

The former preterm infant and risk of post-operative apnoea: recommendations for management

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The preterm infant presenting for anaesthesia during the first 6 months of life is a major anaesthetic challenge. One of the most serious post-operative complications is apnoea with or without bradycardia. For this review, we conducted a search of the current literature in order to formulate a set of evidence-based clinical guidelines to help clinicians in the management of the former preterm infant to avoid post-operative apnoea. Only a small number of patients have been enrolled into prospective, randomized, controlled studies. Based on the current literature, regional anaesthesia is strongly recommended, preferably neuraxial block, but general anaesthesia is also used and in this setting, opioids and muscle relaxants should be avoided. Infants with a post-conceptual age of less than 46 weeks should be admitted for continuous monitoring for at least 12 h post-operatively. In infants with a post-conceptual age (PCA) between 46 and 60 weeks, a careful assessment of the child is mandatory and 12 h of

respiratory monitoring is recommended if the patient's history reveals episodes of apnoea at home, chronic lung disease (CLD), neurological disease or anaemia. The otherwise healthy infant could be scheduled for theatre as the first patient on the list and subsequently monitored in the post-anaesthetic care unit for 6 h. The risk of apnoea in former preterm infants can be further reduced by the administration of intravenous caffeine (10 mg/kg). All of these patients should be referred to a tertiary centre for anaesthesia and surgery.

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PRETERM infants, defined as infants whose gestational age at birth is less than 37 weeks, are at higher risk of respiratory depression and apnoea after anaesthesia conducted within the first months of life.

In otherwise healthy preterm infants, breathing irregularities and periodic breathing are commonly seen during sleep (1). In contrast, prolonged apnoea defined as apnoeas lasting ≥ 15 s or accompanied by bradycardia is always pathologic. In the study by Steward, the incidence of post-operative prolonged apnoea was 12% for former preterm infants undergoing minor surgery (2). Based on this finding, it has been recommended to extend the period of post-operative respiratory monitoring in former preterm infants. Careful selection of anaesthetic technique and drugs has also been suggested to decrease the incidence of respiratory depression in this patient group but there is no general consensus regarding optimal management of these infants in connection with anaesthesia and surgery.

As a result of improvements in perinatal medicine, an increasing number of former preterm infants are now presenting for anaesthesia. The most common surgical procedures are repair of an inguinal hernia and laser photocoagulation for retinopathy of prematurity. The incidence of these conditions is inversely related to birthweight and gestational age, for example, the incidence of inguinal hernia is 10–20% in preterm infants.

The preterm infants are a heterogeneous group of children ranging from the healthy child born at week 36 to the former extreme low birthweight child with severe chronic lung disease on home oxygen. Some infants will be scheduled for surgery in general hospitals on an inpatient or even outpatient basis. It is therefore important to apply clinically useful guidelines for the peri-operative management of preterm infants. These guidelines should help the paediatric but also the general anaesthesiologist to identify the children at increased risk of post-operative apnoea.

This review article is based on a search of the literature and aimed at covering the following

aspects: risk factors for post-operative apnoea, anaesthetic management, drug prophylaxis and post-operative monitoring.

Methods

A literature search was made of PubMed. Selection criteria were publications written in English from the past 25 years using the following search terms: expremature, anaesthesia, post-operative apnoea with an upper age limit of 23 months.

We specifically extracted information that could elucidate risk factors for post-operative apnoea, anaesthetic management, drug prophylaxis, and duration and type of post-operative monitoring. According to the evidence rating scale outlined in Table 1, the two authors evaluated the studies independently and consensus was obtained if disagreement was found initially.

Results of the literature search and interpretation

In total, 327 references were identified. Of these 327, 69 references (randomized, controlled studies, review articles, case stories and descriptions of anaesthetic techniques) could be used to elucidate the problems associated with anaesthesia for the former preterm infant.

Using the evidence rating scale presented in Table 1, we assessed the power of evidence in 22 references with evidence rating of grade I or II (Table 2). Several studies were retrospective. Only a small number of patients were enrolled into ran-

Table 1

Evidence rating scale.	
Grade	Description
I	Evidence is obtained from at least one properly randomized, controlled trial (RCT).
II-1	Evidence is obtained from well-designed controlled trials without randomization.
II-2	Evidence is obtained from well-designed cohort or case-controlled analytical studies, preferably from more than one centre or research group.
II-3	Evidence is obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940) could also be regarded as this type of evidence.
III	Opinions of respected authorities are based on clinical experience, descriptive studies and case reports or reports of expert committees.

