiratory performance, tracheomalacia and mental health).[5,22,23] As far as we know, associations between intraoperative variables and long-term motor outcome have not yet been studied. Our group previously reported normal cognitive performance and impaired psychomotor outcome in children with esophageal atresia born in 1999-2003 and assessed at ages 6 to 24 months.[11] In a cohort born between 1999 and 2006, we found significantly decreased z-scores on motor performance at ages 5 and 8 years.[8] Duration of anesthesia within the first 24 months of life of patients

in that cohort born with esophageal atresia between 1999 and 2003 was negatively associated with motor function at the age of eight years.[8] The cohort in the present study, born between 2007 and 2013, showed impaired motor outcome at 5 years of age, similar to the previous cohort born between 1999 and 2006 (z-score MABC -0.66 vs -0.75).[8] The findings indicate that 17% of our study population scored below the 5th percentile. A score < p5 on the M-ABC is indicative of serious motor problems, and is an indication for early intervention, such as pediatric physical therapy or targeted advice for parents and other caregivers. A lower motor performance score has impact on different facets in the child's life. Sufficient motor skills provide children with the opportunity to interact with their social environment and their physical surroundings. If motor skills are impaired, a child is likely to have impaired social functioning, resulting in difficulty creating relations with peers and, additionally, academic performance could be negatively affected.[24,25]

As reported previously, several severe perioperative metabolic derangements may occur during primary esophageal atresia repair (Table 1).[13,26,27]

Hypercapnia ($PaCO_2$ >6.4 kPa) has proven relevant to the long-term neurodevelopmental outcome because it can affect the cerebral metabolism and may cause apoptosis in the neonatal brain.[28-30] In a previous study, we found that the majority of esophageal atresia patients had hypercapnia during the surgical procedure: median 7.6kPa (IQR 5.8-9.3kPa).[13] High $PaCO_2$ levels lead to acidosis, which may affect children's neurologic development.[31] However, in the present study we did not find a significant association of intraoperative pH with long-term motor outcome in the univariable regression analysis. Since the missing pH data mainly concerned the years 2007 and 2008, we may reasonably assume that these data are missing at random.[20,32] Associations were neither found after imputing missing pH values.

Furthermore, hemodynamic instability could potentially lead to cerebral hypoxia, which might be associated with impaired outcome.[33,34] The present results show that the lowest blood pressure and highest heart rate were not associated with impaired motor outcome, whereas the highest blood pressure was associated with better long-term outcome. The median highest and lowest MAP in our study is 61 and 29 mmHg respectively, which values fall within the +2SD and -2SD margin for blood pressure in neonates; still, value for some patients were above and below these thresholds.[35] The highest MAP was not significantly different between patients with and without supplementation of vasopressors.

The high number of surgeries suggest that these patients are suffering critical illness or had complications or concomitant (congenital) diseases. The high numbers of surgeries for the patients in the present study led to many hospital admissions, repeated anesthesia exposure and more complications. The univariable analysis of this study showed a negative association between the number of surgeries performed within 3 years after esophageal atresia repair and the motor outcome at age 5 years. We did not find an

association between the motor outcome and the duration of the primary esophageal atresia repair. In a previous study, the total anesthesia time (of repeated anesthesia) before the age of 3 years was negatively associated with long-term outcome.[36] Another study found an association between the number of surgeries in the first year of life and the motor function at age 12 months.[37]

As we did not find an association between the duration of the primary surgery and the motor outcome at age 5 years, we hypothesize that impaired motor function might be related to repeated anesthesia rather than to one lengthy anesthesia exposure for primary esophageal atresia repair.[8,36,38] The association between number of surgeries in the first 3 years of life and motor function in the univariate regression analysis might indicate that the surgeries, but also the hospital stays as such, may negatively affect the long-term neurodevelopment.

The univariable regression and multivariable regression analyses showed a positive association of preoperative nasal oxygen supplementation, compared to room air, with motor outcome at age 5 years. As this was unexpected and we could not explain it, we had a closer look at the data and found a few high outliers on the MABC score in the patients who had received preoperative nasal oxygen supplementation (Supplementary figure 1). Due to the retrospective nature of this study, we could not identify why nasal oxygen supplementation had been started in these patients. In our hospital, there are no protocols for the use of nasal oxygen supplementation in this patient population prior to surgery. Therefore, it is highly dependent on the health professional whether a patient receives nasal oxygen supplementation or not. The potential role of preoperative nasal oxygen suppletion should be further investigated.

Furthermore, preoperatively endotracheally intubated patients in this study had been primarily intubated in a less well specialized center without prenatal diagnosis of the esophageal atresia. Previous reports have shown the benefits of in-born versus out-born neonates for the management of complex neonatal conditions.[39,40]

The results of the present and other studies[37,41] show an association between the duration of endotracheal intubation postoperatively and long-term cognitive and motor outcomes after surgery for non-cardiac malformations. Prolonged postoperative intubation might be required on account of comorbidities and other factors that might be associated with impaired long-term motor outcome.

Due to the retrospective nature of the data collection, only few perioperative variables could be included for analysis. Therefore, we predefined those variables which we considered most clinically relevant for the long-term outcome and could be retrieved from the patient files: duration of surgery, highest heart rate, highest and lowest MAP and lowest pH. We did not find significant associations between each of those variables and motor outcome. This might indicate that we are overlooking potential critical peri-

operative parameters. Thus, protocolized treatment of esophageal atresia patients and prospective registration of perioperative events are recommended for future studies.

Unfortunately, the number of variables to be analyzed was hampered by the limited number of patients since we are working with a rare congenital anomaly, leading to a small number of patients. Therefore, we chose 11 variables to be included in the univariable and multivariable regression models. We may have missed other variables possibly associated with long-term motor outcome, such as surgical approach, sex, gestational age, SpO2, prematurity and open or thoracoscopic surgical approach. Due to the limited sample size and the relatively large number of potentially relevant predictors, we preferred to prespecify our statistical analysis plan as much as possible. Adding more independent variables in a post-hoc analysis would have been problematic due to the risk of overfitting. Furthermore, many other confounders may affect outcome but have not been incorporated in the present analyses. It might have been that many other physiologic insults and major life events in their childhood may affect outcome. Yet, a previous study on the perioperative management of esophageal atresia/tracheoesophageal fistula did not find any differences in perioperative variables between open, thoracoscopic, and converted thoracoscopic to open surgical approach.[13] Research on long-term motor outcome of extremely premature children show impaired motor function on the long-term.[42] As the number of extremely premature children in the present cohort was one (32 weeks of gestation), we decided to include weight at birth in the regression analysis, as a proxy of many other risk factors including prematurity and dysmaturity.

Our data do not allow for speculations regarding a change in treatment protocols but emphasize the need for re-evaluation of treatment protocols and more advanced perioperative monitoring. Prospective registration of perioperative data and prolonged follow-up may be useful to detect and reduce long-term motor function impairment, since early interventions could be advantageous for this population.

CONCLUSIONS

In conclusion, the present study shows that the included children born with esophageal atresia have more motor problems than is to be expected from norm values. Long-term motor outcome at 5 years of age was negatively associated with the duration of endotracheal intubation postoperatively, and positively associated with high blood pressure. We cannot explain the positive association we found with preoperative nasal oxygen supplementation as compared to room air. We found associations between perioperative data and long-term outcome in patients with esophageal atresia, in which specific intraoperative variables were not found to be associated with long-term motor

outcome. Prospective, detailed perioperative monitoring to prove the effects on long-term neurodevelopmental outcome should be our goal.

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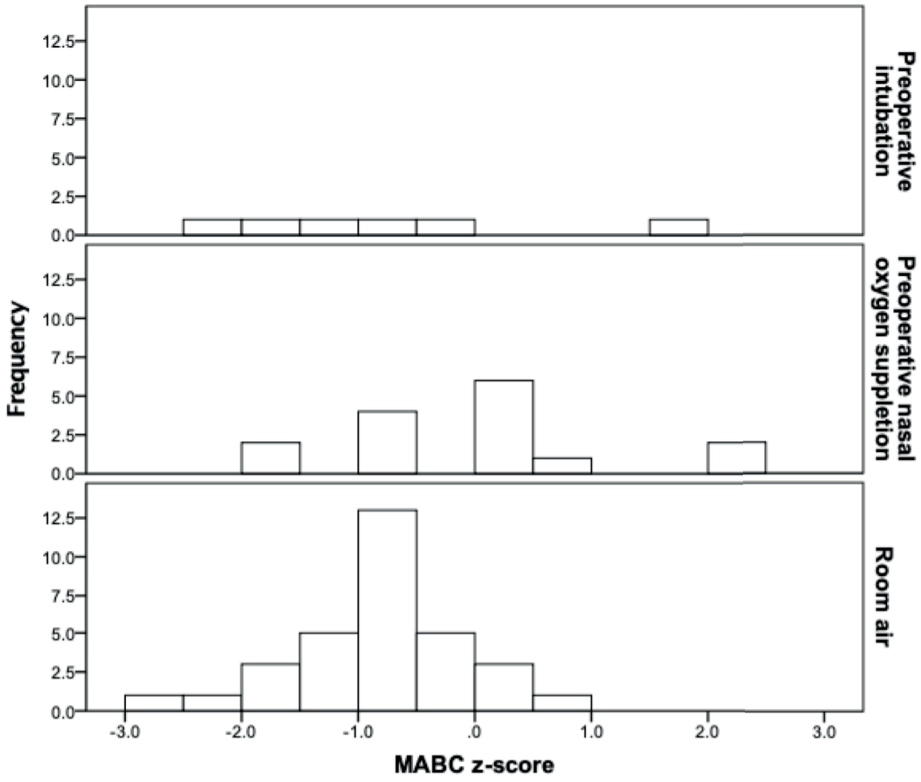
Supplementary Figure 1. MABC z-score outcomes preoperative oxygen suppletion



Supplementary Table 1. Reasons for preoperative endotracheal intubation

Patient	Days postoperative intubated	ICU stay	Reason preoperative intubation	SDS M-ABC
1	8	8	Respiratory insufficiency > intubation > wrong placement tube > reanimation	-1.3
2	2	4	Prematurity, IRDS, infection	-1.7
3	7	119	Persistent tachypnea and dyspnea	-2.3
4	1	9	Respiratory failure > conventional treatment with low pressures	1.7
5	2	13	Aspiration and exhaustion	-0.3
6	2	11	Prematurity	-0.7

Reasons why 6 patients were intubated prior to primary EA repair.

Supplementary Table 2. Reasons for prolonged postoperative endotracheal intubation

Patient	Postoperative days intubated	Reas.on	SDS M-ABC
1	7	Atelectasis, respiratory incidents, sepsis	-1.7
2	8	Pneumothorax, preoperative reanimation	-1.3
3	7	Respiratory failure, sepsis	-2.3
4	5	ALTE, cardiac: ODB, ASD, abnormal venous return	-1
5	5	Great oxygen demand, lots of sputum	-1

Reasons why 5 patients were prolonged intubated following primary EA surgery.

Supplementary Table 3. Reasons for prolonged ICU stay

Patient	ICU stay (days)	Days to extubation	Reason	SDS M-ABC
1	10	1	Phlebitis arm + infection	0
2	21	7	Sepsis	-1.7
3	8	8	Pneumothorax, respiratory insufficiency, preoperative reanimation	-1.3
4	21	1	Pneumothorax, stricture leakage	-1
5	32	1	RS virus	-1
6	53	1	Sepsis	-1.6
7	33	5	ALTE	-1
8	119	7	Sepsis, respiratory failure, cardiac issues	-2.3
9	33	1	Respiratory problems after extubation. Re-intubation necessary	-0.7
10	28	2	Stricture leakage	-1
11	13	2	Pneumothorax	-0.3
12	50	2	Premature	-1.3
13	15	1	Stricture leakage	-1.3
14	17	1	Stricture leakage	-1
15	10	1	Hypokalemia	-1
16	16	3	Lung infiltrations	-1.7
17	11	2	Acidosis	-0.7

Reasons why 17 patients had a prolonged ICU stay after primary EA surgery.

7

Long-term neurodevelopment in children born with esophageal atresia: a systematic review

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ABSTRACT

Background: Although the survival rate of esophageal atresia (EA) has increased to over 90%, the risk of functional long-term neurodevelopmental deficits is uncertain. Studies on long-term outcomes of children with EA show conflicting results. Therefore, we provide an overview of the current knowledge on the long-term neurodevelopmental outcome of children with EA.

Methods: We performed a structured literature search in Embase, Medline Ovid, Web of Science, Cochrane CENTRAL and Google scholar on November 8, 2020 with the keywords ''esophageal atresia'', ''long-term outcome'', ''motor development'', ''cognitive development'', and ''neurodevelopment''.

Results: The initial search identified 945 studies, of which 15 were included. Five of these published outcomes of multiple tests or tested at multiple ages.
Regarding infants, one of six studies found impaired neurodevelopment at 1 year of age. Regarding pre-schoolers, two of five studies found impaired neurodevelopment; the one study assessing cognitive development found normal cognitive outcome. Both studies on motor function reported impairment. Regarding school-agers, the one study on neurodevelopmental outcome reported impairment. Cognitive impairment was found in two out of four studies, and motor function was impaired in both studies studying motor function.

Conclusions: Long-term neurodevelopment of children born with EA has been assessed with various instruments, with contrasting results. Impairments were mostly found in motor function, but also in cognitive performance. Generally, the long-term outcome of these children is reason for concern. Structured, multidisciplinary long-term follow-up programs for children born with EA would allow to timely detect neurodevelopmental impairments and to intervene, if necessary.

INTRODUCTION

Esophageal atresia (EA) is a congenital deformity in which the upper esophagus does not connect to the lower esophagus and the stomach, which occurs in 2.43 per 10,000 live births.[1] After correction of the defect, more than 90% of the children born with EA survive nowadays.[2] Therefore, long-term outcome requires growing attention. The evaluation of long-term outcome in children born with EA focuses on several aspects, such as gastroesophageal reflux, dysphagia, respiratory problems, weight, growth, quality of life, psychological status, social behaviour and neurodevelopment.[2-4]

Most research on long-term outcome of EA has focused on physical impairments or quality of life (QOL), both in children and young adults.[5,6] A recent elaborate review on health related QOL (HrQOL) of patients born with EA concluded that clinical subgroups of children with EA present with impaired HrQOL, and that digestive symptomology negatively influences the HrQOL.[6] Neurodevelopment has been less well studied, and available studies reported conflicting results. Furthermore, the variety of used test instruments and cohorts make it difficult for clinicians to interpret these results, and a comparative study is lacking.

More research on neurodevelopmental outcome has been performed in neonates with other conditions. After extracorporeal membrane oxygenation (ECMO) treatment, 10-50% of children showed cognitive impairment of >2SD, and motor impairment was found in 12%.[7] In children born with diaphragmatic hernia, significantly more problems with motor function, concentration, and behavioural attention were found, compared to reference groups. IQ levels were lower for those who had received ECMO treatment.[8,9]

Neurodevelopment is the brain's ability to develop neurological pathways facilitating performance in daily life. These pathways support the functioning of the brain, including motor function (e.g. agility and balance) and cognitive performance (e.g. think, learn and remember). Motor function and cognitive performance are strongly interrelated and interdependent, displaying marked parallels and multiple points of connection in the brain.[10] Therefore, these factors cannot be seen as separate factors and are always impacted by the other and integrated in a test.

Better insight in long-term neurodevelopmental outcome is important for healthcare professionals as well as for children with EA and their parents, and will be helpful to guide future counselling, follow-up and treatment. In this systematic review we therefore aim to inventory the current knowledge on long-term neurodevelopmental outcome – including cognitive and motor functioning – in children who underwent primary surgery for EA.

METHODS

A broad systematic literature search was performed to identify clinical research on long-term neurodevelopment in children born with EA, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11] A structured electronic search was performed on November 8th, 2020 in the EMBASE, MEDLINE, Web of Science, COCHRANE and Google scholar databases.[12] The search terms were the following: ''esophageal atresia', 'long-term outcome', 'motor development', 'cognitive development' and 'neurodevelopment' (complete search strategy is provided in Supplementary Material). Limits were set to English language and human studies. This systematic review was registered in the PROSPERO database (registration number CRD42020203189).

After deduplication of the retrieved citations in Endnote[13], the titles and abstracts of the remaining studies were screened by two investigators (CvH, CtK), independently and in a systematic fashion. The inclusion criteria were: studies in children born with EA between 6 months and 18 years of age, with long-term neurodevelopment (either motor function and/or cognitive functioning) as primary outcome. Studies including children younger than 6 months old were excluded, since these were considered to describe the short-term effects of surgery and anaesthesia. Neurodevelopment had to be assessed by means of neuropsychological evaluation or a validated questionnaire to assess neurodevelopment. Studies that focused only on quality of life, psychological development, respiratory complications or physical comorbidities were excluded. These types of studies were excluded because clinical presentation of patients EA is very heterogenic which makes it hard to compare outcome variables. Last, studies not originally published in a peer-reviewed journal were excluded.

The remaining studies were selected for full-text analysis. Both investigators (CvH, CtK) independently read the full-texts of these citations. Discrepancies were solved through discussion, or by mediation from a third investigator (JdG), which resulted in the final selection.

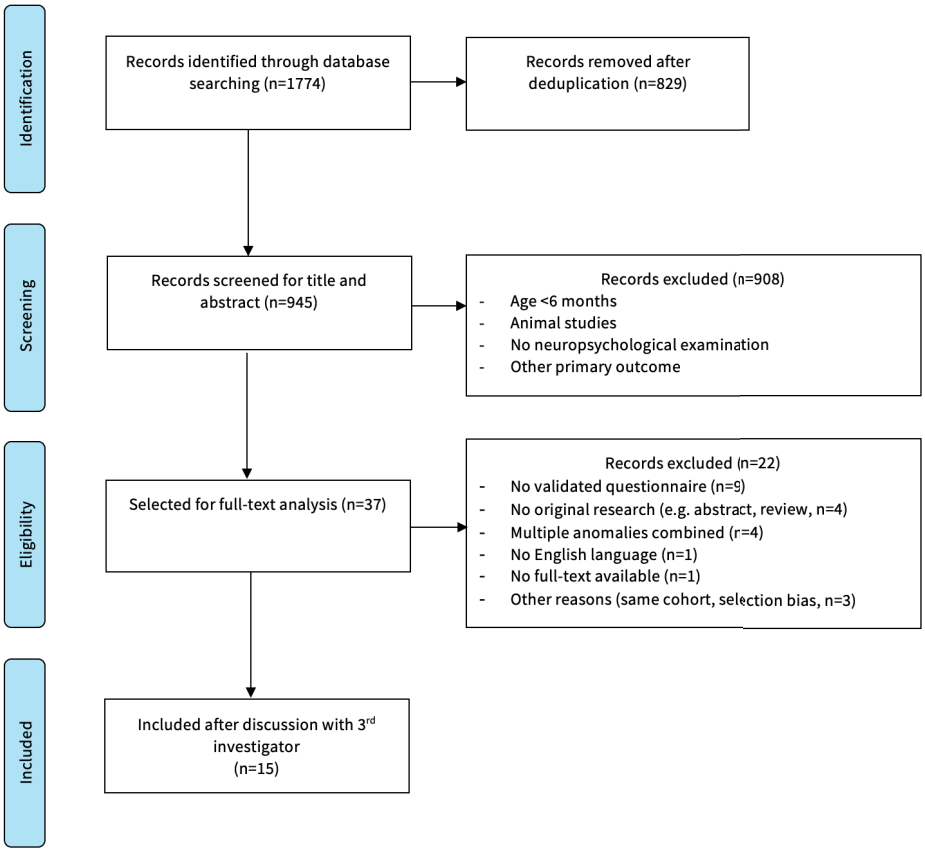
The following data were extracted: number of patients, age, outcome measure (motor or cognitive functioning), test method and test results. As various age-dependent tests are available to assess neurodevelopment in children, we report the search results for three age groups: infants <2 years old, pre-schoolers aged 2-5 years old, and school-aged children of 6-18 years old. This division is based on the age groups used for assessing neurodevelopment in children, based on developmental stages.[14]

Risk of bias was analysed using the Methodological Index for Non-randomized Studies (MINORS).[15] Due to small amount of included studies and the heterogeneity of the data provided by the included studies, we were not able to perform a meta-analysis of the data.

