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[Intervention Review]

Regional (spinal, epidural, caudal) versus general anaesthesia in preterm infants undergoing inguinal herniorrhaphy in early infancy

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ABSTRACT

Background

With improvements in neonatal intensive care, more preterm infants are surviving the neonatal period and presenting for surgery in early infancy. Inguinal hernia is the most common condition requiring early surgery, appearing in 38% of infants whose birth weight is between 751 grams and 1000 grams. Approximately 20% to 30% of otherwise healthy preterm infants having general anaesthesia for inguinal hernia surgery at a postmature age have at least one apnoeic episode within the postoperative period. Research studies have failed to adequately distinguish the effects of apnoeic episodes from other complications of extreme preterm gestation on the risk of brain injury, or to investigate the potential impact of postoperative apnoea upon longer term neurodevelopment. In addition to episodes of apnoea, there are concerns that anaesthetic and sedative agents may have a direct toxic effect on the developing brain of preterm infants even after reaching postmature age. It is proposed that regional anaesthesia may reduce the risk of postoperative apnoea, avoid the risk of anaesthetic-related neurotoxicity and improve neurodevelopmental outcomes in preterm infants requiring surgery for inguinal hernia at a postmature age.

Objectives

To determine if regional anaesthesia reduces postoperative apnoea, bradycardia, the use of assisted ventilation, and neurological impairment, in comparison to general anaesthesia, in preterm infants undergoing inguinal herniorrhaphy at a postmature age.

Search methods

The following databases and resources were searched: the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, 2015, Issue 2), MEDLINE (December 2002 to 25 February 2015), EMBASE (December 2002 to 25 February 2015), controlled-trials.com and clinicaltrials.gov, reference lists of published trials and abstracts published in *Pediatric Research* and *Pediatric Anesthesia*.

Selection criteria

Randomised and quasi-randomised controlled trials of regional (spinal, epidural, caudal) versus general anaesthesia, or combined regional and general anaesthesia, in former preterm infants undergoing inguinal herniorrhaphy in early infancy.

Data collection and analysis

At least two of three review authors (LJ, JF, AL) independently extracted data and performed analyses. Authors were contacted to obtain missing data. The methodological quality of each study was assessed according to the criteria of the Cochrane Neonatal Review Group.

Data were analysed using Review Manager 5. Meta-analyses were performed with calculation of risk ratios (RR) and risk difference (RD), along with their 95% confidence intervals (CI) where appropriate.

Main results

Seven small trials comparing spinal with general anaesthesia in the repair of inguinal hernia were identified. Two trial reports are listed as 'Studies awaiting classification' due to insufficient information on which to base an eligibility assessment. There was no statistically significant difference in the risk of postoperative apnoea/bradycardia (typical RR 0.72, 95% CI 0.48 to 1.06; 4 studies, 138 infants), postoperative oxygen desaturation (typical RR 0.82, 95% CI 0.61 to 1.11; 2 studies, 48 infants), the use of postoperative analgesics (RR 0.42, 95% CI 0.15 to 1.18; 1 study, 44 infants), or postoperative respiratory support (typical RR 0.09, 95% CI 0.01 to 1.64; 3 studies, 98 infants) between infants receiving spinal or general anaesthesia. When infants who had received preoperative sedatives were excluded, the meta-analysis supported a reduction in the risk of postoperative apnoea in the spinal anaesthesia group (typical RR 0.53, 95% CI 0.34 to 0.82; 4 studies, 129 infants). Infants with no history of apnoea in the preoperative period and receiving spinal anaesthesia (including a subset of infants who had received sedatives) had a reduced risk of postoperative apnoea and this reached statistical significance (typical RR 0.34, 95% CI 0.14 to 0.81; 4 studies, 134 infants). Infants receiving spinal rather than general anaesthesia had a statistically significant increased risk of anaesthetic agent failure (typical RR 7.83, 95% CI 1.51 to 40.58; 3 studies, 92 infants). Infants randomised to receive spinal anaesthesia had an increased risk of anaesthetic placement failure of borderline statistical significance (typical RR 7.38, 95% CI 0.98 to 55.52; typical RD 0.15, 95% CI 0.03 to 0.27; 3 studies, 90 infants).

Authors' conclusions

There is moderate-quality evidence to suggest that the administration of spinal in preference to general anaesthesia without pre- or intraoperative sedative administration may reduce the risk of postoperative apnoea by up to 47% in preterm infants undergoing inguinal herniorrhaphy at a postmature age. For every four infants treated with spinal anaesthesia, one infant may be prevented from having an episode of postoperative apnoea (NNTB=4). In those infants without preoperative apnoea, there is low-quality evidence that spinal rather than general anaesthesia may reduce the risk of preoperative apnoea by up to 66%. There was no difference in the effect of spinal compared with general anaesthesia on the overall incidence of postoperative apnoea, bradycardia, oxygen desaturation, need for postoperative analgesics or respiratory support. Limitations on these results included varying use of sedative agents, or different anaesthetic agents, or combinations of these factors, in addition to trial quality aspects such as allocation concealment and inadequate blinding of intervention and outcome assessment. The meta-analyses may have inadequate power to detect a difference between groups for some outcomes, with estimates of effect based on a total population of fewer than 140 infants.

The effect of newer, rapidly acting, quickly metabolised general anaesthetic agents on safety with regard to the risk of postoperative apnoea and neurotoxic exposure has not so far been established in randomised trials. There is potential for harm from postoperative apnoea and direct brain toxicity from general anaesthetic agents superimposed upon pre-existing altered brain development in infants born at very to extreme preterm gestation. This highlights the clear need for the examination of neurodevelopmental outcomes in the context of large randomised controlled trials of general, compared with spinal, anaesthesia, in former preterm infants undergoing surgery for inguinal hernia. There is a particular need to examine the impact of the choice of spinal over general anaesthesia on respiratory and neurological outcomes in high-risk infant subgroups with severe respiratory disease and previous brain injury.

PLAIN LANGUAGE SUMMARY

Regional (spinal, epidural, caudal) versus general anaesthesia in preterm infants undergoing inguinal herniorrhaphy in early infancy

Lay title: Regional versus general anaesthesia in preterm infants undergoing inguinal hernia repair in early infancy

Review question: In preterm infants undergoing inguinal hernia repair, does the use of regional anaesthesia compared to general anaesthesia reduce postoperative complications including apnoea, bradycardia and the use of assisted ventilation?

Background: babies born preterm (before 37 weeks) often have serious health problems and sometimes need surgery. Inguinal hernia (IH) (where the intestine protrudes through the abdominal wall) is the commonest condition where surgery is needed. General anaesthetics for surgery can disrupt breathing and cause other complications in preterm babies. Regional anaesthetics including spinal block (injection) might avoid complications such as pauses in breathing in the first 24 hours after surgery. Whether this improves outcomes for preterm babies having surgery is unclear because no trials have looked at the effects of anaesthetics on brain function in older children.

Study characteristics: seven small trials comparing spinal with general anaesthesia in the repair of IH were identified.

Results: there was no statistically significant difference in the risk of postoperative apnoea/bradycardia, postoperative oxygen desaturations, the use of postoperative analgesics, or postoperative respiratory support between infants receiving spinal or general anaesthesia. When infants who had received preoperative sedatives were excluded, the meta-analysis supported a reduction in the risk of postoperative apnoea in the spinal anaesthesia group. Infants with no history of apnoea in the preoperative period and receiving spinal anaesthesia (including a subset of infants who received sedatives) had a reduced risk of postoperative apnoea. Infants receiving spinal rather than general anaesthesia had a statistically significant increased risk of anaesthetic agent failure. Infants randomised to receive spinal anaesthesia had an increased risk of anaesthetic placement failure of borderline statistical significance.

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Conclusions: there is some evidence to suggest that spinal anaesthesia without the addition of sedative drugs to assist in keeping the baby still and provide additional pain relief during the procedure may be safer than general anaesthesia for a former preterm baby having surgery for inguinal hernia. A recently completed but as yet unpublished large multicentre trial comparing general anaesthesia or awake spinal anaesthesia may help give more precise answers to this question.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Regional (spinal, epidural, caudal) versus general anaesthesia for preterm infants having inguinal herniorrhaphy in early infancy

Regional (spinal, epidural, caudal) versus general anaesthesia for preterm infants having inguinal herniorrhaphy in early infancy

Patient or population: Preterm infants requiring surgery for inguinal hernia in early infancy

Settings: Neonatal/Paediatric intensive care.

