COCHRANE COMMENTARIES

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Title: Agitation on emergence from sevoflurane anaesthesia can be reduced.

Effect of sevoflurane versus other general anaesthesia on emergence agitation in children (review)

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What is this review about?

Post-operative behavioural disturbance when emerging from a general anaesthetic, known as emergence agitation (EA), is an important adverse effect. EA is a mental disturbance during recovery from general anaesthesia that may consist of hallucinations, delusions and confusion manifested by moaning, restlessness, involuntary physical activity and thrashing about in bed (Sikich, 2004)(1). However delirium is not required for a diagnosis of EA.

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Sevoflurane is an inhalational anaesthetic agent that has been widely used in paediatric anaesthetic practice since 1995. It is non-pungent and leads to rapid and smooth induction and rapid recovery. However, its use is associated with EA, especially in pre-school children. EA usually lasts about 30 minutes, during which the child may cause self-injury or disrupt the operative or recovery setting. The long-term effects of EA are largely unknown. EA is more common in surgical procedures that involve post-operative pain and in otorhinolaryngology and ophthalmological procedures. The patient risk factors for the development of EA include young age and pre-operative anxiety.

This review examines whether using alternative general anaesthetics instead of sevoflurane or usingadjunctive intra-operative medications with sevoflurane decreases the occurrence of EA.

What are the findings?

The risk of EA is lower for propofol than sevoflurane, but not for isoflurane or desflurane. If sevoflurane is used for induction and maintenance of anaesthesia, the addition of some agents reduces EA compared to sevoflurane alone. Parental presence at emergence from anaesthesia does not reduce EA.

What are the findings based on?

158 trials involving 14,045 children were included, with 69 studies using alternative GA agents (halothane, propofol, desflurane, isoflurane, ketamine) to sevoflurane and 100 studies using an adjuvant with sevoflurane (propofol, thiopentone induction, clonidine, dexmedetomidine, fentanyl, tramadol, nonsteroidal anti-inflammatory analgesia, magnesium, midazolam, ketamine).

Relative risks (RR) with 95% confidence intervals (CI) for most synthesised data are presented in Table 1. In addition, two studies with 180 participants assessed the effect of parents being present at emergence (RR 0.91, 95%CI 0.51, 1.6). Seven studes with 370 participants assessed midazolam premedication (RR 0.81, 95%CI 0.59, 1.1).

Of the 158 trials, 157 were randomised, only three were not blinded, most (65%) had no withdrawal of participants after randomisation, and only three had more than 15% participant withdrawal. All studies included pre-school age children, with most (57%) limiting age to less than 8 years. Twelve studies (8%) included children beyond the age of 12 years and 25 (16%) studies included infants.

While the risk of bias of most studies was low and the age range of participants relevant there were three main features that limit interpretation or applicability of findings. Firstly, most analyses were limited to non-painful procedures, such as MRI, or procedures with effective regional analgesia. Pain is an important factor because the behaviour of a child in pain may be misdiagnosed as EA and pain may also increase the risk of EA. Including mainly non-painful or pain-managed procedures increases certainty that the behaviour at the end of the anaesthesia is EA, but limits generalisabiltiy of findings to other operations. Some studies did include painful procedures without adequate analgesia, such as paracetamol alone for tonsillectomy. To assess the impact of this the review authors conducted analyses exluding trials in which pain could have contributed to findings for each intervention if there was significant heterogeneity between trials.

Secondly, the outcomes measures used and the threshold for diagnosis of EA varied between studies. Emergence agitation (EA) has no universal definition. The first validated scale to measure it developed in 2004, the Paediatric Anesthesia Emergence Delirium (PAED) scale, assesses severity of EA and includes 5 items, with the maximum score of 20 indicating a lack of eye contact, purposelessness of action, restlessness, inconsolability and lack of awareness of surroundings.

Although it was used in most studies, different authors used different cut-off points for EA, between a score of 10 and 16. One author used a modification of PAED scale, and others used different scales.

Finally all studies excluded children with major systemic illnesses (American Society of Anaesthetist status classification more than 2), children with chronic illness, developmental and behavioural problems.

Implications for practice

- Consider propofol for both induction and maintenance; or for maintenance; or as a 1mg/kg dose at the end of operation to decrease the risk of EA if sevoflurane is being used as well.
- If using sevoflurane for induction and maintenance of anaesthesia, consider adding clonidine, dexmedetomidine or fentanyl at any time during anaesthesia or a ketamine or midazolam bolus at the end of the operation.
- Halothane, although associated with lower risk of EA, is no longer widely used because of its other severe adverse effects, including myocardial sensitisation and arrhythmias.
- Isofluane and desflurane for induction and maintainence are not effective for decreasing risk of EA, nor is midazolam premedication or midazolam bolus at induction.

- Parental presence at emergence from anaesthesia does not reduce risk of EA.

Clinical perspective

This review is consistent with two previous reviews, one that compared halothane with sevoflurane (2) and another by Dahmani 2010(3) that studied using additional medications such as propofol, midazolam, ketamine, fentanyl and alpha-2 agonists to reduce the risk of EA in patients receiving sevoflurane or desflurane (3). The new finding in the current review is that intravenous fentanyl reduces the risk of EA. However at the present time, there is no accepted recommendation for best practice to decrease the risk of EA.

Given that a large number of studies were included and the Grade of Recommendation, Assessment, Development and Evaluation Working Group (GRADE) assessment of the evidence was moderate to high (see Table 1), anaesthetists have several effective interventions that reduce EA, especially in preschool aged children having non-painful procedures or those in which pain is well managed. While it is not clear whether EA reduction would be the same for painful procedures, some of the effective additional interventions provide additional analgesia,

and adequate analgesia should always be ordered for the post-operative period. Paediatricians may need to bring these findings to the attention of anaesthetic staff working outside paediatric centres.

Table 1: Summary of findings (SOF) table for other general anaesthesia /adjunct versus sevoflurane anaesthesia for reducing risk of emergence agitation, adapted from the SOF table in the Cochrane review

Type of administration	**Agents used**	**Relative risk 95% CI***	**Number of participant**	**Quality of evidence**
Induction & maintenance	Propofol	0.35 (0.25-0.51)	1098 (14 studies)	High
	Isoflurane	0.76 (0.46-1.23)	379 (6 studies)	Moderate
	Desflurane	1.46 (0.92-2.31)	408 (6 studies)	Moderate
Adjunct agent	Dexmedetomidine	0.37 (0.29-0.47)	851 (12 studies)	High
	Fentanyl	0.37 (0.27-0.5)	1247 (15 studies)	High
	Clonidine	0.45 (0.31-0.66)	739 (9 studies)	High
	Halothane	0.51 (0.41-0.63)	3534 (34 studies)	High

	Ketamine 0.25 mg/kg at the end	0.3 (0.13-0.69)	231 (3 studies)	Moderate

*results including all available studies

References

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