Journal of Clinical Anesthesia 49 (2018) 19–25

Contents lists available at ScienceDirect

Journal of Clinical Anesthesia

journal homepage: www.elsevier.com/locate/jclinane

Intravenous versus inhalational anesthesia for pediatric inpatient surgery – A systematic review and meta-analysis

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ARTICLE INFO

MeSH-Keywords:
Oculocardiac reflex
Postoperative nausea and vomiting
Inhalation anesthetics
Propofol
Treatment outcome

ABSTRACT

Study objective: General anesthesia is commonly used in pediatric inpatient surgery. It can be induced and maintained by either intravenous or volatile anesthetic agents. We aimed to elucidate whether intravenous or volatile anesthetic agents are superior with regards to preventing anesthesia-related complications.

Design: Using a predefined standardized study protocol we conducted a systematic review of randomized controlled trials (RCTs) with meta-analysis where appropriate searching the following data bases: CENTRAL, MEDLINE, EMBASE, metaRegister of Controlled Trials (until June 2016).

Setting and patients: We included any RCT comparing the adverse effects of intravenous or volatile anesthetic agents in pediatric inpatients. More specifically, primary endpoints were the appearance of cardiopulmonary complications or postoperative nausea and vomiting (PONV) or any cognitive dysfunction within 24 h following general anesthesia. Secondary endpoints were any other complication besides the aforementioned primary endpoints.

Measurements and main results: In total, nine RCTs (762 children) were analyzed. Regarding primary endpoints, the use of propofol during strabismus surgery significantly increased the relative risk (RR) of oculocardiac reflex (RR 4.96, 95% confidence interval [CI]: 3.13–7.87, $p < 0.00001$; two studies, 257 children). PONV was significantly less frequent after general anesthesia with intravenous than with volatile anesthetic agents (RR 0.68, 95% CI: 0.48–0.98, $p = 0.04$; five studies, 563 children). We did not find identify any further difference with regards to the predefined primary or secondary endpoints due to clinical or statistical heterogeneity.

Conclusions: Taken together, propofol increased the risk of oculocardiac reflex whereas PONV was less frequent following intravenous anesthetics compared to volatile anesthetics. The study results may help tailoring the use of either intravenous of volatile anesthetics onto the needs of pediatric inpatients. Given the clinical or statistical heterogeneity among the studies, we call for a scientific effort to increase the body of evidence on anesthetic agents in pediatric general anesthesia.

1. Introduction

General anesthesia is often required for surgery in children and may induce anesthesia-related adverse effects. Among those, the most frequent are postoperative nausea and vomiting (PONV), cardiopulmonary complications, behavioral disturbances during convalescence following general anesthesia, and postoperative pain sensation [1]. PONV is the most frequent anesthesia-related adverse effect, which may cause considerable morbidity especially in children [2,3]. Ear, nose and throat (ENT) surgery as well as strabismus surgery have been identified as predisposing surgical factors for PONV, which varies with the patients' age [4,5]. The incidence of PONV increases with the duration of surgery, with the repetitive administration of opioids, and with episodes of arterial hypotension [2,6]. While the incidence of PONV correlates with a history of previous PONV [6], the efficacy of a PONV prophylaxis medication has already been elucidated by a systematic

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https://doi.org/10.1016/j.jclinane.2018.05.014
Received 30 January 2018; Received in revised form 9 May 2018; Accepted 18 May 2018

review [7]. Cardiovascular complications may arise from general anesthesia in a considerable amount of pediatric inpatients regardless of underlying heart diseases [8]. Those complications range from bradycardia and rhythm disorders to cardiac arrest and may present during induction or maintenance of general anesthesia as well as postoperatively [9–11]. Cognitive dysfunction during convalescence following general anesthesia include hallucinations, emergence delirium, and psychomotor agitation. According to a randomized controlled trial (RCT) and a systematic review, intravenous anesthetic agents like propofol reduce the incidence of cognitive dysfunction following general anesthesia compared to inhalational anesthesia with sevoflurane [12,13]. Postoperative pain sensation may also impair postoperative convalescence in children and will require a multidisciplinary therapeutic approach [14,15].

Given that pediatric surgery is nowadays mostly performed on a day-case basis, anesthesia for pediatric inpatient surgery represents only a small proportion of all anesthetics given [17,18]. Nevertheless, extrapolating results from pediatric outpatients to pediatric inpatients may not be appropriate as inpatient surgery leads to the inclusion of a broad variety of surgeries and procedures, respectively, including cardiothoracic, gastrointestinal, and orthopedic surgery [17,19]. Of note is that a systematic review in pediatric outpatients undergoing surgery concluded that there is insufficient evidence to determine whether intravenous anesthesia with propofol reduces the risk of PONV and the risk of behavioral disturbances compared with inhaled anesthesia [16]. In addition, there was no difference between the groups with regards to respiratory or cardiovascular complications [16]. Moreover, the effect of the anesthetic agent on the incidence of cardiovascular complications during general anesthesia in pediatric inpatients remains unclear. Thus far, there has not been a systematic attempt to analyze the effect of the anesthetic agent on the incidence of postoperative pain sensation following general anesthesia in pediatric inpatients.