RESULTS

The search strategy yielded 1774 citations, of which 945 studies remained after deduplication. Based on the predetermined exclusion criteria, 908 studies were excluded after initial screening of title and abstract. Of the remaining 37 studies selected for full-text analysis, 22 studies were excluded (Figure 1). We found 9 studies in which questionnaires were used to assess neurodevelopment of the patients. These studies did not use validated questionnaires and were therefore not included in this systematic review. Only one study used the Ages and Stages Questionnaire (ASQ) to screen patients for patients to be tested with Bayley-3 (see further).[16] Four studies were published as conference abstract or as a review only, and two reported on a subgroup of another study.[17,18] Four other studies combined multiple congenital anomalies without specifying the test results for the patients with EA. One article was not written in English, and another article was excluded as we had no access to the full-text. One article was excluded due to an inclusion bias; development was only evaluated when a developmental disorder was already suspected.

Figure 1. Inclusion flowchart



Ultimately, fifteen studies were included in this systematic literature review, with a large variation of tests and age groups. Some studies investigated neurodevelopment of the study group at various ages (Table 1, Figure 2A and Figure 2B).

Neurodevelopmental outcome was described for infants (<2 years old) in six studies, for pre-schoolers (2-5 years old) in eight studies[16,19-25] and for school-aged children (>6 years old) in six studies[19,22,23,26-28] (Table 2-4). The sample size ranged from 6 to 182 children; the children's ages ranged from 6 months to 17 years old. A total of 769 tests were conducted, in which the Bayley Scales of Infant and Toddler Development (BSID-I, BSID-II and Bayley-3), the Movement assessment battery for children (M-ABC) and the Wechsler Intelligence Scale for Children (WISC) were most frequently used. The Bayley Scales of Infant and Toddler Development (BSID) has been internationally validated for children up to 42 months old; the most recent version measures five domains of development, including motor skills and cognition.[29] To measure motor skills of children aged 4 up to and including 16 years old, the Movement Assessment Battery for Children (M-ABC) has been developed and validated internationally.[30,31] For cognitive performance, the Wechsler Intelligence Scale for Children (WISC) is available for children from 6 to 16 years old.[32]

Characteristics of the included studies are summarized in Table 1. Risk of bias was present in all studies (Table 5). None of the studies had performed a sample size calculation. One study was retrospective, whereas all others were prospective studies that included patients in consecutive order.

Infants (<2 years old)

Six studies evaluated neurodevelopmental outcome in children under two years old (Table 2, Figure 2A, 2B). One study used BSID-I, one study used BSID-II and two studies used the Bayley-3. The BSID-I and the BSID-II contain two domains (motor and cognitive functioning), while the Bayley-3 also contains a domain on language skills. The other studies used the CAT/CLAMS (Capute Scale Clinical Adaptive Test/Clinical Auditory Milestone Scale) and the GMDS-II (Griffiths Mental Development Scales-II).

At 6 months of age, normal neurodevelopment was found in two longitudinal cohort studies: Gischler et al (BSID-I, ages 6, 12, 18 and 24 months, n=13)[21] and Francesca et al (Bayley-3, ages 6 and 12 months, n=82).[33] At 12 months of age, both these studies again found normal motor and cognitive functioning.[21,33] Francesca et al found a delay with time. They found a significantly lower median motor score at 12 months, compared to the score at 6 months old (p=0.033), but higher cognitive function at 12 months compared to the score at 6 months (p=0.000). Gischler et al found no differences at 12 months compared to the scores of the same cohort at age 6 months, and results at age 18 months also showed normal motor and cognitive functioning.[21]

Table 1. Baseline characteristics of included studies (n=15)

Author, year	Type of study	Operated /born/ tested	Age tests	Tests	Reference population	No. of patients included *	Mortality (n)	No. at follow-up	Type of EA	Gestational age (weeks) Birth weight	Comorbidities
Bouman[26] Netherlands, 1999	Prospective cohort study	NR	8-12y	WISC-RN	Dutch references	36	NR	36	Isolated EA n=5 EA with TEF n=31	NR NR	NR
Faugli[35] Norway, 2009	Prospective cohort study	Born 1999-2002	1y	BSID-II	US references	44	2	39 (36)	10% delayed repair	23% born <37 wks 2830 (595-4570) [A]	20% ≥1 associated anomaly (tetralogy of Fallot, biliary atresia, anorectal malformation, tracheomalacia)
Gischler[35] Netherlands, 2009	Prospective longitudinal cohort study	Tested 1999-2003	6, 12, 18 and 24 months	BSID I/II **	Dutch references	17	NR	13	NR	38.6 (36.9-40.1) [B] 3000 (2600-3200) [B]	Syndromal/ chromosomal n=1, severe neurologic impairment n=2, major congenital anomalies n=1 [#]
Van der Cammen-van Zijp[24] Netherlands, 2010	Prospective cohort study	Born 1999-2003	5y	MABC	Dutch references	29	NR	29	NR	38.4 (28.6-42.0) [A] 2900 (800-4500)	31% ≥1 associated anomaly
Kubota[28] Japan, 2011	Prospective cohort study	NR	6-17y	WISC-3 KSPD	Japanese references	23	NR	23	NR	NR NR	NR
Walker[34] Australia, 2013	Prospective case-control study	Operated Aug2006-Dec 2008	1y	Bayley-3	Study control group	34	1	31	NR	37.6 [C] 2718± 717 [D]	44% ≥1 associated anomaly

Table 1. Baseline characteristics of included studies (n=15) (continued)

Author, year	Type of study	Operated /born/ tested	Age tests	Tests	Reference population	No. of patients included *	Mortality (n)	No. at follow-up	Type of EA	Gestational age (weeks) Birth weight	Comorbidities
Francesca[33] Italy, 2020	Observational prospective cohort study	Born 2009 - 2017	6 and 12 months	Bayley-3	Age-normed	90	NR	82 59	Type C and D	38 (37-39) [B] 2700 (2450-3030)	NR
Bakal[19] Turkey, 2016	Cross-sectional study	Operated Jan1996-Dec 2011	6-16y	ADSI WISC-R	Turkish references	57	18	24 ADSI 15 WISC-R	Type A n=6 Type C n=50 Type E n=1	40% born <37 wks 2255.26 ± 600.27 [D]	35% ≥1 associated anomaly
Giúdici[22] Argentina, 2016	Prospective cohort study	Born Jan2003-Dec2014	1, 3 and 6y	CAT/ CLAMS PRUNAPE	Argentinian references	23	4	21 at 1y 14 at 3y 10 at 6y	Type A n=3 Type C n=20	38.3 ± 1.6 [D] 2917 ± 440 [D]	Trisomy 21 n=1, Edwards syndrome n=1
Walker[25] Australia, 2016	Prospective case-control study	Operated Aug2006-Dec 2008	3y	Bayley-3	Study control group	31	0	24	NR	38 [C] 2765 [C]	NR
Harmsen[23] Netherlands, 2017	Prospective cohort study	Born Jan1999-May2006	5 and 8y	MABC I/II WISC-3-NL RAKIT	Dutch references	78	7	54 motor 49 cognitive	91% type C	39 (29-42) [A] 2830 (750-4505) [A]	12% cardiac anomaly, 5% VACTERL association
König[27] Germany, 2018	Cross-sectional study	NR	3-12y	Deutscher Motorik Test	German references	17	NR	12	NR	54% born <37 wks 23% <1500 grams	46% congenital heart disease, 38% developmental delay, 28% skeletal deformity, 15% anorectal malformation

Table 1. Baseline characteristics of included studies (n=15) (continued)

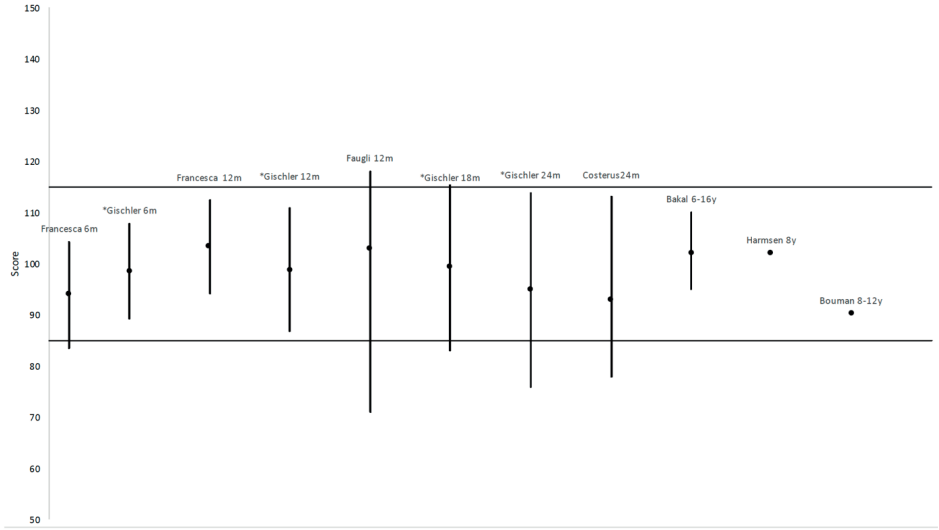
Author, year	Type of study	Operated /born/ tested	Age tests	Tests	Reference population	No. of patients included *	Mortality (n)	No. at follow-up	Type of EA	Gestational age (weeks) Birth weight	Comorbidities
Mawlana[16] Canada, 2018	Retrospective chart review	Operated Jan2000-Dec2015	2-3y	Bayley-3	US references	253	21	182	Type A n=13 Type B n=2 Type C n=149 Type D n=4 Type E n=14	36.8 ± 3.2 [D] 2589 ± 800 [D]	NR
Costerus[20] Netherlands, 2019	Prospective cohort study	Operated Aug2011-Aug2013	1 and 2y	BSID-II	Dutch references	6	NR	5	NR	39.0 (34.0-40.0) [A] 2850 (1941-3338) [A]	Tetralogy of Fallot n=1, kidney dysplasia n=1, Feingold syndrome n=1, intestinal malrotation n =1
Batta[36] Australia, 2020	Retrospective study	Born 2005-2014	1y	GMDS-II	General population references	44	1	27	NR	37.6 (36.4-39.1) [B] 3000 (2590-3405} [B]	NR

EA = esophageal atresia, TEF = tracheoesophageal fistula, NR = not reported. Type of EA according to Gross classification.(15) VACTERL = vertebral, anorectal, tracheoesophageal, renal or limb defects(16) [A] median (range), [B] median (IQR), [C] mean, [D] mean ± SD. [#] These four patients were excluded from neurodevelopmental assessment

* included in neurodevelopmental assessment

** Dutch version of the BISD I/II: BOS 2-30

Figure 2A. Outcome scores cognitive performance



Each line represents cognitive performance (mean (SD)) per study at the specified age in month (m). The dot represents the mean test result, the line represents the SD. Studies from which no crude test scores could be obtained are not included in this graph.
*95% CI reported instead of mean (SD)
The normal score ranges from 85 to 115, displayed by the lines at 85 and 115.

One other study that administered the Bayley-3 at 12 months of age found normal motor, cognitive and receptive language functions but a significantly impaired expressive language functioning (n= 31, $p<0.05$).[34] A study using the BSID-II reported a normal neurodevelopment (n=36).[35] A retrospective study using the GMDS-II at age 12 months (n=27) found normal neurodevelopment.[36]

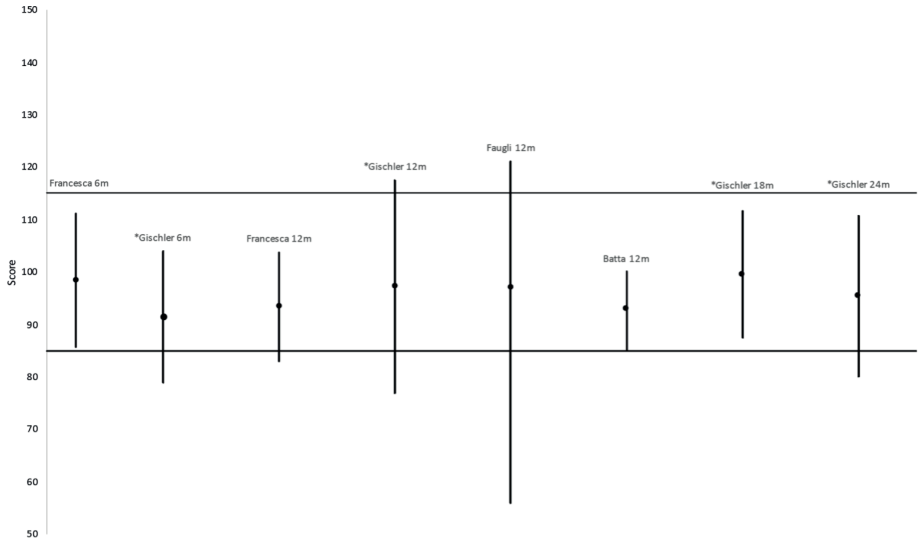
A longitudinal study from Argentina (CAT/CLAMS, ages 1, 2 and 6 years, n=23) found an abnormally low neurologic-psychomotor developmental index (NPDI) in five (24%) children at 1 year of age.[22]

In summary, most studies in infants show normal neurodevelopment compared to healthy controls, whereas only one study found impaired expressive language functioning at 12 months of age.[34]

Pre-schoolers (2-5 years old)

Eight studies assessed childrens neurodevelopment at preschool age (Table 3, Figure 2A, 2B). Full-range neurodevelopment was assessed in five studies; two used the BSID-I or -II [16,20]; two used the Bayley-3[21,25]; and one the CAT/CLAMS.[22] One study measured cognitive functioning with the Ankara Developmental Screening Inventory (ADSI), a validated Turkish instrument, to measure cognitive functioning.[19] Motor functioning was assessed with the M-ABC in two studies.[23,24]

Figure 2B. Outcome scores motor function



Each line represents motor outcome (mean (SD)) per study. The dot represents the mean test result, the line represents the SD at the specified age group in months (m)
*95% CI reported instead of mean (SD)
The normal score ranges from 85 to 115, displayed by the lines at 85 and 115.
Outcome data from van der Cammen-van Zijp and Harmsen could not be included in this graph due to their reported outcome measures lacking mean (SD) data.

Within the framework of a structured longitudinal follow-up program, Gischler et al (BSID-I, ages 6, 12, 18 and 24 months, n=13) showed normal motor and cognitive functioning at age 24 months.[21] Costerus et al (BSID-II, age 2 years, n=5) found normal outcome scores, although one child, diagnosed with Feingold syndrome, showed delayed cognitive functioning and one other child slightly delayed motor function.[20]

A retrospective study in Canadian children (Bayley-3, age 24 months, n=182) found a significant delay of >1 SD for all domains of the Bayley-3.[16] During the first period of this study, children were only assessed if the result of the Ages and Stages Questionnaire (ASQ) – a validated screening instrument for communication, gross motor, fine motor, problem solving and personal-social skills – had raised concerns.[37] During the remaining study period, each child was standardly assessed with the Bayley-3. Another cross-sectional study from a Turkish group (ADSI, age 0-6 years, n=24) found intellectual levels in accordance with the children's age.[19]

The children in the Australian study who had been tested at the age of one year[34], showed at 3 years of age no significant differences in all subdomains of the Bayley-3, but significantly improved receptive language skills (p=0.001, Bayley-3, age 3 years, n=24).[25] The Argentinian group (CAT/CLAMS, ages 1, 2 and 6 years, n=14) found abnormal NPDI in 7 out of 14 (50%) children.[22]

Table 2. Neurodevelopmental outcome in infants (<2 years old) born with esophageal atresia

Age (mo)	Author, year	No. of patients (n)	Test method	Outcome measure	Test result	Conclusion
6	Gischler*[21] Netherlands, 2009	13	BSID I	Motor	98.5 (89.3-107.7) [A]	Normal
				Cognition	91.5 (79.0-104.0)	
	Francesca[33] Italy, 2020	82	Bayley-3	Motor	98.4 ± 12.8 [B]	Normal
				Cognition	93.9 ± 10.4	
12	Gischler[21] Netherlands, 2009	13	BSID I	Motor	98.8 (86.8-110.8) [A]	Normal
				Cognition	97.2 (77.0-117.5)	
	Faugli[35] Norway, 2009	36	BSID-II	Motor	97 (56-121) [C]	Normal
				Cognition	103 (71-118)	
	Walker[34] Australia, 2013	31	Bayley-3	Fine motor	9.16 [D]	Expressive language impaired (p<0.05), other scales normal
				Gross motor	8.37	
				Cognition	11.00	
				Receptive language	10.23	
				Expressive language	9.03	
	Francesca[33] Italy, 2020	59	Bayley-3	Motor	93.4 ± 10.3 [B]	Normal
				Cognition	103.3 ± 9.1	
	Giúdici[22] Argentina, 2016	21	CAT/CLAMS	Visomotor & receptive and expressive language skills	Normal in n=16 (76%) Abnormal n=5 (24%)	Significantly lower than normal
	Batta[36] Australia, 2020	27	GMDS-II	Neurodevelopment	93 (85–100) [E]	Normal
18	Gischler[21] Netherlands, 2009	13	BSID I	Motor	99.2 (83.0-115.4) [A]	Normal
				Cognition	99.6 (87.5-111.6)	
				Cognition	93 (78-113)	

mo = months, US = United States, BOS = Bayley Ontwikkelings Schalen (Dutch version of BSID-I), BSID = Bayley Scales of Infant and Toddler Development, CAT/CLAMS = Capute Scale Clinical Adaptive Test/Clinical Auditory Milestone Scale, GMDS = Griffiths Mental Development Scales. [A] mean (95% confidence interval), [B] mean ± standard deviation, [C] mean (range), [D] mean, [E] median (IQR)

Two studies – with partly the same cohort – appraised the motor function of 5-year-old children with the use of the M-ABC, within the framework of a structured longitudinal follow-up program. Van der Cammen-van Zijp et al (M-ABC, age 5.9 years, n=29, cohort born 1999 – 2003) found a significantly lower total impairment score ($p<0.05$), ball skills and balance skills ($p<0.01$), whereas manual dexterity was within normal ranges, compared to Dutch reference values.[24] Harmsen et al (M-ABC and M-ABC II, ages 5 and 8 years, n=54, cohort born 1999-2006) showed a significantly ($p<0.001$) reduced motor function at 5 years, characterized by impaired gross motor skills, although fine motor skills were not impaired.[23]

Table 3. Neurodevelopmental outcome in preschoolers (2-5 years old) born with esophageal atresia

Age (months)	(year)	Author, year	No. of patients (n)	Test method	Outcome measure	Test result	Conclusion
	2	Gischler[21] Netherlands, 2009	13	BSID I	Motor Cognition	94.8 (75.9-113.7) [A] 95.4 (80.0-110.8)	Normal
	2	Costerus[20] Netherlands, 2019	5	BSID-II-NL	Motor Cognition	87 (83-96) [B] 93 (78-113)	Normal
24 ± 9 [C]		Mawlana[16] Canada, 2018	182	Bayley-3	Motor Cognition Language	Delay >1SD n=32 (18%) Delay >1SD n=44 (24%) Delay >1SD n=40 (22%)	Significantly lower than normal
	3	Walker[25] Australia, 2016	24	Bayley-3	Fine motor Gross motor Cognition Receptive language Expressive language	10.96 [D] 9.25 9.71 11.42 10.67	Receptive language improved (p<0.001), other scales normal
	3	Giúdici[22] Argentina, 2016	14	CAT/CLAMS	Visomotor & receptive and expressive language skills	Normal in n=7 (50%)	Significantly lower than normal
	5	Harmsen[23] Netherlands, 2017	54	M-ABC & M-ABC-II	Motor	z-score -0.75 ± 0.83 [E]	Impaired (p<0.001)
	5.9 ± 0.5 [A]	Van der Cammen-van Zijp[24] Netherlands, 2010	29	M-ABC	Total impairment score Manual Dexterity Ball skills Balance skills	Impaired p≤15 n=10 (34%) Impaired p<≤5 n=2 (7%) Impaired p≤15 n=14 (48%) Impaired p≤15 n=12 (41%)	Total impairment score (p<0.05), ball skills (p<0.01) and balance skills (<0.01) impaired, manual dexterity normal
	0-6 [C]	Bakal[19] Turkey, 2016	24	ADSI	Cognition	Normal in all (100%)	Normal

mo = months, yr = years, US = United States, BSID = Bayley Scales of Infant and Toddler Development, CAT/CLAMS = Capute Scale Clinical Adaptive Test/Clinical Auditory Milestone Scale, M-ABC = Movement-Assessment Battery for Children, ADSI = Ankara Developmental Screening Inventory.

