Mol Neurobiol (2017) 54:4353–4364
DOI 10.1007/s12035-016-9982-3

Emergence and Recovery Characteristics of Five Common Anesthetics in Pediatric Anesthesia: a Network Meta-analysis

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Received: 10 March 2016 / Accepted: 14 June 2016 / Published online: 24 June 2016

Abstract Desflurane, halothane, isoflurane, propofol, and sevoflurane are widely used anesthetics in pediatric anesthesia. Adverse effect including emergence agitation, postoperative nausea and vomiting, and postoperative pain are common. Prolonged extubation time and emergency time are also troubling anesthesiologists. Previous studies have noted the characteristics of various anesthetics in pediatric anesthesia, while the results were inconclusive and conflicting. In this study, we aimed at performing a comprehensive network meta-analysis concerning the emergence and recovery characteristics of pediatric anesthetics. Relevant articles were retrieved and selected according to our inclusion criteria. Network meta-analysis was performed with a random-effect model within a Bayesian framework. ORs and corresponding 95 % credible intervals were calculated by Markov chain Monte Carlo methods. Node-splitting method was used to calculate the inconsistency. Rank probabilities were assessed by the surface under the cumulative ranking curve (SUCRA). Propofol was recommended as the most efficient and safe anesthetic in pediatric anesthesia with few adverse effects. Desflurane has the highest incidence of emergence agitation and worst recovery characteristics. Halothane was regarded as an efficient anesthetic with the best recovery characteristics, while postoperative nausea and vomiting is a common adverse effect. Isoflurane was reported to be the safest concerning postoperative pain, and cases using sevoflurane in pediatric anesthesia reported the highest incidence of analgesic requirement. Our network meta-analysis demonstrated that propofol was suggested as the first choice in the clinical practice for its efficiency and safe in pediatric anesthesia.

Keywords Pediatric anesthesiology · Anesthesiology · Pharmacology · Adverse effect

Introduction

Patient safety has always been the dominant issue in the specialty of anesthesia, especially in pediatric anesthesia. Desflurane, halothane, isoflurane, propofol, and sevoflurane are five widely used anesthetics in general anesthesia by pediatric anesthesiologists. Desflurane is an inhalational anesthetic agent. It has the advantage of rapid emergence and recovery from general anesthesia, especially in pediatric patients [1]. Volatilized halothane often acts as an inhalation anesthetic in general anesthesia as well. The induction and recovery are fast, and the depth of anesthesia can be rapidly altered. Isoflurane is a volatile anesthetic. It has been used in pediatric anesthesia for more than 30 years. Propofol is an intravenous anesthetic. It is short-acting with rapid induction and emergence. It was believed that the use of propofol in general anesthesia could reduce the incidence of emergence agitation. Sevoflurane is another inhalational anesthetic agent. It has been widely used in the induction and maintenance of anesthesia. Sevoflurane also yield rapid onset and offset of action in general anesthesia [2].

Electronic supplementary material The online version of this article (doi:10.1007/s12035-016-9982-3) contains supplementary material, which is available to authorized users.

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However, in the daily use of anesthetics, adverse effect including emergence agitation (a mental disturbance during recovery from general anesthesia that may consist of hallucinations, delusions, and confusion manifested by moaning, restlessness, involuntary physical activity, and thrashing about in the bed [3]), postoperative nausea and vomiting, and postoperative pain which requires analgesics are common. As reported by 30-month survey, postoperative nausea and vomiting had an overall incidence of 6 % [4]. The incidence rate of emergence agitation is also relatively high, varying from 20 to 80 % depending on surgical procedure, adjunct medication, age, and physiological status of patients [5, 6]. Postoperative emergence agitation is detrimental which may result in prolonged post anesthesia care unit (PACU) stay. All these adverse effects result in sufferings and influence the recovery of patients. Unrelieved pain in childhood may also increase pain vulnerability in later life [7]. Besides, prolonged extubation time and emergency time are troubling anesthesiologists as well.

Previous studies have also noted the characteristics of various anesthetics in pediatric anesthesia, while the results were inconclusive and conflicting. For example, according to Sethi et al., desflurane and sevoflurane have comparable effect on postoperative emergence agitation [8]. Whereas He et al. reviewed in their meta-analysis that desflurane may have less adverse effects than sevoflurane in pediatric anesthesia [9].

In this study, we aimed at performing a comprehensive and credible network meta-analysis concerning the emergence and recovery characteristics of desflurane, halothane, isoflurane, propofol, and sevoflurane. The results of our analysis may provide some evidence for pediatric anesthesiologists in their selection of anesthetics.

Material and Methods

Search Strategy

Relevant articles published from 2000 to 2015 were retrieved from MEDLINE, Embase, and Cochrane Library. Keywords as follows were used for searching: "Child, Anesthesia, Desflurane, Halothane, Isoflurane, Propofol, Sevoflurane"; we searched MEDLINE using medical subject headings (MeSH) and text words. Initial search was performed by two reviewers screening titles and abstracts of retrieved articles independently. Irrelevant studies were expelled, and full text of enrolled articles were evaluated for inclusion. Reference list of acquired articles were also checked manually for relevant studies.

Inclusion and Exclusion Criteria

Studies involved in this research have to meet the following criteria. (1) The study was designed as randomized or quasi-randomized controlled trial (RCT). (2) Subjects enrolled in the study were children younger than the age of 18 presenting for pediatric anesthesia with or without surgical intervention. (3) The study should mention the comparison between at least two of the five studied anesthetics interventions, i.e., sevoflurane anesthetic with or without nitrous oxide, propofol, volatile desflurane, halothane, and isoflurane. The effect of pharmacological adjuncts such as fentanyl or other opioids and non-pharmacological adjuncts such as parental presence was not investigated in the present research. (4) Clinical outcomes of the enrolled study should include emergence agitation, postoperative nausea and vomiting, requiring an analgesic, extubation time, emergency time, or duration of PACU stay. (5) Sufficient data should be provided in original studies. Duplicated studies and publications in the form of reviews, meeting or conference abstracts, and case reports were excluded from the present analysis.

