PROSPERO International prospective register of systematic reviews

Systematic review of adverse events of propofol infusion in pediatric patients

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Citation

Liliane Zorzela, Sunita Vohra, Ari Joffe, Lisa Hartling, Yoon Loke, Salima Punja, Katherine Pohlman. Systematic review of adverse events of propofol infusion in pediatric patients. PROSPERO 2013:CRD42013005397 Available from http://www.crd.york.ac.uk/PROSPERO_REBRANDING/display_record.asp?ID=CRD42013005397

Review question(s)

Question: Is propofol infusion assocaited with serious adverse events in pediatric patients?

Objectives: 1. Identify the incidence of serious adverse events associated with propofol infusion in pediatric patients.

2. To identify the propofol dose and duration of infusion associated with serious adverse events (PRIS and cardiac arrest)

3. To describe the patient characteristics associated with serious adverse events during the use of propofol infusion

4. To identify a possible association between serious adverse events related to propofol use and the patient care setting (pediatric intensive care, operating room, paediatric emergency or other)

Searches

The searches will be done in 3 main databases (MEDLINE, EMBASE and CENTRAL). We will search the websites of regulatory pharmaceutical (1) Current Problems in Pharmacology (www.mhra.gov.uk); (2) Australian Adverse Drug Reaction Bulletin (www.tga.gov.au/adr/aadrb.htm); (3)European Public Assessment Reports fromthe European Medicine Evaluation Agency

(www.emca.eu) (4) Food and Drug Administration FDA Medwatch (www.fda.gov/medwatch).

We will screen references of all retrieved articles to identify additional publications. No conference or meeting abstracts will be searched.

No language restrictions and no publication period restrictions will be applied.

Types of study to be included

We will include randomized or quasi-randomized controlled trials of parallel group or cross-over design, which use individual or cluster randomization. In the case of cross-over trials, we will include only the first arm (we will consider events that happened after the cross-over in a sensitivity analysis).

Condition or domain being studied

Propofol is an anaesthetic agent with short onset of action and short half life. These two characteristics make the drug clinically useful. However, there have been case reports of an association between propofol used in prolonged infusions and in high dosages with metabolic acidosis, liver dysfunction, arrhythmias and death. This was called Propofol infusion syndrome (PRIS). Regulatory bodies, such as FDA and Health Canada contraindicate the use of propofol as a continuous infusion in critically ill paediatric patients, mostly based on case reports but propofol is freely used in paediatric emergency rooms and operating rooms. We understand that PRIS in not exclusive to the paediatric population but, due to limitations of propofol use in critically ill

children and no restriction of its use in other paediatric populations, we believe it is important to systematically review the use of propofol infusion in children in an attempt to identify risk factors and address its safety concerns.

Participants/ population

The target population consists of paediatric patients (age ranging from 28 days to 19 years) receiving sedation using propofol for more than 60 minutes in a hospital (intensive care unit, operating room, emergency room, or any other location within the hospital) or other medical setting (for example dentist offices). The indication for sedation will not be a restriction at this time; instead,

it will be the subject of a subgroup analysis. This is a review of adverse events of propofol infusion in paediatric patients, so it has broad inclusion criteria (any children receiving propofol infusion for sedation).

Intervention(s), exposure(s)

The intervention being studied is the use of propofol as an anaesthetic drug given by continuous infusion. It is not clear the length of infusion necessary to cause PRIS. The case reports are usually associated with prolonged use (more than 48 hours) and in high doses (more than 4 mg/kg/hour). We will include patients receiving infusions lasting 60 minutes or longer, as an arbitrary number.

Further, we will exclude studies in which propofol bolus or infusion was given in more than one study arm, in order to have a propofol free comparison group and to limit the possible risk factor to one single arm. As propofol does not provide analgesia, the group receiving propofol can also receive other sedative, analgesic drugs concomitantly.

Comparator(s)/ control

The comparison group, will be any sedative or analgesic agent different from propofol, alone or in combination.

Outcome(s)

Primary outcomes

The primary outcome is the report of PRIS or any other serious adverse events resulting in cardiac arrest (with return to spontaneous circulation or use of extra-corporeal life support) or death associated with propofol use as a continuous infusion in paediatric patients. The follow-up time to measure the primary outcome for this study will be the development of the outcome of interest (PRIS or cardiac arrest) or time of hospital discharge for patients who did not develop the primary outcome.

The primary outcomes will be defined as the following:

Cardiac arrest, a reduction of cardiac output requiring any of the following: chest compressions; defibrillation, epinephrine boluses or cardiac mechanical support (extra-corporeal life support (ECLS); or ventricular assist device (VAD)).

Propofol infusion syndrome (PRIS) will be defined as metabolic acidosis, arterial pH □7.3 along with a serum bicarbonate□ 18 mg/dL; plus the presence of any signs in any the below categories (adapted from Roberts 2009):

1. rhabdomyolysis (the breakdown of muscle fibres resulting in the release of muscle fibre contents (myoglobin) into the bloodstream), defined as creatine phosphokinase (CPK) □ 10,000 IU/L or positive serum or urine myoglobin test or positive urinary casts for haemoglobin;

2. hypotension (initiation of a vasopressor agent or increase of □ 20% from baseline;

3. hepatic transaminitis (increase in aspartate aminotransferase or alanine aminotransferase, or both, □3 times above baseline);

4. hypertriglyceridaemia (serum triglyceride concentration □400 mg/dL);

5. hypoxia (partial pressure of arterial oxygen □ 60 mm Hg);

6. hyperthermia (temperature □ 38.3 °C);

7. cardiac dysfunction that includes asystole, pulseless electrical activity, ventricular fibrillation, sustained ventriculartachycardia of 30 seconds or longer, myocardial failure (ejection fraction□ 40%), or bradycardia (heart rate

□ 60 bpm);

8. renal failure that includes oliguria (urine output □ 0.5 mL/kg/hr for □ 6 hours), anuria (urine output □ 10 mL/hr for □6 hours), elevation in serum creatinine increase of □ 1 mg/dL from baseline), or hyperkalaemia (serum K+ □ 6 mg/dL

(excluding other known causes or haemolyzed specimens).