US Preventive Service Task Force Guide to Clinical Preventive Services (USPSTF, 1996, Second Edition).

Table 2

Level of evidence in relation to post-operative apnoea in former preterm infants.

Aspect	References	Evidence classification
Post-conceptual age	7, 8, 10, 12	Grade II-1
Apnoea at home	10, 27	Grade II-1
Anaemia	14	Grade II-1
Neurological disease	7	Grade II-2
Chronic lung disease	7,12,13,16,23	Grade II-1
Choice of general anaesthetic technique	13,16,17	Grade II-3
Regional vs. general anaesthesia	16, 19, 20, 22, 23, 25-30	Grade I
Caffeine prophylaxis	31, 32, 33	Grade I
Type and duration of post-operative respiratory monitoring	7, 13, 34	Grade II-3

domized, controlled studies. We found a remarkable heterogeneity regarding the type of patient, anaesthetic and surgical approach as well as the degree of monitoring resulting in methodological problems in the attempt to establish appropriate evidence. To overcome problems with sample size, some investigators used a Cochrane meta-analysis (3,4) or a 'combined analysis' (5).

Risk factors for post-operative apnoea and timing of surgery

Post-conceptual age

Post-conceptual age (gestational age + postnatal age) (PCA) is probably the single most important patient characteristic that enables identification of a high-risk patient. PCA has been shown to be inversely related to post-operative apnoea (5-10). Although the aetiology is multifactorial, neurological immaturity is an important factor (11).

Recommendations for optimal timing of surgery vary from 44 to 46 (7,10) to 60 post-conceptual weeks (8), but they are based on studies with major differences in the selection of patients, monitoring and detection of post-operative apnoea. It is thus clear that this patient characteristic cannot be used alone (12).

In a 'combined analysis' pooling data from several studies, Cote's analysis has more statistical power than studies from any single institution (5). The conclusion of this analysis being that each institution must decide what risk is acceptable in their population setting. Factors that should be included in a risk analysis other than post-conceptual age are: apnoea at home, history of chronic lung disease, central nervous system (CNS) morbidity and anaemia (5,13).

Based on the literature, the former otherwise healthy preterm child with a PCA above 60 weeks can be sent home using standard discharge criteria. Infants with a PCA less than 44–46 weeks should be admitted for monitoring at least 12 h post-operatively. Between 46 and 60 weeks, the peri-operative course must be individualized depending on PCA and comorbidity. In otherwise healthy ex-preterm infants, 6 h of monitoring will be sufficient.

Co-morbidity

Apnoea at home. Several conditions in newborns are associated with apnoea, and recurrent apnoea can be documented over longer periods of time. Episodes of apnoea at home seem to predispose to post-operative respiratory complications (5,10).

Anaemia. Anaemia is defined as haemoglobin of less than 6 mmol/l (100 g/l). Many factors contribute to the anaemia of prematurity. Important factors are the impaired erythropoietin response to the decreasing haemoglobin levels, a shorter red cell survival and frequent blood sampling.

Although limited by a small number of patients, it seems that anaemia predispose to post-operative apnoea (5,14). There is no evidence that transfusion of red blood cells will lower the incidence of post-operative apnoea. Instead it is recommended delaying elective surgery until haemoglobin levels are above 6 mmol/l and that can be achieved by prescription of iron-supplemented food.

Neurological disease. Several serious CNS disorders are accompanied by apnoeic attacks, for example intraventricular haemorrhage, seizures, arteriovenous malformations (AVM) and congenital central hypoventilation syndrome. These children should be considered at risk of post-operative apnoea even though no systematic studies are available (7).

Chronic lung disease. Any sign of respiratory dysfunction should be included in risk assessment prior to planning of the peri-operative course in the former preterm infants. The concentration and duration of supplemental oxygen are good indicators of the severity of chronic lung disease (CLD). Other indicators are days on mechanical ventilation, continuous positive airway pressure (CPAP) and need for supplemental oxygen.

To summarize, infants with a history of continuing apnoea, anaemia, neurological disease or chronic lung disease might be predisposed to significant

post-operative apnoea and must be considered at risk although the evidence for this relationship is not firmly established (7,12,13).

