Pediatric Anesthesia

Pediatric Anesthesia ISSN 1155-5645

REVIEW ARTICLE

# Perioperative care of infants with pyloric stenosis

Mineto Kamata[1], Richard S. Cartabuke[1,2] & Joseph D. Tobias[1,2,3]

1 Department of Anesthesiology & Pain Medicine, Nationwide Children's Hospital, Columbus, OH, USA
2 Department of Anesthesiology & Pain Medicine, The Ohio State University College of Medicine, Columbus, OH, USA
3 Department of Pediatrics, The Ohio State University College of Medicine, Columbus, OH, USA

**Keywords**
pyloric stenosis; neonatal anesthesia; airway management

**Correspondence**
Dr. Joseph D. Tobias, Department of Anesthesiology & Pain Medicine, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205, USA
Email: Joseph.Tobias@Nationwidechildrens.org

Section Editor: Mark Thomas

Accepted 7 September 2015

doi:10.1111/pan.12792

## Summary

Pyloric stenosis (PS) is one of the most common surgical conditions affecting neonates and young infants. The definitive treatment for PS is surgical pyloromyotomy, either open or laparoscopic. However, surgical intervention should never be considered urgent or emergent. More importantly, emergent medical intervention may be required to correct intravascular volume depletion and electrolyte disturbances. Given advancements in surgical and perioperative care, morbidity and mortality from PS should be limited. However, either may occur related to poor preoperative resuscitation, anesthetic management difficulties, or postoperative complications. The following manuscript reviews the current evidence-based medicine regarding the perioperative care of infants with PS with focus on the preoperative assessment and correction of metabolic abnormalities, intraoperative care including airway management (particularly debate related to rapid sequence intubation), maintenance anesthetic techniques, and techniques for postoperative pain management. Additionally, reports of applications of regional anesthesia for either postoperative pain control or as an alternative to general anesthesia are discussed. Management recommendations are provided whenever possible.

## Introduction

Pyloric stenosis (PS) is one of the most common surgical conditions affecting infants with an incidence of 0.9–5.1 per 1000 live births (1–4). Although the underlying etiology remains unclear, it has been well established that PS arises from a polygenic mode of inheritance with modification by several environmental factors (5). PS occurs 4–5 times more commonly in male infants and there is a general decline in incidence with increasing birth order, rather than the previously cited increased incidence in the first-born child (6). The incidence is reportedly less common in African-American or Asian ethnic groups than Caucasians in the United States (7). Presentation typically occurs at an average of 5 weeks of age (8). The primary symptom of PS is progressively worsening projectile vomiting. At times, the infant has a ravenous appetite even immediately after vomiting, but progressive deterioration in the clinical status with dehydration eventually results in poor feeding. The primary pathological cause is gastric outlet obstruction. The obstruction is at the level of the pylorus and the vomitus does not contain the usual alkaline secretions of the small intestine. Persistent vomiting results in a loss of gastric juices rich in hydrogen and chloride ions and, to a lesser extent, sodium and potassium ions, causing hypochloremia, hypokalemia, and metabolic alkalosis.

The classic diagnostic finding is the palpation of an olive-sized mass in the upper abdomen, but an 'olive' can be palpated during examination in only 48% of patients on admission (9). The diagnosis is usually confirmed by radiographic study, with ultrasound replacing fluoroscopic upper gastrointestinal barium contrast examination. Ultrasound has also become a substitute for physical examination and may be responsible for recent reports of earlier diagnosis. Accuracy of ultrasonography approaches 100% in experienced hands with 99.5% sensitivity and 100% specificity.

Hirschsprung is credited with authoring the first manuscript regarding PS. In 1888, he reported the death of two infants who had hypertrophied pyloric muscles on postmortem examination (10). Initial medical

treatments were aimed mainly at releasing the pyloric spasm, including the use of gastric lavage, the administration of various anti-spasmodic medications, and dietary measures. Since the end of the 19th century, surgical interventions have been used to bypass or relieve the obstruction. The open pyloromyotomy, which is an extramucosal longitudinal pyloromyotomy, was first performed by Ramstedt in 1911. Ramstedt pyloromyotomy became the standard treatment of this condition and has been performed for decades as on open procedure via a right upper quadrant transverse incision or circumumbilical incision. More recently, laparoscopic pyloromyotomy (LAP), first described in 1990, has been gaining popularity (11). However, controversy remains regarding the advantages and disadvantages of the two surgical approaches, specifically regarding the relative incidence of duodenal perforation and incomplete pyloromyotomy.

Pyloromyotomy for PS is not an emergent procedure, as these patients do not require immediate surgical intervention. Death from PS should generally not occur, but may result from poor preoperative resuscitation, from anesthetic difficulties, or from sepsis due to unrecognized duodenal perforation. The operative mortality rate has declined significantly from as high as 10% during the first half of the 20th century to close to zero in specialized pediatric centers (12,13). Atwell *et al.* (13) reported no mortality in a review of 566 cases from specialized pediatric centers compared to a mortality risk of 0.7% from 459 cases in nonspecialist centers. The following manuscript reviews the perioperative preparation and care of patients requiring surgical intervention for PS. The literature review included a Medline search last updated in June 2015 using PubMed. The following search terms were used: PS, pyloromyotomy, and anesthesia. The search was limited to human studies in English. The hierarchy of evidence from the Centre for Evidence-Based Medicine was applied using levels of evidence for treatment and prognosis. In addition, the authors searched the reference lists of published studies for further potential articles. A published systematic review was also examined for references. Preoperative preparation is discussed, options for anesthetic induction and maintenance reviewed, and options for postoperative care including pain management are presented. Although the majority of centers still rely on general anesthesia, reports regarding the use of regional anesthetic techniques are also reviewed.

## Preoperative preparation

The classic triad of hypochloremia, hypokalemia, and metabolic alkalosis that are classically described as the typical metabolic derangements on presentation of PS is becoming less frequent, perhaps related to early diagnosis by ultrasound. A retrospective analysis of 205 patients diagnosed with PS by ultrasound between 2000 and 2009 revealed hypochloremia in 25%, hypokalemia in 8%, and alkalosis in 18% (14). The frequency of profound hypochloremia, defined as a serum chloride <85 mM, decreased from more than 25% in the 1985–1989 epoch to <10% in the 2004–2010 epoch (9).

### Electrolyte disturbances

The major preoperative consideration remains recognizing and treating dehydration and electrolyte abnormalities before proceeding with anesthetic care. The majority of infants respond to therapy within 12–48 h, after which surgical correction can proceed in a nonemergent manner. Miozzari reviewed 139 consecutive infants between 1 and 20 weeks of age who underwent pyloromyotomy to determine the preoperative fluid resuscitation requirements (15). The authors described a functional relationship between chloride administration and changes in circulating bicarbonate, whereby a chloride dose of approximately 10 $mmol \cdot kg^{-1}$ reduced plasma bicarbonate an average of 3 mM (15). As lactated Ringer's has 10.9 mmol per 100 ml, the average patient would require 90–100 $ml \cdot kg^{-1}$ of fluid to correct the alkalosis. Normal saline has 15.4 mmol per 100 ml, requiring 60–70 $ml \cdot kg^{-1}$ to achieve the same correction. Typically, anesthesia can be safely performed when the serum chloride is >100 $mEq \cdot l^{-1}$ and the infant is voiding, indicating adequate volume resuscitation.

Although severe metabolic alkalosis has potentially life-threatening risks including cardiac arrhythmias, vascular collapse, and seizures, there is limited evidence-based medicine to provide insight into what level of alkalosis is acceptable prior to proceeding with anesthetic care (16,17). A theoretical concern in the infant with alkalosis is the potential effect on central control of ventilation and respiratory drive. Control of ventilation is primarily dependent on the partial pressure of carbon dioxide ($PaCO_2$) and secondarily the partial pressure of oxygen in the blood ($PaO_2$) (18). $PaCO_2$ impacts minute ventilation through a secondary mechanism by altering the hydrogen ion concentration or pH in the cerebrospinal fluid while the impact of $PaO_2$ results from a peripheral effect on chemoreceptors in the aorta and carotid artery (19,20). While a decrease in $PaO_2$ generally stimulates minute ventilation, there is a paradoxical effect in neonates and infants with depressed central control of ventilation with hypoxemia (21,22). Therefore, particularly in the neonatal and infant population, the primary stimulus for ventilation remains $PaCO_2$

and, hence, the pH of the CSF. As such, metabolic alkalosis may have a significant impact on respiratory function especially during the perioperative period in a neonate or infant. Abreu *et al.* (23) reported the polysomnographic findings of five infants with PS who presented with serum bicarbonate levels between 29.3 and 40.6 mM (base excess of 6.6–21.6 mM). Two of the five infants demonstrated central apnea and four of the five infants had episodes of obstructive sleep apnea. All polysomnograms were normal when assessed at the postoperative visit. Andropoulos *et al.* reported postoperative apnea in four term infants following pyloromyotomy, one of whom had preoperative apnea attributed to preexisting metabolic alkalosis. This patient received preoperative and postoperative caffeine citrate, but polysomnography was not performed (24). Given these concerns, correction of alkalosis (serum bicarbonate <30 $mEq \cdot l^{-1}$) is generally indicated prior to pyloromyotomy.