Consequently, there is the need for guidance to choose the best anesthesia regimen for pediatric inpatients. Therefore, we conducted this systematic review in order to elucidate whether intravenous or inhalational anesthetic agents are superior in reducing PONV, cardiovascular complications or cognitive dysfunction in pediatric inpatients.

2. Material and methods

2.1. Protocol and registration

For this systematic review of RCTs we performed meta-analyses according to the current recommendations of the Cochrane Collaboration [20] and reported results according to the criteria of the PRISMA statement [21].

2.2. Eligibility criteria

For the present study, we included RCTs in children < 18 years old (excluding neonates) undergoing elective inpatient surgery with general anesthesia. We excluded quasi- or non-RCTs. Prespecified primary or secondary endpoints had to be reported within the study reports. Patients were to remain within the hospital for at least 24 h following the surgical intervention. We compared general anesthesia performed with any kind of intravenous hypnotic agents with general anesthesia with any kind of volatile anesthetic agent. Re-admission to the hospital was not considered to be an endpoint since it would most likely reflect surgical issues. In addition, undesired effects of general anesthesia were to be reported by the parents.

2.3. Information sources and search

We searched CENTRAL, MEDLINE via Ovid SP and EMBASE via Ovid without any restriction in terms of language or date of publication. The complete search terms are listed as Supplementary material 1. Ongoing and unpublished trials were searched via the metaRegister of Controlled Trials (search terms: “pediatric anesthesia” and “pediatric surgery”). The search was conducted on June 09th, 2016. We also retrieved information from the Cochrane Database of Systematic Reviews. Finally, we contacted the first authors of published trials with regards to missing data or unclear study protocols as well as well as experts in the field of pediatric anesthesia in order to access any unpublished data or additional information regarding ongoing trials.

2.4. Study selection

Two reviewers (PS and FH) independently screened all titles and abstracts identified by the literature search. After exclusion of irrelevant studies, the remaining studies were assessed for relevance as full-texts. In case of conflicting opinions regarding the relevance of certain publications, a third independent reviewer (RS) was involved. Translation service was used when necessary.

2.5. Data collection process

Following identification of relevant literature, data were extracted by two independent researchers (FH and RS) using a predefined standardized data extraction form for each publication. Extracted parameters included study population and criteria for patient selection, severity of the reported disease, relevant comorbidities, general conditions and endpoint analyses. In case of substantial clinical heterogeneity no meta-analysis was performed. We screened for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting according to the risk-of-bias tool [20] in order to assess the methodical quality of any included study. We screened the individual studies for selection bias, performance bias, detection bias, and attrition bias.

2.6. Clinical endpoints

The following endpoints were a priori defined.

Primary endpoints: appearance of cardiopulmonary complications (including arterial hypotension) or PONV or any cognitive dysfunction within 24 h following general anesthesia.

Secondary endpoints: pain sensation following general anesthesia, the need for re-intubation and mechanical ventilation, time to discharge from post-anesthesia care unit to the regular ward, in-hospital mortality rate, patients' and parents' satisfaction with general anesthesia (as proven by questionnaire), and any other complication besides the aforementioned primary endpoints.

2.7. Summary measures and synthesis of results

For quantitative data synthesis we used Cochrane's Review Manager (RevMan [Computer program]. Version 5.3: The Nordic Cochrane Centre, The Cochrane Collaboration 2014, Copenhagen, Denmark). Dichotomous and continuous endpoints were analyzed. To evaluate whether dichotomous endpoints of individual studies were statistically significant, we calculated p values for the effect measures using Fisher's exact test. The pooled studies were evaluated for clinical and for statistical heterogeneity. In case of moderate clinical heterogeneity, a meta-analysis was performed using the random-effects model otherwise using the fixed-effect model [22]. In case of severe clinical heterogeneity no meta-analysis was performed. Statistical heterogeneity was assessed with Cochran's Test und subsequent calculation of I^2. Substantial statistical heterogeneity was assumed if I^2 was > 50%. If I^2 was > 80% individual studies were not compared with each other but the results of each study were reported separately. In order to assess the pooled relative risk (RR) we used the Mantel-Haenszel method. In case of continuous endpoints, the effect measure of the mean difference or