[A] mean (95% confidence interval) [B] Median (range), [C] mean ± SD, [D] mean, [E] range

Table 4. Neurodevelopmental outcome in school-aged children (≥6 years old) born with esophageal atresia

Age (yr)	Author, year	No. of patients (n)	Test method	Outcome measure	Test result	Conclusion
6	Giúdici[22] Argentina, 2016	10	PRUNAPE	Fine and gross motor function, language skills and social area	Normal in n=3 (30%)	Significantly lower than normal
7 (3-12) [A]	König[27] Germany, 2018	12	KTT/DMT	Motor	2.19 [B]	Impaired compared to controls (p=0.04) and norm values (p=0.00)
8	Harmsen[23] Netherlands, 2017	49	M-ABC & M-ABC-II	Motor	z-score -0.53 ± 0.91 [C]	Impaired (p<0.001)
		46	WISC-III-NL & RAKIT	Full-scale IQ Total verbal IQ Total performance IQ	102 ± 14 [C] 103 ± 14 [C] 98 ± 14 [C]	Normal
6-17 [D]	Kubota[28] Japan, 2011	20	WISC-III & KSPD	Cognition	IQ<70 in n=5 (25%)	Higher incidence of mental retardation compared to the reference population (2-3%).
6-16 [D]	Bakal[19] Turkey, 2016	15	WISC-R	Cognition	IQ 95-110 [E]	Normal
10.2 (8-12) [E]	Bouman[26] Netherlands, 1999	36	WISC-RN	Cognition	IQ 90.2 ± 16 [C]	Impaired (p<0.01)

yr = years, US = United States, PRUNAPE = Prueba Nacional de Pesquisa (Argentine Screening Test), KTT/DMT = Kinderturntest Plus/Deutscher Motorik Test, M-ABC = Movement-Assessment Battery for Children, WISC = Wechsler Intelligence Scale for Children, RAKIT = Revised Amsterdam Intelligence Test, KSPD = Kyoto Scale of Psychological Development
[A] median (range), [B] mean, [C] mean ± SD, [D] range, [E] mean (range)

In summary, preschoolers show impaired neurodevelopment in 2/5 studies,[16,22] normal cognitive performance in 1/1 study,[19] and impaired motor function in 2/2 studies.[23,24]

School-aged children (≥6 years old)

Six studies assessed the neurodevelopment of children aged six years or older (Table 4, Figure 2A, 2B). One study assessed the full-range neurodevelopment using the Prueba Nacional de Pesquisa (PRUNAPE, Argentine Screening Test).[22] Cognitive performance was assessed in four studies with the WISC,[19,23,26,28] and in one of these additionally with the Revised Amsterdam Intelligence Test (RAKIT).[23] The two other studies assessed motor functioning; one with the M-ABC[23] and the other with the Kinderturntest Plus/Deutscher Motorik Test (KTT/DMT).[27]

The Argentinian study group (CAT/CLAMS, ages 1, 2 and 6 years, n=10) found borderline or impaired neurodevelopment in seven patients (70%). Four out of the seven patients with a normal NPDI at age 1 year had abnormal rest results at age 6 years (McNemar's test, p=0.04).[22]

Table 5. Risk of bias analysis MINORS

Study	A clearly stated aim	inclusion of consecutive patients	Prospective collection of data	Endpoint appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow-up less than 5%	Prospective calculation of the study size	An adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analysis	Total
Bouman[26]	2	2	2	2	2	2	NR	0	NR	NR	NR	NR	**12/24**
Francesca[33]	2	2	2	2	2	2	0	0	0	NR	NR	2	**14/24**
Gischler[21]	2	2	2	2	2	2	2	0	NR	NR	NR	NR	**14/24**
Walker 2013[34]	2	2	2	2	2	2	NR	0	2	2	2	2	**20/24**
Faugli[35]	2	2	2	2	2	2	NR	0	NR	NR	NR	2	**14/24**
Costerus[20]	2	2	2	2	2	2	2	0	NR	NR	NR	NR	**14/24**
Giudici[22]	1	2	2	2	2	2	0	0	NR	NR	NR	NR	**11/24**
Walker 2016[25]	2	2	2	2	2	2	1	0	2	2	2	2	**21/24**
Mawlana[16]	2	2	2	2	2	2	NR	0	NR	NR	NR	NR	**12/24**
Konig[27]	2	2	2	2	2	2	1	0	2	NR	2	2	**19/24**
van der Cammen[24]	2	2	2	2	2	2	NR	0	NR	NR	NR	NR	**12/24**
Harmsen[23]	2	2	2	2	2	2	1	0	NR	NR	NR	NR	**13/24**
Bakal[19]	2	2	2	2	2	2	NR	0	NR	NR	NR	NR	**12/24**
Kubota[28]	2	2	2	2	2	2	NR	0	NR	NR	NR	NR	**12/24**
Batta[36]	2	2	0	2	2	2	0	0	2	NR	NR	2	**14/24**

NR: not reported

Four studies evaluated cognitive performance with the WISC in school-aged children. Kubota et al (WISC-III & KSPD, age 6-17 years, n=20) showed that five of the children (25%) had IQ-scores lower than 70, defined as intellectual disability, which proportion was significantly higher than the 2-3% incidence in the general Japanese population.[28] Bakal et al (WISC-R, age 6-16 years, n=15) found IQ levels within normal range (range 95-110).[19] Bouman et al (WISC-RN, age 10.2 years, n=36) found a 10-points lower IQ (90.2 vs 100, $p<0.01$) than Dutch reference norms ($p<0.01$).[26] The prospective study of Harmsen et al (WISC-III-NL & RAKIT, age 8 years, n=46) found normal IQ levels ($p=0.26$).[23]

This study also assessed motor function (M-ABC and M-ABC II, ages 5 and 8 years, n=49); the mean M-ABC z-score was significantly lower than normative values (p<0.001), and did not improve significantly from age 5 years to 8 years (linear mixed model, z-score +0.24, p=0.074).[23]

A German cross-sectional study (KTT/DMT, age 7 years, n=17) assessed motor functioning. The children born with EA scored significantly lower than both age-matched healthy controls and the reference population.[27]

In summary, school-aged children show impaired neurodevelopment in 1/1 study,[22] impaired cognitive performance in 2/4 studies[26,28] and impaired motor function in 2/2 studies compared to healthy controls.[23,27]

Associations with neurodevelopment

In total, five studies reported statistical data on the association between covariables and neurodevelopment. Gischler et al used random regression modelling, which revealed that a higher number of congenital anomalies, higher severity of illness during admission, the higher number of surgical interventions in the first 24 months and additional medical problems (e.g. O_2 or tracheostomy at home) were associated with an impaired motor and cognitive functioning (all p<0.05). Length of stay in the first six months was negatively associated with motor functioning as well (p<0.05).[21] With multivariate regression, Francesca et al found birth weight to be positively associated with motor function at 6 months of age, whereas length of stay and weight at 12 months beneath the 5th percentile were both negatively associated with motor function at 12 months.[33]

The total number of major congenital anomalies correlated negatively with motor functioning (Spearman, p=0.007) in the study of van der Cammen-van Zijp et al. They also found a significant negative correlation with duration of hospitalization (p=0.003) and number of surgical interventions (p=0006).[24] Furthermore, a longitudinal linear mixed model analysis of Harmsen et al revealed that duration of anaesthetic exposure within the first 24 months was negatively associated with motor functioning (p=0.018). Sports participation was positively associated with motor functioning at 8 years (p=0.002).[23] The study of Batta et al found that birthweight and length of stay in the hospital were associated with neurodevelopment at one year of age.[36]

DISCUSSION

We conducted this systematic review to provide an overview on the current knowledge on the long-term neurodevelopmental outcome – including both motor function and cognitive performance– of children born with EA. Most studies found cognitive performance comparable to the reference population (Figure 2A) and motor function below

normal (Figure 2B). Two of the six studies in infants found developmental problems; i.e., impaired expressive language and impaired overall neurodevelopment, respectively. Regarding pre-schoolers, five of eight studies found developmental problems. One of these found receptive language to be improved, two found overall neurodevelopment to be impaired, and two found motor function to be impaired. Regarding school-aged children, five of six studies found developmental problems, three in overall neurodevelopment and two in motor function.

Heterogeneity of included studies

The overview provided by this systematic review highlights the heterogeneity of the published data on the neurodevelopmental outcome of children with EA. Unfortunately, various studies only report a dichotomous outcome, without detailed results.[16,19,22,24,28,38] Moreover, both the data and the reference values differ between studies which complicates drawing conclusions on neurodevelopment over time. Therefore, given the wide variety in tests, ages and sample sizes, a meta-analysis could not be performed.

Interpretation of the results

Infants (0-2 years): Up to 12 months of age, both cognitive and motor functioning were within normal limits in most studies, and only one study found an impairment for expressive language.[34] This would indicate that infants do not suffer neurodevelopmental impairments. More problems were revealed, however, at older ages.

Pre-schoolers (2-5 years): In pre-schoolers, two neurodevelopmental studies found cognitive impairments.[16,22] Both motor function studies found mild motor problems and two out of five studies that assessed neurodevelopment also found motor function impairments.[16,22-24] This would indicate that pre-schoolers start showing neurodevelopmental impairments, more than found in studies performed in infants.

School-aged children (6-18 years): Two out of four cognitive studies found an impaired cognitive performance with lower IQ levels.[26,28] Both studies assessing motor function found an impaired motor functioning.[23,27] Additionally, one neurodevelopment study found motor impairment.[22] This would indicate that the eldest studied patients suffer the most neurodevelopmental impairments of all assessed subgroups.

A study analysing change over time, found unchanged impaired motor function at ages 5 and 8 years.[23] Sports participation was reported for 8-year-old children only, and correlated positively with motor function at that age.

Giúdici et al reported a significant decrease in the number of patients with a normal NPDI with increasing age.[22] However, the NPDI had been assessed with the CAT/CLAMS at ages 1 and 3 years, and with the PRUNAPE at age 6 years. The results should therefore be interpreted with caution. Since 11 out of the 21 children in that study were lost to follow-up and characteristics of those children were not reported, an inclusion bias cannot be

ruled out. Lastly, although described in two separate papers, Walker et al evaluated the same study population at ages 1 and 3 years and found impaired expressive language at age 1 year and improved receptive language at age 3 years.[25,34]

Causes of neurodevelopmental impairments

Neurodevelopment has already been studied in critically ill children and children born with other anatomical malformations than EA. Neurodevelopmental impairments have been reported in children who received ECMO treatment and children who received ECMO treatment after surgery for congenital diaphragmatic hernia.[7,8] The systematic review on ECMO treatment also struggled with the heterogeneity of the included studies, but their results suggested a wide range of disabilities.[7]

There is an ongoing discussion on the cause of impaired neurodevelopment in children born with a congenital malformation. Previous research in anaesthesia showed that this impairment might be associated with various intraoperative surgical and anaesthesiologic events.[39] Ventilator time and repeated exposure to anaesthesia have been associated with impaired long-term neurodevelopmental outcome.[40] Repeated exposure is of increased importance in patients undergoing complex surgeries and surgical complications.[23,41,42] Animal studies showed a clear relationship between anaesthetic dose and duration of anaesthesia and impaired development, but doses administered in animals are not comparable to doses administered in human populations.[43] However, the potential neurotoxic effect of anaesthetics is less clear in clinical studies. A review found only little evidence for the risk of adverse developmental outcome after neonatal surgery.[44]

Potentially, the harmfulness of anaesthetic exposure is determined by the combination of the type of anaesthesia, the duration of exposure, the child's age, and the effects of anaesthetics on the perfusion of the brain, but future research is required to explore this hypothesis. Another hypothesis has it that impaired neurodevelopment is inherent to the congenital malformation.

Furthermore, it has been hypothesized that after neonatal critical illness the hippocampus is affected by a combination of factors including hypoxia, neuroinflammation, (surgical) stress, and exposure to anaesthetics.[45] Comparative studies on this issue can gain more insight in the potential causes of long-term developmental impairment in all patient groups, and in ways to stimulate cognitive development.[46]

The results from the present review show that children born with EA are at risk for impaired neurodevelopmental outcome as well as for impaired cognitive and motor development. A structured, longitudinal follow-up program focused on motoric and neurodevelopment run by a multidisciplinary team may help to solve uncertainties for the parents and to offer timely intervention, for instance physiotherapy, when necessary. If there is indeed a developmental problem in this population, longitudinal studies

with standardized follow-up at various ages could be helpful to reveal potential causes and give insight in the effects of interventions.[47]

Strengths, limitations and recommendations

To our knowledge, this is the first systematic review addressing neurodevelopmental outcome in children with EA. One of the strengths is the thorough search strategy. Also, the wide age spread gives an overview of the neurodevelopment during multiple stages of a child's life. However, several limitations need to be addressed. First, although the quality of each included study seems good (Table 5), a broad range of tests were used to assess neurodevelopment, including national instruments such as the PRUNAPE, ADSI, RAKIT and KSPD. Nevertheless, these instruments have all been validated, and test results were compared with local reference norms.[48-51] In some cases, different versions of an instrument sometimes assessed slightly different developmental skills. For example, the cognitive scale of the BSID-II included more linguistic skills than the Bayley-3. This variety in tests complicates the comparison between studies.

Secondly, selection bias could have affected results. An example is the retrospective chart review of Mawlana et al, in which during an unspecified part of the study period the Bayley-3 was assessed only if the ASQ was abnormal.[16] Nevertheless, we have decided to include this study because of its large sample size. Moreover, data on non-participants, which could have influenced the outcomes of the tested cohorts for better or for worse, were missing in all studies but one. Only Harmsen et al disclosed background information about the non-participants.[23] Furthermore, referral bias may have occurred in that parents of children without problems may have not to participate in follow-up programs. Overall, inclusion criteria varied among studies. Four studies clearly stated to have excluded patients with syndromal or chromosomal abnormalities, neurological impairment or intellectual disability,[21,23,24,36] whereas others did not. For example, the cohort of Giúdici et al contained one patient with trisomy 21, one with Edwards syndrome and two with cerebral palsy.[22]

Our search did not identify studies that used validated questionnaires to assess the neurodevelopment of patients born with EA. This type of studies could be of additional value to the studies discussed in this systematic review, which all used validated physical assessment tools to assess the neurodevelopment.

The present study highlights the potential neurodevelopmental impairments of these children. International standardization of testing protocols is advocated.[52] Recommendations would include testing with the instruments and reporting more detailed data, for instance using standard deviation and/or z-scores. This would facilitate meta-analyses and drawing accurate conclusions.

CONCLUSION

In conclusion, this systematic review shows that impairments were mostly found in motor function, but also in cognitive performance. In general, the findings of this review raise concerns regarding the long-term outcome of children after congenital EA surgery. Participation in a structured long-term follow-up program for this patient population is recommended, because this allows timely detection and treatment of neurodevelopmental problems.

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SUPPLEMENTARY MATERIAL. SEARCH STRATEGY

Embase.com

('esophagus atresia'/exp OR ('esophagus anastomosis'/de AND atresia/de) OR (((esophag* OR oesophag*) NEAR/3 (atresia* OR atretic*))):ab,ti) AND ('surgery'/de OR 'pediatric surgery'/de OR 'newborn surgery'/de OR 'surgical technique'/de OR anastomosis/de OR 'esophagus anastomosis'/de OR surgery:lnk OR (surger* OR surgical OR anastomo* OR repair* OR replacement* OR operation* OR operative* OR technique* OR procedure* OR operated* OR approach*):ab,ti) AND ('long term care'/de OR 'quality of life'/exp OR 'quality of life assessment'/exp OR 'child development'/exp OR 'motor dysfunction'/exp OR 'motor activity'/exp OR 'intelligence'/exp OR 'social psychology'/de OR 'cognition'/exp OR 'speech and language'/exp OR 'motor performance'/exp OR (long*-term* OR (qualit* NEAR/3 life*) OR qol OR hrql OR hrqol OR (development* NEAR/3 (child* OR physical*)) OR ((motor OR psychomotor*) NEAR/3 (skill* OR function* OR dysfuntion* OR impair* OR acivit* OR outcome* OR performan*)) OR intel* OR (social NEAR/3 psycholog*) OR psychosocial* OR cognit* OR well-being OR wellbeing OR emotion* OR speech OR language):ab,ti) NOT ([Conference Abstract]/lim) AND [english]/lim

Medline Ovid

(Esophageal Atresia/ OR (((esophag* OR oesophag*) ADJ3 (atresia* OR atretic*))).ab,ti.) AND (Surgical Procedures, Operative/ OR Anastomosis, Surgical/ OR surgery.fx. OR (surger* OR surgical OR anastomo* OR repair* OR replacement* OR operation* OR operative* OR technique* OR procedure* OR operated* OR approach*).ab,ti.) AND (Long-Term Care/ OR Quality of Life/ OR Child Development/ OR Psychomotor Performance/ OR Motor Activity/ OR Intelligence/ OR Psychology, Social/ OR Cognition/ OR exp Language/ OR (long*-term* OR (qualit* ADJ3 life*) OR qol OR hrql OR hrqol OR (development* ADJ3 (child* OR physical*)) OR ((motor OR psychomotor*) ADJ3 (skill* OR function* OR dysfuntion* OR impair* OR acivit* OR outcome* OR performan*)) OR intel* OR (social ADJ3 psycholog*) OR psychosocial* OR cognit* OR well-being OR wellbeing OR emotion* OR speech OR language).ab,ti.) NOT (news OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt. AND english.la.