### Neonatal anesthesia concerns

Other preoperative concerns are generally those issues faced by anesthetic providers when anesthetizing an infant. Associated comorbid conditions, other than electrolyte disturbances and dehydration already discussed, are uncommon in this population, as are associated congenital anomalies. The need for additional investigation is limited unless other concerns are raised during the preoperative anesthetic evaluation. The majority of infants with PS are born at term (≥ 37 weeks gestation), but those infants <44 weeks postgestational age should receive appropriate monitoring for postoperative apnea (25). For preterm infants, the window requiring monitoring may be even more prolonged and the practitioner should adhere to individual institutional guidelines (26,27). One of the risk factors associated with an increased incidence of postoperative apnea is a hemoglobin <10 $gm \cdot dl^{-1}$ (25–27). There is no evidence-based

**Table 1** Summary of perioperative care for pyloric stenosis[a]

Preoperative care
1. The gastric fluid volumes were independent of a history of barium study, preoperative nasogastric suction, and fasting interval (28) (2b)
2. Preoperative decompression of the stomach by a nasogastric tube does not guarantee evacuation of gastric fluid (28) (2b)
3. Correction of electrolyte disturbances should target a serum chloride >100 $mEq \cdot l^{-1}$ and serum $HCO3^-$ < 30 $mEq \cdot l^{-1}$ (5)

Intraoperative care
1. Aspiration of gastric contents by insertion of a large (e.g. 14 French), multiorifice orogastric catheter prior to the induction of anesthesia is warranted for avoiding aspiration of gastric fluid (5).
2. Atropine may be administered prior to endotracheal intubation in neonates to prevent reflex bradycardia during laryngoscopy (5).
3. Awake endotracheal intubation is not superior to rapid sequence intubation (RSI) or modified RSI (41) (2b).
4. Classic RSI including cricoid pressure is controversial and there is little to no evidence-based medicine supporting the role of that in preventing gastric aspiration (47,48) (3b).
5. Inhalation induction may be safe in children undergoing pyloromytomy (51) (4).
6. Succinylcholine continues to be employed because of its rapid onset and short duration of action (63,64) (2a).
7. A small dose of rocuronium (0.3–0.45 $mg \cdot kg^{-1}$) can achieve neuromuscular blockade, a shorter duration, but the onset of neuromuscular blockade may be delayed (67,68) (2b).
8. Desflurane has shorter recovery times (first movement, tracheal extubation, etc.) compared with sevoflurane (82) or isoflurane (81) (2b).
9. Desflurane or sevoflurane is better in terms of the risk of postoperative apnea than isoflurane (81,82) (2b).
10. Nitrous oxide has the potential for the expansion of bowel gas. Its use should be limited especially during laparoscopic procedures (5).
11. Postoperative analgesia can generally be achieved with a combination of infiltration of the surgical site with a local anesthetic agent and the use of a nonopioid agents such as acetaminophen or a nonsteroidal anti-inflammatory agent (4).
12. During laparoscopic procedures, the intra-abdominal pressure should be limited to ≤10 mmHg (135) (2b).
13. There is no strong evidence which shows that regional anesthesia is superior to general anesthesia for pyloromyotomy.

Postoperative care
1. The majority of patients can be managed with nonopioid analgesic agents and infiltration of the surgical site with a local anesthetic agent (2a).
2. Regional anesthesia can be employed to provide postoperative analgesia (49,112,113) (2b).
3. Acetaminophen may be a safer analgesic than ketorolac for postoperative pain control (120) (4).
4. Preterm infants <44–60 weeks postgestational age should receive appropriate monitoring for postoperative apnea (25–27) (2a,2b).
5. The risk of postoperative apnea in preterm infants may be increased by anemia (hemoglobin <10 $gm \cdot dl^{-1}$) (25–27). (2a,2b)

[a]The evidence is graded using the following system with the type of evidence listed: (1a) Systematic review with homogeneity of randomized controlled trials; (1b) individual randomized control trial with a narrow confidence interval; (1c) All or none related outcome; (2a) Systematic review with homogeneity of cohort studies; (2b) Individual cohort study including low quality randomized control trials; (2c) Outcomes research; (3a) Systematic case review with homogeneity of case–control studies; (3b) Individual case–control study; (4) Case series, poor quality cohort and case–control studies; and (5) Expert opinion without explicit critical appraisal.

medicine to prove that a preoperative hemoglobin evaluation is required, although institutional requirements vary. Hemoglobin evaluation should be undertaken if apnea develops or persists in the postoperative period.

## Intraoperative care

### The full stomach and aspiration risk

Once hypovolemia and electrolyte disturbances have been corrected, elective pyloromyotomy is scheduled. Pyloric hypertrophy causes gastric outlet obstruction and gastric fluid retention which can increase the risk of aspiration of gastric contents during the induction of anesthesia. Preoperative decompression of the stomach is generally provided by placement of a nasogastric tube, but this does not guarantee evacuation of gastric fluid. Cook-Sather and colleagues evaluated the gastric fluid volume in 72 infants with PS (28). For those who had undergone preoperative nasogastric suction, the nasogastric tube was aspirated and removed. After anesthetic induction, a 14 French multiorifice orogastric catheter was blindly passed to aspirate gastric fluid for measurement. Gastric fluid volume removed by blind aspiration averaged $4.8 \pm 4.3$ ml·kg$^{-1}$ with 83% of patients having more than 1.25 ml·kg$^{-1}$. The large gastric fluid volumes were independent of a history of barium study, preoperative nasogastric suction, and fasting interval. Fifteen of the 75 subjects underwent gastroscopy to measure residual gastric fluid following orogastric suctioning. Although 14 of the 15 patients evaluated by endoscope had ≤1 ml of residual gastric fluid, one patient had 7 ml residual volume (1.8 ml·kg$^{-1}$). Recovery of total gastric fluid volume by blind aspiration averaged $96 \pm 7\%$. Given this data, gastric evacuation is warranted prior to the induction of anesthesia. The infant should be placed in the lateral decubitus position and an orogastric tube placed prior to induction. Some clinicians recommend the administration of a dose of an anticholinergic agent, such as atropine, prior to this maneuver because of the increased potential for parasympathetic responses during stimulation of the oral or nasopharynx (29–31). No difference has been noted when comparing the bradycardic response between use of an oral or nasal gastric tube (32).

### Intraoperative monitoring and anticholinergic use

Intraoperative monitoring includes use of standard American Society of Anesthesiologists' monitors. Endotracheal intubation/laryngoscopy can cause physiological responses such as systemic and pulmonary hypertension, bradycardia, intracranial hypertension, and hypoxemia. The bradycardia is largely of vagal origin and therefore, although there is significant variation in practices among centers throughout the world, atropine may be administered prior to endotracheal intubation in neonates if it was not administered prior to gastric emptying (30,31). However, this practice cannot be called the standard of care and is not evidence-based.

## Anesthetic induction technique

The choice of anesthetic induction technique, including the benefits of rapid sequence intubation (RSI) and cricoid pressure, is controversial (33–37). Given the potential for residual volumes despite thorough gastric suctioning and the risk of aspiration of gastric contents, we would suggest that, whenever feasible, anesthetic induction should include a modified RSI (38,39). Although once a common practice, particularly when barium contrast study was employed in the diagnosis of PS, awake endotracheal intubation in neonates and infants has decreased significantly over the years given the potential harm that may result including soft tissue injury, bradycardia, breath-holding, laryngospasm, and even aspiration (40). Cook-Sather et. al. demonstrated that awake endotracheal intubation had no benefit compared to standard or modified RSI for PS patients (41). In their prospective, nonrandomized, observational study of 76 infants with PS, the investigators compared three methods of endotracheal intubation including awake intubation with an oxygen-insufflating laryngoscope, RSI, or modified RSI including ventilation through cricoid pressure (41). The percentage of successful endotracheal intubation on the first attempt was 64% for the awake group vs 87% in the two groups who received a neuromuscular blocking agent (NMBA) ($P = 0.028$). Median time to endotracheal intubation was shorter in the two groups that received a NMBA when compared to the awake technique (34 s vs 63 s, $P = 0.004$). There was no difference in the incidence of bradycardia, oxygen desaturation, or complications including bronchial or esophageal intubation, emesis, and oropharyngeal trauma.

In the neonate, several factors speed the onset of oxygen desaturation during apnea including small airway closure secondary to a high closing capacity to functional residual capacity relationship and higher oxygen consumption. As such, neonates and infants may not tolerate even brief periods of apnea with clinically significant oxygen desaturation despite effective preoxygenation prior to the onset of neuromuscular blockade (42,43). These processes generally make performance of classical RSI (no bag-valve-mask ventilation) more difficult, thereby leading many clinicians to use a modified

approach with gentle bag-valve-mask ventilation prior to the onset of full neuromuscular blockade. As with many airway management techniques in our practice, there are practitioner-dependent modifications of RSI techniques (44). Especially in the neonate and infant, correct application of cricoid pressure (site and pressure) may be difficult, while inappropriate use of cricoid pressure may lead to increased difficulties with both bag-valve-mask ventilation and endotracheal intubation (37,45,46).