Intervention: Spinal anaesthesia

Comparison: General anaesthesia

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk* ¹	Corresponding risk*				
	General anaesthesia	Spinal anaesthesia				
Neurodevelopmental status at 2 years corrected age	See comment ²	See comment ²	Not estimable	0 (0)	See comment ²	
Apnoea/bradycardia occurring 12-24 hours following completion of operation	477 per 1000	343 per 1000 (229 to 506)	RR 0.72 (0.48 to 1.06)	138 (4 studies)	⊕⊕⊕⊖ moderate ³	
Any oxygen desaturation occurring 12-24 hours following completion of the operation	870 per 1000	713 per 1000 (530 to 965)	RR 0.82 (0.61 to 1.11)	48 (2 studies)	⊕⊕⊕⊖ moderate ³	
Use of post-operative respiratory support	91 per 1000	8 per 1000 (1 to 149)	RR 0.09 (0.01 to 1.64)	98 (3 studies)	⊕⊕⊖⊖ low ^{3,4,5}	
Post-operative apnoea with pre-operative sedatives excluded	477 per 1000	253 per 1000 (162 to 391)	RR 0.53 (0.34 to 0.82)	129 (4 studies)	⊕⊕⊕⊖ moderate ³	
Anaesthetic agent failure	0 per 1000	0 per 1000 (0 to 0)	RR 7.83 (1.51 to 40.58)	92 (3 studies)	⊕⊕⊖⊖ low ^{3,4,5}	
Anaesthetic placement failure	0 per 1000	0 per 1000 (0 to 0)	RR 7.38 (0.98 to 55.52)	90 (3 studies)	⊕⊕⊖⊖ low ^{3,4,5}

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Assumed control risks are based on the relative baseline number of events per outcome for infants receiving general anaesthesia.

² No studies reported on this outcome. When available, final results from the GAS study will be assessed for inclusion.

³ All studies inadequately described randomisation and allocation concealment. El-Gohary 2004 excluded an unspecified number of infants with inadequate spinal anaesthesia. Somri 1998 did not analyse outcomes as intention to treat and excluded four infants randomised to spinal anaesthesia from the analysis. Williams 2001 excluded four infants with inadequate spinal anaesthesia.

⁴ Wide confidence intervals (CI).

⁵ Low event rates, small sample size.

BACKGROUND

Description of the condition

Inguinal hernia in preterm infants

With improved neonatal intensive care management protocols, more preterm infants are surviving the neonatal period. With this increase, more infants are presenting for surgery in early infancy (Welborn 1997). Inguinal hernia (IH) is a common developmental problem in infants and children (Kumar 2002). Patency of the processus vaginalis is the major factor in the development of IH in female infants (Kumar 2002). By 32 weeks' gestation, the testes in males have normally entered the scrotum and contraction of the inguinal canal has begun. Contraction of the female inguinal canal normally occurs at a similar gestation (Kumar 2002).

Preterm gestation is the single most important predisposing factor for the development of IH (Grosfeld 1989). The incidence increases with decreasing birthweight (Kumar 2002); and appears in 38% of infants whose birth weight is between 751g and 1000g (Peevy 1986); and in 16% of those whose birth weight is between 1001g and 1250g (Peevy 1986; Rajput 1992). Bronchopulmonary dysplasia has also been associated with an increased incidence of IH (Kumar 2002). It has been proposed that increased intra-abdominal pressure resulting from chronic lung disease or gastrointestinal dysfunction could be a predisposing factor to the development of IH (Powell 1986). In addition, inadequate calorie or protein intake can lead to poor muscle and tissue growth (Georgieff 1986).

Description of the intervention

IH requires early surgical repair because of the risk of bowel incarceration and vascular compromise of bowel and gonadal tissue (Rescorla 1984). The interventions to be evaluated in this review include the effect of different anaesthetic approaches (general versus spinal) on postoperative respiratory dysfunction and analgesic requirements.

Postoperative respiratory dysfunction

A major concern in the management of the preterm infant undergoing surgery is the incidence of postoperative apnoea, with or without bradycardia, associated with general anaesthesia. Apnoea in preterm infants has been defined as a pause in breathing of greater than 20 seconds; or one less than 20 seconds and associated with cyanosis, marked pallor, hypotonia or bradycardia (NIH 1987). It appears to be related to an immature respiratory central control mechanism and musculature, and is characterised by an unstable elastic rib cage, an upper airway that is prone to obstruction, a lower airway prone to collapse, plus a predisposition to hypothermia and anaemia (Henderson-Smart 1995). Apnoea and bradycardia reduce cerebral blood flow in preterm infants (Perlman 1985; Coté 1995); and have been associated with significant oxygen desaturations in former preterm infants recovering from anaesthesia (Kurth 1991; Coté 1995). Alterations in cerebral blood flow and tissue oxygenation increase the risk of brain ischaemia and intracranial bleeding and have the capacity to affect long-term brain development (Perlman 1985).

Earlier postoperative studies have demonstrated that approximately 10% to 30% of otherwise healthy preterm infants undergoing inguinal herniorrhaphy under general anaesthesia at greater than term corrected (postmature) age will have one or

more episodes of apnoea in the postoperative period (Gollin 1993; Sims 1994; Kumar 2002), a risk which is inversely proportional to postmenstrual age (PMA: gestational age plus postnatal age) (Welborn 1990; Gollin 1993). More recent observational studies suggest that the risk of postoperative apnoea is much lower when newer anaesthetic agents (for example sevoflurane and desflurane) are used, occurring in fewer than 5% of infants born at less than 32 weeks' gestation (Murphy 2007; Lee 2011). Other specific risk factors for apnoea include anaemia (hematocrit less than 30%), bronchopulmonary dysplasia and ongoing apnoea at home (Coté 1995). The risk period for apnoea, bradycardia or periodic breathing extends from the intraoperative period until many hours later. The peak period for onset of apnoea is within the first 12 hours after surgery, continuing until 48 hours, and up to 72 hours postsurgery (Sims 1994).

Anaesthetics produce dose-dependent and drug-specific changes in the mechanics and central control of the respiratory centre. Inhaled anaesthetics decrease muscle tone within the airways, chest wall and diaphragm, in addition to inhibiting central respiratory drive and responsiveness to ventilatory stimulants such as carbon dioxide. Intravenous anaesthetics may also alter respiratory function whilst opioids produce a dose-dependent depression of medullary respiratory centres, also resulting in decreased responsiveness to partial pressure of carbon dioxide (PaCO₂) (Welborn 1997).

In view of the high incidence of postoperative apnoea in former preterm infants undergoing anaesthesia, a number of investigators have postulated that a safe operating period does not commence until a postmenstrual age of greater than 44 weeks (Liu 1983; Malviya 1993); or even greater than 60 weeks (Kurth 1991).

Neurological outcomes

Experimental studies have indicated a link between the use of anaesthetic agents and brain cell destruction. Infants having undergone surgery demonstrated smaller brain grey matter volumes which may arise from thalamic susceptibility to brain cell apoptosis from exposure to sedative and anaesthetic agent combinations (Filan 2012). Infants undergoing IH surgery and receiving general anaesthetic agents performed worse on academic testing at 15 to 16 years of age compared to non-surgical infants (Hansen 2011). However, the differences in mental development indices and test scores were no longer statistically significant between exposed and unexposed groups after adjusting for confounders commonly associated with mortality and poor neurosensory outcomes: gestational age, gender, birthweight, and severity of lung disease. It is possible that the lower scores reflected the greater overall risk of morbidity in the population of infants (greater proportion of low birth weight and chronic lung disease) requiring IH surgery. Another explanation is that the lack of difference in cognitive ability in later life between former preterm infants receiving regional, compared with general, anaesthesia for IH surgery in these studies may be related to the theoretical effect of neuroplasticity on the recovery of synaptic function (Hansen 2011). In contrast, children undergoing IH surgery at less than three years of age and exposed to anaesthetic agents including ketamine were twice as likely to be diagnosed with a developmental disorder or behavioural disorder or both at follow-up (mean age of 30 months, range 12 to 48 months) compared with those unexposed to IH surgery (DiMaggio 2009).

Other related Cochrane reviews

Prophylactic caffeine has also been used to prevent postoperative apnoea following general anaesthesia (Henderson-Smart 2001).