Cochrane CENTRAL

((((esophag* OR oesophag*) NEAR/3 (atresia* OR atretic*))):ab,ti) AND ((surger* OR surgical OR anastomo* OR repair* OR replacement* OR operation* OR operative* OR technique* OR procedure* OR operated* OR approach*):ab,ti) AND ((long* next term* OR (qualit* NEAR/3 life*) OR qol OR hrql OR hrqol OR (development* NEAR/3 (child* OR physical*)) OR ((motor OR psychomotor*) NEAR/3 (skill* OR function* OR dysfuntion* OR impair* OR acivit* OR outcome* OR performan*)) OR intel* OR (social NEAR/3 psy-

cholog*) OR psychosocial* OR cognit* OR well next being OR wellbeing OR emotion* OR speech OR language):ab,ti)

Web of science

TS=(((((esophag* OR oesophag*) NEAR/2 (atresia* OR atretic*)))) AND ((surger* OR surgical OR anastomo* OR repair* OR replacement* OR operation* OR operative* OR technique* OR procedure* OR operated* OR approach*)) AND ((long*-term* OR (qualit* NEAR/2 life*) OR qol OR hrql OR hrqol OR (development* NEAR/2 (child* OR physical*)) OR ((motor OR psychomotor*) NEAR/2 (skill* OR function* OR dysfuntion* OR impair* OR acivit* OR outcome* OR performan*)) OR intel* OR (social NEAR/2 psycholog*) OR psychosocial* OR cognit* OR well-being OR wellbeing OR emotion* OR speech OR language))) AND LA=(english) AND DT=(article)

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“esophagus|oesophagus|esophageal|oesophageal atresia|atretic” surgery|surgical|anastomosis “long-term”|”quality*life”|”child|physical development”|”motor skill|function|dysfuntion|impairment|acivit|outcome|performance”|intelligence|cognition|wellbeing

8

Towards integrative neuromonitoring of the surgical newborn; a systematic review

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ABSTRACT

Background: The altered neurodevelopment of children operated on in the neonatal period might be due to perioperative changes in the homeostasis of brain perfusion. Monitoring of vital parameters is standard of care, but it usually does not include monitoring of the brain.

Objectives: To evaluate methods with potential and/or suggested additional value towards monitoring of the brain. In addition, we want to clarify if there are specific risk factors resulting in perioperative changes and how this can be evaluated.

Design: Systematic review.

Data sources: A structured literature search was performed in MEDLINE in Ovid, Embase, Cochrane CENTRAL, Web of Science and Google Scholar.

Eligibility criteria: Studies in neonates who received perioperative neuromonitoring were eligible for inclusion; studies on neurosurgical procedures or cardiac surgery with cardiopulmonary bypass and/or deep hypothermia cardiac arrest were excluded.

Results: Nineteen of the 24 included studies, totalling 374 infants, reported about the use of near-infrared spectroscopy. Baseline values of cerebral oxygenation greatly varied (mean 53% to 91%) and consequently, no coherent results were found. Two studies found a correlation between cerebral oxygenation and mean arterial blood pressure. Five studies, with in total 388 infants, used (amplitude-integrated) electroencephalography to study perioperative brain activity. Overall, the brain activity decreased during anaesthesia and epileptic activity was more frequent in the perioperative phase. The association between intraoperative cerebral saturation or activity and neuroimaging abnormalities and/or neurodevelopmental outcome was investigated in six studies, but no association was found.

Conclusion: Currently used techniques for perioperative neuromonitoring lack specificity and are not related to clinical (long-term) outcome or prognostics. To create a better understanding of the altered neonatal physiology and to signal risk of brain injury, we suggest to combine multiple neuromonitoring modalities which provides continuous information about the interactions between the various organ systems and might signal risk of brain injury.

INTRODUCTION

The past decades have seen improved outcomes of the operative treatment and non-operative treatment and care for the surgical newborn with congenital anomalies.[1] Survival rates increased due to changes in resuscitation time, optimization of homeostasis preoperatively, and subsequently better surgical timing and approach.[2,3] Yet, the few studies that investigated long–term outcomes of neonatal surgery show impaired neurodevelopment.[4–7] Causes of impairment are largely unknown, but a previous study suggested a crucial role for the complex interactions between cerebral oxygenation, activity and perfusion in the perioperative period.[8]

Monitoring of vital parameters as a surrogate for end-organ perfusion is standard of care, but it usually does not include monitoring of the brain, except in neonatal cardiac surgery with cardiopulmonary bypass, where, perioperative neuromonitoring is advocated in view of the high risk of brain injury and the existence of abnormal cerebral flow antenatally in some complex cardiac anomalies.[9,10] No valid indications for neuromonitoring of the non-cardiac surgical newborn are reported. However, a recent study also reported a high incidence, 58% in full-term born infants, of anatomical signs of brain injury on MRI after non-cardiac neonatal surgery as well.[11] Hence, surgical newborns may be prone to perioperative brain injury, although it is not clear from previous research whether these injuries occurred in the pre-, intra- or postoperative period. Yet, after birth, the biggest changes in the neonatal physiology might occur in the intraoperative period.

The brain can be monitored during surgery and anaesthesia by means of various techniques, such as near-infrared spectroscopy (NIRS), (amplitude-integrated) electroencephalography ((a)EEG), or cerebral Doppler ultrasound (CDU). Measurements with these techniques alongside continuous vital parameter measurements can provide insight into the altered physiology of the surgical newborn and their brain in the perioperative period.

However, a systematic evaluation of indications and treatment algorithms for neuromonitoring is lacking. The aim was to evaluate methods with potential and/or suggested additional value towards monitoring of the brain. In addition, we want to clarify if there are specific risk factors resulting in perioperative changes and how this can be evaluated.

METHODS

Eligibility criteria

We performed a structured literature search to identify clinical studies using perioperative neuromonitoring in neonates, defined as children under 90 days of life or postmenstrual age less than 52 weeks. The search was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[12,13] The studies needed to be originally published in a peer-reviewed journal. Limits were set on human and English-language studies.

Studies were excluded if the article did not match the inclusion criteria; if the article was a case report; if the surgical procedure was neurosurgery or cardiac surgery with cardiopulmonary bypass and/or deep hypothermia cardiac arrest; or if the article did not contain original patient data.

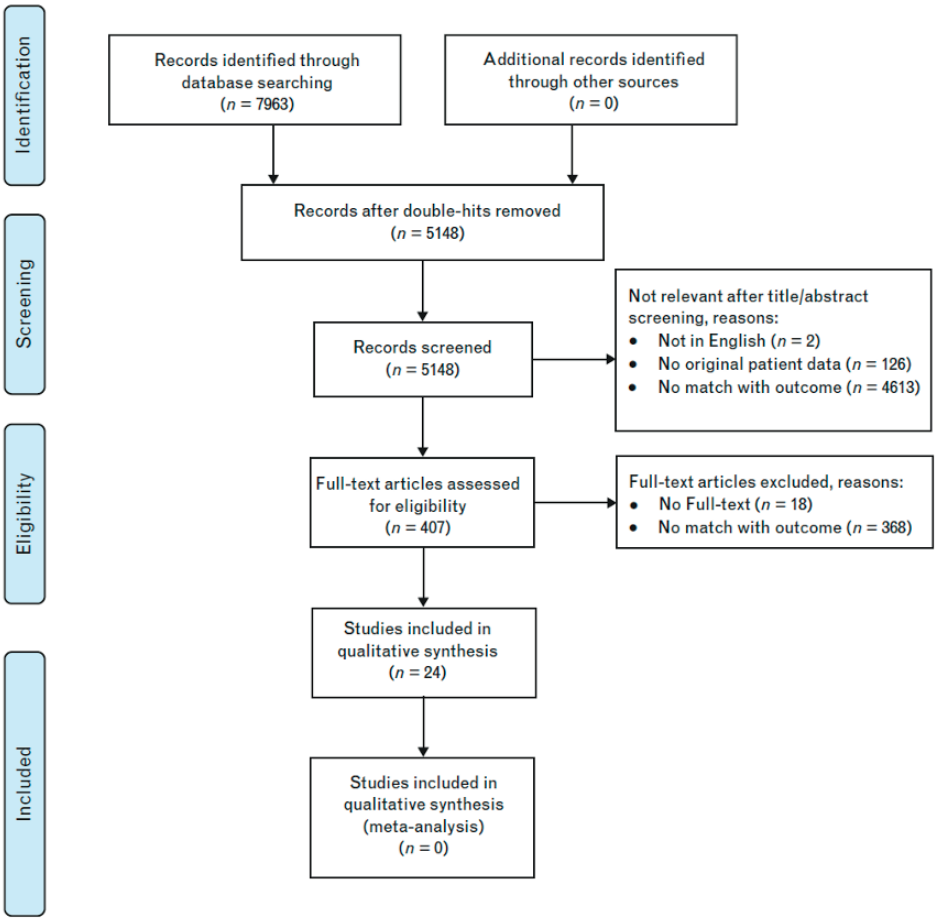
Information sources

The search strategy included expanded Medical Subjects Headings (MeSH) terms and predefined search terms (see appendix 1). On 11 December 2018, the electronical literature search was performed in MEDLINE in Ovid (PubMed), Embase, Cochrane CENTRAL, Web of Science and Google Scholar.

Search

The following search terms were used for Medline Ovid: (General Surgery/ OR exp "Surgical Procedures, Operative"/ OR (surgic* OR operation* OR operate* OR reoperation* OR reoperate* OR surgery OR surgeries OR intraoperativ* OR intra-operativ* OR peroperativ* OR thoracoscop* OR pleuroscop* OR thoracotom* OR pleuracotom* OR pleuratom* OR laparoscop* OR peritoneoscop* OR videolaparoscop* OR abdominoscop* OR celioscop* OR VATS OR laparotom*).ab,ti.) AND (electroencephalography monitoring/ OR neuromonitoring/ OR near infrared spectroscopy/ OR cerebral oximeter/ OR electroencephalogram/ OR brain function/ OR (EEG OR aEEG* OR NIRS OR ((near*-infrared*) ADJ (spectro*)) OR neuromonitor* OR neuro-monitor* OR ((electroencephalograph*) ADJ3 (monitor*)) OR ((cerebr* OR brain*) ADJ3 (oximeter* OR oxygenat*)) OR electroencephalogram*).ab,ti.) AND (infant/ OR neonatology/ OR neonatal intensive care unit/ OR pediatric surgery/ OR (infan* OR newborn* OR new*-born* OR baby OR babies OR neonat* OR child* OR NICU).ab,ti.) NOT (letter* OR news OR comment* OR editorial* OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt. AND english.lg. NOT (exp animals/ NOT humans/). The full search is added as appendix.

Figure 1. PRISMA flow diagram of manuscript selection



Study selection

After removing the duplicates of the retrieved citations, two authors (SC and CvH) independently screened the titles and abstracts of the remaining citations on relevance, and reviewed the full texts of eligible articles on inclusion criteria (figure 1). All studies were methodological scored (appendix 2). The following data was extracted: study design, sample size, study patient characteristics, modality, device and period of neuromonitoring, results of neuromonitoring, outcome and – if applicable – the follow-up data.

RESULTS

Structured literature search

The systematic search retrieved 7963 records (Figure 1), of which 24 articles met the inclusion criteria. All studies had a prospective observational design and were methodological scored (appendix 2). The median sample size was 16 (range 5 to 226) and the total number of children studied was 762 (Tables 1 and 2). Nineteen studies used NIRS.[14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32] Fourteen of these measured only cerebral oxygenation [15, 16, 19, 20, 22–28, 30–32] and five combined cerebral oxygenation with cerebral blood flow[16, 17, 28] or cerebral autoregulation[20, 32] (Table 1). Five studies used aEEG – in four to measure cerebral activity [33–36] and in one, a large cohort study, to detect epileptic activity only [37] (table 2).

Clinical outcome was reported in five studies. Postoperative neuro-imaging was performed in three of these studies [20, 35, 38], in one of which the findings of the neuro-imaging were combined with neurodevelopmental outcome at the age of 2 years.[38] The two other studies reported about neurodevelopmental outcome [26, 29] (table 4).

NIRS - cerebral oxygen saturation

Nineteen of the 24 included studies made use of NIRS (table 1). All but one monitored the patients over time, most commonly starting before surgery and continuing until end of surgery (table 3). The reported mean and median baseline NIRS values range widely (table 3). Results of the four studies that investigated the effect of ligation of (hemodynamic significant) patent ductus arteriosus ((hs)PDA) on cerebral oxygenation conflict: one reported no significant changes after ligation, one a significant decline, and two a significant increase in cerebral oxygenation after ligation (table 3).[16–19] The other studies concern different types of surgical approach. Four studies investigated NIRS during open abdominal surgery; one during laparoscopic surgery, and two during thoracoscopic surgery. Two studies did not specify the surgical approach. In these studies, measurements at different perioperative moments in the periods were compared with each other; coherent results were not found (table 3). Five studies showed a significant decrease in cerebral oxygenation; four a significant increase; and eight no significant change.

NIRS – correlations with other physiological variables

In the five studies that reported a decrease of cerebral oxygenation, three reported no significant changes in blood pressure[15, 16, 27] and two did not report blood pressure values.[24, 28] In the four studies that reported an increase in cerebral oxygenation, two studies found no significant changes in blood pressure, [18, 32] and the other two studies did not report blood pressure values. [19, 31] (table 3). Four studies aimed to find associations for cerebral oxygen desaturations and other perioperative monitoring techniques.[22, 25, 26, 28]

Table 1. Overview of included studies reporting about NIRS as intraoperative neuromonitoring technique

Demographics								Measurement			Results		
Study	**N**	**Device**	**Pathologies**	**Surgery**	**Age at surgery (d)**	**GA (wk)**	**BW (kg)**	**Cerebral oxygenation**	**Cerebral blood flow**	**Cerebral autoregulation**	**Comparison over time**	**Neuro-imaging**	**Neuro-development**
Fortune (2001)	49	NIRO-300	Acute abdomens	NR	Neonates, not specified	26.8-40.0‡	1100-4000‡	X					
Dotta (2005)	25	NIRO-300	CDH	Laparotomy	3.5*±2.5 (2-14)‡.	37.8*±1.8	3057*± 354	X			X		
Zaramella (2006)	16	NIRO-300 + TCD	PDA	Ligation	7-29‡	27.3* (24-34)‡	1036* (680–1740) ‡	X	X		X		
Hüning et al (2008)	10	NIRO-300	PDA	Ligation	14† (12–22)	24† (23–27)‡	748† (590–1070)‡		X		X		
Vanderhaegen (2008)	10	INVOS	PDA	Ligation	33*±30.9 (6–88)‡	27*±2.64 (24–32)‡	987.5*±391 (555–1855) ‡	X			X		
Chock (2011)	12	INVOS	PDA	Ligation	16*±9	26*±1	841*±159	X			X		
Chock (2012)	10	INVOS	PDA	Ligation	NR	26*±1	830*±170		X	X	X	x	
Conforti (2014)	13	INVOS	EA	Laparotomy	NR	33 - 41+5‡	1170-3740‡	X			X		
Michelet (2015)	60	INVOS	Emergency thoracic or abdominal surgery, CVC insertion, urological procedures, imperforate hymen, pharyngeal teratoma and endoscopy	NR	22*±22	37*±4	NR	X			X		

Table 1. Overview of included studies reporting about NIRS as intraoperative neuromonitoring technique (continued)

Study	N	Device	Pathologies	Surgery	Age at surgery (d)	GA (wk)	BW (kg)	Cerebral oxygenation	Cerebral blood flow	Cerebral autoregulation	Comparison over time	Neuro-imaging	Neuro-development
Tytgat (2015)	12	INVOS	HPS	Laparoscopy	38† (15-62)‡	39†(36-41)‡	3500† (2400-4400)‡	X			X		
Conforti (2016)	13	INVOS	CDH	Laparotomy	3† (2-9)‡‡	38† (35-40)‡‡	3055† (2660-3620)‡‡	X			X		
Koch (2016)	21	NIRO-300	CDH, EA, Intestinal artesias, exomphalos, PDA, HPS, circumcision, oophorectomy	NR	12.8*±10.1	35.7*±5.4	2878*±1002	X			X		
Razlevice (2016)	43	INVOS	General, thoracic or urologic surgery for congenital anomalies or disease	NR	6† (0-70)‡	38† (25–41)‡	3400† (800–5000)‡	X			X		X
Tytgat (2016)	15	INVOS	EA	Thoracoscopy	2†(1-7)‡	39† (36-42)‡	2962† (2155-4490) ‡	X			X		
Beck et al (2017)	19	INVOS	Gastroschisis, omphalocele, CDH, EA, NEC, neonatal bowel obstruction, abdominal tumor	NR	2† ±5‡‡	38† ±6.1‡‡	2945† ±801‡‡	X	X		X		
Costerus (2017)	10	INVOS	CDH, EA	Thoracoscopy	1.3-4.5‡	34-40.2‡	1941-3338‡	X			X		X
Stolwijk (2017)	5	INVOS	LGEA	Thoracoscopy	4† (2–53)‡	35+3† (33+4 to 39+6)‡	1580-2825	X			X	X	X
Nissen (2017)	12	INVOS	HPS	NR	43† (20-74)‡	38† (35-40)‡	3105† (2380-4000)‡	X			X		
Kuik (2018)	19	INVOS	NEC, SIP	Laparotomy	9† (7–12) ‡‡	27.6† (26.6–31.0) ‡‡	1090† (924–1430) ‡‡	X		X	X		

NR: not reported, CDH: congenital diaphragmatic hernia, EA: esophageal atresia, LGEA: long gap esophageal atresia, NEC: necrotizing enterocolitis, PDA: patent ductus arteriosus, CVC: central venous catheter, SIP: spontaneous intestinal perforation, HPS: hypertrophic pyloric stenosis , : mean ± standard deviation, † :median, ‡ :range, ‡‡: IQR*

Table 2. Overview of included studies reporting about aEEG as intraoperative neuromonitoring technique