Given these concerns, some authors have suggested alternative RSI techniques while others have suggested that RSI has no place in the practice of pediatric anesthesia (34,47,48). A controlled RSI technique defined as bag-valve-mask ventilation with peak inflating pressure <10–12 $cmH_2O$, avoidance of cricoid pressure, and the use of a nondepolarizing NMBA has been offered as an alternative technique for emergency endotracheal intubation in pediatric patients (47). Neuheus *et al.* conducted a retrospective review of 1001 pediatric patients undergoing controlled RSI that included 64 infants of whom 30 were neonates. In these patients, oxygen desaturation before endotracheal intubation occurred in four patients or 6.3% of the study cohort (47). However, none of the four patients developed bradycardia or hypotension. The authors concluded that, when compared with the classical RSI, there were fewer episodes of hypoxemia, no bradycardia, and improved conditions for endotracheal intubation with controlled RSI. Despite its continued widespread use in the practice of anesthesia, there is little to no evidence-based medicine supporting the role of classic RSI in preventing gastric aspiration (see below) (48).

### Use of inhalation induction

While the majority of patients present with preexisting intravenous access, the anesthesia provider may occasionally be presented with a patient without such access or in whom awake vascular access is challenging. Although the awake placement of an intraosseous needle or ultrasound-guided peripheral or central venous access may be considered, several authors have reported the successful inhalation induction of general anesthesia with intravenous cannulation after anesthetic induction (49,50). Scrimgeour *et al.* retrospectively reviewed the inhalation induction of anesthesia in patients presenting for pyloromyotomy during an 8-year period from 2005 to 2012. Of the 269 patients, 252 patients underwent inhalation induction, while 17 patients received intravenous induction (51). All of the infants came to the operating room with a nasogastric tube and intravenous access in place. Following aspiration of the nasogastric tube to empty the stomach, anesthesia was induced with sevoflurane in oxygen ± nitrous oxide. The authors reported no aspiration events. Although the investigators concluded that the inhalation induction is safe in children undergoing pyloromyotomy, they cautioned that the aspiration of gastric contents during induction is extremely rare in pediatric anesthesia and that further study is needed to demonstrate that inhalation induction is superior to modified RS in patients with existing intravenous access.

The other concern with inhalation induction, especially in the absence of intravenous access, is the potential for hemodynamic instability. Although inhalation induction in the setting of hypovolemia can result in hemodynamic instability, this is less common with sevoflurane, which has replaced halothane in the majority of operating rooms throughout the world (52). Oral or intramuscular atropine should be considered to reduce the parasympathetic response to gastric emptying with NG placement, support hemodynamic status, and decrease airway complications during inhalation induction in this population (53,54). Another useful safeguard is the ready availability of an intraosseous needle (55–57). Its use has been described for both elective and emergent use when attempts at peripheral access fail.

### Medications for intravenous anesthetic induction

When intravenous induction is chosen, careful selection of both the sedative agent and the NMBA may improve the chances of successful intubation with limited morbidity. Vomiting and the resultant gastric aspiration are often related to an inadequate depth of anesthesia and insufficient neuromuscular blockade during induction and endotracheal intubation (58). As such, the use of a rapidly acting NMBA and effective sedative/analgesic agents is required prior to the initiation of laryngoscopy and endotracheal intubation. For classical RSI, the traditional agent for neuromuscular blockade has been succinylcholine. Although the potential adverse effects include acute rhabdomyolysis, hyperkalemia, arrhythmias, and cardiac arrest with undiagnosed skeletal muscle myopathy or other comorbid conditions, the relative incidence of such problems is minimal in neonates and young infants (59–62). Per discussion with experts from the North American MH Registry of MHAUS, the youngest patient reported in the literature who developed rhabdomyolysis and hyperkalemia following the administration of succinylcholine was a 4-month-old infant. Succinylcholine continues to be employed because of its rapid onset and short duration of action. Ghazal *et al.* (63) retrospectively reviewed the use of

either succinylcholine or rocuronium during LAP in 246 infants. The infants received propofol for anesthetic induction, sevoflurane for maintenance, no intraoperative opioids, and either rocuronium or succinylcholine to facilitate endotracheal intubation. The primary outcome measure was time to transport after the end of surgery, which was used as a measure of recovery from anesthesia and neuromuscular blockade. Time to transport in minutes (median, interquartile range) was 13 (7–21) in patients receiving only succinylcholine compared to 18 (11–24) in those receiving only rocuronium ($P = 0.03$). In addition, the conditions for endotracheal intubation conditions may be better with succinylcholine when compared to 0.6–0.7 mg·kg$^{-1}$ of rocuronium (64). Although larger doses of rocuronium (up to 1.2 mg·kg$^{-1}$) have been recommended to improve the conditions for endotracheal intubation, a significantly prolonged effect can be expected especially in neonates and infants given the immaturity of the hepatic microsomal enzyme systems (65,66). If rocuronium is used for neuromuscular blockade, a shorter duration can be achieved with the use of a lower dose (0.3–0.45 mg·kg$^{-1}$), with the understanding that the onset of neuromuscular blockade may be somewhat delayed (67,68). The use of controlled RSI would minimize this concern. Alternatively, the availability of sugammadex may mitigate the concerns and clinical impact of the prolonged duration of action of rocuronium. Although there are limited data, simulations indicates that sugammadex has faster reversal times for rocuronium in this population compared with adults (69). Plaud *et al*. (70) evaluated the time to train-of-four (TOF) ≥0.9 after sugammadex (2 mg·kg$^{-1}$) administration. A TOF ≥ 0.9 was achieved in 0.6, 1.2, 1.1, and 1.2 min in infants (28 days to 23 months old), children (aged 2 years), adolescents (aged 12–17 years), and adults (aged 18–65 years), respectively. Although RSI without the use of a NMBA using a combination of propofol and remifentanil has been described in older children and adults, there is potential for hypotension and there is no literature to demonstrate the safety of this technique in neonates and infants (71,72).

During intravenous induction of anesthesia, the other decision in addition to choice of a NMBA revolves around the choice of the sedative/hypnotic agent. Given the lack of availability of thiopental in the United States, propofol has become the favored agent for intravenous induction. The limited data in the infant population suggest that propofol may be a preferred agent for induction with a more rapid awakening and fewer postoperative respiratory adverse effects (73). In a cohort of 59 infants, 30 were 1–6 months of age and 29 were 7–12 months of age, anesthesia was induced with either propofol (3 mg·kg$^{-1}$) or thiopental (5 mg·kg$^{-1}$) and then maintained with halothane. Neuromuscular blockade was achieved with succinylcholine. There was more rapid recovery (5.5 ± 2.5 vs 10.2 ± 1.4 min in the infants 1–6 months of age) and fewer postoperative complications with propofol. Four patients in the thiopental group experienced problems, including three with postextubation airway obstruction and oxygen desaturation and one with prolonged awakening, while no patients in the propofol group exhibited adverse postoperative events. However, there was no difference in recovery and discharge times. When used as the sole agent, the induction dose of propofol in infants is greater than older children and adolescents (74–76). The propofol dose ($ED_{50}$) needed for satisfactory induction of anesthesia as judged by loss of the lid reflex in 22 infants, ranging in age from 1 to 6 months of age, was 3.0 ± 0.2 vs 2.4 ± 0.1 mg·kg$^{-1}$ in children ranging in age from 10 to 16 years (74). Pain on injection occurred in 50% of the infants and 18% of the children. The major concern with such doses in this population is the potential for hemodynamic depression with reports of hypotension in 30–40% of neonates and infants (77,78). Although there are limited data in this population, ketamine (2 mg·kg$^{-1}$) has been shown to be a safe and effective agent with limited effects on hemodynamic function even in infants with congenital heart disease (79,80). Advantages include its hemodyanic stability with maintenance of heart rate, blood pressure, and systemic cardiac output.

### Maintenance anesthesia

Following successful endotracheal intubation, maintenance anesthesia is generally provided with a volatile anesthetic agent. Given the age range, these infants may be at risk for postoperative apnea, the incidence of which may be magnified by the effects of metabolic alkalosis on the central control of ventilation (23,24). Theoretically, the impact of the metabolic derangement on the central control of ventilation would persist until there is equilibration of the CSF pH with the serum pH. As this process may take hours, it is possible that the serum pH and serum bicarbonate could return to normal and yet there be a persistent alkalosis within the CSF. Wolf *et al*. (81) compared the postoperative recovery effects following general anesthesia with either desflurane or isoflurane in 20 infants undergoing general anesthesia for pyloromyotomy. Following a modified RSI with thiopentone, atracurium 0.5 mg·kg$^{-1}$ was administrated, and mechanical ventilation was initiated to normocapnia with either 1 minimal alveolar concentration (MAC) of desflurane or isoflurane in 100% oxygen without opioids. Recovery

time in the desflurane group was significantly shorter than in the isoflurane group with mean times to swallowing (3.89 vs 8.82 min), movement (5.33 vs 10.73 min), and tracheal extubation (7.5 vs 13.45 min) being shorter in the desflurane group when compared with the isoflurane group. No apnea was noted in the desflurane group vs three episodes in the isoflurane group. The same authors noted no difference when comparing the risk of apnea with desflurane vs sevoflurane although recovery times were slightly shorter with desflurane (82).