How the intervention might work

Reducing the risk of episodes of postoperative apnoea

In addition to a suggested safe period of operation, awake regional anaesthesia has been suggested to reduce, but not abolish, the incidence of postoperative apnoea, with an even lower incidence observed when no sedation is used (Frumiento 2000). Observational studies support a lower incidence of apnoea in infants receiving regional rather than general anaesthesia (Geze 2011; Lee 2011).

Risks of using regional anaesthesia

There is an attendant 'small but potentially catastrophic risk' of spinal cord injury, the exact frequency of which is unknown (Berde 2005). However, existing studies imply low incidence for this complication (Giaufré 1996). The benefit of regional anaesthesia may also be limited if placement or anaesthetic failure rates (or both) result in repeated attempts, increased operative time and the addition of a general anaesthetic. The ease of placement and effectiveness of caudal compared to spinal anaesthesia has been evaluated in case reports (Tobias 1998; Geze 2011); and small observational studies (Geze 2011).

Why it is important to do this review

A large proportion of extremely low and very low birth weight infants develop inguinal hernias and these infants are at highest risk of postoperative apnoea and altered brain development. Anaesthetic and sedative agents are postulated to cause neurotoxic changes within the infant brain, and animal studies indicate increased vulnerability during periods of rapid brain growth and synaptogenesis (Jevtovic-Todorovic 2003; Fredriksson 2007). The developing brain of the preterm infant is at particular risk of neurotoxicity. Therefore it is important to determine whether avoiding a brief exposure to anaesthetic agents during surgery with the use of regional, in preference to general, anaesthesia improves long-term neurodevelopmental outcomes in former preterm infants requiring inguinal herniorrhaphy. The potential benefit of this on longer term neurological outcomes needs to be balanced against the risk of incorrect needle placement, need for repeated attempts at placement and unsatisfactory depth of anaesthesia and analgesia in an awake infant. An increasing number of studies have evaluated the use of regional anaesthesia. This updated review contributes to current knowledge on the risks of postoperative respiratory dysfunction in former preterm infants with inguinal hernia who have received regional or general anaesthesia or both, to assist anaesthetists, neonatologists, paediatric surgeons and parents in making decisions on the best anaesthetic approach.

OBJECTIVES

To determine if regional anaesthesia, used in preterm infants undergoing inguinal herniorrhaphy, reduces postoperative apnoea, bradycardia and the use of assisted ventilation, in comparison to those infants undergoing inguinal herniorrhaphy with general anaesthesia.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials or quasi-randomised controlled trials (including abstracts).

Types of participants

Preterm infants born at less than 37 weeks' gestation, undergoing inguinal herniorrhaphy before 60 weeks' postmenstrual age.

Types of interventions

Any form of regional anaesthesia (epidural, spinal or caudal) compared to general anaesthesia administered in the repair of inguinal hernia or coadministration of regional and general anaesthesia.

Types of outcome measures

Primary outcomes

Respiratory

- Apnoea - any episodes of apnoea in the first 24 hours postoperatively or mean rate of apnoea per 24 hours. Apnoea is defined as a pause in breathing of greater than 20 seconds; or one less than 20 seconds and associated with cyanosis, marked pallor, hypotonia or bradycardia (NIH 1987).
- Desaturations - any episodes of desaturation in the first 24 hours postoperatively or mean rate of desaturation per 24 hours. Desaturation is defined as a haemoglobin oxygen saturation (SpO₂) of less than 90% for more than 10 seconds. Again this will be recorded in the 24 hour period immediately postoperatively and the frequency of episodes will be recorded over a 24 hour period.
- The use of postoperative respiratory support (continuous positive airways pressure or intermittent positive pressure ventilation) beyond the end of the surgical procedure. Once neuromuscular blockade has been antagonised we classify postoperative respiratory support as an adverse effect if it is required for more than 1 hour past reversal of anaesthesia.

Neurological

- Neurodevelopmental state at two-year follow-up as reflected in the Bayley scales of infant development (MDI/PDI).

Secondary outcomes

Anaesthetic effectiveness

- Operator satisfaction (anaesthetic administered provided sufficient infant immobility to allow satisfactory completion of the operation).
- Any anaesthetic failure (use of additional anaesthetic agents either due to placement failure or agent failure). 'Anaesthetic placement failure' and 'Repeated attempts to achieve successful agent failure' are measures of failure to achieve lumbar puncture in the spinal group; and 'Anaesthetic agent failure' is failure to achieve adequate anaesthesia after the administration of either spinal or general anaesthetic agents.

- Postoperative pain, as measured by a validated pain scale and by the use of pain relief.
- Duration of surgery (from admission to operating theatre until admission to recovery room).
- Temperature on admission to recovery room/NICU/PICU.

Health Service use

- Duration of postoperative hospital stay.
- Non-routine postoperative admission to PICU/NICU.

Search methods for identification of studies

See: Neonatal Collaborative Review Group search strategy.

Electronic searches

For the 2015 updated review, we searched MEDLINE (Dec 2002 to 25 February 2015), EMBASE (Dec 2002 to 25 February 2015), PubMed (December 2002 to 25 February 2015), and the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, 2015, Issue 2), clinicaltrials.gov and controlled-trials.com using the following key words: apnoea or apnoea, anaesthesia or anaesthesia and the MeSH term infant, newborn. Other than the date ranges specified, no other search limits were applied.

Searching other resources

We also searched the US 'Society for Pediatric Research', the European Society for Paediatric Research and Pediatric Anesthesia databases (December 2002 to 24th November 2012).

Data collection and analysis

We used the standard methods of the Cochrane Neonatal Review Group. Two review authors (AL, LJ) scrutinised all titles and abstracts of research identified from the search strategy for their suitability and relevance to this review. The RCTs were selected, analysed and considered for inclusion and graded for their methodological quality using concealment of randomisation, blinding of intervention, completeness of follow-up and blinding of outcome assessment. Review authors discussed any conflicts and we involved a further party if needed to help resolve these conflicts. We addressed any unclear issues regarding the trials by contacting the authors where possible.

At least two review authors out of five (AL, LJ, JF, PC, NB) independently extracted the data. Two review authors (LJ, JF) checked the data and entered it into the Cochrane Review Manager software ([RevMan 5.3](#)). We checked any missing information or data inconsistencies, where necessary, with the authors of the study.

We carried out meta-analysis using the [RevMan 5.3](#) software using the fixed-effect model. Results were expressed as risk ratio (RR), risk difference (RD) and number needed to treat for an additional beneficial (NNTB) or harmful outcome (NNTH) for categorical data and weighted mean difference for continuous data with 95% confidence intervals (CI) for each summary estimate. Heterogeneity of treatment effect was evaluated for each meta-analysis. For effects where RD but not RR was statistically significant, we termed the result as of "borderline statistical significance" in this review.

Assessment of risk of bias in included studies

The criteria and standard methods of the Cochrane Neonatal Review Group were used to assess the methodological quality of the included trials. Quality of the included trials was evaluated in terms of adequacy of randomisation and allocation concealment, blinding of parents or caregivers and assessors to intervention, and completeness of assessment in all randomised individuals.

For the 2015 update, the previous assessments were incorporated into RevMan 5 'Risk of bias' tables ([RevMan 5.3](#)). Risk of bias for each study was calculated using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). The following were assessed:

(1) Sequence generation (checking for possible selection bias)

- adequate (any truly random process, e.g. random number table; computer random number generator);
- inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear.

(2) Allocation concealment (checking for possible selection bias)

- adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear.

(3) Blinding (checking for possible performance bias)

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

- adequate (less than 20% missing data);
- inadequate;
- unclear.

(5) Selective reporting bias

- adequate (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest are reported incompletely and so cannot be used; or study fails to include results of a key outcome that would have been expected to have been reported);
- unclear.

(6) Other sources of bias

The possibility of other possible sources of bias (e.g. early termination of trial due to data-dependent process, extreme baseline imbalance, etc) was assessed as:

- yes;
- no;

- unclear.

(7) Overall risk of bias

Explicit judgements were made about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, the likely magnitude and direction of the bias and whether it is likely to impact on the findings.

Subgroup analysis and investigation of heterogeneity

The following subgroup analyses were prespecified:

- gestational age (above and below about 32 weeks);
- birth weight (above and below about 1500 grams);
- postmenstrual age at time of surgery (less than or more than 50 weeks PMA);
- presence of chronic lung disease (as defined by an oxygen requirement at 36 weeks corrected gestational age);
- anaemia (hematocrit less than 30%);
- administration of prophylactic caffeine/theophylline to prevent apnoea;
- preoperative use of sedatives.