Demographic								Measurement			Results		
Study	**N**	**Device**	**Pathologies**	**type of surgery**	**Age at surgery (d)**	**GA (wk)**	**Birth weight (kg)**	**Cerebral activity**	**Epileptic activity**	**Sleep depth**	**Comparison over time**	**Neuro-imaging**	**Neuro-development**
Kohelet (2004)	226	EEG, NR	NEC, PDA	Ligation or laparotomy	NR	>24	Very low birthweight		X				
Kasdorf (2013)	17	Olympic CFM 6000 Infant aEEG Cerebral Function Monitor	PDA	Ligation	24*±13 (8-55)‡	26.6*±3.4 (22.6-35.1)‡	867*±337 (538-1735)‡	X			X		
Leslie (2013)	17	Cerebral Function Monitor aEEG	PDA	Ligation	27† (14–42)‡	25† (23–27) ‡	680† (500–1140) ‡	X			X		
Stolwijk (2017)	111	BrainZ Monitor aEEG	EA, Abdominal wall defects, intestinal atresia/volvulus, anorectal malformation, urogenital malformation	NR	2† (0-32)‡	38.28† (28–42)‡	NR	X	X	X	X	X	
Cornelissen (2018)	17	Waveguard EEG cap & EMU40EX; Natus Medical Incorporated	Elective surgery	NR	2.9† (2.6-3.5) ‡‡ **months**	NR	NR	X					

*NR: not reported, NEC: necrotizing enterocolitis, PDA: patent ductus arteriosus, EA: esophageal atresia, * :mean ± standard deviation, † :median, ‡:range, ‡‡: IQR*

Table 3. Studies using NIRS and reporting the changes in rSO_2

Study	Type of surgery	Baseline values (%)	Comparison between different time points		Significant change
Dotta et al (2005)[§]	Laparotomy	NR	Begin surgery	End surgery	↓
Zaramella et al (2006)[§]	Ligation PDA	61.6 (3,8)**	Before ligation	After ligation	↓
Hüning et al (2008)[§]	Ligation PDA	53±15*	Changes during closure		NS
Vanderhaegen et al (2008)[§]	Ligation PDA	NR	Before ligation	After ligation	↑
Chock et al (2011)	Ligation PDA	63±13*	Before ligation	After ligation	↑
Conforti et al (2014)	Laparotomy	NR	Before surgery	During vs after surgery	NS
Michelet et al (2015)	NR	78±10*	NR	NR	NR
Tytgat et al (2015)	Laparoscopy	68±15*	Before insufflation	During and after cessation	NS
Conforti et al (2016)	Laparotomy	HFO 81[†] (70-98)[‡‡]	Before surgery	During surgery	↓
		CMV 82[†] (76-91)[‡‡]			
Tytgat et al (2016)	Thoracoscopy	77±10*	After anesthesia induction	After CO2 insufflation	↓
Beck et al (2017)	NR	79.11±9.92*	Changes during surgery		NS
			0 hours postoperative	24 hours postoperative	NS
Costerus et al (2017)	Thoracoscopy	CDH 82*	Before surgery	During surgery	NS
		EA 91*			
Nissen et al (2017)	NR	77.89±5.84*	Before surgery	After surgery	↑
Kuik et al (2018)	Laparotomy	NR	Before surgery	During surgery	NS
			During surgery	After surgery	↑

*[§] TOI, NR: not reported, NS: not significant, PDA: patent ductus arteriosus, * : mean ± standard deviation,** mean (standard error) , [†] :median, [‡] :range, [‡‡]: IQR*

One of these investigated the applicability of NIRS in neonates undergoing surgery by comparing the event rate of hypoxia (defined as SpO2<90%,) measured with the conventional peripheral pulse oximeter with the event rate of hypoxia measured with NIRS (defined as >20% decline from rSO_2 baseline or an absolute decline in rSO2 <40%, lasting for a minimum of 3 min) and found that NIRS hypoxia events occurred two to three more than hypoxia measured with the conventional peripheral pulse oximeter. During desaturation, the decline in SpO_2 was similar to that of cerebral oxygen saturation (rSO_2) in pattern and duration. Both SpO_2 and blood pressure were positively correlated with rSO_2.[25] Other studies found that cerebral oxygen desaturation (defined as delta rSO_2 > 20% from baseline) occurred in almost 20% of the patients and that a decrease in rSO_2 values was associated with a decrease in mean arterial blood pressure.[26] Yet, another of these studies measured perioperative rSO_2 in 60 infants <3 months of age with 960 data points and found cerebral desaturations (defined as delta rSO_2 > 20% from baseline) in 6.1% data points. The data suggests that a decrease in systolic blood pressure of more than 20.5%, or a decrease in mean blood pressure of more than 15.5%, is associated with a decrease in cerebral oxygenation of more than 10%. Furthermore, at the measurement points where delta rSO_2 was > 20% from baseline, the absolute blood pressure was lower (62±15 mmHg) than that at the normally saturated measurement points (71±15 mmHg).[22] By contrast, the fourth study – with 19 neonates during a variety of surgical procedures – reported intraoperative desaturations (defined as delta rSO_2 > 20% from baseline) in 6 (6.7%) of the measurement points and did not find a correlation between mean arterial blood pressure and cerebral rSO_2.[28] An overview of physiological variables correlated to NIRS are shown in appendix 3.

NIRS - cerebral autoregulation

Two studies used NIRS to evaluate perioperative cerebrovascular autoregulation.[20, 32] Chock et al. compared the effect of different treatments for hsPDA on cerebral autoregulation. Autoregulation impairment was defined as an increase in the pressure passivity index. This is calculated by the concordance between the mean arterial blood pressure (MABP) and rSO_2. Surgical ligation of the hsPDA was associated with an increased risk for impaired cerebral autoregulation in the first 6 hours after ligation compared to neonates who had a conservative treatment.[20] The other study concerned neonates undergoing abdominal surgery; impaired cerebral autoregulation was seen more frequently in the intraoperative period than in the pre- and postoperative periods. Elevated P_aCO_2 as well as elevated end-tidal sevoflurane levels negatively affected the cerebral autoregulation.[32]

NIRS – cerebral blood flow/volume

One study investigated the effect of PDA ligation on the cerebral tissue oxygenation index with NIRS and the cerebral blood volume and cerebral blood flow (CBF) velocity with cerebral Doppler ultrasound in relation to changes in arterial pH.[16] Overall, the cerebral tissue oxygenation index declined after PDA ligation, while the cerebral blood volume remained the same. Furthermore, both a lower pH and an increase in arterial CO_2 were found to be associated with an increase in CBF. In another study, cerebral blood volume changes directly after surgical closure of PDA were measured with NIRS. [17] Total haemoglobin corresponded to cerebral blood volume and was calculated by the sum of oxygenated haemoglobin and deoxygenated haemoglobin. Cerebral oxygenation decreased in the first minutes after ligation (table 3), although not significantly. Cerebral blood volume increased significantly in the first 2 minutes after ligation by a mean (SD) of 0.14 (0.12)ml per 100 grams tissue and returned to baseline within 2–5 minutes.

aEEG – cerebral activity

Interpretation of aEEG is based on pattern recognition of background activity.[39] One study in 111 neonates showed that overall the background pattern regressed two classes during surgery and anaesthesia compared to preoperatively.[35] Postoperatively, the trace returned to continuous normal voltage within 24 hours in 86% of the preterm and 98% of the term neonates. A higher sevoflurane dose was significantly associated with more suppressed background patterns. Furthermore, epileptic activity during surgery was seen in four of the 111 neonates, in one directly after starting sevoflurane induction. Postoperatively, epileptic activity was observed in eight neonates.[35] Another study aimed to determine the incidence of seizures in 6525 very low birthweight infants and to identify perinatal and postnatal factors associated with the occurrence of these seizures. Seizures had occurred in 23/95 (24%) of the infants operated on for PDA versus 10% of the conservatively treated infants and in 21/131 (16%) of the infants operated on for necrotizing enterocolitis versus 12% of the conservatively treated infants.[37] A third study, on age-related changes in EEG traces, showed that in neonates undergoing sevoflurane anaesthesia for elective surgery, slow-delta oscillations were present at all ages, but that theta and alpha oscillations emerged by approximately 4 months; seizures were not investigated.[40]

Another study investigated if aEEG could be useful to detect pain during hsPDA ligation in preterm neonates and investigated the relation between vital signs and aEEG during anaesthesia. There was no correlation between vital signs and aEEG voltage; aEEG was suppressed during surgery and remained suppressed during the 2-hours postoperative monitoring; seizures were not investigated.[33]

The fifth study investigated aEEG during ligation of hsPDA under fentanyl and rocuronium. During the procedure, the aEEG lower border of the background pattern trace

decreased and continuity decreased. Five of the 17 neonates already had a discontinuous background pattern preoperatively and none demonstrated complete recovery of the lower margin 24 hours postoperatively.[34]

Neuro-imaging and neurodevelopmental outcome

Neuro-imaging and neurodevelopmental outcome were reported in six studies (table 4). In a study in five children with long-gap oesophageal atresia, two of the children had postoperative intracranial abnormalities on MRI. Signs of changes resulting from altered cerebral perfusion (based on hypotension or hypocarbia) or cerebral oxygenation were absent in these two infants. All five children showed normal cognitive development and motor development at the age of 2 years (assessed with the Bayley Scales of Infant and Toddler Development, Third Edition and the Griffith Mental Development Scales).[38]

Two other studies examined perioperative neuromonitoring in relation to neurodevelopment after neonatal surgery. One examined the relation between cerebral desaturation (defined as at least once delta rSO_2 > 20% from baseline) during anaesthesia and neurologic function during clinical follow-up at 14 days till 6 months. Neurological function had deteriorated in three out of eight infants who had desaturated and in none of the 35 infants who had not desaturated. This deterioration might also be related to other clinical factors than perioperative cerebral desaturation, since all three infants with deteriorated neurological function had received cardiopulmonary resuscitation after birth. Moreover, two of them were born prematurely and had not undergone preoperative imaging. The absolute minimal rSO_2c value in the desaturation group was 66% (41.5–71%), versus 76.5% (60.5–90%) in the group without desaturation.[26] The other study reported NIRS values and neurodevelopmental outcome at the age of 2 years in seven infants after surgery for congenital diaphragmatic hernia and oesophageal atresie neonates. Correlations between intraoperative rSO_2 and neurodevelopmental outcome were not investigated.[29]

Chock et al. performed MRI and/or cranial ultrasound in 40 infants after the diagnosis of PDA was made (baseline) and at discharge or hospital transfer, next to perioperative cerebral autoregulation measurements calculated by the pressure passivity index with NIRS as mentioned above. Ten infants showed worsening neuroimaging findings compared to baseline, of whom three were treated with indomethacin alone, four were surgically ligated after failed indomethacin closure, and three received primary surgical ligation. An association between impaired cerebral autoregulation and neuroimaging abnormalities was not found. The neurodevelopmental outcome of these infants was not reported.[20]

Another study investigated perioperative aEEG in relation to MRI in 111 various non-cardiac surgical newborns. Preoperatively, 10% of the neonates had brain injury on

Table 4. Results of neuroimaging and neurodevelopmental outcome

Demographics			Neuroimaging			Neurodevelopmental outcome		
Study	**N**	**Device**	**Timing/Age**	**Type**	**Results**	**Test**	**Timing/Age**	**Results**
Razlevice (2016)	43	INVOS, NIRS	NP	NP	NP	Clinically documented neurological function by pediatric neurologist	In-hospital follow-up (range 14 days- 6 months)	Desaturated group: declined in 3 patients Normal group: in normal range
Costerus (2017)	10	INVOS, NIRS	NP	NP	NP	BSID-II, MDI, PDI	24 months	All in normal range
Stolwijk (2017)	5	INVOS, NIRS	Preoperative Postoperative	Ultrasound MRI	2 patients with a small thalamic infarction	Griffith Mental Development Scales and BSID-III	24 months	All in normal range
Chock (2012)	10	INVOS, NIRS	Baseline Before discharge or hospital transfer	Ultrasound and MRI	25% increased abnormalities compared to baseline*	NP	NP	NP
Stolwijk (2017)	111	BrainZ Monitor aEEG	Preoperative postoperative	Ultrasound MRI	10% intracranial lesions 58% parenchymal lesions and 37% non-parenchymal injury	NP	NP	NP

NP: not performed, NR: not reported, MRI: magnetic resonance imaging, *abnormalities not specified
BSID-II or III: Bayley's Scales of Infant Development, MDI: mental developmental index, PDI: psychomotor developmental index

ultrasound scan; 58% of all neonates had parenchymal lesions and 37% had non-parenchymal injury on the postoperative MRI. An association between MRI-abnormalities and type of aEEG background patterns was not found.[35]

DISCUSSION

This review included 24 articles reporting NIRS, aEEG and cerebral Doppler ultrasound as perioperative neuromonitoring modalities in infants less than 90 days of age undergoing surgery without cardiac bypass. Nineteen studies, with in total 374 infants, reported NIRS. These studies show a large heterogeneity in patient age, pathology, surgical approaches, practical clinical use and measurement timing. Furthermore, baseline values of cerebral oxygenation and definitions of hypoxia greatly varied. Clear associations between changes in cerebral oxygenation and vital parameters were not reported. Treatment algorithms for cerebral oxygenation were not found.

Five studies made use of aEEG studying perioperative brain activity – 388 infants in total. Overall, brain activity decreased and epileptic activity occurred more frequently in the perioperative phase. These studies also show a large heterogeneity in patient characteristics such as gestational age, birth weight and pathology.

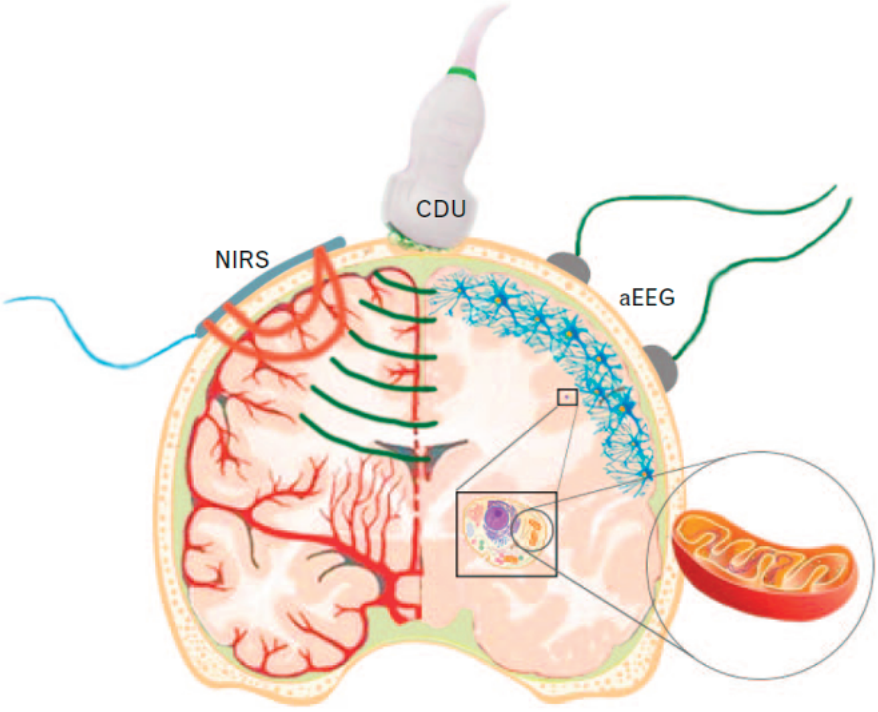
Six studies investigated association between intraoperative cerebral saturation or activity and neuroimaging abnormalities and/or outcome. One reported impaired neurodevelopmental outcome after cerebral desaturation episodes. A clear correlation with cerebral desaturation could not be established, however, as these infants had also received cardiopulmonary resuscitation. Another study showed that seizures are associated with a higher mortality rate in very-low-birth-weight neonates.[37] One study combined neuroimaging findings with neurodevelopmental outcome and found no impaired neurodevelopment in infants with intracranial pathology at the age of 2.[38]

Unfortunately, it was not possible to perform statistical analysis on the correlation between neuromonitoring and outcome due to limited data. Overall, there is minimal clinical evidence for using a single neuromonitoring device during non-cardiac surgery in neonates. Yet, a previous systematic review suggests that these neonates have an increased risk on delayed cognitive and motor development at the age of two.[5] It is important to stress that (possible) long term morbidity of neonatal surgery might not been seen before school-age. Motor function, concentration and attention deficits are reported from the age of 8 and later as extensive neuropsychological evaluation is only feasible from that age.[41]

Neonatal physiology may be too complex to detect insufficient cerebral perfusion with one device only, but may be better understood when combining different modalities. Therefore, we searched for broader monitoring techniques and new ways of integrated

data analysis. We suggest that 'integrative' neuromonitoring might be more beneficial, as visualized in figure 3 and 4. In this context, the term 'integrative' refers to multimodal neuromonitoring which combines multiple modalities for better understanding of the pathophysiology. This starts with monitoring standard vital parameters which provide information about particular organ systems and reflect end-organ perfusion, but lack specificity for brain perfusion.[42, 43] To overcome this, NIRS is increasingly used in neonatal intensive care units. NIRS is based on the relative transparency of biological tissue to light. The technique is limited by inter- and intra-patient variance, because it depends on physiologic variability, the NIRS device and the type of probe that is used for monitoring. [44, 45, 46] Previous research on liquid phantoms showed device- and sensor-specific hypoxic thresholds.[44] In that study, the NIRO large sensor was associated with a hypoxic threshold of 62%; the INVOS small adult sensor with a hypoxic threshold of 55%; and the INVOS neonatal sensor with a hypoxic thresholds of 63%.[47] In this light, NIRS provides information about changes from an relative arbitrary zero-point, which means that you can only monitor a trend at best.[47] Besides that, cerebral oxygenation varies from 40-56% directly after birth and stabilizes 3 till 6 weeks postnatal between 55%-

Figure 2. Broad outlines of the different neuromonitoring modalities and its shortcoming to provide information on cellular level

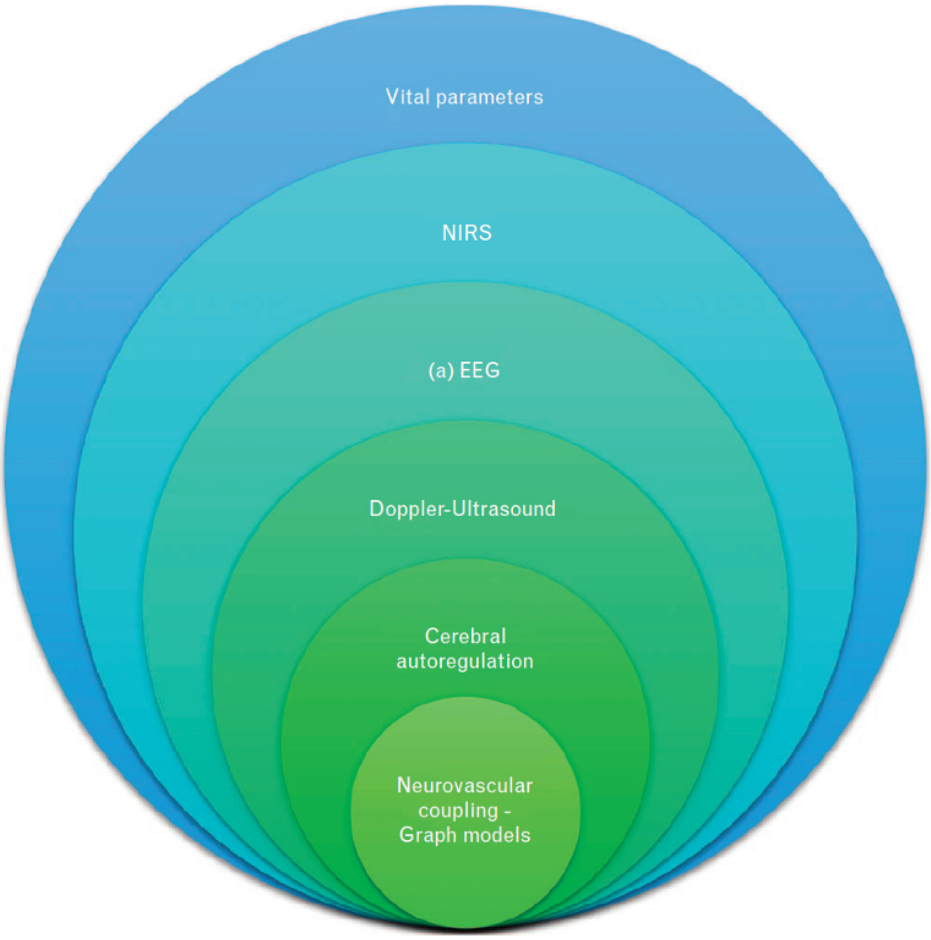


85%.[45] Changes in cerebral perfusion due to fluctuations in MABP or end-tidal CO_2 and changes in saturation effects cerebral oxygenation, so it should be stressed that NIRS values can only be interpreted together with standard vital parameter monitoring.[47, 48] Anesthesiologists should use NIRS as a warning signal, needing to check everything else.