Secondary outcomes
We will also capture events that do not clearly fulfil the above inclusion criteria. These events will be reported as an unclear outcome definition and will be the subject of a sensitivity analysis.

Data extraction, (selection and coding)
All studies meeting the following criteria will be included.

1. Paediatric population: age ranging from 28 days to 19 years, exclusively;

2. Use of propofol as a continuous infusion for more than 60 minutes.

3. The comparison group will be any other sedative or analgesic agents (alone or in combination) different from propofol.

Risk of bias (quality) assessment
Clinical trials

Two review authors (LZ and SP) will independently assess the methodological quality of each trial using the Cochrane 'Risk of bias' tool (Higgins 2011). We will assess the following sources of bias for all study designs.

1. Selection bias, including randomization: describes the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. Describes the method used to conceal the allocation sequence in sufficient detail to determine whether

intervention allocations could have been foreseen in advance of, or during, enrolment.

2. Performance bias: describes all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provides any information relating to whether the intended blinding was effective.

3. Detection bias: describes all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provides any information related to whether the intended blinding was effective.

4. Attrition bias: describes the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. States whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition or

exclusions where reported, and any re-inclusions in analyses performed by the review authors.

5. Selective reporting bias: states how the possibility of selective outcome reporting was examined by the review authors, and what was found. We are aware that the adverse events related to a therapy are poorly reported in clinical trials.

6. Other source of bias: states any important concerns about bias not addressed in the other domains in the tool.

If particular questions or entries were pre-specified in the study's protocol, responses should be provided for each question or entry.

Two authors will assess the risk of bias of each trial, following the domain-based evaluation as described in the

Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). The authors will assess the domains for risk of bias; in the first three domains as 'Low risk of bias'; 'High risk of bias' and 'Unclear', which means there is an uncertain risk of bias.

Strategy for data synthesis

The main comparison will be propofol infusion and control. In this review, the control group will be called standard care and it will include the most common sedative agents used for paediatric sedation.

All analyses will be performed using the ReviewManager software. For rare events such as PRIS, we will use the Peto one-step odds ratio method. It is the least biased and most powerful method and provides the best confidence interval coverage provided there is no substantial imbalance between treatment and control group sizes within studies, and treatment effects are not exceptionally large (Higgins 2011).

We will pool data from studies that are sufficiently homogenous and with the same study design in order to perform a meta-analysis.

Analysis of subgroups or subsets

We will perform subgroups for the primary outcome (PRIS and cardiac arrest) based on the following:

1. Comparison group: if two or more trials are found using the same comparison group (for example ketamine), these studies will be subgrouped in an attempt to identify any risk increase or reduction for developing the primary outcome.

2. Dosage of propofol: we will subgroup studies using propofol infusion at equal to or less than 4mg/kg/h or more than 4mg/kg/h as this seems to be the dosage cut-off for reporting PRIS in children, but it is not clear what dose of propofol is necessary to cause PRIS. This subgroup analysis will be done as

an attempt to measure a dose-effect relationship between propofol and the development of PRIS.

3. Duration of propofol infusion: we will subgroup studies with propofol infusion lasting less than or equal to 12 hours, between 12 and 24 hours and more than 24 hours. This subgroup analysis was chosen as the duration of exposure of

propofol required to cause PRIS is unclear. It will be done in an attempt to determine if there is any relationship between duration of infusion of propofol and the development of PRIS.

4. Indication for sedation: if enough trials are found under similar settings, for example sedation for mechanical ventilation in intensive care unit or sedation procedures in the operating room, these studies will be subgrouped in an attempt to identify patient setting (location within the healthcare facility) and

indication in an association with the primary outcome.

Dissemination plans

Publication in a pediatric critical care journal, for example Pediatric Critical Care or Pediatric Anesthesia.

Contact details for further information

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Details of any existing review of the same topic by the same authors
Protocol has been published for a Cochrane review, although differently to this one, the cochrane review includes observational studies.

Anticipated or actual start date
15 August 2013

Anticipated completion date
15 January 2014

Funding sources/sponsors
This systematic review is part of Dr Liliane Zorzela's PhD thesis, Dep Pediatric, University of Alberta. Dr Sunita Vohra is her PhD supervisor and Dr Ari Joffe, Dr Lisa Hartling and Dr Yoon Loke are Liliane's thesis advisory committee. There are no direct funders for this review.

Conflicts of interest
None known

Language
English

Country
Canada

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Adolescent; Anesthetics, Intravenous; Child; Death; Heart Arrest; Humans; Infant; Propofol;

Any other information
It is part of a PhD Thesis, to compare reviews using different study designs will provide different assessment of adverse events.

Stage of review
Ongoing

Date of registration in PROSPERO
16 August 2013

Date of publication of this revision
16 August 2013

Stage of review at time of this submission	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No

Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No