RESULTS

Description of studies

This 2015 review update identified three new randomised controlled trials by [Kunst 1999](#), [El-Gohary 2004](#) and [Das 2005](#), assessing the impact of regional versus general anaesthesia in preterm infants undergoing inguinal herniorrhaphy in addition to the original four randomised controlled trials ([Welborn 1990](#); [Krane 1995](#); [Somri 1998](#); [Williams 2001](#)). [Krane 1995](#) is included in the review although some of the data were incomplete and we were not able to obtain this information via personal communication. Two of the newly identified studies are awaiting further classification: [Das 2005](#) did not specify the infant population as preterm and reported a minimum age at operation of less than two months; and [Kunst 1999](#) was excluded in the original version of this review as the published results were of insufficient detail. The newly identified [El-Gohary 2004](#) trial qualified for inclusion in this review: similar to the other studies in this review, this was published as a complete article.

Details of each study are given in the table '[Characteristics of included studies](#)'. Overall, the studies attempted to include ex-preterm infants. The inclusion criteria, the intervention (type of anaesthetic agent) and outcomes varied between studies.

All studies compared single-shot spinal versus general anaesthesia in premature infants (less than 37 weeks) undergoing inguinal herniorrhaphy.

[Krane 1995](#) enrolled 18 infants born at less than 36 weeks' gestation who were post-term but less than 60 weeks' corrected gestational age at time of surgery, with an American Society of Anesthesiologists (ASA) physical class of I or II, undergoing inguinal herniorrhaphy. The authors excluded significant chronic lung disease, known symptomatic congenital heart disease or symptomatic central nervous system disease. Preoperative respiratory function of the included infants was assessed by a 12

hour study of respiratory rate, haemoglobin oxygen saturation and ECG in the infant's home. On the day of surgery 10 infants received a single shot of spinal anaesthetic with 0.6 mg/kg tetracaine hydrochloride made hyperbaric with an equal volume of 10% dextrose. Three infants in the spinal group who cried during surgical manipulation received brief mask blow-over of 50% nitrous oxide (N₂O). In the general anaesthesia group, eight infants received balanced anaesthesia, with halothane and muscle relaxation. At the end of the surgery the ilioinguinal nerve was infiltrated with 0.25% bupivacaine for pain relief. When necessary, at the conclusion of surgery, neuromuscular blockade was antagonised with neostigmine and atropine. One infant in the spinal anaesthetic group had inadequate spinal anaesthetic blockade and was then given a general anaesthetic in addition to a local nerve block. The outcome measures of postoperative apnoea (cessation of respiratory movement for more than 10 seconds), bradycardia and periodic breathing were reported to be equal in each group, but individual data were not supplied. Postoperative haemoglobin oxygen desaturation (a decrease in peripheral oxygen saturation (SpO₂) to less than 90% for 10 seconds or more), anaesthetic placement failure and anaesthetic agent failure were measured and reported for the two groups. Postoperative pain relief in both groups was managed with paracetamol and no opioids were administered.

[Somri 1998](#) enrolled 40 infants born at less than 37 weeks' gestation who were post-term but less than 60 weeks' corrected gestational age at time of surgery and with one of the following: a history of neonatal respiratory distress syndrome, bronchopulmonary dysplasia documented by radiography or a history of preoperative apnoea. They did not exclude any infants on entry criteria but excluded from analysis those infants in whom failure to achieve spinal needle placement occurred. On the day of surgery, 20 infants received a spinal anaesthetic with isobaric bupivacaine 0.6 to 0.8 mg/kg. A pacifier was used to soothe restless infants. In the general anaesthesia group 20 infants received thiopentone intravenous induction, 4 to 5 mg/kg, followed by balanced anaesthesia of halothane 0.5% to 1.5% and muscle relaxation with atracurium, 0.5 mg/kg. Neuromuscular blockade was reversed at the end of surgery with neostigmine and atropine. The outcome measures were postoperative apnoea (defined as a respiratory pause of 15 seconds or longer; or less than 15 seconds with bradycardia (defined as a heart rate of less than 100 beats/minute)); postoperative analgesia; postoperative respiratory support; average length of hospital stay; anaesthetic placement failure; and multiple spinal placement attempts. Six infants in the spinal anaesthesia group became restless despite successful spinal blockade and supplementary anaesthesia was administered to obtain sufficient motionlessness for completion of the operative procedure: four infants received inhaled halothane and two received intravenous propofol. Paracetamol was the only analgesic agent used in the postoperative period.

[Welborn 1990](#) (the third study) enrolled 36 infants born at less than 37 weeks' gestation who were post-term but less than 51 weeks' corrected gestational age at time of surgery and who were healthy, with an ASA physical status I or II. The authors excluded infants who had cardiac, neurological or metabolic disease and those who were receiving methylxanthines or caffeine. In the spinal anaesthesia group, during the early part of the study, nine infants received intramuscular ketamine for sedation prior to performance of lumbar puncture. These results were presented separately. As

the authors gained experience the ketamine sedation was stopped due to the high incidence of side effects observed. The remaining 11 infants in the spinal group were comforted with sugar solution. In all infants the spinal anaesthesia was achieved by 1% tetracaine 0.4 to 0.6 mg/kg with an equal volume of 10% dextrose. The 16 infants in the general anaesthesia group received a balanced anaesthetic with halothane and neuromuscular blockade. Neuromuscular blockade was reversed at the end of surgery with neostigmine and atropine. The outcomes measured were episodes of postoperative apnoea (defined as a respiratory pause of less than 15 seconds not associated with bradycardia); and prolonged episodes of apnoea (defined as a respiratory pause of 15 seconds or longer; or less than 15 seconds accompanied by bradycardia (defined as a heart rate less than 100 beats per minute for at least 5 seconds). Other outcomes measured included postoperative respiratory support, length of surgery and temperature on admission to the recovery room.

Williams 2001 (the fourth study) enrolled 28 infants born at less than 36 weeks' gestation, who were post-term but less than 46 weeks' postconceptional age at time of surgery. The authors excluded infants with pre-existing cardiac, neuromuscular or metabolic diseases. Pre-existing abnormal respiratory function with or without the need for supplemental oxygen therapy was noted. On the day of surgery 14 infants received a spinal anaesthetic consisting of 0.5% bupivacaine 1 mg/kg. The 14 infants in the general anaesthesia group received a 2 minimum alveolar concentration (MAC) equivalent value for age of sevoflurane in 100% oxygen and muscle relaxation with atracurium. At the end of surgery, neuromuscular blockade was antagonised with neostigmine and glycopyrrolate. Both groups received a single injection of bupivacaine 0.25% 2 mg/kg into the caudal epidural space for analgesic effects extending into the postoperative period. The outcome measure was postoperative apnoea (a sustained respiratory pause of 15 seconds or longer, or less than 15 seconds if accompanied by an SpO₂ less than 90% or bradycardia). Bradycardia was defined as a heart rate of less than 100 beats/minute for at least five seconds. Anaesthetic placement failure was also measured.

El-Gohary 2004 (the fifth study) enrolled 30 infants born at less than 37 weeks' gestation who were post-term but less than 46 weeks' postconceptional age at time of surgery. The authors excluded infants with pre-existing cardiac, neuromuscular or metabolic diseases; coagulopathy; systemic infection; meningitis; infection at the site of puncture; and cases of inadequate block. On the day of the surgery, 15 infants received a single dose of EMLA cream 0.5 g applied to the skin over the sacrococcygeal membrane 90 minutes before receiving a spinal anaesthetic consisting of 1 mL/kg of 0.375% ropivacaine. The 15 infants in the general anaesthesia group received 2 MAC sevoflurane in 100% oxygen. Restlessness or discomfort in the presence of adequate block was alleviated with mask inhalation of nitrous oxide. The outcome measures were episodes of pre and post-operative apnoea (a sustained respiratory pause of 15 seconds or longer; or less than 15 seconds if accompanied by an SaO₂ less than 90%; or bradycardia, where bradycardia was defined as a heart rate of less than 100 beats/minute for at least 5 seconds; and desaturation was defined as an SaO₂ of less than 90% for more than 10 seconds).

Ongoing studies: the GAS study is a multi-centre trial that has recently completed recruitment of 722 infants undergoing inguinal

herniorrhaphy repair ([NCT0075660](#)). Infants were randomised to regional anaesthesia versus combined general/regional anaesthesia. In addition to neurosensory outcomes at two years' corrected age, investigators intend to follow longer term intelligence quotients of study infants at five years' corrected age.