Adding NIRS, which mainly reflects changes in venous oxygenation,[49] enables detecting changes in oxygen delivery to the brain and in oxygen consumption in the brain. These changes are generally quantified using the fractional tissue oxygen extraction parameter.[50]

Neuromonitoring with NIRS during sedation is complicated because of changes in oxygen consumption due to changes in cerebral metabolism.[51] Measurements of cerebral oxygenation are therefor often complemented with measurements of cerebral activity by means of aEEG.[51] The EEG is an electrophysiological technique for the record-

Figure 3. Our proposal of 'integrative' neuromonitoring



ing of electrical activity arising from the brain.[52] EEG can be measured in its conventional format or in an amplitude integrated form (aEEG). At the neonatal intensive care unit, aEEG is most commonly used in hypoxic ischemic encephalopathy and therapeutic hypothermia. Hence, it may also be helpful in infants with encephalopathy of varying etiologies.[53, 54] The infants presented in the work by McCann ME et al., all developed new-onset epileptic seizures postoperative within 25 hours of administration of anaesthetics.[55] In here, all patients underwent relative small surgical procedures with an uneventful perioperative course. In this light, we think that perioperative monitoring with aEEG might be useful for early detection of (severe) postoperative encephalopathy and epileptic seizures. To identify the potential value of aEEG in the operation theatre, a randomised controlled trial could be performed in which the anaesthesiologists is or is not blinded for aEEG.

Cranial ultrasound with Doppler is still the only way to image and quantify real-time cerebral perfusion and flow velocity.[56] Yet, mathematical approaches to measure the regulation mechanism of cerebral blood flow are being developed. Cerebral autoregulation is the most extensively studied regulation mechanism in preterm and term neonates. At its core, cerebral autoregulation maintains a constant cerebral blood flow (CBF) in a wide range of cerebral perfusion pressures (CPP). NIRS measurements present an attractive method for non-invasive assessment of CBF.[57] In studies on cerebral autoregulation, cerebral oxygenation parameters generally serve as a measure for CBF and MABP as a measure for CPP. A marker for cerebral autoregulation can be obtained by combining CBF and CPP measurements. Note, however, that NIRS measurements are valid surrogates for CBF only in the absence of large variations in arterial saturation and under the assumption of a constant cerebral metabolism.[58] Besides the partial pressures of arterial blood gases (CO_2 and O_2), the primary controllers of CBF are the cerebral metabolism and the autonomic nervous system, which implies that CBF is mainly determined by neural activity.[59] An increase in neural activity results in a higher oxygen consumption, which, in turn, triggers an increase in CBF, in order to deliver more oxygen to the brain.[60] This regulation mechanism is called neurovascular coupling.[59] General physiological markers of neurovascular coupling can be obtained by studying the interaction between NIRS and EEG measurements. From a mathematical point of view, a straightforward framework to integrate all of the different regulation mechanisms in one model can be constructed using graph theory, which allows to compute signal interaction graphs.[61] From a clinical point of view, signal interaction graphs allow to capture the dynamic coordinated interactions of organ systems. These interactions are essential to maintain homeostasis; distinct physiological states can be captured using these models. Examples includes the differentiation between sleep and awake states, between consciousness and unconsciousness and the effect of particular medication.[62] More importantly, altered or disrupted organ communications could be detected that,

when not managed, might lead to dysfunction of individual systems or to the collapse of the entire organisms, e.g., fever, hypertension, coma, or multiple organ failure.[63]

The presently used techniques for perioperative neuromonitoring – NIRS, aEEG, and cerebral Doppler ultrasound – lack specificity, standardized reporting and are not related to clinical (long-term) outcome or prognostics. We narrowed our literature search to neonates up to 90 days old. For this group, the results of this review indicate that neuromonitoring with any of these techniques will neither help to better understand the altered neonatal pathophysiology, nor enable early detection of deviation from the norm. A meta-analysis could not be performed due to the absence of standardized reported results and led to the inability to draw up a clear monitoring guideline.

aEEG monitoring has proved to be useful to detect epilepsy or status epilepticus, but there is no demonstrated additional value of NIRS or cerebral ultrasound with Doppler over standard monitoring of blood pressure, end-tidal CO2 and SpO2. The value of these monitoring modalities in the neonate requires further prospective trials with clinical meaningful outcome.

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Appendix 2. Methodological index for non-randomized studies

Methodological items for non-randomized studies	**Fortune** (18)	**Dotta** (19)	**Zaramella** (20)	**Hüning** (21)	**Vanderhaegen** (22)	**Chock** (23)	**Chock** (24)	**Conforti** (25)	**Michelet** (26)	**Tytgat** (27)	**Conforti** (28)	**Koch** (29)	**Razlevice** (30)	**Tytgat** (31)	**Beck** (32)	**Costerus** (33)	**Stolwijk** (34)	**Nissen** (35)	**Kuik** (36)	**Kohelet** (41)	**Kasdorf** (37)	**Leslie** (38)	**Stolwijk** (39)	**Cornelissen** (40)
A clearly stated aim	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Inclusion of consecutive patients	2	1	1	2	1	1	1	1	1	1	2	2	1	1	1	1	1	1	2	2	2	2	2	2
Prospective collection of data	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2
Endpoints appropriate to the aim of the study	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Unbiased assessment of the study	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Follow-up period appropriate to the aim of the study	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Loss to follow up less than 5%	NA	NA	NA	NA	NA	1	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Prospective calculation of the study size	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Additional criteria in the case of comparative study																								
An adequate control group	1	NA	NA	NA	NA	2	2	2	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Contemporary groups	2	NA	NA	NA	NA	2	2	2	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Baseline equivalence of groups	2	NA	NA	NA	NA	1	2	1	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Adequate statistical analyses	2	NA	NA	NA	NA	2	2	2	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total score (out of)	**17 (22)**	**9 (14)**	**9 (14)**	**10 (14)**	**8 (14)**	**17 (22)**	**19 (22)**	**16 (22)**	**18 (22)**	**9 (14)**	**10 (14)**	**10 (14)**	**9 (14)**	**9 (14)**	**9 (14)**	**9 (14)**	**9 (14)**	**8 (14)**	**10 (14)**	**10 (14)**	**11 (14)**	**10 (14)**	**11 (14)**	**10 (14)**

The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). NA: not applicable.

Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (Minors): Development and validation of a new instrument. *ANZ Journal of Surgery*2003; doi 10.1046/j.1445-2197.2003.02748.x.

Appendix 3. Overview of cerebral oxygenation, vital parameters and anaesthesia

Study	Cerbral oxygenation & Vital parameters					Significance		Induction anaesthesia	Maintenance anaesthesia
Dotta (2005)		Begin surgery	End surgery					Fentanyl 2ug/kg/h & pancuronium 0.1mg/kg/h	Fentanyl 2ug/kg/h & pancuronium 0.1mg/kg/h
	rSO_2	Δ -6.05±10.6				↓			
	HR	149.5±9.1*	165.2±14.2*			↑			
	SaO_2	94.1±4.6*	93.4±4.4*			NS			
	FiO2	0.25±0.05*	0.37±0.14*			↑			
	MABP	54.7±7.7*	55.6±8.1*			NS			
Zaramella (2006)		Before ligation	After ligation					Fentanyl 10-15ug/kg & Pancuronium 0.05-0.1mg/kg or Vecuronium bromide 0.08-0.1mg/kg	Fentanyl 2ug/kg/h
	rSO_2	61.6 (3.8)**	55.8 (2.6)**			↓			
	HR	162 (4.29)**	163 (5.1)**			NS			
	SaO_2	95.6 (1.07)**	95.4 (0.93)**			NS			
	MABP	47.25 (2.96)**	45.75 (3.26)**			NS			
Hüning (2008)		Before ligation	+0-2min	+2-5min	+5-10min	NS		Midazolam/Disoprivan & fentanyl/ alfentanil & vecuronium	Fentanyl/alfentanil
	rSO_2	53 (15)*	47 (22)*	48 (21)*	51 (22)*	↓			
	HR	165.4 (18.9)	0.1 (1.0)	0.7 (1.6)	2.0 (2.1)	NS			
	SaO_2	90.4 (8.3)	-2.8 (1.2)	-2.9 (4.3)	-1.3(4.3)	NS			
	MABP	31.9 (9.9)	33.8 (9.7)	31.9 (8.9)	30.9 (9.4)	NS			
Vanderhaegen (2008)		Before surgery vs after surgery (A)	5 min before vs 5 min after clipping (B)			A	B	Fentanyl 10 µg/kg & ancuronium 0.1 µg/kg	Fentanyl 3 µg/kg/h
	rSO_2	$3.1^{\dagger}$ (-6.8-5.9)‡‡	$2.9^{\dagger}$ (0.49-6.5)‡‡			NS	↑		
	HR	$7.9^{\dagger}$ (-4.4-26.7)‡‡	$6.5^{\dagger}$ (0.82-9.9)‡‡			NS	↑		
	SaO_2	$-1.04^{\dagger}$ (-2.2-0.12)‡‡	$0.78^{\dagger}$ (-0.68-6.08)‡‡			NS	NS		
	MABP	$3.9^{\dagger}$ (1.2-9.1)‡‡	$3.3^{\dagger}$ (-1.3-9.5)‡‡			NS	NS		

Appendix 3. Overview of cerebral oxygenation, vital parameters and anaesthesia (continued)

Study	Cerbral oxygenation & Vital parameters					Significance	Induction anaesthesia	Maintenance anaesthesia
Chock (2011)		Before ligation	After ligation				Fentanyl, ketamine, & rocuronium	NR
	rSO_2	63±13*	NNR			↑		
	MABP	35.8±5*	NR			NR		
Conforti (2014)		Before surgery	During vs after surgery				NR	NR
	rSO_2	NNR	NNR			NS		
	MABP	NR	NR			NR		
Michelet (2015)		Baseline	NR			NR	Propofol 5–7 mg/kg & suxamethonium 1.5 mg/kg & sufentanil 0.2ug/kg + atracurium 0.5 mg/kg after intubation OR sevoflurane 6% followed by sufentanil 0.2 ug/kg & atracurium 0.5 mg/kg	Sevoflurane 1,5-3% (endtidal expired concentration)
	rSO_2	78±10*	NR			NR		
	MABP	64±13*	NR			NR		
Tytgat (2015)		Before insufflation	Start insufflation	Stop insufflation	After cessation		Sevoflurane (inspired fraction) up to 8%, with a 100% FiO2 & atracurium	Sevoflurane. Acetaminophen/ paracetamol.
	rSO_2	68±14*	69±15*	69±11*	71±9*	NS		
	HR	141±12*	146±14*	139±15*	136±14*	NS		
	SpO_2	98±2*	97±3*	98±2*	98±2*	NS		
	MABP	35±5*	38±5*	43±9*	41±6*	↑ tov baseline		
Conforti (2016)		Before surgery	During surgery				NR	NR
	rSO_2	81† (70-98)‡‡	61† (52-74)‡‡	HFO group		↓		
	MABP	NR	NR			NR		
	rSO_2	82† (76-91)‡‡	65† (67-93)‡‡	CMV group		↓		
	MABP	NR	NR			NR		

Appendix 3. Overview of cerebral oxygenation, vital parameters and anaesthesia (continued)

Study	Cerbral oxygenation & Vital parameters				Significance	Induction anaesthesia	Maintenance anaesthesia
Tytgat (2016)		Baseline	After induction	After insufflation	↓	Sevoflurane 6–8 % (inspired concentration) & atracurium 0.5 mg/kg	Sevoflurane & sufentanil
	rSO_2	NR	77±10	73±7	↓		
	SaO_2	97±3	NR	90±6	↓		
	MABP	NNR	NNR	NNR	NS		
Beck (2017)		Start surgery	24 hours postoperative			NR	NR
	rSO_2	79.11±9.92*	-0.6±9.1 (IQR)		NS		
	MABP	NR	NR		NR		
Costerus (2017)		Before surgery	During Surgery			Propofol 2-3 mg/kg & sufentanil 0.3 µg/kg & cisatracurium 0.1 mg/kg	NR
	rSO_2	82*	Range 81-89	CDH	NS		
	MABP	NNR	NNR		↓ 30 min and ↑ 90 & 120 min after insufflation		
	rSO_2	91*	Range 79-91	OA	NS		
	MABP	NNR	NNR		NS		
Nissen (2017)		Admission	Before surgery	After surgery		?	?
	rSO_2	72.74±4.60*	77.89±5.84*	80.79±5.29*	Sign ↑ admission vs after surgery		
	MABP	NR	NR	NR	-		
Kuik (2018)		Before surgery	During surgery	After surgery		Sevoflurane & fentanyl & rocuronium.	Sevoflurane
	rSO_2	64† (53-75)‡	65† (53-73)‡	72† (60-82)‡	Sign ↑ during vs after surgery		
	MABP	35(28-38)	32(30-36)	35(32-41)	NS		

NR: not reported, NS: not significant, NNR: no numbers reported, *MABP: mean arterial blood pressure, HR: heart rate, HFO: high frequency oscillation, CMV: conventional mechanical ventilation, *: mean ± standard deviation,** mean (standard error) , † :median, ‡:range, ‡‡: IQR,*

APPENDIX 2.1 STRUCTURED LITERATURE SEARCH

The following search terms were used for Embase.com:

('surgery'/exp OR 'peroperative care'/exp OR 'intraoperative monitoring'/exp OR 'perioperative monitoring'/exp OR 'thoracoscopy'/exp OR (surgic* OR operation* OR operate* OR reoperation* OR reoperate* OR surgery OR surgeries OR intraoperativ* OR intra-operativ* OR peroperativ* OR thoracoscop* OR pleuroscop* OR thoracotom* OR pleuracotom* OR pleuratom* OR laparoscop* OR peritoneoscop* OR videolaparoscop* OR abdominoscop* OR celioscop* OR VATS OR laparotom*):ab,ti) AND ('electroencephalography monitoring'/exp OR 'neuromonitoring'/exp OR 'near infrared spectroscopy'/exp OR 'cerebral oximeter'/exp OR 'electroencephalogram'/exp OR 'brain function'/de OR (EEG OR aEEG* OR NIRS OR ((near*-infrared*) NEXT/1 (spectro*)) OR neuromonitor* OR neuro-monitor* OR ((electroencephalograph*) NEAR/3 (monitor*)) OR ((cerebr* OR brain*) NEAR/3 (oximeter* OR oxygenat*)) OR electroencephalogram*):ab,ti) AND ('infant'/exp OR 'neonatology'/exp OR 'neonatal intensive care unit'/de OR 'pediatric surgery'/exp OR (infan* OR newborn* OR new*-born* OR baby OR babies OR neonat* OR child* OR NICU):ab,ti) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [ENGLISH]/lim NOT ([animals]/lim NOT [humans]/lim)

The following search terms were used for Medline Ovid:

(General Surgery/ OR exp "Surgical Procedures, Operative"/ OR (surgic* OR operation* OR operate* OR reoperation* OR reoperate* OR surgery OR surgeries OR intraoperativ* OR intra-operativ* OR peroperativ* OR thoracoscop* OR pleuroscop* OR thoracotom* OR pleuracotom* OR pleuratom* OR laparoscop* OR peritoneoscop* OR videolaparoscop* OR abdominoscop* OR celioscop* OR VATS OR laparotom*).ab,ti.) AND (electroencephalography monitoring/ OR neuromonitoring/ OR near infrared spectroscopy/ OR cerebral oximeter/ OR electroencephalogram/ OR brain function/ OR (EEG OR aEEG* OR NIRS OR ((near*-infrared*) ADJ (spectro*)) OR neuromonitor* OR neuro-monitor* OR ((electroencephalograph*) ADJ3 (monitor*)) OR ((cerebr* OR brain*) ADJ3 (oximeter* OR oxygenat*)) OR electroencephalogram*).ab,ti.) AND (infant/ OR neonatology/ OR neonatal intensive care unit/ OR pediatric surgery/ OR (infan* OR newborn* OR new*-born* OR baby OR babies OR neonat* OR child* OR NICU).ab,ti.) NOT (letter* OR news OR comment* OR editorial* OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt. AND english.lg. NOT (exp animals/ NOT humans/)

The following search terms were used for Cochrane CENTRAL:

((surgic* OR operation* OR operate* OR reoperation* OR reoperate* OR surgery OR surgeries OR intraoperativ* OR intra-operativ* OR peroperativ* OR thoracoscop* OR pleuroscop* OR thoracotom* OR pleuracotom* OR pleuratom* OR laparoscop* OR

peritoneoscop* OR videolaparoscop* OR abdominoscop* OR celioscop* OR VATS OR laparotom*):ab,ti) AND ((EEG OR aEEG* OR NIRS OR (near* NEXT/1 infrared* NEXT/1 spectro*) OR neuromonitor* OR neuro-monitor* OR ((electroencephalograph*) NEAR/3 (monitor*)) OR ((cerebr* OR brain*) NEAR/3 (oximeter* OR oxygenat*)) OR electroencephalogram*):ab,ti) AND ((infan* OR newborn* OR (new* NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR NICU):ab,ti)

The following search terms were used for Web Of Science:

TS=(((surgic* OR operation* OR operate* OR reoperation* OR reoperate* OR surgery OR surgeries OR intraoperativ* OR intra-operativ* OR peroperativ* OR thoracoscop* OR pleuroscop* OR thoracotom* OR pleuracotom* OR pleuratom* OR laparoscop* OR peritoneoscop* OR videolaparoscop* OR abdominoscop* OR celioscop* OR VATS OR laparotom*)) AND ((EEG OR aEEG* OR NIRS OR (near* NEAR/1 infrared* NEAR/1 spectro*) OR neuromonitor* OR neuro-monitor* OR ((electroencephalograph*) NEAR/2 (monitor*)) OR ((cerebr* OR brain*) NEAR/2 (oximeter* OR oxygenat*)) OR electroencephalogram*)) AND ((infan* OR newborn* OR new*-born* OR baby OR babies OR neonat* OR child* OR NICU)) NOT ((animal* OR rat OR rats OR mouse OR mice OR murine OR dog OR dogs OR canine OR cat OR cats OR feline OR rabbit OR cow OR cows OR bovine OR rodent* OR sheep OR ovine OR pig OR swine OR porcine OR veterinar* OR chick* OR zebrafish* OR baboon* OR nonhuman* OR primate* OR cattle* OR goose OR geese OR duck OR macaque* OR avian* OR bird* OR fish*) NOT (human* OR patient* OR women OR woman OR men OR man))) AND DT=(Article) AND LA=(English)

The following search terms were used for Google Scholar (First 200 references):

Surgery|intraoperative|peroperative EEG|NIRS|”near infrared spectroscopy” |neuromonitoring|”cerebral monitoring”|electroencephalography|”cerebral oximeter”|electroencephalogram infants|newborns|”new born|borns”|baby|babies|neonate|neonatology|child|NICU

9

General discussion

The research presented in this thesis showed that children born with esophageal atresia encounter multiple problems during and following the primary esophageal atresia repair. They are prone to encounter metabolic derangements during this operation, followed by various complications. These children undergo multiple surgeries in the first 12 years of life and may suffer motor function impairment. Our results show that they will need continued care beyond the repair of the anatomical malformation presented at birth. Important questions raised from these results are:

- What are the causes of the neurodevelopmental impairments this patient group encounters?
- How can we prevent and treat these neurodevelopmental impairments?

