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Review Article

REVIEW ARTICLE

Systematic review of the neurocognitive outcomes used in studies of paediatric anaesthesia neurotoxicity

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Abstract

Neurotoxicity of anaesthetics in developing brain cells is well documented in preclinical studies, yet results are conflicting in humans. The use of many and different outcome measures in human studies may contribute to this disagreement. We conducted a systematic review to identify all measures used to assess long-term neurocognitive outcomes following general anaesthesia (GA) and surgery in children. The quality of studies was assessed according to the Newcastle-Ottawa Scale (NOS) for observational studies. PubMed/MEDLINE, EMBASE, Cinahl, Web of Science, and the Cochrane Library were searched for studies investigating neurocognitive outcome after GA in children <18 yr. Sixty-seven studies were identified from 19 countries during 1990–2017. Most assessments were performed within cognition, sensory-motor development, academic achievement or neuropsychological diagnosis. Few studies assessed other outcomes (magnetic resonance imaging, serum-biomarkers, mortality, neurological examination, measurement of head circumference, impairment of vision). Rating according to the NOS rewarded a mean of six stars out of nine. Some concerns prevail regarding potential inter-rater variability because of equivocal description of rating criteria. Specific features such as stability over lifetime and inter-relations of outcomes (e.g. prediction of subsequent development or diagnosis of neuropsychological conditions) are discussed. The importance of validity and reliability of the various test instruments are described. The studies vary immensely in important characteristics. Future observational studies should be more consistent in the choice of study population, age at exposure, follow-up, indication for and type of surgery, and outcomes. Assessment of sensory-motor development seems feasible in young children (age <4 yr), intelligence/cognition in older children.

Keywords: anaesthesia; general; child development; infant; review

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Confronted with the lack of definite answers, researchers continue to investigate whether anaesthetics cause harm to the developing brain in children. Evidence from preclinical studies on various species including non-human primates, a variety of anaesthetic drugs, modes of administration, and durations, substantiate this concern. In humans, an association between general anaesthesia (GA) in young children and subsequent impaired neurodevelopment remains to be properly established or rejected. Single and short exposures lasting <1 h are considered 'safe' regarding neurodevelopmental outcome.[1] In a recent sibling-matched cohort study it was reported that children exposed once for inguinal hernia repair before age 3 yr showed no difference in intelligence quotient testing compared with their unexposed siblings.[2] A Swedish population-based cohort study detected a low overall difference in academic achievement and intelligence after single and multiple exposures before age 4 yr for miscellaneous types of surgeries.[3] These findings concur with the results of an international randomised trial comparing neurodevelopmental outcome at age 2 yr between infants exposed to a brief sevoflurane anaesthesia or an awake spinal-/caudal anaesthetic for inguinal herniorrhaphy; no difference was found between groups.[4] Quite the opposite, some studies focusing on exposure in ≤3- or ≤4-yr-old children to anaesthesia for miscellaneous types of surgery indicate long-term effects on cognition, learning, and behavioural disorders.[5,6] As an example, exposure to GA and surgery before age 3 yr was found to associate with a remarkably increased risk of being diagnosed with a developmental/behavioural disorder.[7]

Interestingly, various authorities interpret the existing results differently. While European scientific societies agree, that at present, there is no human evidence to support any change in anaesthetic practice in children and pregnant women,[1] the Food and Drug Administration recently warned against anaesthesia in children <3 yr of age prolonged anaesthesia.[8] Such different interpretations might have serious clinical implications for patients (e.g. postponement of surgery).

The majority of studies within the field of anaesthesia-related neurotoxicity are cohort studies, which knowingly are vulnerable to confounding. As a consequence, recent literature calls for the use of other modalities (e.g. neuroimaging and biomarkers), to evaluate neuro-apoptosis and neuro-inflammation.[9] Furthermore, other factors that might mitigate morbidity after GA and surgery in children are increasingly acknowledged and subjected to intensive research.[10–13] Despite this broadened search for answers, anaesthesia-related neurotoxicity has not yet been properly clinically defined. Consequently, it is unknown where clinical research should be focused. Multiple factors, for example, sample size; selection of exposed cohort; age at exposure; type of, and indication for, surgery; follow-up as well as type of outcome measures could likely influence results.

We hypothesised that inconsistency in the choice of outcome measures, age at exposure, and differences in study quality are major confounding factors for divergent results obtained in human studies.

The aims of this systematic review were to identify the type of outcomes used in studies investigating neurodevelopmental consequences of anaesthesia/surgery exposure in infancy and early childhood. Further, we wished to compare the studies with regard to other crucial factors and assess the methodological quality of these studies.

Methods

The study protocol was published at PROSPERO (registration ID: CRD42016042450) and reported according to the PRISMA guidelines.[14]

Search strategy

We searched PubMed/MEDLINE, EMBASE, Cinahl, Web of Science and the Cochrane Library (last search on June 16, 2017) using relevant terms concerning 'general anaesthesia' and 'neurocognitive outcome'. Via the MESH database and the EMTREE thesaurus we identified relevant search terms. Additionally, the reference list of included studies was hand-checked for other potentially relevant publications. 'Neurobehavioral outcome' was part of the search. However, most articles on postoperative behaviour assessed temporary changes (e.g. emergency delirium and anxiety). These were not considered to be long-term results of anaesthesia-related neurotoxicity and articles using only behaviour as outcomes were not included in the content analyses. Librarians at the Medical Research Library, part of The University Library of Southern Denmark, Odense University Hospital, Denmark approved the construction of the final search. The exact search for the respective databases is available as Supplementary Material (Supplementary 1).

Study selection

To be eligible for this review studies must report on:

- Age at exposure <18 yr
- Exposure to single/multiple GA or surgery (it is assumed, that surgery is only delivered with a concomitant GA)
- Evaluation of cognitive function after the exposure(s)

Studies must be published in peer reviewed journals, identified by experts within the field, or have been cited by peer reviewed papers.

We excluded studies that were not reported in English, evaluated neurotoxic effects of topically/locally administered anaesthetics, or studies conducted in animals.

Two authors (N.G.C. and S.K.) independently assessed title, abstract and full text for eligibility using the Covidence software (Covidence systematic review software, Veritas Health Innovation, Melbourne Australia. Available at https://www.covidence.org).

Outcomes

We identified all outcome measures used in studies investigating neurocognitive consequences of surgery and GA exposure in children (primary outcome).

Further, the quality of studies regarding selection and comparability of study participants, as well as ascertainment of outcomes were evaluated based on the Newcastle-Ottawa Scale (NOS).[15]

Data extraction

We recorded study ID, design, reason for anaesthesia (type of surgery or diagnostics), and specifics on anaesthetic procedure (type, drugs, doses, means of administration) if provided. We also recorded information on the population studied (study base, number of exposed/non-exposed individuals), age at exposure, male/female distribution, type of outcome, and age at assessment.