Risk of bias in included studies

See: [Characteristics of included studies](#) table.

Overall, the studies included in this review were of inadequate quality. Due to the nature of the intervention contrast, it was deemed impractical to blind the intervention in any of the studies. Three of the five studies attempted to account for this by using blinded assessment. Specific methodological issues of individual trials are discussed below:

Krane 1995

Randomisation in this study was not described adequately. There was no mention of allocation concealment and there was no blinding of intervention but there was adequate blinding of the outcome, with the results being interpreted by a trained technician unaware of the treatment group assignment. There was complete follow-up of all enrolled infants. One infant with a failed spinal anaesthetic who subsequently received a general anaesthetic was counted as a member of the general anaesthetic group. We have re-analysed this according to intention-to-treat analysis by including the infant in the spinal group. Unfortunately, despite contacting the author, further clarification of this infant was not available.

Somri 1998

Randomisation in this study was inadequately described. Allocation concealment was not mentioned and there was no blinding of either intervention or outcome. There was complete follow-up of all enrolled infants. Bias was introduced by omitting three infants in which lumbar puncture was unsuccessful and one infant was excluded because of hypothermia.

Welborn 1990

Randomisation in this study was inadequately described. Allocation concealment was not mentioned and there was no blinding of intervention, but a pulmonologist unaware of treatment group assessed outcome. There was complete follow-up. Subgroup analyses were performed, with and without pre-anaesthetic ketamine sedation, in the spinal group, following initial concerns by study investigators that pre-anaesthetic sedation contributed to greater incidence of postoperative apnoea. Results were reported by the investigators in three groups: general anaesthesia, spinal plus ketamine, and spinal without ketamine.

Williams 2001

Randomisation in this study was adequately described with the use of random number tables. There was no mention of allocation concealment and there was no blinding of intervention but the results were analysed by a blinded observer. There was complete follow-up. Four infants were excluded following randomisation due to anaesthetic failure in the spinal anaesthesia group. These four infants were given a general anaesthetic but were excluded from further analysis by the authors.

El-Gohary 2004

Randomisation in this study was inadequately described. There was no mention of allocation concealment, blinding of intervention or outcome assessment. Although the number analysed equalled

those initially randomised, follow-up is assessed as incomplete due to the exclusion of an unspecified number of cases with inadequate block. Whether cases of inadequate block were excluded pre- or postrandomisation was not mentioned. Two cases in the spinal group requiring nitrous oxide via mask inhalation were analysed as intention to treat.

Effects of interventions

See: [Summary of findings for the main comparison Regional \(spinal, epidural, caudal\) versus general anaesthesia for preterm infants having inguinal herniorrhaphy in early infancy](#)

All five studies in this review reported on the impact of spinal versus general anaesthesia in preterm infants undergoing inguinal herniorrhaphy. The five studies reported different postoperative outcomes. Where different studies reported similar outcomes there was no significant heterogeneity of treatment effect between the studies. However, due to the small number of studies and participants in a proportion of the meta-analyses, a complete lack of heterogeneity cannot be assumed.

Spinal anaesthesia versus general anaesthesia (Comparison 1)

Primary outcome measures

Apnoea/bradycardia (Analysis 1.1; Figure 1): four studies adequately reported on apnoea/bradycardia. In all four studies the definition of apnoea did not fulfil the [NIH 1987](#) definition of a pause in breathing of greater than 20 seconds or one less than 20 seconds and associated with cyanosis, marked pallor, hypotonia or bradycardia. [El-Gohary 2004](#), [Somri 1998](#), [Williams 2001](#), and [Welborn 1990](#) defined apnoea as a pause in breathing of 15 seconds, or less if associated with bradycardia. [Krane 1995](#) defined apnoea as a pause greater than 10 seconds, or less if associated with bradycardia, but the results were not adequately reported. Only [Somri 1998](#) demonstrated a statistically significant reduction in the risk of apnoea/bradycardia among infants having received a spinal anaesthetic (RR 0.12, 95% CI 0.02 to 0.89). The remaining three studies showed no significant difference between intervention groups. Meta-analysis showed no statistically significant difference between the intervention groups (typical RR 0.72, 95% CI 0.48 to 1.06; 4 studies, 138 infants).

Figure 1. Forest plot of comparison: 1 Spinal anaesthesia versus general anaesthesia, outcome: 1.1 Apnoea/bradycardia occurring 12 to 24 hours following completion of operation.

Any oxygen desaturation (Analysis 1.2; Figure 2): two studies reported on oxygen desaturation ([Krane 1995](#); [El-Gohary 2004](#)). Neither study, alone or in combination, showed a statistically significant difference in the rate of oxygen desaturation between

infants who received a spinal anaesthetic and those who received a general anaesthetic (typical RR 0.82, 95% CI 0.61 to 1.11; 2 studies, 48 infants).

Figure 2. Forest plot of comparison: 1 Spinal anaesthesia versus general anaesthesia, outcome: 1.2 Any oxygen desaturation occurring 12-24 hours following completion of the operation.

Postoperative respiratory support (Analysis 1.3): of three studies ([Krane 1995](#); [Somri 1998](#); [Welborn 1990](#)) reporting this outcome; only [Somri 1998](#), reported the need for respiratory support for longer than one hour postoperatively in four infants having received a general anaesthetic compared to no infants having received spinal anaesthesia. In the meta-analysis there was a

reduced need for respiratory support in infants receiving spinal anaesthesia but this was not statistically significant (typical RR 0.09, 95% CI 0.01 to 1.64; 3 studies, 98 infants).

Postoperative apnoea with preoperative sedatives excluded (Analysis 1.4; Figure 3): four studies reported postoperative apnoea

in infants who had not received preoperative sedatives (Welborn 1990; Somri 1998; Williams 2001; El-Gohary 2004). Only Somri 1998 showed a significant reduction in risk of apnoea/bradycardia among infants who received spinal anaesthetic (RR 0.12, 95% CI 0.02 to 0.89). Welborn 1990 ceased the usage of preoperative ketamine because of apnoea: once ketamine was ceased the incidence of apnoea was dramatically reduced. We have performed subgroup analyses with and without the ketamine group. The effect on postoperative apnoea was statistically significant in the

subgroup of infants that had not received preoperative ketamine (typical RR 0.53, 95% CI 0.34 to 0.82; 4 studies, 129 infants). The use of spinal rather than general anaesthesia was associated with a 47% reduction in the risk of postoperative apnoea for those infants not receiving any sedation. The number needed to treat to benefit (NNTB) from receiving spinal rather than general anaesthesia in preventing an episode of postoperative apnoea was approximately four infants (4.40).

Figure 3. Forest plot of comparison: 1 Spinal anaesthesia versus general anaesthesia, outcome: 1.4 Postoperative apnoea with preoperative sedatives excluded.

Postoperative apnoea with no episodes of preoperative apnoea (Analysis 1.5; Figure 4): this subgroup was determined post hoc. Four studies reported postoperative apnoea in infants with no history of preoperative apnoea (Welborn 1990; Somri 1998; Williams 2001; El-Gohary 2004). This outcome did not reach statistical significance in any of the studies taken separately. In the updated review and meta-analysis, there was a statistically significant reduction in the risk of postoperative apnoea in preterm infants without a history of preoperative apnoea and having

received a spinal anaesthetic (typical RR 0.34, 95% CI 0.14 to 0.81; 4 studies, 134 infants). The use of spinal rather than general anaesthesia was associated with a 66% reduction in the risk of postoperative apnoea for those infants without preoperative apnoea. The number needed to treat to benefit (NNTB) from receiving spinal rather than general anaesthesia in preventing an episode of postoperative apnoea in infants with no history of preoperative apnoea was approximately six infants (5.72).

Figure 4. Forest plot of comparison: 1 Spinal anaesthesia versus general anaesthesia, outcome: 1.5 Postoperative apnoea with no preoperative apnoea.

Neurodevelopmental state at two year follow-up as reflected in the Bayley scales of infant development (MDI/PDI): none of the trials in this review reported on neurodevelopmental state at two year follow-up or any other neurological outcomes.