### Intraoperative administration of opioids

Given the concerns regarding postoperative apnea, opioids are generally not included in the perioperative care of these infants. With limited surgical trauma and the rapid recovery, postoperative analgesia can generally be achieved with a combination of infiltration of the surgical site with a local anesthetic agent and the use of a nonopioid agent such as acetaminophen or a nonsteroidal anti-inflammatory agent (NSAID) (see below). One opioid that has been specifically studied in this population is remifentanil (83–86). In a prospective, randomized trial comparing maintenance anesthesia with nitrous oxide combined with either remifentanil or halothane, new onset postoperative apnea was observed in 3 of 13 (23%) infants who received halothane group vs none of the 22 who received remifentanil. However, in a subsequent study, no difference in emergence time or time to tracheal extubation was noted when comparing remifentanil to isoflurane (inspired concentration of 0.75%) (87).

### Nitrous oxide

Given the rapid recovery from the newer volatile agents and the potential adverse effect profile of nitrous oxide, it is generally no longer included as part of the maintenance anesthetic (87,88). While many of the newer concerns regarding nitrous oxide may be theoretical at this point especially in the pediatric-aged patient, the potential for the expansion of bowel gas should limit its use during laparoscopic procedures especially. As such, either sevoflurane or desflurane are administered in a mixture of oxygen in air. Even during brief procedures, the administration of 100% oxygen is not recommended (89). The inspired oxygen concentration should be decreased as clinically indicated by pulse oximetry.

### Neuromuscular blocking agent for maintenance anesthesia

If succinylcholine has been used to facilitate endotracheal intubation during anesthetic induction, neuromuscular blocking with a short-acting, nondepolarizing NMBA may be required during open or LAP. Increased sensitivity to all NMBAs has been demonstrated in neonates and infants when compared to children and adults. In clinical practice, rocuronium has been used to provide neuromuscular blockade for brief procedures such as pyloromyotomy. When rocuronium is compared with other age groups, as a result of decreased hepatic clearance and increased sensitivity of the neuromuscular junction, its effect is prolonged in neonates (90,91). Given similar pharmacokinetic properties, vecuronium should also be considered a long-acting NMBA in this population (92). On the other hand, atracurium and cisatracurium show different recovery patterns compared to rocuronium and vecuronium in the infant population, acting more like intermediate-acting agents with an average clinical duration of action of cisatracurium (recovery of evoked response to 25% of control) of approximately 40 min (93–95). As only brief surgical relaxation is usually required, the clinical duration can be further shortened by the administration of a smaller dose (cisatracurium 0.075–0.1 $mg \cdot kg^{-1}$). Neuromuscular blockade should be reversed at the termination of the procedure.

### Regional anesthesia instead of general anesthesia

Although pyloromyotomy is most commonly performed under general anesthesia with endotracheal intubation, there are case series describing the use of regional blockade including spinal anesthesia, thoracic epidural anesthesia, and caudal epidural block as the primary anesthetic technique with avoidance of endotracheal intubation. Kachko *et al.* (96) retrospectively compared spinal anesthesia with general anesthesia in 60 infants undergoing open pyloromyotomy primarily assessing the anesthesia time. General anesthesia ($n = 36$) included RSI following atropine, propofol, and succinylcholine. Maintenance anesthesia included 1 MAC isoflurane with atracurium for neuromuscular blockade. Spinal anesthesia ($n = 24$) was provided by administrating 0.7–0.8 $mg \cdot kg^{-1}$ of 0.5% isobaric bupivacaine without epinephrine. Intravenous midazolam was administered if the infant was crying or restless despite adequate spinal anesthesia. In the spinal group, one dose of midazolam was needed in 25% of patients due to agitation, but none of the patients required conversion to general anesthesia because of inadequate block or its complications. Total operating room time (50.9 vs 69.5 min) and emergence time (3.6 vs 17.2 min) were significantly shorter with spinal anesthesia compared with general anesthesia.

Similar results were reported by Somri *et al.* (97) using spinal anesthesia (0.8 mg·kg$^{-1}$ of 0.5% isobaric bupivacaine) as an alternative to general anesthesia in 23 premature and full-term infants during open pyloromytomy. Intraoperatively, there were no clinically significant changes in respiratory rate, heart rate, blood pressure, and oxygen saturation following spinal anesthesia. Five of the patients (22%) required intraoperative doses of intravenous propofol (0.5–1 mg·kg$^{-1}$) to provide optimal intraoperative surgical conditions. Lumbar puncture was unsuccessful in two of the 23 patients (8%).

Even somewhat more intriguing is a report regarding the use of spinal anesthesia during LAP. Given the impact of abdominal insufflation with carbon dioxide and the increase in intra-abdominal pressure on respiratory mechanics, endotracheal intubation with general anesthesia and controlled ventilation are generally required during such procedures (98). Islam *et al.* (99) retrospectively reviewed their experience with spinal anesthesia for LAP in 12 infants and compared it to 12 infants receiving general anesthesia. Although, no difference was noted in induction times, the interval time from the termination of surgery to operating room exit was significantly shorter for the spinal group than general anesthesia group (14 vs 28 min, $P < 0.001$). Although there were no complications in spinal anesthesia group, 3 of the 12 cases (25%) had to be converted to general anesthesia due to inability to access the intrathecal space in two and inadequate block in one.

Two different reports outline the use of single shot epidural anesthesia instead of general anesthesia during open pyloromyotomy (100,101). The first of these used thoracic epidural anesthesia in 20 infants (100). After sedation with nalbuphine and propofol, ultrasound-guided, single-shot epidural anesthesia was performed at $T_{10\text{-}11}$ with 0.75 ml·kg$^{-1}$ of 0.475% ropivacaine. Although the surgical procedure could be performed under single-shot thoracic epidural anesthesia and sedation, oxygen desaturation to 92% occurred in one patient which required assisted positive pressure ventilation via face mask. The largest report of regional anesthesia to date is a retrospective review detailing the use of caudal epidural block in 232 infants presenting for pyloromyotomy (101). The authors reported a success rate of 96% with a shorter hospital stay and faster return to oral feedings than patients who received general anesthesia. Complications secondary to the caudal administration of bupivacaine occurred in three patients including respiratory depression, bradycardia, and ventricular extrasystoles (1.3%). Of note, the author's dose of bupivacaine exceeded those that are routinely recommended to avoid local anesthetic toxicity (bupivacaine 4 mg·kg$^{-1}$).

Both spinal and single-shot epidural anesthesia (thoracic or caudal) have been anecdotally reported as an alternative to general anesthesia for pyloromyotomy. Of particular note is that one of the reports using spinal anesthesia was performed in patients undergoing LAP. Although these regional anesthetic techniques have been anecdotally proven to be safe and effective, they have not been thoroughly evaluated with strict evidence-based medicine protocols. Although the series were large, they come from centers with significant experience in regional anesthesia. With the two reports of epidural techniques, the doses of bupivacaine administered (3.6 and 4 mg·kg$^{-1}$) approach or exceed the upper recommended dosing limit. If these techniques are considered, they should only be practiced by those with significant experience with regional anesthesia in neonates and infants with careful attention to dosing of the local anesthetic agent.

Animal models have revealed that exposure to a variety of general anesthetic agents cause central neuroapoptosis resulting in long-term developmental problems (102–106). In humans, some studies have suggested that exposure to general anesthetic agents, particularly during the neonatal period, may result in cognitive delay later in life (107–109). Walker *et al.* (110) reported on the developmental outcome in 52 infants treated for PS. At 1 year of age, the infants underwent developmental assessment and were compared to 211 control infants. PS infants performed worse than controls on cognitive, receptive language, fine motor, and gross motor skill scales. The authors advocated future studies to explore alternatives to general anesthesia including spinal, epidural, or regional techniques to ameliorate the potential effects of general anesthesia on neurodevelopmental outcome. Although these regional anesthetic techniques have been used successfully, it should be noted that the use of sedative and/or hypnotic agents was required in the majority of patients. Therefore, exposure to potentially neurotoxic agents has not been eliminated. Future investigation should focus on regional techniques and the use of agents that are not associated with neuroapoptosis, such as remifentanil and dexmedetomidine.

## Postoperative analgesia

Effective postoperative analgesia remains an integral component of anesthetic management. The majority of patients can be managed with nonopioid analgesic agents and infiltration of the surgical site with a local anesthetic agent (111). Alternatively, regional anesthesia

can be employed to provide postoperative analgesia. While higher concentrations of bupivacaine are required for surgical anesthesia, a lower concentration (0.125%) can be used to provide effective postoperative analgesia as an adjunct to general anesthesia. Given the upper abdominal incision, a larger volume of local anesthetic may be required to achieve effective dermatomal spread. In our experience, volumes of 1.5 $ml \cdot kg^{-1}$ of 0.125% bupivacaine administered via the caudal epidural route can be used for postoperative analgesia following general anesthesia. Breschan *et al.* (49) reported the use of ultrasound-guided rectus sheath block for open pyloromyotomy using 0.3 $ml \cdot kg^{-1}$ of 0.3% ropivacaine on both sides during general anesthesia. Two of the 26 infants (7.6%) required a rescue dose of fentanyl intraoperatively and a rescue dose of an NSAID postoperatively while another two infants received an NSAID postoperatively.