Studies will be excluded if they meet the following criteria: (1) the age of enrolled subjects were older than 18 or not descript detailed; (2) the publication type of study were abstract, conference paper, or review; (3) and the study cannot provide sufficient and qualified data.

The outcomes of this study were emergence agitation (defined as the number of subjects with postoperative behavioral disturbance, as measured by the authors of included studies), postoperative nausea and vomiting, requiring an analgesic, extubation time, emergency time, and duration of PACU stay.

Data Extraction and Quality Assessment

Two reviewers (Jianrong Guo and Xiaoju Jin) extracted the data from the enrolled studies independently using a standardized data collection form. Discrepancies between reviewers were resolved by discussion; otherwise, a third reviewer would decide (Huan Wang). We also contacted the authors of the relevant study when additional information was required. Important information extracted from original articles including the first author's name, year of publication, numbers of enrolled subjects, age of subjects, type of surgery, premedication and doses, pharmacological adjuncts and doses, anesthetic interventions, and clinical outcomes (emergence agitation, postoperative nausea and vomiting, requiring an analgesic, extubation time, emergency time, or duration of PACU stay). The quality of eligible studies was evaluated according to the Cochrane Collaboration Handbook (www.cochrane.de).

Statistical Analysis

A pair-wise meta-analysis was performed to combine studies addressing the same clinical outcome and studied anesthetics; the results were evaluated by the odds ratio (OR) with 95 % confidential interval (CI). Heterogeneity was assessed by the

I^2 test, with an $I^2 > 50$ % considered as the existence of significant heterogeneity. For groups without significant heterogeneity, fixed-effect model was applied, ORs were calculated by the Mantel-Haenszel method, whereas ORs for subgroups with significant heterogeneity were calculated by random-effect model and the DerSimonian and Laird method. Calculations in traditional meta-analyses were performed by STATA 12.0 (Stata Corp, College Station, TX) software.

In addition to pair-wise meta-analyses making direct comparison between two anesthetics, a network meta-analysis concerning multiple treatments was performed with a random-effect model within a Bayesian framework [10]. ORs and corresponding 95 % credible intervals (CrIs) were calculated by Markov chain Monte Carlo methods with WinBUGS (MRC Bio-statistics Unit, Cambridge, UK). Sensitivity analysis was conducted to verify the robustness of the results. This network analysis enabled the incorporation of indirect comparisons constructed from two trials that have one anesthetic study in common. The method combined both direct and indirect evidence for any given pair of anesthetics and certain outcomes.

Besides, the pooled ORs from the network meta-analysis and ORs from pair-wise meta-analyses of direct comparisons were compared to estimate the consistency between direct and indirect comparisons. To assess the consistency, the node-splitting method was used to calculate the inconsistency of the model. The method separated the evidence concerning certain comparison into direct and indirect evidence, and the inconsistency was reported by its Bayesian P value [11]. We also sorted the studied anesthetics for each outcome based on their rank probabilities. The rank probabilities were assessed for each anesthetic by the surface under the cumulative ranking curve (SUCRA) as previously described [12].

To assess the influence of single study on the overall results, sensitivity analyses were conducted by discarding individual studies sequentially. The publication bias was evaluated by Deek's funnel plot asymmetry test, with Egger's linear regression test applied to measure funnel plot asymmetry. A two-side P less than 0.1 was considered as significant. Sensitivity analysis and publication bias were calculated by STATA 12.0 (Stata Corp, College Station, TX) software as well.

Result

Study Characteristics

Nine hundreds and fifty-six studies were identified from literature search, 908 studies were excluded after screening titles, abstracts, and full text. Forty-eight eligible studies were enrolled in this meta-analysis, with a total of 4485 children aged from 0 to 18 involved [2, 8, 13–58]. Subjects involved in this meta-analysis were anesthetized by desflurane, halothane, isoflurane, propofol, or sevoflurane. Outcomes including emergence agitation, postoperative nausea and vomiting, requiring an analgesic, extubation time, emergency time, or duration of PACU stay were recorded and analyzed (Table 1). Eligible publications were categorized by studied anesthetics and summarized in Fig. 1. The results of sensitivity analysis verified the robustness of the results of pair-wise meta-analysis (Table S1, Table S2, Table S3, Table S4, Table S5 and Table S6). Figure S1 exhibited that there was no publication bias in the included studies.

Results from Network Meta-analysis

Emergence Agitation

As a primary outcome of this analysis, a network pair-wise meta-analysis was performed concerning the effect of five anesthetics on emergence agitation. A total of 39 studies including direct or indirect comparisons between studied anesthetics were involved. Anesthetics were compared with each other independently; ORs and corresponding 95 % CrIs were calculated. As indicated in the result, compared to desflurane, halothane and propofol have significantly lower incidence rate of emergence agitation (OR = 0.39, 95 % CrI 0.18–0.88; OR = 0.17, 95 % CrI, 0.07–0.41, separately, Table 2); the effect of isoflurane and sevoflurane on emergence agitation is similar to desflurane (OR = 0.53, 95 % CrI 0.19–1.50; OR = 0.69, 95 % CrI: 0.34–1.40, separately, Table 2). Of all the five studied anesthetics, propofol has the lowest incidence rate of emergence agitation (Fig. 2).

Postoperative Nausea and Vomiting

Thirty-three studies were involved in the investigation concerning the effect of anesthetics on postoperative nausea and vomiting. However, we did not get much significant results from the calculation. We observed that propofol has a lower incidence rate of postoperative nausea and vomiting than halothane (OR = 0.41, 95 % CrI 0.20–0.80, Table 2).

Requiring an Analgesic

We enrolled 19 studies in the calculation about the use of anesthetics and the need of analgesics. As indicated in Table 2, sevoflurane has significantly higher rate of analgesics requirement than isoflurane (OR = 4.06, 95 % CrI 1.02–17.55).

