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Lower versus higher oxygen concentrations titrated to target oxygen saturations during resuscitation of preterm infants at birth

Authors: Lui K, Jones LJ, Foster JP, Davis PG, Ching S, Oei J, Osborn DA

Background

For infants born at full term, the use of air (21% oxygen) for resuscitation is generally well tolerated and may be associated with better outcomes. Infants born preterm (before 37 weeks' gestation) require more resuscitation after birth and have more problems with adaptation to life.

Review question

This review set out to investigate whether the use of lower or higher concentrations of oxygen (adjusted according to the infant's oxygen saturation, or percentage of hemoglobin binding sites in the bloodstream occupied by oxygen) are better for resuscitating preterm infants, when used in the first ten minutes after birth.

Results

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We included ten trials in this review. The trials included a total of 914 infants, the majority of which were born before 32 weeks' gestation. The review found no evidence of an effect from use of a lower compared to a higher initial oxygen concentration targeted to infant oxygen saturation for resuscitation on mortality or other newborn health outcomes. There was also no difference in the rate of airway intubation (placement of a flexible plastic tube into the windpipe) during resuscitation between the infants who received lower concentrations of oxygen and those who received higher concentrations of oxygen. There was not enough information to determine the effect on long-term outcomes including neurodevelopmental disability (impairment in physical, learning, language, or behaviour areas). We judged the overall quality of the evidence to be low because of the uncertainty of the effects we found and also because we had concerns about the way in which many of the studies were carried out. The evidence in this review is current to October 2017.

Conclusions

When targeted to the infant's oxygen saturation, it is currently unclear whether the initial oxygen concentration used for resuscitation of preterm infants affects short- or long-term infant outcomes. Further trials enrolling preterm infants at birth assessing both the initial oxygen concentration and the best level of oxygen saturation to target are needed.

Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents - assessment of harmful effects

Authors: Storebø O, Pedersen N, Ramstad E, Kielsholm M, Nielsen S, Krogh HB, Moreira-Maia CR, Magnusson FL, Holmskov M, Gerner T, Skoog M, Rosendal S, Groth C, Gillies D, Buch Rasmussen K, Gauci D, Zwi M, Kirubakaran R, Håkonsen SJ, Aagaard L, Simonsen E, Gluud C

Review question

Is methylphenidate administration associated with harmful effects in children and adolescents with attention deficit hyperactivity disorder (ADHD)?

Background

ADHD is one of the most common neurodevelopmental disorders in childhood and is associated with impaired functioning and negative outcomes for development. Individuals diagnosed with ADHD are often hyperactive and impulsive. Methylphenidate, a psychostimulant, is the drug most often prescribed for children and adolescents with ADHD.

Study characteristics

We searched for available research up to January 2016 and found 260 studies with different designs. We included a number of non-randomised designs (where investigators did not assign participants to a certain treatment):

– 7 comparative cohort studies (a group of people followed over time; six studies compared 968 patients who were taking methylphenidate to 166 controls who were not taking methylphenidate; and 1 study included 1224

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patients that were taking or not taking methylphenidate during different time periods);

– 4 patient-control studies (comparing two groups of people: 53,192 were taking methylphenidate, and 19,906 were not);

– 177 non-comparative cohort studies (2,207,751 participants) with no control group (i.e. who were not taking methylphenidate);

– 2 cross-sectional studies (96 participants were taking methylphenidate at a single time point); and

– 70 patient reports/series (206 participants were taking methylphenidate).

We also included methylphenidate groups from randomised clinical trials (RCTs; experiments in which participants are randomly put into independent groups that compare different treatments). All RCTs assessed methylphenidate versus other interventions for ADHD and follow-up periods from RCTs. We only used the data from the intervention arm with methylphenidate. In all the included non-comparative cohort studies, 2,207,751 participants were taking methylphenidate. Participants' ages ranged from 3 years to 20 years.