Anaesthetic management

Choice of general anaesthetic technique

Randomized prospective studies have not been conducted. In a retrospective study, intra-operative opioids and muscle relaxants were more frequently used in ex-preterm infants with failed extubation attempts, possibly indicating more respiratory complications (13).

Infants in this age group are generally very sensitive to the respiratory depressant action of opioids and the half-life of non-depolarizing muscle relaxants and opioids are longer than in older children. Muscle relaxants block nicotine-induced carotid body chemoreceptor responses, which may explain the respiratory depressant action (15). General anaesthesia without these drugs would be preferable to avoid post-operative respiratory complications. Sevoflurane (16) and remifentanyl (17) have a rapid offset but experience in this patient population is limited. Based on reports of serious complications with the use of propofol for intensive care unit (ICU) sedation in children, this drug is not licensed or recommended for use in anaesthesia in this age group (18).

Although evidence from the literature is limited, the anaesthetic technique could have an impact on the risk of post-operative apnoea in former preterm infants. It is therefore recommended to use an anaesthetic technique based on inhaled anaesthetics with avoidance of muscle relaxants and opioid whenever possible.

General vs. regional anaesthesia

Comparison of regional and general anaesthesia for inguinal herniotomy in former preterm infants has been carried out in several studies. Spinal analgesia with bupivacaine provides a profound block but the duration of block is often regarded insufficient, with a significant number of patients requiring supplementation with general anaesthesia. A further problem is a significant failure rate of this technique (16). Caudal epidural analgesia (single shot or infusion) or a combination of spinal and caudal analgesia has been proposed (19,20). Another alternative has been to lengthen the duration of spinal or caudal block by addition of epinephrine or clonidine (21,22). Limited information is available about the dose-response relationship (21) and clonidine has been related to hypotension and post-operative apnoea (23,24). A reduction in the incidence of post-operative

respiratory complications has been reported after the use of regional analgesia (16,25–29). Another study found no such benefits (30). A meta-analysis revealed a lower incidence of post-operative apnoea with spinal anaesthesia if infants given pre-operative sedatives were excluded (4).

Thus regional analgesia seems promising in selected patients. A rational choice would be the use of bupivacaine with the addition of clonidine that may prolong the duration of anaesthesia. Ropivacaine and levobupivacaine are new long-acting local anaesthetics thought to be less cardio- and neurotoxic than bupivacaine indicated by studies in full-term infants. These agents could in future challenge the position of bupivacaine as the long-acting local anaesthetic of choice.

Drug prophylaxis

Caffeine or methylxanthine (bio transformed to caffeine) may be used to prevent apnoea in preterm infants. Caffeine is usually preferred as it has been proposed to have lesser haemodynamic consequences, a greater therapeutic index and a longer half-life. Three studies have shown a significant prophylactic effect of intravenous caffeine (31–33) and a Cochrane review concluded that caffeine was effective even although the number of patients was small (3). A dose of 10 mg/kg intravenous caffeine seems to be effective and safe but further dose–response studies are needed to determine the effective dosing regime.

The duration and type of post-operative monitoring

When significant risk factors are present (CLD, anaemia, recurrent apnoea or neurological disease), 12 h of monitoring are recommended as the initial apnoea always occurs within the first 12 post-operative hours (5–7,11). Extension of monitoring is necessary if pathological apnoea arises during this time period. In otherwise healthy ex-preterm infants, 6 h of monitoring seems sufficient. In retrospective studies including ASA I–II infants, all ‘first’ apnoea events occurred within the first 4 h post-operatively (13,34).

Nursing observation and pulse oximetry failed to detect apnoea in 4 out of 5 and 3 out of 5 patients, respectively, compared with computerized pneumocardiography (35). There is no doubt that the detection of apnoea is related to the level of monitoring. A combination of nursing observation, pulse oximetry and ECG allows detection of bradycardia and/or hypoxemia. There is currently no evidence that any one form of monitoring will lead to reduced morbidity or mortality (36–38).