Table 1 Main characteristics of included studies

Study	Size	Age	Type of surgery	Premedication (mg/kg)	Analgesia	Intervention	Endpoints
Sethi 2013	88	2–6 y	Cataract surgery	None	Subtenon block	Desflurane, sevoflurane	①②③⑤⑥
Hasani 2013	88	3–6 y	Hernia repair surgery	Midazolam, 0.3	0.5 % bupivacaine, fentanyl 3 mcg/kg, paracetamol 40 mg/mg	Propofol, sevoflurane	①②
Locatelli 2013	260	1–6 y	Sub-umbilical surgery	Midazolam, 0.5	Paracetamol 40 mg/kg, codeine 1 mg/kg, 0.25 % bupivacaine 1 ml/kg	Desflurane, sevoflurane	①⑤
Singh 2012	75	4 m–7 y	Sub-umbilical surgery	None	0.2 % bupivacaine, paracetamol 30 mg/kg	Isoflurane, desflurane, sevoflurane	①③④⑤⑥
Zand 2011	167	2–7 y	Sub-umbilical surgery	None	0.25 % bupivacaine	Halothane, sevoflurane	①⑤⑥
Pieters 2010	42	3–7 y	Adenotonsillectomy	None	Fentanyl 2 mcg/kg	Propofol, sevoflurane	①②④⑥
Singh 2009	80	1–12 y	Spinal surgery	Atropine, 0.04	Fentanyl 2 mcg/kg	Isoflurane, sevoflurane	①②④⑤
Konig 2009	179	2–12 y	Dental surgery	Acetaminophen, 20 Midazolam, 0.5	Fentanyl 2 mcg/kg	Propofol, sevoflurane	①②③
Bryan 2009	200	18 m–7 y	MRI	None	None	Propofol, sevoflurane	①
Nakayama 2007	186	2–5 y, 6–11 y	Otorhinolaryngological surgery	Atropine, 0.01	Lidocaine 10 mg, fentanyl 2 mcg/kg, flurbiprofen axetil 1 mg/kg	Propofol, sevoflurane	①②④⑤⑥
Meyer 2007	59	1–6 y	Sub-umbilical surgery	Midazolam, 0.4	Caudal block	Isoflurane, sevoflurane	①②③④⑥
Mayer 2006	38	12 m–7 y	Minor ear-nose-throat surgery	Midazolam, 0.5	Paracetamol 30 mg/kg	Desflurane, sevoflurane	②③④⑥
Isik 2006	80	5–15 y	Hypospadias/orchidopexy/ skin grafting/tympanoplasty/ debridement/pyeloplasty	Midazolam, 0.5	Fentanyl 1 mcg/kg	Desflurane, sevoflurane	②④⑤
Bortone 2006	110	1–6 y	Sub-umbilical surgery	None	Paracetamol 20 mg/kg, 0.25 % bupivacaine	Isoflurane, sevoflurane	①⑤
Kain 2005	102	3–10 y	Adenoidectomy/strabismus/ herniorrhaphy/endoscopy/ hydrocele/orchiopexy/ circumcision	None	None	Sevoflurane, halothane	①
Demirbilek 2004	120	2–7 y	Adenoidectomy/ tonsillectomy	Midazolam, 0.5	Fentanyl 2.5 mcg/kg	Sevoflurane, desflurane	①②④⑤⑥
Cohen 2004	56	0–3 y	NR	None	Caudal block or fentanyl 1 mcg/kg	Propofol, sevoflurane	①③④⑤⑥
Valley 2003	48	1–7 y	Sub-umbilical surgery	Midazolam	Regional or local anesthetic block	Desflurane, sevoflurane	⑤⑥
Cohen 2003	53	2–36 m	General surgery/urology/otolaryngology/ orthopedics/plastic surgery/ ophthalmology	None	Caudal block or fentanyl 2 mcg/kg	Sevoflurane, propofol	①②③④⑤
Murray 2002	130	0–7 y	Short otolaryngology procedures	None	None	Halothane, sevoflurane	①
Cohen 2002	100	2–7 y	Adenoidectomy	None	Fentanyl 2.5 mcg/kg	Desflurane, sevoflurane	①②③④⑤
Le Berre 2001	40	2 m–6 y	Sub-umbilical surgery	Midazolam, 0.2	Caudal block	Sevoflurane, isoflurane	④⑤
Hallen 2001	60	3–8 y	Myringotomy	Midazolam, 0.3	Paracetamol 25 mg/kg	Sevoflurane, halothane	①②⑤⑥
Viitanen 2000	80	1–3 y	Adenoidectomy	None	Diclofenac 12.5 mg/kg	Sevoflurane, halothane	②③⑤
Uezono 2000	16	1–5 y	Eye examination	Midazolam, 0.5	Acetaminophen 30 mg/kg	Sevoflurane, propofol	①④⑤⑥
Picard 2000	50	3–10 y	Tonsillectomy	None	Bupivacaine 2 mg/kg, acetaminophen 20 mg/kg, ibuprofen 10 mg/kg	Propofol, sevoflurane	①②④⑥
Galinkin 2000	265	9 m–6 y	Myringotomy	Midazolam, 0.5; acetamino-phen, 10	Fentanyl 2 mcg/kg	Sevoflurane, halothane	①②⑥
Cravero 2000	43	6 m–10 y	Bilateral myringotomy	None	Acetaminophen 25 mg/kg	Sevoflurane, halothane	①②⑥
Cravero 2000	32	6 m–10 y	MRI	None	None		①②⑥

Table 1 (continued)