Key results

The findings suggest that methylphenidate administration might lead to serious adverse (harmful) events, including death, cardiac problems, and psychotic disorders. About 1 in 100 patients treated with methylphenidate seemed to suffer a serious adverse event. Withdrawal from methylphenidate due to serious adverse events occurred in about 1.2 out of 100 patients treated with methylphenidate. Withdrawal from methylphenidate due to any adverse events occurred in about 7.3 out of 100 patients treated with methylphenidate. We also noted a large proportion of non-serious adverse events. More than half the patients exposed to methylphenidate seemed to suffer one or more adverse events. Withdrawal from methylphenidate due to non-serious adverse events occurred in about 6.2 out of 100 patients exposed to methylphenidate. Withdrawal of methylphenidate for unknown reasons was 16.2 out of 100 patients exposed to methylphenidate.

Quality of the evidence

The quality of the evidence and hence the certainty or reliability of the evidence for the comparative studies is very low. The reliability of the evidence for the non-comparative studies is low due to weaknesses in study design. Accordingly, it is not possible to accurately estimate the risks of adverse events in children and adolescents prescribed methylphenidate.

Conclusions

Methyphenidiate might be associated with a number of serious adverse events. Methylphenidate produces a large number of other non-serious harmful effects in children and adolescents with ADHD. We suggest that clinicians and parents are alert to the importance of monitoring adverse events in a systematic, meticulous manner. If methylphenidate is to continue to have a place in ADHD treatment in the future, we need to identify subgroups of patients in whom the benefits of methylphenidate outweigh the harms. Just as we need to be able to identify who is

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likely to benefit from treatment, we also need to be able to identify those who are most at risk of experiencing adverse events. In order to do this, we need to undertake large-scale, high-quality RCTs along with other studies aimed at identifying those who respond and those who do not respond to treatment.

Early intensive behavioral intervention (EIBI) for increasing functional behaviors and skills in young children with autism spectrum disorders (ASD)

Authors: Reichow B, Hume K, Barton EE, Boyd BA

What is the aim of this review?

The aim of this review was to find out whether early intensive behavioral intervention (EIBI) can improve functional behaviors and skills, reduce the severity of autism, and improve intelligence and communication skills for young children (less than six years old) with autism spectrum disorders, also called ASD. Cochrane researchers gathered and analysed all relevant studies to answer this question and found five relevant studies.

Key messages

The evidence supports the use of EIBI for some children with ASD. However, the results should be interpreted with caution, as the quality of the evidence is weak; only a small number of children were involved in the studies, and only one study had an optimum design in which children were randomly assigned to treatment groups.

What was studied in the review?

We examined EIBI, which is a commonly used treatment for young children with ASD. We looked at the effect of EIBI on adaptive behavior (behaviors that increase independence and the ability to adapt to one's environment); autism symptom severity; intelligence; social skills; and communication and language skills.

What are the main results of this review?

We found five relevant studies, which lasted between 24 months and 36 months. Of the five studies, three were conducted in the USA and two in the UK. Only one study randomly assigned children to a treatment or comparison group, which is considered the 'gold standard' for research. The other four studies used parent preference to assign children to groups. A total of 219 children were included in the five studies; 116 children in the EIBI groups and 103 children in generic, special education services groups. All children were younger than six years of age when they started treatment; their ages ranged between 30.2 months and 42.5 months. These studies compared EIBI to generic, special education services for children with ASD in schools.

Review authors examined and compared the results of all five studies. They found weak evidence that children receiving the EIBI treatment performed better than children in the comparison groups after about two years of treatment on scales of adaptive behavior, intelligence tests, expressive language (spoken language), and receptive language (the ability to understand what is said). Differences were not found for the severity of autism

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symptoms or a child's problem behavior. No study reported adverse events (deterioration in adaptive behaviour or autism symptom severity) due to treatment.

How up-to-date is this review?

The review authors searched for studies that had been published up to August 2017.

Grommets for children with recurring acute middle ear infections

Authors: Venekamp RP, Mick P, Schilder AGM, Nunez DA

Review question

Do children with recurring acute middle ear infections benefit from placement of grommets in both ears (with or without surgical removal of the adenoids at the same time)?