Kumar *et al.* (112) retrospectively reviewed patients who underwent supraumbilical pyloromyotomy comparing postoperative analgesia between patients receiving ultrasound-guided, preincisional rectus sheath block ($n = 12$) and those receiving wound infiltration with a local anesthetic agent ($n = 18$) at the end of the procedure. There were no differences between the groups in time to first feeding, hospital discharge time, and time to administration of first analgesic agent after surgery. Mata-Gómez *et al.* (113) anecdotally reported the use of ultrasound-guided paravertebral block for open pyloromyotomy using 0.25 $ml \cdot kg^{-1}$ of 0.25% bupivacaine in three neonates following pyloromyotomy. None of the infants required the administration of opioids or NMBAs. The authors noted hemodynamic stability and analgesia that allowed for early tracheal extubation after completion of the surgery.

Although the use of opioid analgesic agents increases the potential for postoperative respiratory depression, in common clinical practice their administration continues intraoperatively. In a survey of the members of the Association of Pediatric Anesthetists of Great Britain and Ireland, 30% of respondents reported that they administered opioids intraoperatively, primarily fentanyl in an average dose of 2.2 $\mu g \cdot kg^{-1}$ (range 0.5–8 $\mu g \cdot kg^{-1}$). Fifty percent prescribed opioids postoperatively, usually morphine at an average dose of 60 $\mu g \cdot kg^{-1}$ (range: 10–150 $\mu g \cdot kg^{-1}$) (114). Habre *et al.* (115) examined postoperative analgesia in 72 patients undergoing pyloromyotomy who received bupivacaine wound infiltration. Twenty-five percent of the infants received fentanyl, meperidine, or morphine following induction. Three patients required naloxone reversal postoperatively. Leclair *et al.* (116), comparing laparoscopic vs open pyloromyotomy, utilized a standardized anesthetic protocol that included 20 $\mu g \cdot kg^{-1}$ of alfentanil prior to incision.

As an alternative to the use of perioperative opioids in this population, NSAIDs and acetaminophen are frequently employed as the primary agent for postoperative analgesia. There are no prospective trials evaluating the use of NSAIDs in providing analgesia following pyloromyotomy (117–119). Currently, ketorolac is the most commonly used intravenous NSAIDs for postoperative analgesia in neonates and infants in the United States (115). Concern has been expressed regarding the use of ketorolac in young infants due to the potential effects on renal function and bleeding (120). In a retrospective review of 57 infants, ranging in age from 0 to 3 months, 10 of 57 (17.2%) had a bleeding event after the administration of 0.5 $mg \cdot kg^{-1}$ of ketorolac and that risk was significantly increased in infants younger than 21 days of life and <37 weeks corrected gestational age. Given these data, the use of acetaminophen may be a safer option. To achieve an analgesic plasma concentration (10–20 $\mu g \cdot ml^{-1}$), the initial per rectum loading dose of acetaminophen should be 40 $mg \cdot kg^{-1}$ (121,122). Although there was significant interpatient variability, the authors recommended the loading dose be followed by 20 $mg \cdot kg^{-1}$ every 6 h to reach analgesic plasma concentrations. Additional pharmacokinetic data have been reported by Anderson et. al. outlining dose regimens based on gestational age, chronologic age, and acetaminophen preparation (123). Alternatively, an intravenous preparation of acetaminophen has recently been introduced for clinical use in the United States while intravenous paracetamol (propacetamol) has been available for some time in many other countries (124,125). However, carefully conducted prospective trials demonstrating the benefits of intravenous acetaminophen in infants following pyloromyotomy are lacking. Our retrospective, unpublished data have failed to show a benefit when comparing intravenous vs rectal acetaminophen in a study cohort that included 66 infants, 33 of whom received acetaminophen per rectum vs 33 who received it intravenously (unpublished data from Arlyne Thung *et al.*, Nationwide Children's Hospital, Columbus, Ohio – presented in abstract form at the Society for Pediatric Anesthesia Meeting March 2015). In the intravenous group, $7.6 \pm 1.8$ $mg \cdot kg^{-1}$ of acetaminophen was administrated intraoperatively and in the rectal group, $30.2 \pm 5.5$ $mg \cdot kg^{-1}$ of acetaminophen was administrated after anesthetic induction. There was no significant difference regarding pain (Face, Legs, Activity, Cry, and Consolability, FLACC) scores, length of PACU stay, and hospital stay. Except for two patients in the IV group, all others received wound infiltration of local anesthetics by surgeons. The average FLACC

score in PACU of the patients with or without local anesthesia were 0.35 vs 2.75, respectively. These data suggest that there is no advantage when comparing intravenous and rectal acetaminophen and that local anesthetic infiltration plays an important role in this population.

### Change in surgical technique—minimally invasive approach

As with other surgical procedures, there has been a change in surgical practice when performing pyloromyotomy, using minimally invasive laparoscopic techniques (11,126) rather than an open procedure. Although controversy remains as to which procedure is most effective, the laparoscopic approach may have some clinical benefit in terms of time to full feeds and postoperative hospital stay (127–130). The first meta-analyses (127) comparing laparoscopic and open pyloromyotomy by Hall *et al*. indicated the complication rate was higher in LAP group; however, recent studies have demonstrated no significant differences in regard to postoperative complications including incomplete pyloromyotomy, perforation, and the need for re-operation (128–130). However, the results are not the same across all studies (131). In a prospective, randomized trial comparing open and LAP in a cohort of 102 infants with PS, LeClair *et al*. (116) reported no difference in the incidence of postoperative vomiting between the two groups. The overall incidence of complications was similar, but the duration of surgery and anesthesia were significantly longer in the laparoscopic group and there were three cases of incomplete pyloromyotomy after laparoscopy, requiring a repeat procedure. The authors concluded that LAP does not decrease the incidence of postoperative vomiting, and has a similar complication rate compared with the open umbilical approach, but may expose patients to a risk of inadequate pyloromyotomy. Furthermore, in their randomized control trial, Siddiqui *et al*. (132) found that the cosmetic results were significantly better in the laparoscopic group.

Lemoine *et al*. (133) prospectively compared postoperative pain in LAP and open transumbilical pyloromyotomy (UMBP). Each group had 19 patients with comparable demographic and no comorbid condition. After surgery, the patient's pain was assessed using the FLACC scale. Postoperative analgesia included acetaminophen and if the infant's pain was not controlled, opioids were administered. During the postoperative period, more patients in the UMBP group required acetaminophen than in the laparoscopic (LAP) group (78% vs 53%, $P = 0.03$). One patient in the UMBP group required given morphine vs none in the LAP group (5% vs 0%, $P$ = NS). The authors concluded that UMBP patients may have more postoperative pain than those in the LAP group.

With the use of peritoneal insufflation during laparoscopy, specific alterations may be required in the anesthetic technique. To facilitate port placement, some degree of neuromuscular blockade is required during the initial portion of the procedure. However, the surgical relaxation required is generally not different from that required for open pyloromyotomy. Recent studies have shown that pneumoperitoneum techniques can be safely applied to small infants and neonates (134). Potential effects of pneumoperitoneum on the respiratory system include limitation of diaphragmatic motion, decreased pulmonary compliance and functional residual capacity, increased airway resistance, resulting in decreased tidal volume and minute ventilation. Given these concerns, it is generally recommended that the intra-abdominal pressure be limited to ≤10 mmHg (135). In addition, the absorption of $CO_2$ through the peritoneum may cause hypercapnia. The use of general anesthesia with endotracheal intubation is generally recommended to allow ventilator support. Local infiltration and use of nonopioid analgesics provide postoperative pain relief.

## Conclusions

After the initial reports of success by Ramstedt, pyloromyotomy quickly became the standard treatment for PS. Over the years, the mortality rate has steadily declined to the point where mortality from PS should generally not occur. Although PS still remains a common surgical condition affecting young infants, it can be diagnosed earlier related to the use ultrasound. Earlier diagnosis has led to a reduction in the magnitude of hypochloremia, hypokalemia, and alkalosis. Preoperative preparation generally includes intravascular resuscitation with the knowledge that surgical correction is generally performed on an elective basis. Anesthesia can be safely performed when the serum chloride is >100 $mEq \cdot l^{-1}$ and the infant is voiding, indicating adequate volume resuscitation.

Given gastric outlet obstruction, there may be a risk of aspiration during anesthetic induction. Gastric fluid should be aspirated immediately before anesthetic induction. The optimal technique for anesthetic induction has not been proven with evidence-based medicine. Awake endotracheal intubation is no longer recommended. Induction techniques vary from true RSI using a sedative and succinylcholine to a controlled RSI, defined as bag-valve-mask ventilation with peak inflating pressure <10–12 $cmH_2O$, with or without cricoid

pressure, and the use of a nondepolarizing NMBA. Inhalation induction may be also considered in rare circumstances where intravenous access cannot be achieved in the awake state. Maintenance of anesthesia is generally provided with a volatile anesthetic agent, and sevoflurane or desflurane with the provision of postoperative monitoring in patient at risk for apnea related to their gestational and chronological age. The intraoperative use of opioids increases the risk of postoperative respiratory depression. Given this, the use of remifentanil rather than fentanyl has been favored by some. As the postoperative pain can generally be managed with nonopioid agents and local infiltration of the surgical site, the use of opioids for rescue analgesia should be rare. As alternatives to general anesthesia, regional block including spinal anesthesia, thoracic epidural anesthesia, and caudal block have been reported as the primary anesthetic technique with avoidance of general anesthesia and endotracheal intubation. The reader is referred to Table 1 for a summary of perioperative care for pyloric stenosis with references and level of evidence. Recently, minimally invasive surgical approaches (laparoscopy) have been introduced, although advantages over open techniques have not been rigorously and uniformly proven in prospective trials. Future investigation to determine the optimal induction and airway technique would be useful, but likely require a multi-institutional effort. Similarly, the role of regional anesthetic techniques, either as the sole anesthetic or in conjunction with general anesthesia, deserves further study.