Training and organization

The continuing experience of the individual anaesthesiologist is of major importance in reducing peri-operative morbidity and mortality in infants (39,40). It is not known if personal experience with regional anaesthetic techniques in newborns and infants, airway management, etc. influences outcome such as post-operative respiratory complications. A detailed review of anaesthesia for preterm infants is beyond the scope of this review but safe airway management is a crucial part of the anaesthetic management. Airway management is preceded by assessment of anatomic and functional abnormalities. The preterm infants have limited respiratory reserve. A laryngeal mask airway may be used for short surgical procedures in the presence of subglottic stenosis or chronic lung disease and hyper reactive airways. Otherwise safe airway control is achieved by insertion of an endotracheal tube and is preferred by many paediatric anaesthesiologists. Hypoxemia and hypercapnia and acidosis carry the risk of transition to a fetal circulation with right-to-left shunting. Recurrent/reactive pulmonary hypertension, right-side cardiac decompensation or reactive bronchiolar symptoms in inexperienced hands may cause serious and ‘unexpected’ problems.

Regional analgesia in newborns and infants can be difficult and meticulous attention to technique and dosing is mandatory. This is another example suggesting that sub-specialists in paediatric anaesthesia in a tertiary centre should manage the care of these children.

Summary

Former preterm infants are a heterogeneous group of children and risk assessment must be individualized and guidelines for peri-operative management must be formulated for each institution.

Based on the literature, it must be considered an established fact that elective surgery whenever

Table 3

Suggested recommendation for managing former preterm infants presenting for surgery.

Post-pone surgery until PCA \geq 60 weeks
 Refer to a tertiary centre
 Assessment of comorbidity or anaemia
 Decide level of post-operative monitoring (see Fig. 1)
 Choose appropriate anaesthesia technique
 Administer caffeine

PCA: post-conceptual age; co-morbidity: CLD, continuing apnoea or neurological disease; anaemia: Hct $<$ 30%.

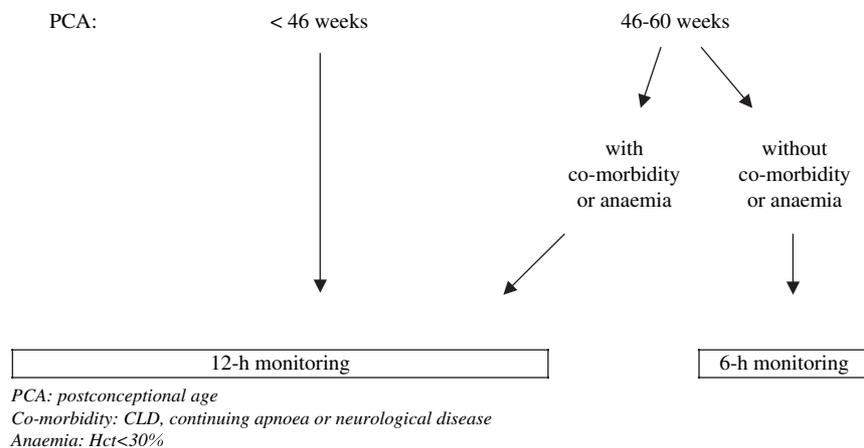


Fig. 1. Post-operative monitoring of the former preterm infant with a post-conceptual age (PCA) < 60 weeks.

possible should be postponed until a PCA of 60 weeks (Table 3). By that time, respiratory control is mature and no special measures should be taken in relation to post-operative apnoea in the otherwise healthy child scheduled for in- or outpatient surgery. Infants with a PCA of less than 46 weeks should be admitted for continuous monitoring for a period of at least 12 h post-operatively (Fig. 1).

In infants with a PCA between 46 and 60 weeks, careful assessment is mandatory: a decision has to be made whether the child should be monitored for 6 or 12 h. Although less well established, infants with continuing apnoea at home, a history of CLD, neurological disease or anaemia should be identified and considered as high risk. These patients require 12-h post-operative monitoring. We suggest that the otherwise healthy infant can be monitored for 6 h post-operatively, with surgery scheduled early in the day and standard monitoring (ECG and pulsoximetry) in the post-anaesthetic care unit.

General anaesthesia without opioids (supplemented with a central or peripheral block) and without muscle relaxants is an option; however, regional anaesthesia (spinal and/or caudal block with clonidine) is recommended. Intravenous caffeine (10 mg/kg) may be given to all former preterm infants with a PCA less than 60 weeks presenting for anaesthesia.

Former preterm infants should be referred to a tertiary centre for anaesthesia and surgery in the first 6 months of life.

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