Study	Size	Age	Type of surgery	Premedication (mg/kg)	Analgesia	Intervention	Endpoints
						Sevoflurane, halothane	
Viitanen 1999	52	1–3 y	Adenoidectomy	None	Lidocaine 10 mg	Propofol, sevoflurane	①②③⑤⑥
Valley 1999	40	4 m–14 y	Sub-umbilical surgery	None	Regional or local anesthetic block	Isoflurane, sevoflurane	①
Lopez Gil 1999	120	6 m–12 y	Sub-umbilical surgery	Midazolam, 0.5	Fentanyl 3 mcg/kg	Propofol, sevoflurane	①③
Lapin 1999	100	6 m–6 y	Myringotomy	Midazolam, 0.5	Acetaminophen 15–30 mg/kg	Halothane, sevoflurane	①⑥
Gurkan 1999	40	3–15 y	Strabismus surgery	None	Acetaminophen 10 mg/kg	Propofol, sevoflurane	①②③
Davis 1999	200	1–5 y	Bilateral myringotomy	Midazolam, 0.2	Ketorolac 1 mg/kg	Halothane, sevoflurane	①②③
Chiu 1999	40	1–10 y	Urological procedures	Trimeprazine, 2	Ilioinguinal or caudal block	Sevoflurane, halothane	①②⑤
Beskow 1999	62	8 m–18 y	Hernia repair/circumcision/cystoscopy/ orchidofunicolysis/anometry/ coloscopy/incision of abscess/removal of surgical dressings	Midazolam, 0.4; atropine, 0.02	Lidocaine 1 mg/ml	Halothane, sevoflurane	①②③⑤
Guard 1998	50	2–8 y	Urological surgery	None	Lumbar or caudal epidural block	Sevoflurane, propofol	②③④⑤⑥
Crawford 1998	60	3–12 y	Orthopedic/urological surgery	None	Fentanyl 2 mcg/kg, ilioinguinal/ iliohypogastric nerve blocks	Propofol, halothane	②③
Welborn 1996	80	1–7 y	Adenoidectomy	Midazolam, 0.5	None	Sevoflurane, halothane, desflurane	①②⑤⑥
Sury 1996	40	6 m–6 y	Urological, plastic or orthopedic surgery	Atropine, 0.02	0.25 % bupivacaine 2.5 mg/kg or diclofenac 0.5–1 mg/kg or both	Sevoflurane, halothane	①②③⑤⑥
Rieger 1996	41	2–10 y	Adenotomy	Midazolam, 0.5; atropine, 0.02	None	Sevoflurane, halothane	①②④⑤
Kataria 1996	428	0–18 y	Inpatient surgical procedures	Midazolam	Fentanyl	Sevoflurane, halothane	①②④⑤
Epstein 1995	40	9 m–16 y	Otorhinolaryngologic/orthopedic surgery	None	Fentanyl 1 mcg/kg	Sevoflurane, halothane	①④⑤
Hannallah 1994	100	2–12 y	Eye muscle surgery/ plastic surgery/dental restoration/ urological procedures	None	0.25 % bupivacaine	Propofol, halothane	②④⑤
Reimer 1993	75	2–12 y	Strabismus surgery	None	Acetaminophen 10 mg/kg, codeine 1.0 mg/kg	Halothane, propofol	②③
Naito 1991	30	1–7 y	Pulsed dye laser therapy	None	None	Sevoflurane, halothane	①②④
Borgeat 1990	40	3–8 y	Ent procedures	Atropine, 0.04	None	Propofol, halothane	①②③④

m month, *y* year, *NR* not report

① Emergence agitation

② Postoperative nausea and vomiting

③ Requiring an analgesic

④ Extubation time

⑤ Emergency time

⑥ Duration of PACU stay

Extubation Time

Twenty-one eligible studies mentioned the effect of anesthetics on extubation time. Cases using desflurane have a significantly longer duration before extubation compared to other anesthetics (halothane: WMD = 7.48, 95 % CrI 4.05–10.96; isoflurane: WMD = 4.37, 95 % CrI: 0.74–7.90; propofol: WMD = 3.82, 95 % CrI 0.82–7.04; sevoflurane: WMD = 3.27, 95 % CrI 0.95–5.64). Besides, halothane was observed to have significantly longer extubation time than propofol (WMD = 3.66, 95 % CrI: 0.85–6.30) and sevoflurane (WMD = 4.19, 95 % CrI 1.74–6.70).