In the following section, the main findings are placed in the broader perspective of other studies and findings in surgical newborns.

ESOPHAGEAL ATRESIA

Over the last decades, survival rates of children born with esophageal atresia have increased to over 90%.[1] The attention of healthcare professionals has, therefore, shifted towards long-term outcome and co-morbidity of the survivors. Most of the long-term outcome studies performed in this patient population have focused on the incidence and impact of reflux issues, airway infections and lung problems.[1-3 4,5] But this population is also thought to suffer neurodevelopmental impairments: their motor function, cognitive performance and overall neurodevelopment may be at risk due to exposure to various variables. Potential risk factors include the impact of the anatomical malformation itself, feeding problems leading to malnutrition, repeated and/or lengthy ICU admission, repeated and/or lengthy endotracheal intubation, use of potentially neurotoxic drugs, and repeated and/or lengthy surgery and anesthesia and its complications. Each and any of these factors could affect the long-term neurodevelopment.

As the hippocampus regulates memory encoding, consolidation and retrieval, it is thought to be involved in the ability to store and retrieve information about events and their contexts, as well as delayed recall of verbal and visuospatial information.[6] The hippocampus undergoes a growth spurt within the first 2 years of life, and is then vulnerable to alterations following neonatal critical illness. This is the period in which children born with esophageal atresia are potentially more at risk due to exposure to risk factors such as general anesthesia, hypoxia, hyperoxia, stress and neuroinflammation. These conditions are specifically harmful for the hippocampus, as shown in animal models.[7] It is assumed that survivors of preterm birth, congenital heart disease and severe respiratory failure are at risk of long-term memory deficits and the related negative influences on

the hippocampus. This assumption may hold as well for survivors of esophageal atresia, as they are exposed to risk factors such as neonatal general anesthesia and hypoxia, and to stress and neuroinflammation. This theory provides an explanation for the findings of Chapters 6 and 7, indicating impaired motor function, cognitive functioning and neurodevelopment.

DISCUSSION AND FUTURE STEPS IN THE TREATMENT OF ESOPHAGEAL ATRESIA

The study results in Chapter 2 showed that the neonates during primary esophageal atresia repair undergo major intraoperative metabolic derangements. The findings in this study underscore the importance of adequate perioperative monitoring. As of today, the anesthetic procedure during primary esophageal atresia repair is not standardized. The metabolic derangements found in Chapter 2 support the need for a protocol that includes the use of an arterial line in each patient, to enable monitoring of metabolic status and hemodynamics at standardized moments during the surgery. Additionally, a dedicated team of anesthesiologists is recommended as well as a dedicated team of pediatric surgeons, as multidisciplinary in-hospital teams have proven to improve patient outcomes.[8]

The metabolic derangements might have negative effects on the long-term neurodevelopment. However, the study in Chapter 6 did not find associations between the intraoperative pH and the motor function at 5 years of age. This does not mean that the intraoperative metabolic derangements, such as hypercarbia, will not cause brain damage. Reasons for not finding associations may be due to the small sample size and missing intraoperative blood gas values, or due to the fact that these metabolic derangements not affected motor function, but for instance cognitive performance, for which we do not have sensitive tests.

The study found a negative association between the number of surgeries in the first 3 years of life and the motor function at 5 years of age in univariate analysis. This implies that multiple surgeries carry risk for impaired neurodevelopment of children born with esophageal atresia. Factors that could underlie this risk are the patient's health, surgical risks, risk factors at the pediatric or neonatal intensive care unit, and anesthesiologic risks. With regard to the latter, neurotoxicity of the anesthetics used could be an important player. Furthermore, repeated anesthetic procedures may serve as a proxy for severity of associated illness, as more severely ill patients are prone to undergo more surgeries. When performing this study, we recognized that other, not included variables, could be associated with long-term outcome. As we had predefined the parameters to be

included for the regression analysis, changing the analysis plan was out of the question. We deemed post-hoc analysis unfit, due to the risks of introducing significant bias.[9] Yet, it would be interesting to investigate the associations between long-term outcome and additional variables such as prematurity, SpO_2, and dose and type of anesthetic agents as well. Ideally, an observational study should be set up to prospectively gather these data of children with esophageal atresia in a large multicenter study with a long-term follow-up program in which the children's cognitive and motor development is assessed with standardized instruments.

Dilatation of the surgical anastomosis made during primary esophageal atresia repair most frequently required general anesthesia in this patient population, as shown in Chapter 5. Anastomotic strictures are found in up to 60% of these cases. The study showed that an anastomotic stricture required on average 3.9 dilatations, most of which in the first two years of life.

Combining surgical interventions and procedures might be useful to reduce the required number of anesthetic periods. However, this might not always be feasible, since anastomotic stricture dilatations are often acute interventions, not elective. A possible alternative is better prevention of anastomotic strictures. A study researching the effects of intralesional steroids to prevent refractory anastomotic strictures is ongoing.[10] In a study on suture techniques during primary esophageal atresia repair, the application of a plus-shaped incision on the anastomosis lead to zero dilatations in 11 patients at age 4 years old.[11] Long-term outcome was not reported in this study. Furthermore, studies with larger cohorts are lacking.

The long-term effects of hospitalization, anesthesia and surgery on the neurodevelopment of children born with esophageal atresia are unknown. As shown in Chapter 7, all studies assessing motor function found an impaired motor function in children born with esophageal atresia, but studies assessing the cognitive performance and the overall neurodevelopment showed conflicting results. In view of the heterogeneity of the research populations and the tests used to assess motor function, cognitive performance and neurodevelopment, we cannot state whether this patient population systematically develops neurodevelopmental problems.

MECHANISMS OF NEUROTOXICITY BASED ON ANIMAL MODELS

The treatment of surgical newborns is increasingly paid attention to, since it is thought that many of the procedures could be associated with neurological impairments. The fragile newborn brain is developing rapidly in the first few years of life. Particular windows of vulnerability in the months after birth creates potential risks for the neu-

rodevelopment.[12] Most information on anesthesia-induced neuroapoptosis is based on animal models. The most vulnerable brain areas are those involved in learning, memory, sensory information processing and cognitive function. Due to the possible neuronal loss or loss of connectivity in these brain regions, fundamental neuronal networks will not be fully developed, which can lead to long-term neurocognitive impairment.[13] It is plausible that a threshold level of neuroapoptosis has to be reached to cause cognitive deficits.[14,15] Anesthetic drugs could induce different levels of apoptosis in the different regions of the brain. We have to keep in mind that neuronal apoptosis is a normal phenomenon in the developing brain, since 50-70% of all neurons will undergo apoptosis in order to maintain the normal structure of the central nervous system.[16] Depending on the degree of apoptosis in the different brain regions, different long-term problems may be expected.

Most commonly used general anesthetics inhibit the NMDA receptors and/or activate GABA receptors.[17] Since the NMDA and GABA receptors have an active role in the survival, maturation and integration of progenitors, is it plausible that anesthetics can interfere with neurogenesis.[18] It is key to understand in which neurodevelopmental stage and to what extent anesthetics can affect the neurogenesis. The window of susceptibility to anesthetic neurotoxicity coincides with synaptogenesis. During synaptogenesis, neurons are sensitive to disturbances in the environment in which their synapses lay. Anesthesia during the peak of synaptogenesis can therefore result in reduction of dendric spines, while the dendric spines are critical for synaptic transmission.[19,20] Considering that anesthesia induces impairment of synapse development, and that synapses play an important part in the long-term potentiation, it may well be that the mechanism of action of anesthetics leads to long-term neurodevelopmental problems.[21]

CONSEQUENCES FOR PEDIATRIC ANESTHESIA

Since most in vivo studies are performed in animals, data on the effects of anesthetics on the pediatric human brain is missing. However, anesthetic drugs bind to the same receptors in humans as they do in animals. If the binding of NMDA receptors and GABA receptors plays a role in the neurotoxicity of the drugs in humans, a shift may be made towards anesthetic drugs that do not bind to these specific receptors. A possible alternative drug is dexmedetomidine, which is a selective alpha-2 adrenergic receptor agonist that has anxiolytic, sedative, sympatholytic and analgesic features.[22] As it binds alpha-2 receptors, the possible neurotoxic effects of anesthetics binding to NMDA and GABA receptors are avoided. Alpha-2 receptors are found in the central nervous system. Binding of the alpha-2 receptor inhibits the release of norepinephrine from the presynaptic neuron. Via the locus coeruleus, a sleep-like sedation is induced; the main analgesic

effect is mediated via the dorsal horn, and insulin release is inhibited from pancreatic beta cells. Subsequently, due to the pre- and post-synaptic alpha-2 receptor activation, hemodynamic side effects can occur when dexmedetomidine is used. Activation leads to early vasoconstriction, and later leads to vasodilatation and reflex bradycardia.[23,24] Dexmedetomidine is cleared via hepatic metabolism. A high inter-individual variability for clearance and distribution volumes has been observed. Hypoalbuminemia, end-organ damage, hemodynamic changes and decreased cardiac output may contribute to this variability, especially in critical ill neonates.[25-27] Pediatric pharmacokinetic models seem to show maturation effects in newborns.[28] However, measured effects differ between studies. The inter-individual variability seems to have greater influence on the clearance than on the maturation effects.[29,30] Animal studies show favorable long-term outcome after dexmedetomidine infusion, when compared to sevoflurane, isoflurane, ketamine and propofol (Chapter 3). Almost all included studies in Chapter 3 tested for immediate apoptosis by marking the caspase-3 protein. Still, anesthesia-induced neuroapoptosis might be delayed and progressive. This means that caspase-3 negative neurons may activate cell death in a later stage, and are thus undetected by these studies.[31] A published pilot from the TREX-study showed that dexmedetomidine/remifentanil combined with caudal anesthesia provided effective anesthesia in infants undergoing surgery for longer than 2 hours.[32] As the TREX-study is still including patients in various countries all over the world, long-term neurodevelopmental outcome of these children has yet to be assessed.

Markers of inflammation, such as tumor necrosis factor-alpha (TNF-a) and cytokine interleukin 6 (IL-6), can be measured in the plasma. The levels of TNF-alfa and IL-6 have been found to be diagnostic indicators for brain damage in neonates with non-asphyxia fetal distress.[33] This observation shows that future research on anesthetic neurotoxicity should focus on more markers besides caspase-3, because caspase-3 might not be the right marker to focus on when one is searching for late neurotoxic effects of the anesthetics used. Factors such as Tau protein and neurofilament light, which are increasingly used in traumatic brain injury research and anesthesiologic research, might also be of additional value when studying neurotoxicity of anesthetics in pediatric patients.[34,35]

DISCUSSION ON NEURODEVELOPMENTAL IMPAIRMENTS

Discussion is ongoing about the neurotoxicity of anesthetic drugs in pediatric settings. Thus far, published clinical studies have not found differences in long-term development between exposed and non-exposed children.[36-39] Of the various studies performed, the PANDA study found no differences in IQ scores at 10 years of age between children

exposed to anesthesia before the age of 3 years and their unexposed siblings.[38] The MASK study showed no deficits in general intelligence in children exposed to anesthesia before the age of 3 years. However, secondary outcomes of this study suggest that multiple exposures to anesthesia are associated with changes in specific neuropsychological domains associated with behavioral and learning difficulties.[39] It has been suggested that a single short exposure to general anesthetic and sedation is unlikely to have negative effects on long-term behavior and learning.[37] This suggestion is supported by evidence from the GAS-study, a randomized controlled trial comparing the effects of one short period (<2 hours) of spinal anesthesia to general anesthesia. This study showed no differences in neurodevelopmental outcome at 2 and 5 years of age between children exposed to general anesthesia and children not exposed to general anesthesia in the period up to 60 weeks postmenstrual age.[37,40]

Children born with esophageal atresia are possibly at risk for long-term neurodevelopmental impairment. This group is not the only group at risk, since neurodevelopmental deficits as well have been shown in children born with congenital diaphragmatic hernia (CDH) or giant omphalocele, and those having received ECMO treatment for other reasons.

Generally, normal intelligence is found in these other risk groups.[41] In an elaborate neuropsychological assessment program, ECMO and/or CDH patients at 2, 5 and 8 years of age showed previously found sustained attention deficits but normal intelligence.[41,42] Also, specific short- and long-term memory deficits were found in over half the patients at school age. This study showed that intraoperative use of inotropic drugs was negatively associated with delayed verbal and visuospatial memory.[42] This suggests that cerebral hypoperfusion might be an important factor in the development of long-term impairments. However, we have to be aware of bias, as merely the patients with the worst hemodynamic state received inotropics. An elaborate study such as the study performed in CHD and/or ECMO patients has not been published for children born with esophageal atresia. However, it is not unlikely that similar results would be found, as esophageal atresia likewise is a major congenital anomaly requiring prompt postnatal surgical repair. Children born with esophageal atresia are therefore at risk of exposure to risk factors such as cerebral hypoperfusion, hyperperfusion and hyperoxia, like children born with different other congenital anomalies, but do not suffer ventilatory problems, except those with problems caused by tracheomalacia.

Children operated on in the neonatal period seem to have altered neurodevelopment, which might be due to perioperative changes in the homeostasis of the brain perfusion. It has been suggested that complex interactions between cerebral oxygenation, activity and perfusion causes the impairment.[43] Accurate neuromonitoring can help elucidate the interactions in the brain and map the reaction of the brain to changing situations such as metabolic derangements and drug administration. Knowing how the brain

reacts to perioperative changes might be important in understanding the mechanism of neurotoxicity after neonatal disease, surgery, hospital admission and anesthesia. Thus far, various monitoring devices are available. However, not all of these devices are fit for neonatal use, as discussed in Chapter 8.

When NIRS was applied to study the brain perfusion of patients with long-gap esophageal atresia, it appeared that the cerebral oxygenation remained stable during most of the surgeries. Outliers occurred during changes in either the respiratory or hemodynamic parameters. After intervention by the anesthesiologist to correct these parameters, cerebral oxygenation normalized.[44] A study in children born with esophageal atresia undergoing thoracoscopic repair reported a decrease in SaO_2 and pH during the surgery, and an increase in pCO_2.[45] Perioperative hypercapnia leads to acidosis, which can cause acidosis-induced cerebral arteriolar dilatation. Previous research in adult men, in whom hypercapnia and hypocapnia was induced by means of inhalation of CO_2 gas, showed that acidosis caused cerebral impairments.[46,47] In adults, hypocapnia leads to cerebral lactate efflux and reduced cerebral bloodflow.[48] The cerebral vasodilatation leads to increased cerebral blood flow, whereas hypocapnia leads to cerebral vasoconstriction, and thus a decreased cerebral blood flow.[49,50]

Besides the effects of carbon dioxide and thus acidosis, high O_2 levels can also impair long-term outcome. During anesthesia and surgery in neonates, oxygen is often maintained at a very high level. Caution is advised, however, because hyperoxia may trigger apoptotic neurodegeneration in neonates, as shown in animal studies.[51] Studies in premature brain injury models show that hypoxia leads to maturation delay in astroglia, neurons and oligodendroglia.[52]

FUTURE STEPS IN THE TREATMENT OF ESOPHAGEAL ATRESIA

There are many things unclear about the treatment of esophageal atresia and the long-term neurodevelopmental effects thereof (Figure 1). By accumulating follow-up data, we can gain a better insight into the pathophysiology of the brain development of this patient population and find out whether they suffer structural long-term neurodevelopmental impairments. Availability of international protocols for the anesthesiologic and surgical treatment and follow-up could be very helpful to achieve this. Internationally standardized treatment and long-term follow-up programs such as the one performed since 1999 in our center, could provide valuable data. Within such a follow-up program, neurodevelopmental problems can be detected early, and timely interventions can be offered to guide the child during early development. But larger cohorts are needed and cooperation between centers, such as European Reference Network of Inherited and Congenital Anomalies (ERNICA), could be helpful in this respect.