Background

An acute middle ear infection is one of the most common childhood illnesses. While most children have an occasional episode, some suffer from recurring ear infections (three or more infections over a period of a six months, or four or more in a year). Such recurring infections cause considerable distress through frequent ear pain, fever, general illness, sleepless nights and time lost from nursery or school for the child and from work for their carers. Grommets, also known as ventilation or tympanostomy tubes, can be offered as a treatment. They are tiny plastic tubes put into the eardrum by an ENT surgeon during a short operation.

Study characteristics

This review includes evidence up to 4 December 2017. We included five randomised controlled trials with a total of 805 children with recurring acute middle ear infections. All studies were performed before the introduction of vaccination against pneumococcus, a bacterium that commonly causes ear infections. Surgical removal of the adenoids was not performed in both groups in any of the trials.

Key results

We primarily looked at the difference in the proportion of children who had no further acute middle ear infections at three to six months follow-up (intermediate-term), and who had a persisting perforation (hole) in the ear drum. We also looked at some other outcomes, including the proportion of children who had no further episodes of acute middle ear infection.

<u>Grommets versus active monitoring</u>

We found low-quality evidence that fewer children who were treated with grommets had further episodes of ear infection at six and 12 months follow-up than those managed with active monitoring; three and eight children needed to be treated with grommets to benefit one, respectively. The number of ear infections at six and 12 months follow-up was also lower in the grommets group; the difference was, however, at best modest with around one fewer episode at six months and a less noticeable effect by 12 months (*low to very low-quality*

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evidence). Children treated with grommets did not have better quality of life at four or 12 months follow-up (*low-quality evidence)*.

Grommets versus antibiotic prophylaxis

It is uncertain whether or not grommets are more effective than antibiotic prophylaxis; we found very low-quality evidence that fewer children who were treated with grommets had further ear infections at six months than those receiving antibiotic prophylaxis (preventative antibiotics); five children needed to be treated with grommets to benefit one. The number of ear infections at six months, however, did not significantly differ between children treated with grommets and those receiving antibiotic prophylaxis (*very-low quality evidence*).

Grommets versus placebo drugs

We found very low-quality evidence that fewer children who were treated with grommets had further ear infections at six months than those receiving placebo drugs; three children needed to be treated with grommets to benefit one. The number of ear infections at six months was also lower in the grommets group; the difference was however at best modest with around one fewer episode (*very low-quality evidence*).

Negative effects of grommets were not systematically reported in the studies. Two studies reported on the number of children with a persistent perforation of the ear drum; this occurred in 0% (0/54) and 4% (3/76) of children receiving grommets, respectively (*low-quality evidence*).

Quality of evidence

We judged the quality of the evidence on the benefits and harms of placement of grommets in both ears for children with recurring acute middle ear infections to be low to very low due to study limitations (risk of bias) and the small to very small sample sizes of included studies (leading to imprecise effect estimates). This means that the findings of this review should be interpreted with caution since the true effects of grommets in this group of children may be different than the numbers presented.

Glucocorticosteroids administered after Kasai surgical procedure for infants with blocked or damaged bile duct

Authors: Tyraskis A, Parsons C, Davenport M

Medications used postoperatively (immediately after surgery) for infants with blocked or damaged bile duct (that is, biliary atresia)

Review question

Do medications, called glucocorticosteroids (steroids), have beneficial or harmful effects in the health of infants with biliary atresia operated by the Kasai surgical procedure (that is, portoenterostomy)? We reviewed if there was any difference in death, need for a liver transplant, postoperative jaundice (yellowish or greenish pigmentation of the skin and whites of the eyes), and harmful effects.

Background

Biliary atresia is a rare condition that may occur once in 30,000 births. In biliary atresia, the common bile duct is

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blocked or damaged; as the bile cannot leave the liver, the liver becomes damaged. An operation called 'Kasai portoenterostomy' is used to replace the damaged bile ducts with a piece of the infant's intestine. This allows the bile to drain directly from the small bile ducts at the edge of the infant's liver, straight into the intestine. Medications called glucocorticosteroids have historically been used in the treatment of biliary atresia after surgery. Two benefits of glucocorticosteroids may be that they are anti-inflammatory, and they increase bile flow. Several studies have been carried out comparing infants taking glucocorticosteroids postoperatively to those who have been given a placebo (an inactive substance that can be made to resemble an active medication or therapy). These studies try to identify if there is any measurable difference in the clearance of jaundice, survival, and need for transplantation. To organise randomised clinical trials large enough to be able to detect differences is, however, challenging.