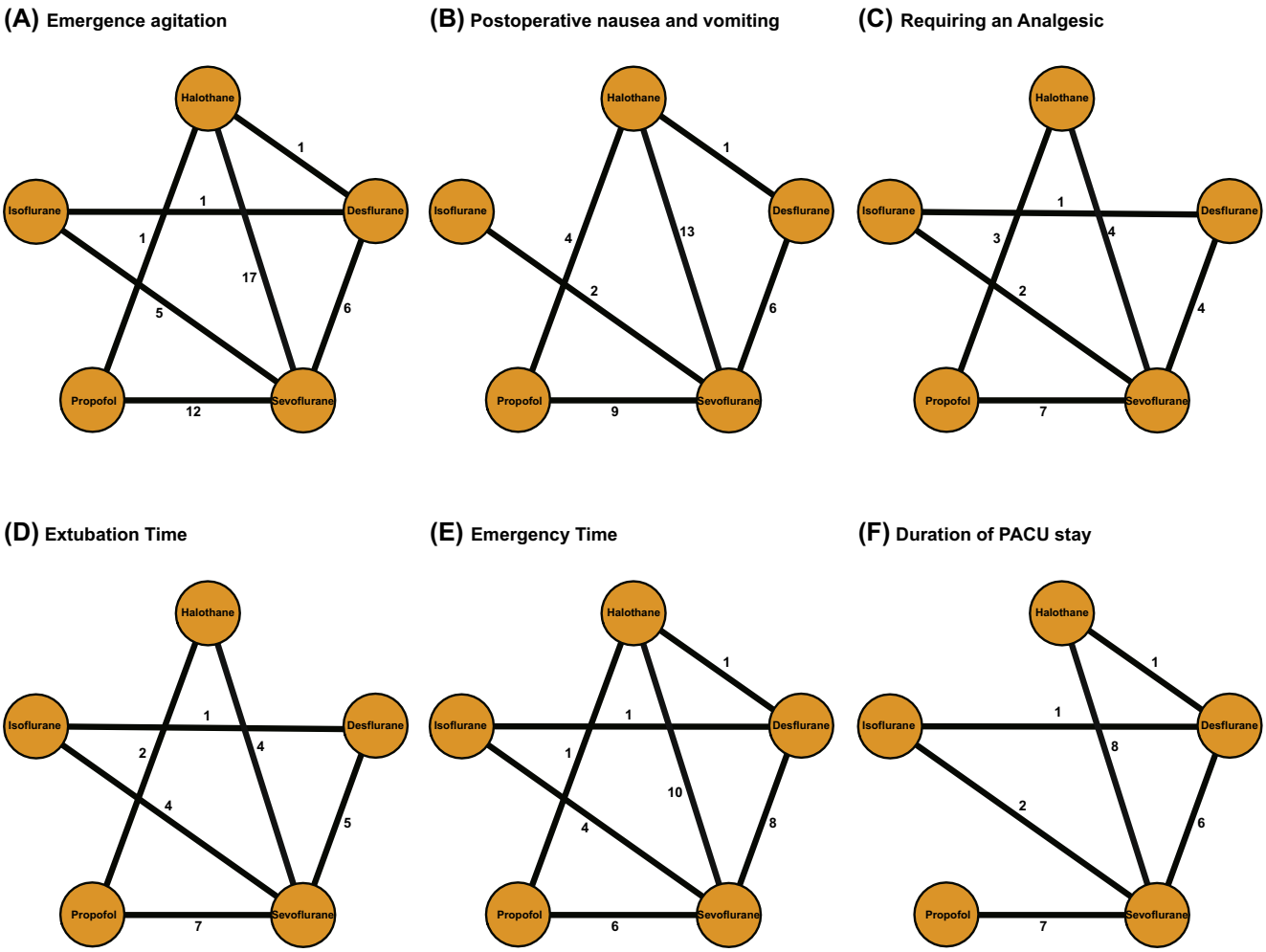

Fig. 1 **a**–**f** Evidence network of eligible comparisons for network meta-analysis. *Numbers* by the lines indicates the cumulative number of enrolled studies for each direct comparison

Emergency Time

Twenty-seven studies were involved in the analysis regarding emergency time, namely the time when spontaneous eye opening was detected without stimulus in a quiet, warm, and calm environment. According to our results, patients using halothane as anesthetics had the shortest emergency time compared to ours (desflurane: WMD = −9.65, 95 % CrI −13.63, −5.86; isoflurane: WMD = −5.77, 95 % CrI −11.20, −0.89; propofol: WMD = −6.60, 95 % CrI −10.94, −2.52; sevoflurane: WMD = −7.31, 95 % CrI −10.25, −4.74).

Duration of PACU Stay

Twenty-one studies focused on the effect of anesthetics on the duration of PACU stay. Halothane was observed to have a significantly longer duration of PACU stay than desflurane (WMD = 6.93, 95 % CrI 0.53–13.32). No other significant results were identified about the duration of PACU stay.

Relative Ranking of Five Anesthetics

In secondary analyses, we compared the estimate rank probabilities of different anesthetics by SUCRA. The results were illustrated in Table 3. As indicated by the data, propofol ranked the highest in emergence agitation and postoperative nausea and vomiting, which means it has the lowest incidence rate concerning the two outcomes. Regarding the requirement of anesthetics, the use of isoflurane indicated the lowest rate of anesthetics requirement. Desflurane ranked the highest for extubation time, emergency time, and duration of PACU stay; however, it had the highest incidence rate of emergence agitation as well. Besides, of all the five studies anesthetics, halothane ranked the lowest in postoperative nausea and vomiting, extubation time, emergency time, and duration of PACU stay, which made it the most unsatisfying anesthetics according to our calculation.

Table 2 The efficacy (emergence agitation) and tolerability (PONV, requiring an analgesic, extubation time, emergency time, duration of PACU stay) of five anesthetics in children according to the network meta-analysis using odds ratios (ORs) and corresponding 95 % credential intervals (Crls)