Secondary outcome measures

Anaesthetic agent failure (Analysis 1.6; Figure 5): three studies assessed anaesthetic agent failure (El-Gohary 2004; Krane 1995; Somri 1998). Although each study indicated a higher incidence of agent failure in the spinal group, none of these studies

when considered separately reached statistical significance. In the meta-analysis, infants who received a spinal anaesthetic had a statistically significantly greater risk of failure of anaesthesia arising from the anaesthetic agent, compared to those receiving general anaesthesia (typical RR 7.83, 95% CI 1.51 to 40.58; 3 studies, 92 infants). One spinal anaesthetic agent failure occurred for every four successfully placed spinal anaesthetics administered (typical RD 0.24, 95% CI 0.11 to 0.38), requiring the use of sedatives or inhalational anaesthesia or both.

Figure 5. Forest plot of comparison: 1 Spinal anaesthesia versus general anaesthesia, outcome: 1.6 Anaesthetic agent failure.

Repeated attempts to achieve successful anaesthetic placement (Analysis 1.7): in the study by [Somri 1998](#), infants undergoing a spinal anaesthetic were more likely to undergo multiple attempts to achieve accurate placement of the spinal needle. This effect was of borderline statistical significance (RR 9.24, 95% CI 0.54 to 157.57; RD 0.21, 95% CI 0.03 to 0.38).

Anaesthetic placement failure (Analysis 1.8; Figure 6): three studies reported on anaesthetic placement failure ([Krane 1995](#); [Somri 1998](#); [Williams 2001](#)). None of the included studies

alone reached statistically significant difference in the proportion of infants with failure of spinal placement between regional anaesthesia and general anaesthesia groups. In the study by [Krane 1995](#), no infant in either group had anaesthetic placement failure. Overall, there was an increased risk of anaesthetic placement failure in the spinal group of borderline statistical significance (typical RR 7.38, 95% CI 0.98 to 55.52; typical RD 0.15, 95% CI 0.03 to 0.27; 3 studies, 90 infants). There was one spinal needle placement failure for every seven infants in whom spinal anaesthesia was intended.

Figure 6. Forest plot of comparison: 1 Spinal anaesthesia versus general anaesthesia, outcome: 1.8 Anaesthetic placement failure.

Use of postoperative analgesic agents (Analysis 1.9): the only study to report on this outcome, [Somri 1998](#), showed no significant difference in the use of postoperative analgesic agents between infants receiving spinal anaesthesia compared to those receiving general anaesthesia (RR 0.42, 95% CI 0.15 to 1.18; 1 study, 44 infants). None of the studies used opioids or other respiratory depressants as analgesic agents in the postoperative period. All studies used paracetamol for pain relief.

Duration of surgery (Analysis 1.10): two studies reported this outcome. [Welborn 1990](#) reported no statistically significant difference between the treatment groups; however, insufficient data were supplied to allow calculation in this systematic review. The study by [El-Gohary 2004](#) showed no statistically significant difference between spinal and general anaesthesia groups (RD -2.00, 95% CI -5.24 to 1.24).

Average length of hospital stay: one study reported on the length of hospital stay with no significant difference between the treatment groups ([Somri 1998](#)). Reporting of data were insufficient to include in the meta-analysis.

Temperature on admission to recovery: one study reported on temperature on admission to recovery ([Welborn 1990](#)). The mean temperature on admission to recovery, 36.5 °C, was the same between the two intervention groups.

With the exception of the subgroups receiving preoperative sedatives and those infants without episodes of preoperative apnoea, other prespecified subgroup analyses were not possible due to inadequate reporting of outcome data and the small numbers of studies and participants.

DISCUSSION

Summary of main results

The 2015 update identified two new randomised trials ([El-Gohary 2004](#); [Das 2005](#)), only one of which was eligible for inclusion ([El-Gohary 2004](#)), bringing the total number of eligible studies in this review to five enrolling 152 infants in total ([Welborn 1990](#); [Krane 1995](#); [Somri 1998](#); [Williams 2001](#); [El-Gohary 2004](#)). Spinal anaesthesia was no more effective than general anaesthesia

in reducing the overall incidence of postoperative morbidity. However, once infants receiving ketamine in the [Welborn 1990](#) study were excluded from the analysis there was a statistically significant reduction in the incidence of episodes of postoperative apnoea in the spinal anaesthetic group. For every four infants treated with spinal anaesthesia one infant was prevented from having an episode of postoperative apnoea. Infants with episodes of postoperative apnoea but no episodes of preoperative apnoea and receiving spinal rather than general anaesthesia had a similar reduction in episodes of postoperative apnoea.

Anaesthetic failure was analysed in three categories: anaesthetic placement failure; anaesthetic agent failure; and repeated attempts to achieve successful placement of anaesthesia. Overall, there were more technical failures in the spinal group. Accurate placement of the spinal needle occurred in one infant in every seven scheduled to receive a spinal anaesthetic. For every four infants having a spinal anaesthetic, one experienced an anaesthetic agent failure requiring additional anaesthetic agent. None of the studies addressed the issue of why there were so many technical failures and they did not describe the degree of training or pre-study experience of the anaesthetic staff involved in the placement of spinal catheters.

The potential benefits of a reduction in postoperative apnoea need to be considered alongside a one in seven likelihood of failing to achieve the accurate placement of a spinal needle and a one in four chance of anaesthetic agent failure associated with spinal anaesthesia.

Overall completeness and applicability of evidence

The included studies reported both short and long episodes of postoperative apnoea. For the purpose of this systematic review, we concentrated on long episodes of postoperative apnoea. Three of the studies used a definition for apnoea as 'a cessation in breathing for 15 seconds, or less if associated with bradycardia'; and in the study by [Krane 1995](#), a definition of '10 seconds, or less if associated with bradycardia' was used. None of these definitions fulfilled the [NIH 1987](#) definition of apnoea or the criteria prespecified in this review.

Continuous outcome variables for length of surgery, average length of hospital stay and temperature on admission to recovery were reported as means. No standard deviations and confidence intervals were available, therefore our interpretation is based on the conclusions of the individual authors.

Neurodevelopmental outcomes were not reported in any of the randomised trials included in this review. As discussed in the background of this review, the effect of general anaesthesia exposure on longer term brain development and function are of great importance in the preterm infant population.

Important outcomes to measure in future studies include neurosensory impairment and anaesthetic effectiveness (operator satisfaction, any anaesthetic failure) in order to better evaluate the effect of anaesthetic-sedative agents on the growing brain balanced with the practicalities and technical challenges of achieving adequate anaesthesia to allow sufficient infant immobility during surgery.

Quality of the evidence

The results of this systematic review should be interpreted with caution due to the poor quality of many of the included studies resulting from small sample sizes, bias introduced by poor randomisation, and the inadequacy of intention-to-treat analyses. Although tests for heterogeneity were non-significant for all outcome measures, the small numbers of studies and infants within each meta-analysis make it difficult to draw any firm conclusions on homogeneity between studies.

Potential biases in the review process

The number of included studies were too few for a formal assessment of publication bias.

AUTHORS' CONCLUSIONS

Implications for practice

There was moderate-quality evidence that spinal anaesthesia may reduce the incidence of postoperative apnoea by up to 47% in ex-preterm infants not receiving additional sedative or analgesic agents whilst undergoing inguinal herniorrhaphy. For every four infants treated, spinal anaesthesia may prevent one infant from having postoperative apnoea (NNTB=4). There was low-quality evidence of a reduction in postoperative apnoea by up to 66% in infants with no prior history of apnoea and receiving spinal rather than general anaesthetic. There was very low-quality evidence of greater risk of anaesthetic agent failure and anaesthetic placement failure when regional anaesthesia was used, with the latter being of borderline statistical significance. None of the trials located in this review reported on neurodevelopmental outcomes. There is currently no evidence from randomised trials to confirm or deny that brief exposure to general anaesthesia affects longer term neurodevelopmental outcomes in former preterm infants undergoing surgery for inguinal hernia.

Implications for research

Although observational studies indicate a potential for neurotoxicity and brain cell destruction in preterm infants receiving sedative and anaesthetic agents, this has not been examined in randomised trials of general, compared with regional, anaesthesia in former preterm infants. There is a clear need for randomised trials evaluating the risk of postoperative apnoea and long-term neurodevelopmental impairment in ex-preterm infants in association with general anaesthesia. It is important for such trials to examine whether the risk of poor neurodevelopmental outcomes is higher in infants with a history of severe respiratory disease or previous brain injury or both compared to lower risk infants, and whether either or both groups of infants may benefit from reduced exposure to anaesthetic agents.