## Funding

The study received no external funding.

## Conflict of interest

The authors report no conflict of interest.

## References

1 St. Peter SD, Ostlie DJ. Pyloric stenosis: from retrospective analysis to prospective clinical trial-the impact on surgical outcomes. *Curr Poin Pediatr* 2008; **20**: 311–314.
2 Nielsen JP, Haahr J. Infantile hypertrophic pyloric stenosis. Decreasing incidence. *Dan Med Bull* 2000; **47**: 223–225.
3 O'Donoghue JM, Connolly KD, Gallagher MM *et al*. The increasing incidence of infantile hypertrophic pyloric stenosis. *Ir J Med Sci* 1993; **162**: 175–176.
4 Applegate MS, Druschel CM. The epidemiology of infantile hypertrophic pyloric stenosis in New York State, 1983 to 1999. *Arch Pediatr Adolesc Med* 1995; **149**: 1123–1129.
5 Chung E. Infantile hypertrophic pyloric stenosis: genes and environment. *Arch Dis Child* 2008; **93**: 1003–1004.
6 Wang J, Walker DK, Hwang LY *et al*. Prevalence of infantile hypertrophic pyloric stenosis in Texas, 1999-2002. *Birth Defects Res Clin Mol Teratol* 2008; **82**: 763–767.
7 MacMahon B. The continuing enigma of pyloric stenosis of infancy: a review. *Epidemiology* 2006; **17**: 195–201.
8 Bissonnette B, Sullivian PJ. Pyloric stenosis. *Can J Anaesth* 1991; **38**: 668–676.
9 Taylor ND, Cass DT, Holland AJA. Infantile hypertrophic pyloric stenosis: has anything changed? *J Paediatr Child Health* 2013; **49**: 33–37.
10 Hirschsprung H. Falle von angeborener pylorus stenose, beobachtet bei sauglingen. *Jahrb der Kinderh* 1888; **28**: 61–68.
11 Alain JL, Grousseau D, Terrier G. Extra-mucosa pyloromyotomy by laparoscopy. *Chir Pediatr* 1990; **31**: 223–224.
12 Allan C. Determinants of good outcome in pyloric stenosis. *J Paediatr Child Health* 2006; **42**: 86–88.
13 Atwell JD. Infantile hypertrophic pyloric stenosis: where should it be treated? *Ann R Coll Surg Engl* 1993; **75**: 36–37.
14 Tutay GF, Capraro G, Spirko B *et al*. Electrolyte profile of pediatric patients with hypertrophic pyloric stenosis. *Pediatr Emerg Care* 2013; **29**: 465–468.
15 Miozzari HH, Tonz M, von Vigier RO *et al*. Fluid resuscitation in infantile hypertrophic pyloric stenosis. *Acta Pediatrica* 2001; **90**: 511–514.
16 Knutsen OH. New method for administration of hydrochloric acid in metabolic acidosis. *Lancet* 1983; **321**: 953–956.
17 Helmy MM, Tolner EA, Vanhatalo S *et al*. Brain alkalosis causes birth asphyxia seizures, suggesting therapeutic strategy. *Ann Neurol* 2011; **69**: 493–500.
18 Haddad GG, Mellins RB. The role of airway receptors in the control of respiration in infants: a review. *J Pediatr* 1977; **91**: 281–286.
19 Pappenheimer JR, Fencl V, Heisey SR *et al*. Role of cerebral fluids in control of respiration as studied in unanesthetized goats. *Am J Physiol* 1965; **208**: 436–450.
20 Kronenberg R, Hamilton FN, Gabel R *et al*. Comparison of three methods for quantitating respiratory response to hypoxia in man. *Respir Physiol* 1972; **16**: 109–125.
21 Cross KS, Oppé TE. The effect of inhalation of high and low concentrations of oxygen on the respiration of the premature infant. *J Physiol* 1952; **117**: 38–55.
22 Rigatto H, Brady JP. Periodic breathing and apnea in preterm infants. II. hypoxia as a primary event. *Pediatrics* 1972; **50**: 219–228.
23 Abreu FA, Silva E, Macfadyen UM *et al*. Sleep apnoea during upper respiratory infection and metabolic alkalosis in infancy. *Arch Dis Child* 1986; **61**: 1056–1062.
24 Andropoulos DB, Heard MB, Johnson KL *et al*. Postanesthesia apnea in full-term infants after pyloromyotomy. *Anesthesiology* 1994; **80**: 216–219.
25 Coté CJ, Zaslavsky A, Downes JJ *et al*. Postoperative apnea in former preterm infants after inguinal herniorrhaphy. A combined analysis. *Anesthesiology* 1995; **82**: 809–822.
26 Welborn LG, Greenspun JC. Anesthesia and apnea. Perioperative considerations in the former preterm infant. *Pediatr Clin North Am* 1994; **41**: 181–198.
27 Malviya S, Swartz J, Lerman J. Are all preterm infants younger than 60 weeks postconceptual age at risk for postanesthetic apnea? *Anesthesiology* 1993; **78**: 1076–1081.
28 Cook-Sather SD, Tulloch HV, Liacouras CA *et al*. Gastric fluid volume in infants for pyloromyotomy. *Can J Anaeth* 1997; **44**: 278–283.
29 Kattwinkel J, Fanaroff AA, Klaus MH. Bradycardia in preterm infants: indications