Study characteristics

We performed a search which included studies up to 20 December 2017. We identified two randomised clinical trials (where participants are divided by chance into the trial groups) which met the requirements for our review and followed-up the participants for at least two years. We identified 19 further observational studies from which we were able to report some findings on harms in a narrative form. The randomised trials included 107 infants who were given glucocorticosteroids and 104 who were given placebo. Trials were funded by charities, public organisations, and received support from private sector companies, all of which did not seem to have any interest in the outcome of the respective trials.

Funding

The included trials outlined their sources of funding, and the review authors deemed that there were no conflicts of interest. Review authors did not receive funding to carry out this review.

Key results

We did not find any differences between the groups of infants treated with glucocorticosteroids compared with placebo in terms of mortality, adverse events, ability to clear jaundice, or need for a liver transplant.

Quality of the evidence

We assessed the two trials as having low risk of bias (we had no concerns that their design and reporting may deviate from the truth), but they were at high risk of imprecision (inexact evaluations of outcomes). They used different categories for adverse events, and we were unable to combine the data from the trials. We could not include enough infants in our analyses (only two published trials) in order to detect small differences between the two intervention groups. The certainty of the evidence was low for mortality, adverse events, ability to clear jaundice, or need for a liver transplant outcomes. One further ongoing trial was identified, with no currently available results.

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Future steps

We need further randomised clinical trials that compare glucocorticosteroids with placebo in order to find out if glucocorticosteroids are of benefit in the postoperative management of infants with biliary atresia. Such trials need to be conducted at different clinical centres.

Interventions for treating urinary stones in children

Authors: Barreto L, Jung J, Abdelrahim A, Ahmed M, Dawkins GP C, Kazmierski M

Review question

What is the evidence for treating stones of the kidney or ureter in children?

Background

Urinary stones occur in up to 5 in 100 children in high-income countries. These rates have been noted to be increasing. To treat urinary stones in children, urologists use medications, shock wave therapy, open surgery, and small scopes that are put into the bladder or through the skin. It is not clear how well each of these treatments work and what the side effects are.

Study characteristics

We included 14 studies with a total of 978 randomised children with stones in either the kidney or ureter, which connects the kidney to the bladder. The number of children in the studies varied from 22 to 221 children. There were seven trials of different types of surgery, four trials of medications and one study that compared medication with surgery. The amount of time the trials followed participants for ranged from one week to one year.

Key results

Shock waves versus medication to dissolve stones: we are uncertain about the effect on successful removal of stones, serious complications and the need for a second procedure to treat the stones.

Shock waves given slowly versus shock waves given fast: we are uncertain about the effect of slow shock waves on successful removal of stones. We are also uncertain about the effect on serious complications and the need for other procedures.

Shock waves versus treatment using a scope through the bladder to break up the stone: we are uncertain about the effect of shock waves on successful removal of stones compared to using a scope. We are also uncertain about the effect on serious complications and the need for other procedures.

Shock waves versus treatment using a scope through the skin into the kidney: shock waves are likely less successful in the removal of stones. Shock waves appears to reduce severe adverse events but more often secondary procedures are needed to remove all the stones.

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Use of a scope through the kidney with a drainage tube afterwards versus without a drainage tube: we are uncertain about the effect on successful removal of stones, serious complications or the need for more procedures.

Use of a scope through the kidney with a regular versus very small ("mini") tube through the skin: successful removal of stones are likely similar in both procedures. We did not find any data relating to serious adverse events. We are uncertain about the effect on the need for another procedure.

Alpha-blockers versus placebo with or without ibuprofen: alpha-blockers may increase successful removal of stones. We are uncertain about serious complications and the need for more procedures.

Quality of the evidence.

The quality of evidence for most outcomes was very low. This means that we are very uncertain about most of the review findings.

If you have any questions or comments with regard to the above document please feel free to contact me.

Kind regards

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