Emergence agitation	*Desflurane*	*0.39 (0.18, 0.88)*	0.53 (0.19, 1.50)	*0.17 (0.07, 0.41)*	0.69 (0.34, 1.40)
	2.58 (1.11, 5.70)	*Halothane*	1.37 (0.53, 3.50)	*0.42 (0.20, 0.84)*	*1.78 (1.10, 2.70)*
	1.88 (0.66, 5.30)	0.74 (0.29, 1.99)	*Isoflurane*	*0.31 (0.11, 0.85)*	1.30 (0.56, 3.00)
	6.50 (2.50, 15.00)	*2.52 (1.21, 4.90)*	*3.43 (1.20, 9.00)*	*Propofol*	*4.20 (2.40, 7.60)*
	1.45 (0.72, 2.90)	*0.57 (0.37, 0.88)*	0.77 (0.33, 1.80)	*0.24 (0.13, 0.42)*	*Sevoflurane*
PONV	*Desflurane*	1.21 (0.46, 3.22)	0.90 (0.14, 5.73)	0.51 (0.18, 1.37)	0.87 (0.38, 2.01)
	0.83 (0.31, 2.17)	*Halothane*	0.72 (0.11, 4.24)	*0.41 (0.20, 0.80)*	0.71 (0.42, 1.22)
	1.13 (0.17, 7.81)	1.39 (0.24, 8.93)	*Isoflurane*	0.56 (0.09, 3.63)	0.99 (0.18, 5.80)
	2.02 (0.73, 5.65)	*2.46 (1.24, 5.06)*	1.78 (0.28, 10.99)	*Propofol*	1.75 (0.98, 3.25)
	1.16 (0.50, 2.64)	1.40 (0.82, 2.38)	1.01 (0.17, 5.43)	0.57 (0.31, 1.03)	*Sevoflurane*
Requiring an analgesic	*Desflurane*	1.22 (0.33, 4.40)	0.37 (0.07, 1.81)	1.08 (0.29, 3.47)	1.59 (0.53, 4.31)
	0.85 (0.23, 3.12)	*Halothane*	0.31 (0.06, 1.45)	0.89 (0.36, 1.94)	1.30 (0.59, 2.70)
	2.70 (0.55, 13.72)	3.20 (0.69, 16.98)	*Isoflurane*	2.80 (0.59, 13.65)	*4.06 (1.02, 17.55)*
	0.96 (0.29, 3.49)	1.15 (0.51, 2.78)	0.35 (0.07, 1.70)	*Propofol*	1.50 (0.79, 2.87)
	0.66 (0.23, 1.90)	0.77 (0.37, 1.72)	*0.24 (0.06, 0.96)*	0.68 (0.35, 1.26)	*Sevoflurane*
Extubation Time	*Desflurane*	*7.48 (4.05, 10.96)*	*4.37 (0.74, 7.90)*	*3.82 (0.82, 7.04)*	*3.27 (0.95, 5.64)*
	−7.48 (−10.96, −4.05)	*Halothane*	−3.10 (−7.08, 0.77)	*−3.66 (−6.30, −0.85)*	*−4.19 (−6.70, −1.74)*
	−4.37 (−7.90, −0.74)	3.10 (−0.77, 7.08)	*Isoflurane*	−0.56 (−4.11, 3.19)	−1.09 (−4.16, 1.97)
	−3.82 (−7.04, −0.82)	*3.66 (0.85, 6.30)*	0.56 (−3.19, 4.11)	*Propofol*	−0.54 (−2.67, 1.43)
	−3.27 (−5.64, −0.95)	*4.19 (1.74, 6.70)*	1.09 (−1.97, 4.16)	0.54 (−1.43, 2.67)	*Sevoflurane*
Emergency time	*Desflurane*	*9.65 (5.86, 13.63)*	3.87 (−1.25, 8.95)	3.06 (−1.50, 7.72)	2.36 (−0.71, 5.29)
	−9.65 (−13.63, −5.86)	*Halothane*	*−5.77 (−11.20, −0.89)*	*−6.60 (−10.94, −2.52)*	*−7.31 (−10.25, −4.74)*
	−3.87 (−8.95, 1.25)	*5.77 (0.89, 11.20)*	*Isoflurane*	−0.78 (−6.39, 4.92)	−1.51 (−5.84, 2.97)
	−3.06 (−7.72, 1.50)	*6.60 (2.52, 10.94)*	0.78 (−4.92, 6.39)	*Propofol*	−0.71 (−4.21, 2.73)
	−2.36 (−5.29, 0.71)	*7.31 (4.74, 10.25)*	1.51 (−2.97, 5.84)	0.71 (−2.73, 4.21)	*Sevoflurane*
Duration of PACU Stay	*Desflurane*	*6.93 (0.53, 13.32)*	3.42 (−9.48, 16.06)	6.44 (−0.63, 13.55)	3.29 (−1.88, 8.36)
	−6.93 (−13.32, −0.53)	*Halothane*	−3.47 (−16.54, 9.11)	−0.48 (−7.05, 6.12)	−3.61 (−7.84, 0.56)
	−3.42 (−16.06, 9.48)	3.47 (−9.11, 16.54)	*Isoflurane*	3.04 (−9.91, 16.34)	−0.13 (−12.00, 11.93)
	−6.44 (−13.55, 0.63)	0.48 (−6.12, 7.05)	−3.04 (−16.34, 9.91)	*Propofol*	−3.12 (−8.22, 1.74)
	−3.29 (−8.36, 1.88)	3.61 (−0.56, 7.84)	0.13 (−11.93, 12.00)	3.12 (−1.74, 8.22)	*Sevoflurane*

P values in italics are significant

PONV postoperative nausea and vomiting, *PACU* post anesthesia care unit

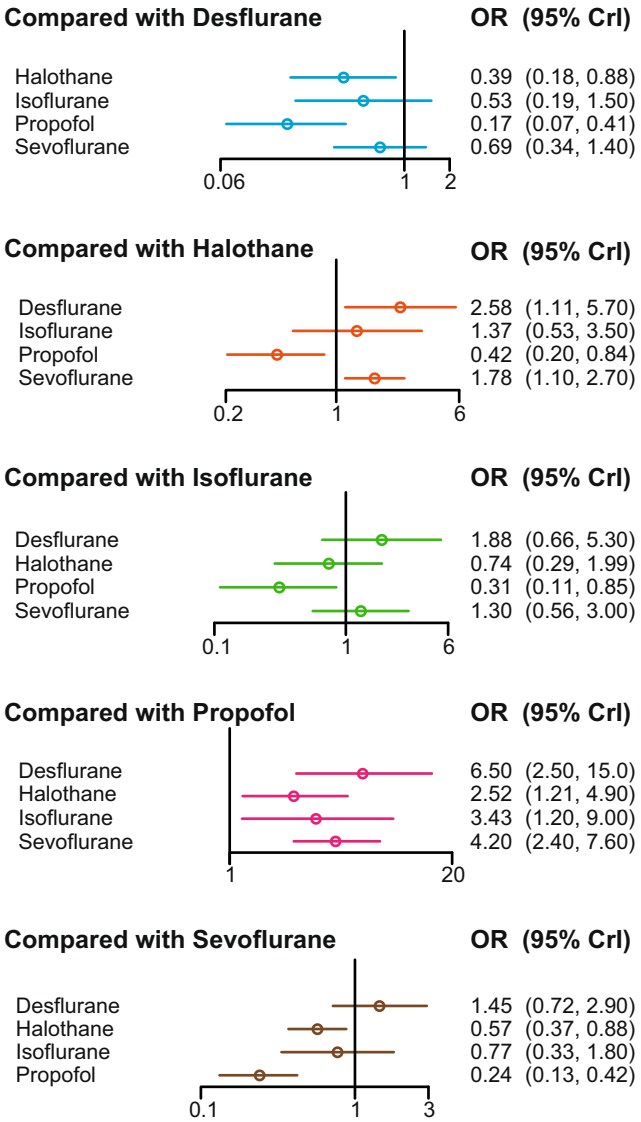

Fig. 2 The effect of anesthetics on emergence agitation

Comparisons Between Direct and Indirect Evidences

We used the node-splitting method and its Bayesian *P* value to report the inconsistency of our results. For the majority of our results, the confidence intervals from direct and indirect evidences are in general consistent, with minor differences. However, significant differences were observed at the comparison, which limited the use of our results. For example, when we compared sevoflurane and halothane for their effect in emergence agitation, both the pooled OR combining both direct and indirect evidences and OR from direct evidence reported a higher incidence rate of sevoflurane, whereas OR from indirect evidence indicated that sevoflurane has a significantly lower incidence rate of emergence agitation than halothane ($P = 0.006$, Fig. 3). Similar results were also observed when we compared propofol and halothane, sevoflurane and propofol concerning emergence agitation (Fig. 3). Nevertheless, no significant difference between direct and indirect evidence was observed in other calculations (Figs. 3, 4, 5, 6, 7 and 8).