and hazards of atropine therapy. *Pediatrics* 1976; **58**: 494–499.
30 Barrington K. Premedication for endotracheal intubation in the newborn infant. *Paediatr Child Health* 2011; **16**: 159–171.
31 Kelly MA, Finer NN. Nasotracheal intubation in the neonate: physiologic responses and effects of atropine and pancuronium. *J Pediatr* 1984; **105**: 303–309.
32 Bohnhorst B, Cech K, Peter C *et al*. Oral versus nasal route for placing feeding tubes: no effect on hypoxemia and bradycardia in infants with apnea of prematurity. *Neonatology* 2010; **98**: 143–149.
33 Neilipovittz DT, Crosby ET. No evidence for decreased incidence of aspiration after rapid sequence induction. *Can J Anaesthesiol Scand* 2009; **53**: 1167–1172.
34 Johr M. Anaesthesia for child with a full stomach. *Curr Opin Anaesthesiol* 2007; **20**: 201–203.
35 Weiss M, Gerber AC. Rapid sequence induction in children – it's not a matter of time!. *Pediatr Anesth* 2008; **18**: 97–99.
36 Gencorelli FJ, Fields RG, Litman RS. Complications during rapid sequence induction of general anesthesia in children: a benchmark study. *Pediatr Anesth* 2010; **20**: 421–424.
37 Allen LG, Engelhardt T, Lendrum RA. Do not know where to press? Cricoid pressure in the very young. *Eur J Anaesthesiol* 2014; **31**: 333–334.
38 Morton HJ, Wylie WD. Anaesthetic deaths due to regurgitation or vomiting. *Anaesthesia* 1951; **6**: 190–201.
39 Tobias JD. Rapid sequence intubation: what does it really mean? *Saudi J Anesth* 2014; **8**: 153–154.
40 Kong AS, Brennan L, Morgan-Hughes J. An audit of induction of anesthesia in neonates and small infants using pulse oximetry. *Anaesthesiology* 1992; **47**: 896–899.
41 Cook-Sather SD, Tulloch HV, Cnaan A *et al*. A comparison of awake versus paralyzed tracheal intubation for infants with pyloric stenosis. *Anesth Analg* 1998; **86**: 945–951.
42 Patel R, Lenczyk M, Hannallah RS *et al*. Age and the onset of desaturation in apneic children. *Can J Anaesth* 1994; **41**: 771–774.
43 Hardman JG, Wills JS. The development of hypoxaemia during apnoea in children: a computational modeling investigation. *Br J Anaesth* 2006; **97**: 564–570.
44 Eich C, Timmermann A, Russo SG *et al*. A controlled rapid-sequence induction technique for infants may reduce unsafe actions and stress. *Acta Anaesthesiol Scand* 2009; **53**: 1167–1172.
45 Landsmann I. Cricoid pressure: indications and complications. *Pediatr Anesth* 2004; **14**: 43–47.
46 Hartsilver EL, Vanner RG. Airway obstruction with cricoid pressure. *Anaesthesia* 2000; **55**: 208–211.
47 Neuhaus D, Schmitz A, Gerber A. Controlled rapid sequence induction and intubation - an analysis of 1001 children. *Pediatr Anesth* 2013; **23**: 734–740.
48 MacDonold NJ, Fitzpatrick GJ, Moore KP *et al*. Anaesthesia for congenital hypertrophic pyloric stenosis. A review of 350 patients. *Br J Anaesth* 1987; **59**: 672–677.
49 Breschan C, Jost R, Stettner H *et al*. Ultrasound-guided rectus sheath block for pyloromyotomy in infants: a retrospective analysis of a case series. *Pediatr Anesth* 2013; **23**: 1199–1204.
50 Engelhardt T. Rapid sequence induction has no use pediatric anesthesia. *Pediatr Anesth* 2015; **25**: 5–8.
51 Scrimgeour GE, Leather NW, Perry RS *et al*. Gas induction for pyloromyotomy. *Pediatr Anesth* 2015; **25**: 677–680.
52 Green DH, Townsend P, Bagshaw O *et al*. Nodal rhythm and bradycardia during inhalation induction with sevoflurane in infants: a comparison of incremental and high-concentration techniques. *Br J Anaesth* 2000; **85**: 368–370.
53 Shaw CA, Kelleher AA, Gill CP *et al*. Comparison of the incidence of complications at induction and emergence in infants receiving oral atropine versus no premedication. *Br J Anaesth* 2000; **84**: 174–178.
54 Miller BR, Friesen RH. Oral atropine premedication in infants attenuates cardiovascular depression during halothane anesthesia. *Anesth Analg* 1988; **67**: 180–185.
55 Neuhaus D, Weiss M, Engelhardt T *et al*. Semi-elective intraosseous infusion after failed intravenous access in pediatric anesthesia. *Pediatr Anesth* 2010; **20**: 168–171.
56 Hamed RK, Hartmans S, Gausche-Hill M. Anesthesia through an intraosseous line using an 18-gauge intravenous needle for emergency pediatric surgery. *J Clin Anesth* 2013; **25**: 447–451.
57 Tobias JD, Ross AK. Intraosseous infusions: a review for the anesthesiologist with a focus on pediatric use. *Anesth Analg* 2010; **110**: 391–401.
58 Warner MA, Warner ME, Warner DO *et al*. Perioperative pulmonary aspiration in infants and children. *Anesthesiology* 1999; **90**: 66–71.
59 Rawicz M, Brandom B, Wolf A. The place of suxamethonium in pediatric anesthesia. *Pediatr Anesth* 2009; **19**: 561–570.
60 Larach MG, Rosenberg H, Gronert GA *et al*. Hyperkalemic cardiac arrest during anesthesia in infants and children with occult myopathies. *Clin Pediatr* 1997; **36**: 9–16.
61 Schulte-Sasse U, Eberlein HJ, Schmücker I *et al*. Sollte die Verwendung von Succinylcholin in der Kinderanästhesie neu überdacht werden. *Anaesthesiol Reanimat* 1993; **18**: 13–19.
62 Breucking E, Reimnitz P, Schara U *et al*. Anesthetic complications. The incidence of severe anesthetic complications in patients and families with progressive muscular dystrophy of the Duchenne and Becker types. *Anaesthesist* 2000; **49**: 187–195.
63 Ghazal E, Amin A, Wu A *et al*. Impact of rocuronium vs succinylcholine neuromuscular blocking drug choice for laparoscopic pyloromyotomy: is there a difference in time to transport to recovery? *Pediatr Anesth* 2013; **23**: 316–321.
64 Perry JJ, Lee JS, Sillberg VA *et al*. Rocuronium versus succinylcholine for rapid sequence induction intubation. *Cochrane Database Syst Rev* 2008; **16**: CD002788.
65 Kara I, Duman I, Duman A. Delayed recovery from rocuronium block in an infant. *Middle East J Anaesthesiol* 2012; **21**: 731–733.
66 Feltman DM, Weiss MG, Nicoski P *et al*. Rocuronium for nonemergent intubation of term and preterm infants. *J Perinatol* 2011; **31**: 38–43.
67 Driessen JJ, Robertson EN, Booij LHDJ. Acceleromyography in neonates and small infants: baseline calibration and recovery of the responses after neuromuscular blockade with rocuronium. *Eur J Anaesthesiol* 2005; **22**: 11–15.
68 Driessen JJ, Robertson EN, Egmond JV *et al*. The time-course of action and recovery of rocuronium 0.3 mg/kg in infants and children during halothane anaesthesia measured with acceleromyography. *Pediatric Anesthesia* 2000; **10**: 493–497.
69 Kleijn HJ, Zollinger DP, van den Heuvel MW *et al*. Population pharmacokinetic-pharmacodynamic analysis for sugammadex-mediated reversal of rocuronium-induced neuromuscular blockade. *Br J Clin Pharmacol* 2011; **72**: 415–433.
70 Plaud B, Meretoja O, Hofmockel R *et al*. Reversal of rocuronium-induced neuromuscular blockade with sugammadex in pediatric and adult surgical patients. *Anesthesiology* 2009; **110**: 284–294.
71 Dewhirst E, Martin DP, Tobias JD. Propofol and remifentanil for rapid sequence intubation in a pediatric patient at risk for aspiration with elevated intracranial pressure. *Pediatr Emerg Care* 2013; **29**: 1201–1203.
72 Politis GD, Tobias JD. Rapid sequence intubation without a neuromuscular blocking agent in a 14-year-old with myasthenia gravis. *Pediatr Anesth* 2007; **17**: 285–288.
73 Schrum SF, Hannallah RS, Verghese PM *et al*. Comparison of propofol and