The relative safety of newer generation rapid onset and offset general anaesthetic agents requires further examination. Older generation inhalational anaesthetic agents have the potential to expose the lungs, heart and brain of former preterm infants to greater toxicity compared with newer generational agents but this has not been tested. Large randomised trials comparing contemporary general with spinal anaesthetic approaches without the co-administration of sedative agents are needed in order to evaluate this.

Inguinal hernia operations are associated with comparatively low requirement for postoperative analgesics and are traditionally treated with low-level analgesic agents such as paracetamol. Trials involving alternative types of neonatal surgery gastrointestinal approaches, such as [Somri 2011](#), may provide a better comparison of postoperative analgesic effectiveness between general and spinal anaesthesia.

Randomised trials should provide complete descriptions of randomisation techniques, allocation concealment, and methods of blinding participants and assessors. Outcome definitions should be prespecified and consistently applied across all study centres. Anaesthetic staff responsible for placement of spinal anaesthetics and surgical staff involved in inguinal hernia repair surgery should receive training and assessment prior to study commencement. Follow-up outcomes should be analysed as intention to treat, with complete reporting on withdrawals or cross-over of treatments. All measured outcomes should be reported.

Larger studies are needed to identify the risk benefit ratio of spinal anaesthesia versus general anaesthesia. To reduce the risk

of postoperative apnoea between regional and general anaesthesia by at least 10% would require a total sample size of 155 infants (90% power and $\alpha = 0.05$). If apnoea incidence is truly as low as 5% with the newer inhalational anaesthetics, then at least 242 infants would be required to detect a statistically significant difference between regional and general anaesthesia. These sample sizes highlight the need for a multicentre randomised controlled trial.

The GAS Study is a multi-centre trial that has recently completed recruitment of 722 infants undergoing inguinal herniorrhaphy repair ([NCT0075660](#)). Infants were randomised to regional anaesthesia versus combined general and regional anaesthesia. In addition to neurosensory outcomes at two years corrected age, investigators intend to follow longer term intelligence quotients of study infants at five years corrected age.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

El-Gohary 2004

Methods	Randomised Single centre trial Blinding of randomisation: can't tell Blinding of intervention: can't tell Blinding of outcome assessment: can't tell Complete follow-up: can't tell
Participants	Ex-premature infants (< 37 weeks gestation). Post conceptual age < 46 weeks Undergoing surgical repair of inguinal hernia Major exclusions: pre-existing cardiac, neuromuscular or metabolic diseases, coagulopathies, systemic infections, meningitis and local infection at the site of puncture. Cases of inadequate block
Interventions	Sevoflurane general anaesthesia (N = 15). Ropivacaine spinal anaesthesia (N = 15)
Outcomes	Apnoea (respiratory pause > 15 seconds or < 15 seconds if accompanied by oxygen saturations < 90% or bradycardia) Bradycardia (HR <100 per minute for at least 5 seconds) Desaturations (oxygen saturations < 90% for > 10 seconds). All within first 12 hours postoperatively Duration of surgery (min) (no definition given)
Notes	Two infants in group 2 (spinal anaesthesia group) became restless during the procedure and required 50:50 N ₂ O/O ₂ via mask inhalation, there is no mention of exclusion from the study
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment (selection bias)	Unclear risk No information provided

El-Gohary 2004 (Continued)

Random sequence generation (selection bias)	Unclear risk	"allocated randomly"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Exclusion of an unspecified number of cases of inadequate spinal anaesthesia

Krane 1995

Methods	Randomised Single centre trial Blinding of randomisation: can't tell Blinding of intervention: no Blinding of outcome assessment: yes Complete follow-up: yes
Participants	Ex-premature infants (< 36 weeks gestation). Corrected gestational age < 51 weeks Undergoing surgical repair of inguinal hernia ASA physical class I or II Major exclusions: significant chronic lung disease, known symptomatic congenital heart disease or symptomatic central nervous system disease. Preoperative 12 hour measure of respiratory rate and respiratory pattern in addition to saturation monitoring
Interventions	Bupivacaine spinal anaesthesia (N = 10). Halothane general anaesthesia (N = 8)
Outcomes	Any postoperative oxygen desaturation Postoperative respiratory support Anaesthetic placement failure Anaesthetic agent failure
Notes	Apnoea:- cessation of respiratory movement for >10 seconds Haemoglobin oxygen desaturation was defined as a decrease of SpO2 to < 90% for 10 seconds or more

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	No information
Random sequence generation (selection bias)	Unclear risk	"assigned randomly"

Regional (spinal, epidural, caudal) versus general anaesthesia in preterm infants undergoing inguinal herniorrhaphy in early infancy (Review)

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Krane 1995 (Continued)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was complete follow-up of all enrolled infants. The one infant with a failed spinal anaesthetic who was given a general anaesthetic was counted as a member of the general anaesthetic group.

Somri 1998

Methods	Randomised Single centre trial Blinding of randomisation: can't tell Blinding of intervention: no Blinding of outcome assessment: unknown Complete follow-up: yes
Participants	Infants born < 37 weeks gestation or < 60 weeks postconceptional age and/or with one or more of the following 1. A history of neonatal respiratory distress syndrome 2. BPD documented by radiography 3. History of pre operative apnoea
Interventions	Bupivacaine spinal anaesthesia (N=24). Halothane/Nitrous oxide general anaesthesia (N=20)
Outcomes	Postoperative apnoea/bradycardia defined as apnoea with bradycardia lasting ≥ 15 sec Effectiveness of postoperative analgesia Postoperative respiratory support Average length of hospital stay Anaesthetic placement failure Multiple placement attempts
Notes	Spinal anaesthetic failures were excluded from analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	No information
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"

Somri 1998 (Continued)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	High risk	Although the handling of all randomised infants is reported, follow-up is assessed as incomplete due to failure to analyse outcomes according to intention to treat . Four infants in whom lumbar puncture was unsuccessful and one infant with hypothermia randomised to receive spinal anaesthesia were excluded from further analysis

Welborn 1990

Methods	Randomised Single centre trial Blinding of randomisation: can't tell Blinding of intervention: no Blinding of outcome assessment: yes Complete follow-up: yes Preterm infants < 37 weeks .
Participants	36 former preterm infants < 37 weeks corrected to 51 weeks postconceptional age (35 to 51 weeks) Healthy infants ASA physical status I or II Anaesthesia < 51 weeks postconceptional age All undergoing inguinal hernia repair Exclusion criteria: cardiac, neurologic, metabolic disease or receiving methylxanthines or caffeine
Interventions	Spinal anaesthesia divided into 2 groups, IIa and IIb. IIa spinal with preoperative ketamine (N = 9), IIb spinal with no ketamine (N = 11). Halothane/Nitrous oxide general anaesthesia (N = 16)
Outcomes	Postoperative apnoea/bradycardia Postoperative respiratory support Length of surgery Temperature on recovery
Notes	Trial protocol was altered during the study to exclude ketamine as preoperative sedation in the spinal anaesthesia group resulting in 2 subgroups. Subgroup IIa received ketamine sedation prior to spinal placement and subgroup IIb were comforted using a pacifier dipped in sucrose or "peach schnapps"

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	No information

Welborn 1990 (Continued)

Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"A pulmonologist blinded to patient group assignment, examined the recorded data"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up assessed as complete

Williams 2001

Methods	Randomised Single centre trial Blinding of randomisation: yes (random number tables) Blinding of intervention: no Blinding of outcome assessment: yes Complete follow-up: yes
Participants	28 infants undergoing inguinal herniotomy. Born < 36 weeks gestation. Postconceptional age < 46 weeks Exclusion criteria: pre-existing cardiac, neuromuscular or metabolic diseases. Preoperative haemoglobin and respiratory function were noted
Interventions	Bupivacaine spinal anaesthesia (N = 14). Sevoflurane general anaesthesia (N = 14)
Outcomes	Postoperative apnoea/bradycardia Anaesthetic placement failure
Notes	Spinal anaesthetic failures were excluded from analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	No information
Random sequence generation (selection bias)	Unclear risk	"randomly assigned, using random number tables"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information

Williams 2001 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"each computer-generated printout was individually analysed by an investigator blinded to the anaesthetic technique used"
Incomplete outcome data (attrition bias) All outcomes	High risk	Exclusion of 4 of cases of inadequate spinal anaesthesia

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Somri 2011	No infants in the study underwent inguinal herniorrhaphy. Surgery included duodenoduodenostomy for repair of duodenal atresia, Meckel's diverticulectomy, ileocaecal resection for repair of complicated meconium ileus, and ileostomy or colostomy for treatment of congenital colorectal malformations.