Discussion

In this meta-analysis, we systematically reviewed the emergence and recovery characteristics of desflurane, halothane, isoflurane, propofol, and sevoflurane. Four thousand and four hundred eighty-five cases from 48 eligible articles were involved. As illustrated in our results, propofol was considered as the most efficient and safe anesthetic with less adverse effect, namely lowest incidence rate of emergence agitation and postoperative nausea and vomiting, as well as relatively short extubation time, emergency time, and duration of PACU stay. Besides, halothane was also regarded as an efficient anesthetic. It had the shortest extubation time, emergency time, and duration of PACU stay, although the use of halothane might lead to a relatively high incidence rate of postoperative nausea and vomiting. However, desflurane did not perform well in our analysis. It had the highest incidence rate of emergence agitation and longest extubation time, emergency time, and duration of PACU stay among all the five studied anesthetics. Regarding the need of analgesic, isoflurane was reported to be the safest, while cases using sevoflurane in pediatric anesthesia reported the highest incidence rate of analgesic requirement. These results may help pediatric anesthetists in the selection of anesthetics.

As far as we are concerned, this is the very first and largest network meta-analysis considering the emergence and recovery characteristics of common anesthetics in pediatric anesthesia. A

Table 3 Relative ranking of five anesthetics assessed by using SUCRA values

Drugs	Emergence agitation (%)	PONV (%)	Requiring an analgesic (%)	Extubation time (%)	Emergency time (%)	Duration of PACU stay (%)
Desflurane	7.50	39.00	51.50	*99.50*	*94.75*	*89.25*
Halothane	68.50	20.00	39.75	1.50	0.25	19.00
Isoflurane	47.25	48.50	*93.50*	38.75	42.75	54.25
Propofol	*99.50*	*90.50*	51.75	48.00	50.25	25.75
Sevoflurane	28.00	51.75	13.25	61.75	61.75	62.00

P-values in italics are significant

PONV postoperative nausea and vomiting, *PACU* post anesthesia care unit

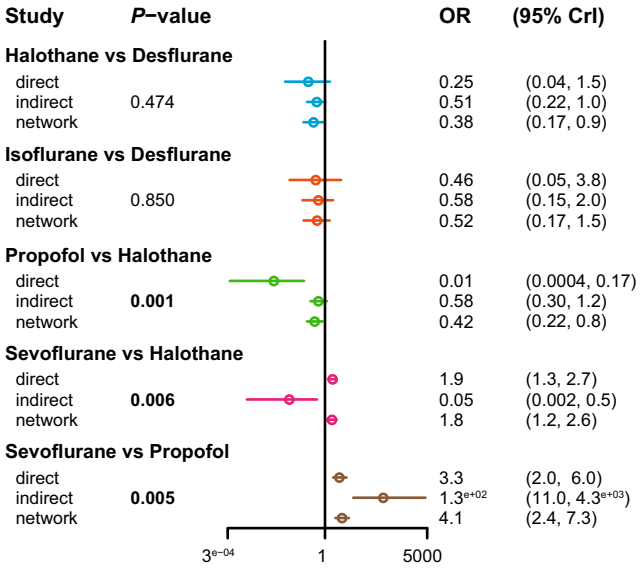

Fig. 3 Comparison between direct and indirect evidence—emergence agitation

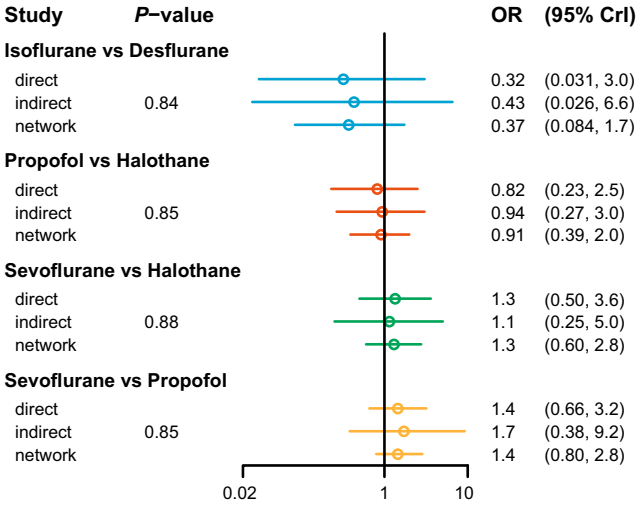

Fig. 5 Comparison between direct and indirect evidence—require an analgesic

large scale of cases was involved in our analysis; both direct and indirect evidences were combined to verify our results. Our results were conclusive and in consistence with previous results. As Ortiz reported in their meta-analysis involving 900 children, when compared to sevoflurane, propofol may reduce the risk of PONV and the risk of behavioral problems [59]. The results were confirmed in our analysis. It has also been demonstrated by Kanaya et al. in their analysis that emergence agitation in children is less likely to occur after propofol anesthesia compared with sevoflurane anesthesia [60]. Similar results were also reported by Costi et al. [61] There is also a meta-analysis revealing that emergence agitation occurred more frequently with sevoflurane than with halothane anesthesia in children [62]. The result is in consistence with ours. However, contradiction also exists between our results and some traditional meta-analyses. As reported by He et al. in their meta-analysis about the effect of desflurane versus sevoflurane in pediatric anesthesia, desflurane was considered as a safer anesthetic with shorter extubation time and emergency time and less agitation [9]. Opposite results were observed in our analysis. This inconsistency may be due to the contribution of indirect evidences.