thiopental for rapid anesthesia induction in infants. *Anesth Analg* 1994; **78**: 482–485.
74 Westrin P. The induction dose of propofol in infants 1-6 months of age and in children 10-16 years of age. *Anesthesiology* 1991; **74**: 455–458.
75 Aun CS, Short SM, Leung DH *et al*. Induction dose-response of propofol in unpremedicated children. *Br J Anaesth* 1992; **68**: 64–67.
76 Morton NS, Wee M, Christie G *et al*. Propofol for induction of anaesthesia in children. A comparison with thiopentone and halothane inhalational induction. *Anaesthesia* 1988; **43**: 350–355.
77 Simons SH, van der Lee R, Reiss IK *et al*. Clinical evaluation of propofol as sedative for endotracheal intubation in neonates. *Acta Paediatr* 2013; **102**: e487–e492.
78 Welzing L, Kribs A, Eifinger F *et al*. Propofol as an induction agent for endotracheal intubation can cause significant arterial hypotension in preterm neonates. *Pediatr Anesth* 2010; **20**: 605–611.
79 Hickey PR, Hansen DD, Cramolini GM *et al*. Pulmonary and systemic hemodynamic responses to ketamine in infants with normal and elevated pulmonary vascular resistance. *Anesthesiology* 1985; **62**: 287–293.
80 Morray JP, Lynn AM, Stamm SJ *et al*. Hemodynamic effects of ketamine in children with congenital heart disease. *Anesth Analg* 1984; **63**: 895–899.
81 Wolf AR, Lawson RA, Dryden CM *et al*. Recovery after desflurane anaesthesia in the infant: comparison with isoflurane. *Br J Anaesth* 1996; **76**: 362–364.
82 Sale SM, Read JA, Stoddart PA *et al*. Prospective comparison of sevoflurane and desflurane in formerly premature infants undergoing inguinal herniotomy. *Br J Anaesth* 2006; **96**: 774–778.
83 Ross AK, Davis PJ, Dear GL *et al*. Pharmacokinetics of remifentanil in anesthetized pediatric patients undergoing elective surgery or diagnostic procedures. *Anesth Analg* 2001; **93**: 1393–1401.
84 Davis PJ, Galinkin J, McGowan FX *et al*. Randomized multicenter study of remifentanil compared with halothane in neonates and infants undergoing pyloromyotomy. I. Emergence and Recovery Profiles. *Anesth Analg* 2001; **93**: 1380–1386.
85 Galinkin JL, Davis PJ, McGowan FX *et al*. A randomized multicenter study of remifentanil compared with halothane in neonates and infants undergoing pyloromyotomy. II. Perioperative breathing patterns in neonates and infants with pyloric stenosis. *Anesth Analg* 2001; **93**: 1387–1392.
86 Ben Khalifa S, Blidi S, Trifa M *et al*. Time to extubation in infants undergoing pyloromyotomy – isoflurane inhalation vs remifentanil infusion. *Middle East J Anaesthesiol* 2009; **20**: 277–280.
87 Ko H, Kaye AD, Urman RD. Nitrous oxide and perioperative outcomes. *J Anesth* 2014; **28**: 420–428.
88 Schallner N, Goebel U. The perioperative use of nitrous oxide: renaissance of an old gas or funeral of an ancient relict? *Curr Opin Anaesthesiol* 2013; **26**: 354–360.
89 Sola A. Oxygen in neonatal anesthesia: friend or foe? *Curr Opin Anaesthesiol* 2008; **21**: 332–339.
90 Wierda JM, Meretoja OA, Taivainen T *et al*. Pharmacokinetics and pharmacokinetic-dynamic modelling of rocuronium in infants and children. *Br J Anaesth* 1997; **78**: 690–695.
91 Saldien V, Vermeyen KM, Wuyts FL. Target-controlled infusion of rocuronium in infants, children, and adults: a comparison of the pharmacokinetic and pharmacodynamic relationship. *Anesth Analg* 2003; **97**: 44–49.
92 Kalli I, Meretoja OA. Duration of action of vecuronium in infants and children anaesthetized without potent inhalation agents. *Acta Anaesthesiol Scand* 1989; **33**: 29–33.
93 Taivainen T, Meakin GH, Meretoja OA *et al*. The safety and efficacy of cisatracurium 0.15 mg/kg during nitrous oxide-opioid anaesthesia in infants and children. *Anaesthesia* 2000; **55**: 1047–1051.
94 Soltész S, Silomon M, Mencke T *et al*. Neuromuscular blockade with cisatracurium in infants and children. Its course under sevoflurane anesthesia. *Anaesthesist* 2002; **51**: 374–377.
95 de Ruiter J, Crawford MW. Dose-response relationship and infusion requirement of cisatracurium besylate in infants and children during nitrous oxide-narcotic anesthesia. *Anesthesiology* 2001; **94**: 790–792.
96 Kachko L, Simhi E, Freud E *et al*. Impact of spinal anesthesia for open pyloromyotomy on operating room time. *J Pediatr Surg* 2009; **44**: 1942–1946.
97 Somri M, Gaitini LA, Vaida SJ *et al*. The effectiveness and safety of spinal anaesthesia in the pyloromyotomy procedure. *Paediatr Anaesth* 2003; **13**: 32–37.
98 Tobias JD. Anaesthesia for minimally invasive surgery in children. *Best Pract Res Clin Anaesthesiol* 2002; **16**: 115–130.
99 Islam S, Larson SD, Kays DW *et al*. Feasibility of laparoscopic pyloromyotomy under spinal anesthesia. *J Pediatr Surg* 2014; **49**: 1485–1487.
100 Willschke H, Machata AM, Rebhandl W *et al*. Management of hypertrophic pylorus stenosis with ultrasound guided single shot epidural anaesthesia-a retrospective analysis of 20 cases. *Pediatr Anesth* 2011; **21**: 110–115.
101 Moyao-García D, Garza-Leyva M, Velázquez-Armenta EY *et al*. Caudal block with 4 mg x kg-1 (1.6 ml/kg) of bupivacaine 0.25% in children undergoing surgical correction of congenital pyloric stenosis. *Pediatr Anesth* 2002; **12**: 404–410.
102 Fredriksson A, Archer T, Alm H *et al*. Neurofunctional deficits and potentiated apoptosis by neonatal NMDA antagonist administration. *Behav Brain Res* 2004; **153**: 367–376.
103 Fredriksson A, Pontén E, Gordh T *et al*. Neonatal exposure to a combination of N-methyl-D-aspartate and gamma-aminobutyric acid type A receptor anesthetic agents potentiates apoptotic neurodegeneration and persistent behavioral deficits. *Anesthesiology* 2007; **107**: 427–436.
104 Jevtovic-Todorovic V, Hartman RE, Izumi Y *et al*. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. *J Neurosci* 2003; **23**: 876–882.
105 Loepke AW, Istaphanous GK, McAuliffe JJ 3rd *et al*. The effects of neonatal isoflurane exposure in mice on brain cell viability, adult behavior, learning, and memory. *Anesth Analg* 2009; **108**: 90–104.
106 Rizzi S, Carter LB, Ori C *et al*. Clinical anesthesia causes permanent damage to the fetal guinea pig brain. *Brain Pathol* 2008; **18**: 198–210.
107 Ing CH, DiMaggio CJ, Malacova E *et al*. Comparative analysis of outcome measures used in examining neurodevelopmental effects of early childhood anesthesia exposure. *Anesthesiology* 2014; **120**: 1319–1332.
108 Ing C, DiMaggio C, Whitehouse A *et al*. Long-term differences in language and cognitive function after childhood exposure to anesthesia. *Pediatrics* 2012; **130**: e476–e485.
109 Flick RP, Katusic SK, Colligan RC *et al*. Cognitive and behavioral outcomes after early exposure to anesthesia and surgery. *Pediatrics* 2011; **128**: e1053–e1061.
110 Walker K, Halliday R, Holland AJA *et al*. Early developmental outcome of infants with infantile hypertrophic pyloric stenosis. *J Pediatr Surg* 2010; **45**: 2369–2372.
111 Bhalla T, Shepherd E, Tobias JD. Neonatal pain management. *Saudi J Anaesth* 2014; **8**: 89–97.
112 Kumar A, Wilson GA, Engelhardt TE. Ultrasound guided rectus sheath blockade compared to peri-operative local anesthetic infiltration in infants undergoing supraumbilical pyloromyotomy. *Saudi J Anaesth* 2014; **8**: 229–232.
113 Mata-Gómez J, Guerrero-Domínguez R, García-Santigosa M *et al*. Ultrasound-guided

paravertebral block for pyloromyotomy in 3 neonates with congenital hypertrophic pyloric stenosis. *Braz J Anesthesiol* 2015; **65**: 302–305.
114 Peutrell JM, Wilkins DG. Pyloric stenosis in full term babies. A postal survey of the management by pediatric anaesthetists. *Paediatr Anaesth* 1994; **4**: 93–97.
115 Habre W, Schwab C, Gollow I *et al*. An audit of postoperative analgesia after pyloromyotomy. *Paediatr Anaesth* 1999; **9**: 253–256.
116 Leclair MD, Plattner V, Mirallie E *et al*. Laparoscopic pyloromyotomy for hypertrophic pyloric stenosis: a prospective, randomized controlled trial. *J Ped Surg* 2007; **42**: 692–698.
117 Burd RS, Tobias JD. Ketorolac for pain management after abdominal surgical procedures in infants. *South Med J* 2002; **95**: 331–333.
118 Papacci P, De Francisci G, Iacobucci T *et al*. Use of intravenous ketorolac in the neonate and premature babies. *Pediatr Anesth* 2004; **14**: 487–492.
119 Cohen MN, Christians U, Henthorn T *et al*. Pharmacokinetics of single-dose intravenous ketorolac in infants aged 2-11 months. *Anesth Analg* 2011; **112**: 655–660.
120 Aldrink JH, Ma M, Wang W *et al*. Safety of ketorolac in surgical neonates and infants 0-3 months old. *J Pediatr Surg* 2011; **46**: 1081–1085.
121 Birmingham PK, Tobin MJ, Henthorn TK *et al*. Twenty-four-hour pharmacokinetics of rectal acetaminophen in children: an old drug with new recommendations. *Anesthesiology* 1997; **87**: 244–252.
122 Birmingham PK, Tobin MJ, Fisher DM *et al*. Initial and subsequent dosing of rectal acetaminophen in children: a 24-hour pharmacokinetic study of new dose recommendations. *Anesthesiology* 2001; **94**: 385–389.
123 Anderson BJ, van Lingen RA, Hansen TG *et al*. Acetaminophen developmental pharmacokinetics in premature neonates and infants: a pooled population analysis. *Anesthesiology* 2002; **96**: 1336–1345.
124 Palmer GM, Atkins M, Anderson BJ *et al*. IV acetaminophen pharmacokinetics in neonates after multiple doses. *Br J Anaesth* 2008; **101**: 523–530.
125 Anderson BJ, Pons G, Autret-Leca E *et al*. Pediatric intravenous paracetamol (propacetamol) pharmacokinetics: a population analysis. *Pediatr Anesth* 2005; **15**: 282–292.
126 Muensterer OJ, Adibe OO, Harmon CM *et al*. Single-incision laparoscopic pyloromyotomy: initial experience. *Surg Endosc* 2010; **24**: 1589–1593.
127 Hall NJ, Van Der Zee J, Tan HL *et al*. Meta-analysis of laparoscopic versus open pyloromyotomy. *Ann Surg* 2004; **240**: 774–778.
128 Sola JE, Neville HL. Laparoscopic vs open pyloromyotomy: a systematic review and meta-analysis. *J Pediatr Surg* 2009; **44**: 1631–1637.
129 Jia WQ, Tian JH, Yang KH *et al*. Open versus laparoscopic pyloromyotomy for pyloric stenosis: a meta-analysis of randomized controlled trials. *Eur J Pediatr Surg* 2011; **21**: 77–81.
130 Oomen MW, Hoekstra LT, Bakx R *et al*. Open versus laparoscopic pyloromyotomy for hypertrophic pyloric stenosis: a systematic review and meta-analysis focusing on major complications. *Surg Endosc* 2012; **26**: 2104–2110.
131 Hall NJ, Eaton S, Seims A *et al*. Risk of incomplete pyloromyotomy and mucosal perforation in open and laparoscopic pyloromyotomy. *J Pediatr Surg* 2014; **49**: 1083–1086.
132 Siddiqui S, Heidel RE, Angel CA *et al*. Pyloromyotomy: randomized control trial of laparoscopic vs open technique. *J Pediatr Surg* 2012; **47**: 93–98.
133 Lemoine C, Paris C, Morris M *et al*. Open transumbilical pyloromyotomy: is it more painful than the laparoscopic approach? *J Pediatr Surg* 2011; **46**: 870–873.
134 Kuebler JF, Ure BM. Minimally invasive surgery in the neonate. *Semin Fetal Neonatal Med* 2011; **16**: 151–156.
135 Bannister CF, Brosius KK, Wulkan M. The effect of insufflation pressure on pulmonary mechanics in infants during laparoscopic surgical procedures. *Paediatr Anaesth* 2003; **13**: 785–789.