Characteristics of studies awaiting assessment *[ordered by study ID]*
Das 2005

Methods	Randomised Single centre trial Blinding of randomisation: can't tell Blinding of intervention: can't tell Blinding of outcome assessment: can't tell Complete follow-up: yes
Participants	30 infants undergoing inguinal herniorrhaphy aged between 1 and 12 months ASA physical status I Excluded infants with spinal deformities, neurological disease, congenital abnormalities, or with any localised infection at the site of injection of spinal anaesthesia
Interventions	Bupivacaine spinal anaesthesia (N = 15). Propofol/nitrous oxide general anaesthesia with atracurium induction and fentanyl analgesia (N = 15). All infants (N = 30) premedicated with triclofos sodium syrup 75 mg/kg 2 hours preoperatively
Outcomes	Pain score at 15 minutes postoperatively Analgesic requirements at 15, 30 and 60 minutes postoperatively Postoperative changes in heart rate Postoperative vomiting Baseline changes in oxygen saturations at 20 minutes postoperatively

Das 2005 (Continued)

Clinically significant oxygen desaturations
Apnoea within 30 minutes postoperatively
Duration of spinal anaesthesia

Notes

Kunst 1999

Methods	Randomised Single centre trial Blinding of randomisation: can't tell Blinding of intervention: can't tell Blinding of outcome assessment: can't tell Complete follow-up: yes
Participants	17 preterm infants undergoing inguinal hernia at gestational ages 26.9 ± 2 weeks (spinal) and 29.7 ± 3.7 weeks (general) with history of apnoea and bradycardia
Interventions	Unsupplemented spinal anaesthesia (N = 8). General anaesthesia (N = 9).
Outcomes	'Worrying apnoea' defined as apnoea > 15 seconds or apnoea 10 to 15 sec with bradycardia (HR < 150 bpm) 'Unworrying apnoea' defined as apnoea without bradycardia lasting 10 seconds

Notes

Characteristics of ongoing studies [ordered by study ID]

NCT0075660

Trial name or title	The GAS study
Methods	The GAS study is a randomised trial design comparing regional and general anaesthesia in infants undergoing inguinal hernia repair. The study was performed at 27 sites in 7 countries.
Participants	The GAS study enrolled 722 infants < 60 weeks PMA, requiring inguinal hernia repair.
Interventions	Infants undergoing inguinal hernia repair were randomised to general anaesthesia or awake spinal anaesthesia. Spinal blocks were carried out as per the clinicians' normal practice; isobaric bupivacaine or levobupivacaine up to 1 mg/kg was administered into the subarachnoid space. Depending on clinician preference, additional local anaesthetic techniques were used for postoperative analgesia. The infant's condition and behaviour was recorded regularly intra-operatively and in the early postoperative period up to discharge from hospital. Parents were also contacted about 5 days postoperatively and questioned regarding potential complications of the technique.
Outcomes	Preliminary results: awake spinal anaesthesia was the predominant choice in the regional group with 339/355 infants receiving this technique; of these 109 also had an additional caudal block. For 279/339 (82%) cases the spinal ($\pm$ caudal) anaesthesia was sufficient on its own for the completion of surgery; in 18/355 (5%) cases some form of additional sedation or brief exposure to sevoflurane was required; and in 42/355 (12%) cases the block was a complete failure and a full general anaesthetic was required.

NCT0075660 (Continued)

Starting date

Contact information

Notes

Presented at European Anaesthesiology Congress, EUROANAESTHESIA 2014 Stockholm Sweden

DATA AND ANALYSES

Comparison 1. Spinal anaesthesia versus general anaesthesia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Apnoea/bradycardia occurring 12-24 hours following completion of operation	4	138	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.48, 1.06]
2 Any oxygen desaturation occurring 12-24 hours following completion of the operation	2	48	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.61, 1.11]
3 Post-operative respiratory support	3	98	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 1.64]
4 Post-operative apnoea with preoperative sedatives excluded	4	129	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.34, 0.82]
5 Post-operative apnoea with no episodes of pre-operative apnoea	4	134	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.14, 0.81]
6 Anaesthetic agent failure	3	92	Risk Ratio (M-H, Fixed, 95% CI)	7.83 [1.51, 40.58]
7 Repeated attempts to achieve successful anaesthetic placement	1	44	Risk Ratio (M-H, Fixed, 95% CI)	9.24 [0.54, 157.57]
8 Anaesthetic placement failure	3	90	Risk Ratio (M-H, Fixed, 95% CI)	7.38 [0.98, 55.52]
9 Use of post-operative analgesics	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.15, 1.18]
10 Duration of surgery	1	30	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-5.24, 1.24]

Analysis 1.1. Comparison 1 Spinal anaesthesia versus general anaesthesia, Outcome 1 Apnoea/bradycardia occurring 12-24 hours following completion of operation.

Study or subgroup	Spinal n/N	General n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
El-Gohary 2004	9/15	12/15		37.28%	0.75[0.46,1.22]
Somri 1998	1/24	7/20		23.72%	0.12[0.02,0.89]
Welborn 1990	8/20	5/16		17.26%	1.28[0.52,3.16]
			Favours spinal 0.01 0.1 1 10 100 Favours general

Analysis 1.2. Comparison 1 Spinal anaesthesia versus general anaesthesia, Outcome 2 Any oxygen desaturation occurring 12-24 hours following completion of the operation.

Analysis 1.3. Comparison 1 Spinal anaesthesia versus general anaesthesia, Outcome 3 Post-operative respiratory support.

Analysis 1.4. Comparison 1 Spinal anaesthesia versus general anaesthesia, Outcome 4 Post-operative apnoea with preoperative sedatives excluded.

Analysis 1.5. Comparison 1 Spinal anaesthesia versus general anaesthesia, Outcome 5 Post-operative apnoea with no episodes of pre-operative apnoea.

Analysis 1.6. Comparison 1 Spinal anaesthesia versus general anaesthesia, Outcome 6 Anaesthetic agent failure.

Analysis 1.7. Comparison 1 Spinal anaesthesia versus general anaesthesia, Outcome 7 Repeated attempts to achieve successful anaesthetic placement.

Analysis 1.8. Comparison 1 Spinal anaesthesia versus general anaesthesia, Outcome 8 Anaesthetic placement failure.

Analysis 1.9. Comparison 1 Spinal anaesthesia versus general anaesthesia, Outcome 9 Use of post-operative analgesics.

Analysis 1.10. Comparison 1 Spinal anaesthesia versus general anaesthesia, Outcome 10 Duration of surgery.

WHAT'S NEW

Date	Event	Description
25 February 2015	New citation required but conclusions have not changed	Three potentially relevant studies were identified of which one was deemed eligible for inclusion. A large multicentre trial (The GAS study) (NCT0075660) has been completed but not as yet reported in the peer reviewed literature.
25 February 2015	New search has been performed	This updates the review 'Regional (spinal, epidural, caudal) versus general anaesthesia in preterm infants undergoing inguinal herniorrhaphy in early infancy' (Craven 2003).

HISTORY

Protocol first published: Issue 2, 2002

Review first published: Issue 3, 2003

Date	Event	Description
28 August 2013	New search has been performed	Initial search updated.
24 November 2012	New search has been performed	New authorship. Updated search November 2012, identified one new study for inclusion. New primary outcome added - Neurosensory development at 2 year follow up (Bayley Scales). New subgroup added: postoperative apnoea in infants without preoperative apnoea.
30 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

LJ and AL performed the literature search and obtained copies of relevant studies for examination.

LJ, AL, JF, PC, NB extracted the data.

LJ revised the text with the assistance of AL and with guidance/review by PC.

DECLARATIONS OF INTEREST

None

Regional (spinal, epidural, caudal) versus general anaesthesia in preterm infants undergoing inguinal herniorrhaphy in early infancy (Review)

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Neurosensory development at two year follow-up was not included in the original review. This has been added in the light of more recent experimental studies evaluating the effect of general anaesthesia on brain function ([Filan 2012](#); [Hansen 2011](#)).

INDEX TERMS

Medical Subject Headings (MeSH)

*Anesthesia, Conduction; *Anesthesia, General; Anesthesia, Epidural; Anesthesia, Spinal; Apnea [prevention & control]; Bradycardia [prevention & control]; Hernia, Inguinal [*surgery]; Herniorrhaphy [*methods]; Infant, Premature; Infant, Premature, Diseases [*surgery]; Postoperative Complications [prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant, Newborn