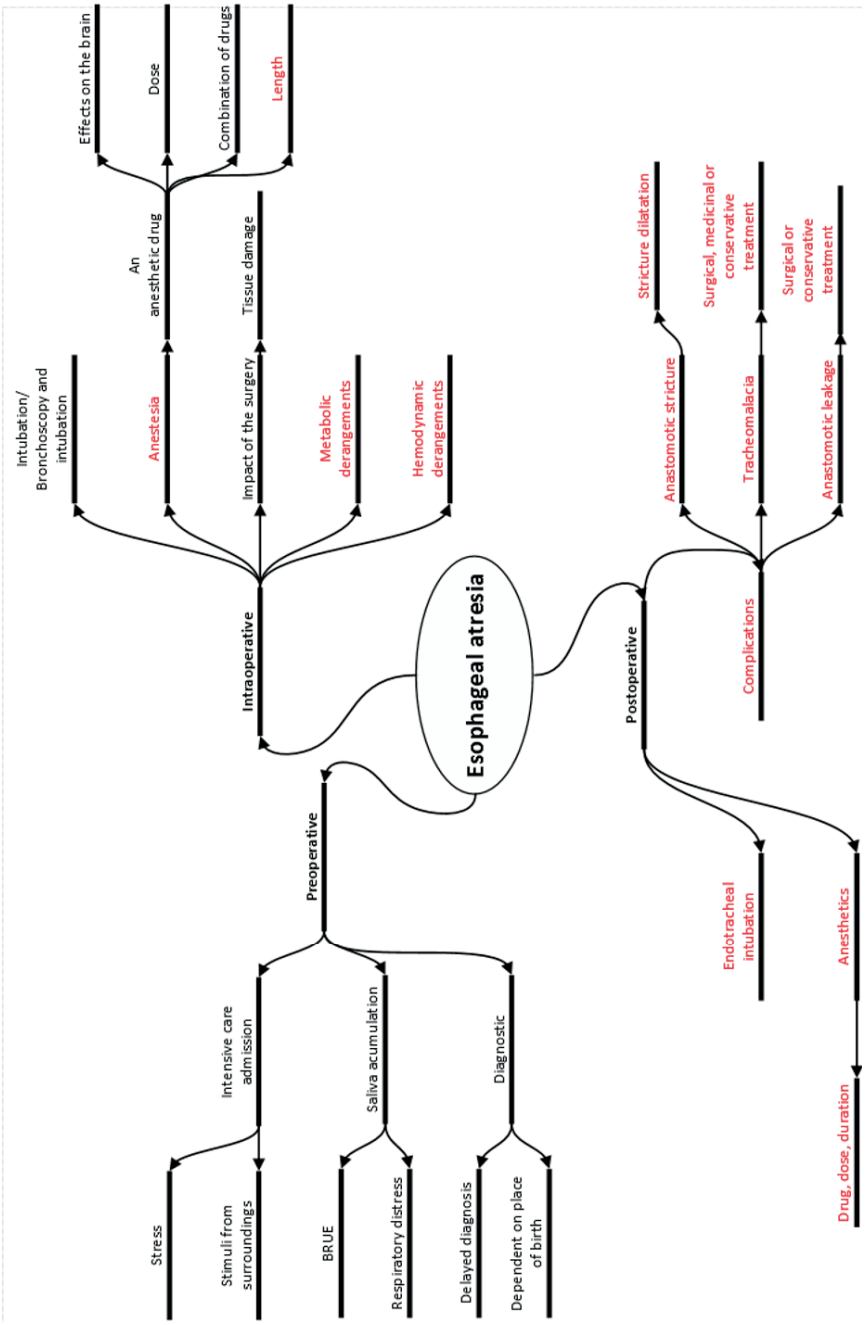

Figure 1. Risk factors for impaired neurodevelopment in patients born with esophageal atresia

Variables in red are discussed in this thesis

FUTURE RESEARCH DIRECTIONS

- Future research should aim to gain insight into the mechanisms of neurotoxicity in surgical neonates.
- Structured, international, multidisciplinary long-term follow-up programs should be created to gain insight into problems children born with esophageal atresia may experience. Different perioperative protocols used in the participating countries can help find the origin of long-term neurodevelopmental problems. To be able to compare outcome data, it is key that the participating countries should use the same follow-up.
- Future pharmacological studies should focus on the long-term effects of neonatal drug exposure.
- Improvement of anesthesia techniques, including monitoring of the brain and metabolic status.

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10

Summary

The overall aim of this thesis was to study the perioperative course of patients with esophageal atresia and its effects on the long-term neurodevelopmental outcome with the ultimate goal to improve the care of these children.

The study in Chapter 2 showed risk of various metabolic derangements during primary esophageal atresia repair, including severe acidosis, hypercapnia and hyperoxia. Acidosis comes with great risk for the brain, leading to concerns regarding neurodevelopmental outcomes (Chapters 6 and 7).

There is concern about the putative neurotoxicity of commonly used anesthetic drugs. Therefore, a search for non-neurotoxic anesthetic drugs is ongoing. A suggested nontoxic sedative drug is dexmedetomidine, which is a selective alpha-2 adrenergic receptor agonist. The systematic review in Chapter 3 presented that the long-term effects of the use of dexmedetomidine are intensively being investigated in neonatal animals. In these animal studies, dexmedetomidine exerted neuroprotective effects when added to the commonly used allegedly neurotoxic anesthetics. This systematic review also showed that long-term effects of dexmedetomidine on the neonatal human brain are not known. Therefore, it is unknown whether dexmedetomidine is a suitable nontoxic alternative. Nevertheless, in the survey study we performed, the majority of respondents from Europe, New Zealand, Australia and the USA claimed to use dexmedetomidine in pediatric anesthesiology for premedication, procedural sedation, IC sedation, anesthesia and/or for postoperative analgesia (Chapter 4).

To improve the long-term outcome, it is important to find the underlying cause of the deteriorations. Chapter 5 showed that the primary esophageal atresia repair is not the sole intervention children born with esophageal atresia have to undergo. It appeared that those with esophageal atresia type C underwent a median number of 4 procedures – mainly in the first 2 years after the primary repair. Esophageal atresia-related procedures account for about 70% of all procedures performed in this patient population. Other procedures were mainly related to the comorbidities.

Next, we aimed to assess the association between motor function at 5 years of age and perioperative variables of the primary esophageal atresia repair and a few postoperative variables, such as number of surgeries in the first 3 years of life (Chapter 6). This assessment showed impaired motor development in children operated on for esophageal atresia type C as compared to the reference population at 5 years of age. The number of postoperative days endotracheal intubation was negatively associated with motor function, whereas high blood pressure was positively associated with motor function. To determine whether neurodevelopmental impairment is a general problem for patients with esophageal atresia, we performed a systematic review to search for results on the long-term neurodevelopment of this group (Chapter 7). From the results of this system-

atic review we concluded that they might suffer impaired motor function and impaired cognitive performance on the long term.

A method to determine whether intraoperative events are associated with the long-term neurodevelopmental impairment, is monitoring of the brain during surgery and anesthesia (Chapter 8). Multiple types of techniques are available to monitor the brain, but not all monitors are fit and validated for monitoring of neonates. We assessed the possibilities and clinical value of neuromonitoring of the neonate during the perioperative period. We found that the monitoring devices that are currently available for neonatal monitoring lack specificity and are not related to clinical outcome or prognosis.

In chapter 9 we discussed our findings of all studies and compared them to the literature from other researchers. Our findings on the care path of children born with esophageal atresia emphasize the need for well-structured postnatal care, with structured long-term follow-up for all. By recognizing the effects of multiple procedures, we might be able to give each patient the best suitable care. Whether long-term neurodevelopmental impairment can also be ascribed repeated anesthesia exposures continuous to be a grey area. Neuromonitoring might help answer questions regarding the neurotoxicity of anesthetics. By combining various methods of neuromonitoring, we might be able to find out how the brain reacts to anesthesia exposure and metabolic derangements during the perioperative period. In this research area, there is still a lot to discover. If we are able to find out how the brain reacts to anesthesia and metabolic derangements, we can have an extra parameter to monitor during surgery. By monitoring the brain during surgery, we might be able to reduce the long-term neurodevelopmental problems often found in patients who underwent long and/or repeated anesthesia exposures.

11

Samenvatting

Het doel van het onderzoek van dit proefschrift was om de gebeurtenissen tijdens de operatie van slokdarm atresie te bestuderen en om te kijken welke gevolgen deze gebeurtenissen hebben op de ontwikkeling van de hersenen van kinderen die geboren worden met een slokdarm atresie.

De slokdarm atresie wordt geopereerd wanneer de kinderen twee dagen oud zijn. Dan worden beide uiteinden van de slokdarm aan elkaar vastgemaakt, zodat eten en drinken via de mond de slokdarm in kan, en vervolgens de maag kan bereiken. In hoofdstuk 2 werd gekeken naar veranderingen in het bloed tijdens deze operatie. Er werd gevonden dat tijdens deze operatie meerdere waarden in het bloed buiten de normaalwaarden vielen. De zuurtegraad en zuurstofwaarden werden te laag, en de hoeveelheid koolstofdioxide werd te hoog. Een te lage zuurtegraad heeft risico's voor de hersenen, waardoor deze bevindingen zorgelijk zijn met oog op hersenontwikkeling op latere leeftijd (Hoofdstuk 6 en 7).

Er is onzekerheid over de mogelijke schadelijke effecten van narcosemiddelen op de ontwikkeling van de hersenen. Daarom wordt er hard gezocht naar narcosemiddelen die geen risico met zich meebrengen wat betreft schadelijke effecten op de hersenen. Dexmedetomidine is een middel wat mogelijk niet schadelijk is voor de hersenen. In het onderzoek in Hoofdstuk 3 werd gevonden dat de lange termijneffecten van dit middel op de hersenen van proefdieren bijna niet is onderzocht. Er werd in de literatuur voornamelijk gekeken naar de korte termijneffecten van dexmedetomidine op de hersenen van deze proefdieren. Hierbij werd gevonden dat dexmedetomidine een beschermend effect had wanneer het tegelijkertijd met andere narcosemiddelen werd gegeven. In dit onderzoek zochten we ook naar bevindingen over de effecten van dexmedetomidine op de hersenen van kinderen, maar hierover was nog helemaal niets bekend in de wereldwijde literatuur. Om te onderzoeken of artsen van over de hele wereld dexmedetomidine al wel gebruiken bij kinderen, hoewel het onbekend is welke gevolgen dit heeft voor de hersenen, hebben we een onderzoek opgezet (Hoofdstuk 4). We hebben artsen van over de hele wereld gevraagd of zij dexmedetomidine gebruiken bij kinderen. Daarnaast vroegen wij waarvoor zij het middel dan gebruikten: als premedicatie voor de narcose, sedatie tijdens procedures, sedatie op de intensive care, als narcosemiddel, of als pijnstiller na de operatie. Uit dit onderzoek bleek dat artsen van over de hele wereld al frequent dexmedetomidine gebruiken wanneer zij kinderen behandelen en dat zij hier over het algemeen positieve ervaringen mee hebben.

In een ander onderzoek, Hoofdstuk 6, hebben we gekeken naar de motorische vaardigheden van kinderen geboren met slokdarm atresie. Dit werd getest wanneer de kinderen 5 jaar oud waren. Met de resultaten hiervan werd gekeken naar welke factoren tijdens de eerste operatie bijdragen aan slechtere motorische vaardigheden op de leeftijd van

5 jaar. Dit werd gedaan door middel van een rekenmodel, waarin meerdere factoren werden beoordeeld op hun bijdrage aan een verslechterde lange termijn uitkomst. Hierbij werd onder andere gekeken of een toenemend aantal operaties in de eerste 3 jaar van het leven had geleid tot een slechtere ontwikkeling van motorische vaardigheden. Met dit rekenmodel werd gevonden dat kinderen met slokdarm atresie minder goede motorische vaardigheden hadden vergeleken met 5-jarige gezonde kinderen. Ook werd gevonden dat patiënten slechtere motorische vaardigheden hadden wanneer ze langer beademd waren op de intensive care. Als de bloeddruk tijdens de operatie hoog was geweest, hadden ze juist wat betere motorische vaardigheden.

Om de lange termijn ontwikkeling van kinderen geboren met slokdarm atresie te verbeteren, moeten we eerst weten wat de oorzaak is van de minder goede algehele ontwikkeling van deze kinderen. Het onderzoek in Hoofdstuk 5 heeft laten zien dat kinderen met slokdarm atresie een heleboel operaties moeten ondergaan. Ze moeten gemiddeld 4 operaties ondergaan, met name in de eerste twee jaar na de geboorte. Van alle operaties is meer dan 70% gerelateerd aan de slokdarm atresie. De andere operaties die bij deze kinderen werden uitgevoerd waren voornamelijk nodig door andere aangeboren afwijkingen.

Om te onderzoeken of patiënten met slokdarm atresie een minder goede ontwikkeling hebben dan andere kinderen, hebben we gekeken naar alle onderzoeken die hierover gedaan zijn (Hoofdstuk 7). Hierbij werd gevonden dat patiënten met slokdarm atresie over het algemeen een minder goede ontwikkeling van motorische en cognitieve vaardigheden hebben.

Een methode om te onderzoeken of gebeurtenissen tijdens een operatie leiden tot minder goede ontwikkeling van de hersenen, is door de hersenen te monitoren tijdens de narcose en de operatie (Hoofdstuk 8). Er zijn veel manieren en apparaten om naar de hersenactiviteit te kijken, maar niet al deze methodes zijn geschikt om te gebruiken bij pasgeborenen. We hebben gekeken naar de mogelijkheden om de hersenen van de pasgeborenen in de gaten te houden. Daarbij hebben we gevonden dat alle beschikbare technieken bij pasgeborenen een slechte specificiteit hebben, en dat de bevindingen niet kloppen met de uitkomsten in de praktijk of de prognose van de patiënt.

In Hoofdstuk 9 zijn alle bevindingen van de studies besproken en bediscussieerd. De bevindingen van de onderzoeken in dit proefschrift benadrukken de essentie voor goed gestructureerde zorgpaden voor pasgeborenen die moeten worden geopereerd, mede met oog op onderzoeken wanneer de kinderen opgroeien en er problemen kunnen ontstaan in de algehele ontwikkeling. Deze problemen wil je zo vroeg mogelijk opsporen, zodat je zo vroeg mogelijk de juiste hulp kan inschakelen. Door te onderzoeken welke

factoren er van invloed zijn op de ontwikkeling, kunnen we per patiënt bekijken of zij groter risico lopen op een verstoring van de ontwikkeling.

Of verstoring van de ontwikkeling van kinderen ook komt door de narcose medicijnen blijft nog steeds een grijs gebied. Monitoring van de hersenen van pasgeborenen tijdens de operatie zou bij kunnen dragen aan het vinden van antwoorden over de schadelijke effecten van narcose medicatie. Door verschillende technieken van monitoring te combineren zou het mogelijk kunnen zijn om in kaart te brengen hoe de hersenen reageren op de narcose medicatie tijdens de operatie. Met deze informatie zou je kunnen werken naar oplossingen om de gevolgen op de ontwikkeling van jonge patiënten die operaties moeten ondergaan, te minimaliseren.

12

List of publications
PhD portfolio
Curriculum Vitae
Acknowledgements

LIST OF PUBLICATIONS

A systematic review and narrative synthesis on the histological and neurobehavioral long-term effects of dexmedetomidine.
van Hoorn CE, Hoeks SE, Essink H, Tibboel D, de Graaff JC.
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Dis Esophagus. 2021 Aug 10:doab054. doi: 10.1093/dote/doab054.

PORTFOLIO

Name PhD student	Camille van Hoorn
Erasmus MC Department:	Anesthesiology and Pediatric Surgery
PhD period:	September 2018 – May 2021
Promotor(s):	Prof. dr. Stolker and prof. dr. Wijnen
Supervisor(s):	Dr. Jurgen de Graaff

Training program	Year	Workload
General academic skills		
BROK	2019	1.5 EC
How to present your poster	2019	0.3 EC
Scientific Integrity	2018	0.3 EC
Erasmus MC-Biomedical English Writing	2019	2.0 EC
Research skills		
Basic course on “R”	2019	1.8 EC
Presentations		
DCEA meeting	2020	0.5 EC
Poster presentation ESPA	2018	0.3 EC
Poster presentation ESPA	2019	0.3 EC
Pharmacology meeting	2019	0.5 EC
Sophia Research Day	2019	0.5 EC
Wetenschapsdag anesthesie	2019	0.3 EC
Wetenschapsdag anesthesie	2020	0.3 EC
Conferences		
ESPA	2018	1.0 EC
ESPA	2019	1.0 EC
ICT and Health conference	2020	0.3 EC
Wetenschapsdag anesthesie	2018	0.3 EC
Wetenschapsdag anesthesie	2019	0.3 EC
Wetenschapsdag anesthesie	2020	0.3 EC
Seminars and workshops		
PhD Day Erasmus MC, several workshops	2019	0.3 EC
Research meetings pediatric surgery (monthly)	2018-2021	2.0 EC
Research meetings pediatric intensive care (weekly)	2018-2021	3.0 EC
Research meetings CHIL (monthly)	2018-2020	1.0 EC
Research meetings anesthesiology (biweekly)	2019-2021	2.0 EC
Research meetings pediatric pharmacology (weekly)	2018-2020	1.5 EC
Grand round (weekly)	2018-2021	3.0 EC
COEUR PhD day	2019	0.3 EC
COEUR PhD day	2020	0.3 EC

COEUR PhD day	2021	0.3 EC
RDO H2020	2019	0.3 EC
RDO	2018	0.3 EC
Presentation workshop TREX	2018	0.3 EC
TRix workshop	2018	0.3 EC
TULIPS PhD day	2019	0.3 EC
Cardiovascular day	2019	0.3 EC
ZonMW workshop	2018	0.3 EC
Pharmacology seminar	2018	0.3 EC
Sophia Research day	2019	0.3 EC
Sophia Research days, several workshops	2021	0.3 EC
Teaching tasks		
Tutor master thesis	2019-2020	3.0 EC

ABOUT THE AUTHOR

Camille van Hoorn was born on October 27, 1995 in Bergen op Zoom. She grew up in Bergen op Zoom, Tholen, Zwolle and Deventer. She completed her athenaeum degree in 2014 at Etty Hillesum Lyceum in Deventer.

That same year, she started her study Medicine at the Erasmus University Rotterdam. During medical school, she worked as a medical student and team leader at the department of obstetrics and maternity ward from 2015 to 2019.

In the second year of her studies, she joined a research group at the department of Anesthesiology. As a part of the minor "Anesthesiology and Intensive care" in the third year of medical training, she visited the department of Anesthesiology in the Sophia Children's Hospital. There, she was introduced to dr. de Graaff (co-promotor), who introduced her to research in pediatric anesthesiology. She started doing research in the field of pediatric anesthesiology and continued this research for her master's thesis on patients born with esophageal atresia. Subsequently, she was offered a PhD position at the department of Anesthesiology in August 2018 (promotor: prof. dr. Stolker). During the research for her PhD, her interest in (pediatric) surgery was fueled. With help of prof. dr Wijnen (promotor), the ongoing research could be combined with surgical subjects, which resulted in a combined PhD trajectory at both the department of Anesthesiology and the department of Pediatric Surgery. In June 2020, she started her clinical rotations.

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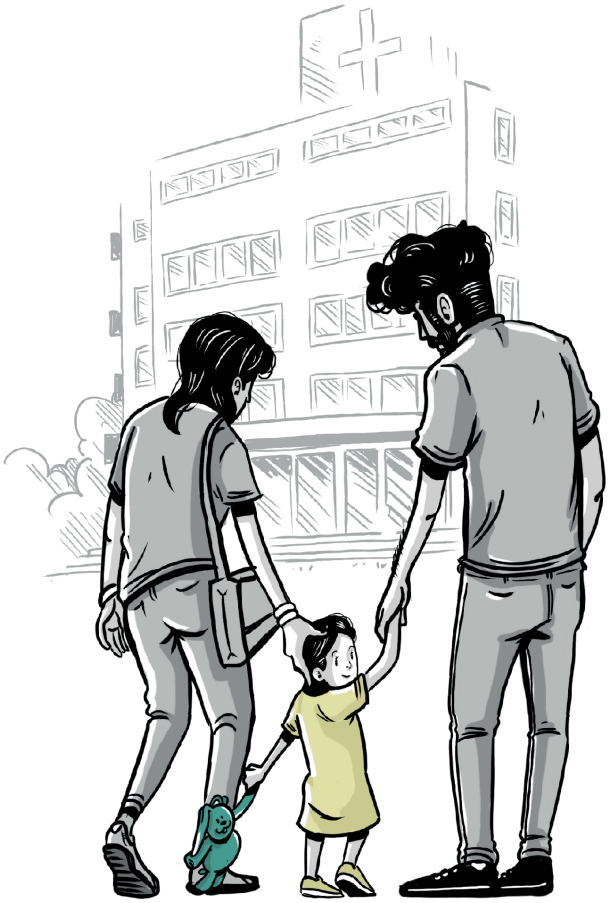

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