Although emergence agitation, postoperative nausea and vomiting and postoperative analgesia are common adverse effects of pediatric anesthesia, the reason for a higher incidence rate of adverse effects after desflurane and sevoflurane had not been elucidated yet. A possible explanation was that the prompt recovery from anesthesia with sevoflurane also facilitates earlier awareness of postoperative pain, which is also considered as etiology of emergence agitation [63]. Also, as has been demonstrated by previous studies, volatile

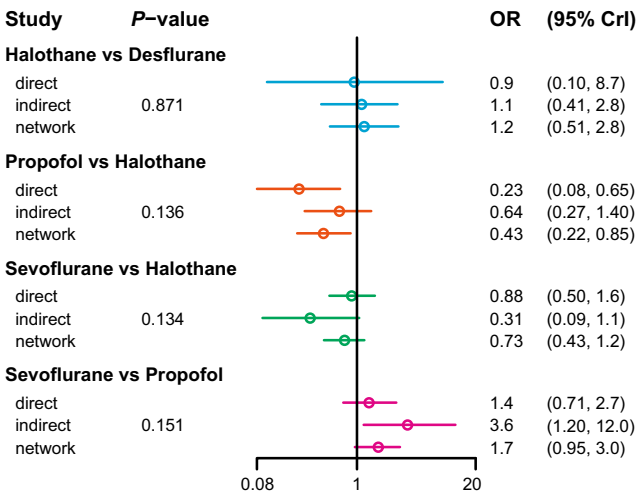

Fig. 4 Comparison between direct and indirect evidence—postoperative nausea and vomiting

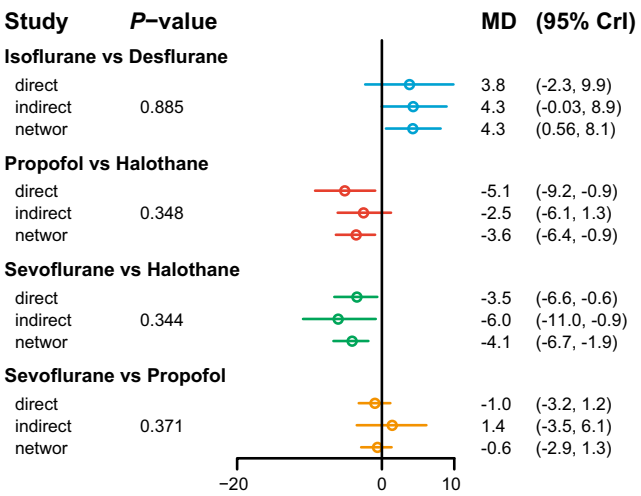

Fig. 6 Comparison between direct and indirect evidence—extubation time

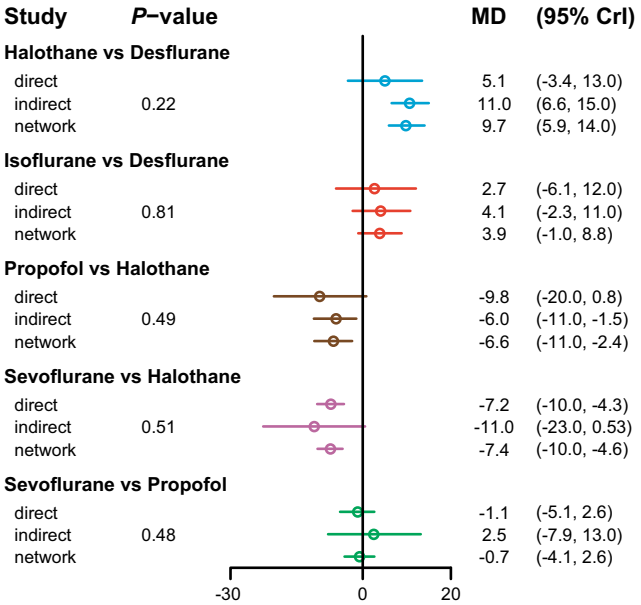

Fig. 7 Comparison between direct and indirect evidence—emergency time

anesthetics like sevoflurane can induce hyperalgesia by activating nociceptive neurons [64, 65]. The biphasic effect of volatile anesthetics might be the explanation for postoperative pain after the use of sevoflurane.

Nonetheless, some limitations of this meta-analysis should be discussed. As we mentioned in the results, the consistency between direct and indirect evidence was not perfect. Some inconsistent results were observed in the calculation, which might affect the validity of our results. Also, since various protocols were applied by eligible studies, significant heterogeneity might be elicited. It was also controversial whether we could combine results from different protocols in the calculation of pooled ORs. Besides, the premedication and anesthetics used in anesthesia induction was not considered as variants in the analysis. A further study with more focus on the effect of premedication on anesthesia in pediatric surgery is therefore suggested. Age and ethnicity of patients involved in the study were also considered as variants that may mislead the results. Further stratified analyses based on larger set of samples are recommended. It might also be an important issue for future research to verify the influence of different genetic background on emergence agitation and other adverse effect.

In conclusion, a network meta-analysis combining both direct and indirect evidences from currently available studies was performed to compare the emergency and recovery characteristics of desflurane, halothane, isoflurane, propofol, and sevoflurane. Propofol was recommended as the most efficient and safe anesthetic in pediatric anesthesia with few adverse effects. Meanwhile, desflurane was reported to have the highest incidence rate of emergence agitation and worst recovery characteristics. Halothane was also regarded as an efficient anesthetic with best recovery characteristics, while postoperative nausea and vomiting is a common adverse effect after the use of halothane. This is the largest network meta-analysis on the emergence and recovery characteristics of anesthetics in pediatric anesthesia so far. Hopefully, we can provide some evidence for pediatric anesthetists in the selection of anesthetics.

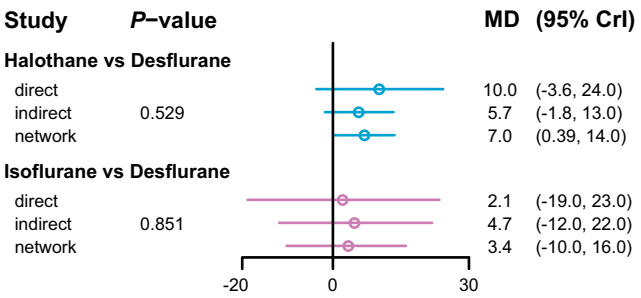

Fig. 8 Comparison between direct and indirect evidence—PACU stay

Acknowledgments This work was funded by the Outstanding Leaders Training Program of Pudong Health Bureau of Shanghai (Grant No. PWR12013-03)

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest.

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