의학석사 학위논문

Effects of remifentanil on induction and recovery profiles during sevoflurane anesthesia in children

-a meta-analysis of randomized controlled trials-

소아에서 세보플루란을 이용한 마취 시 레미펜타닐의 추가 사용이 마취유도와 회복에 미치는 영향

-무작위배정비교임상시험의 메타분석-

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최 재 규

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The Department of Clinical Medical Sciences

Seoul National University College of Medicine

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by

Choi Jaekyu

A thesis submitted to the Department of Clinical Medical Sciences in partial fulfillment of the requirements for the Degree of Master of Science in Clinical Medical Sciences at Seoul National University College of Medicine

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Approved by Thesis Committee:

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Professor _____Vice chairman

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소아에서 세보플루란을 이용한 마취 시 레미펜타닐의 추가 사용이 마취유도와 회복에 미치는 영향

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지도교수 서 정 화

이 논문을 의학석사 학위논문으로 제출함

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최 재 규

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ABSTRACT

Background: Although sevoflurane is widely used in pediatric anesthesa, its single use may be insufficient to prevent noxious stimuli induced by tracheal intubation or cause emergence agitation during recovery. Therefore, this meta-analysis was performed to determine whether administration of remifentanil may improve induction and recovery profiles during sevoflurane anesthesia in children.

Methods: A comprehensive literature search was conducted to identify randomized controlled trials involving children < 18 years of age who received sevoflurane anesthesia combined with or without intravenous remifentanil. Two authors independently assessed study quality and extracted data from included studies. Random-effects models were applied to calculate pooled risk ratios (RRs) for dichotomous data and standardized mean differences (SMDs) for continuous data with the corresponding 95% confidence intervals (CIs). The primary outcomes were hemodynamic changes during tracheal intubation and the incidence of emergence agitation during recovery.

Results: Out of 1920 studies screened, 13 studies involving 1237 children were included in the analysis. The use of remifentanil reduced changes of blood pressure [SMD (95% CI) -1.33 (-1.89, -0.77), $P < 0.001$, $I^2 = 87\%$] and heart rate [SMD (95% CI) -1.21 (-1.81, -0.61), $P < 0.001$, $I^2 = 89\%$] during tracheal intubation. The incidence of emergence agitation decreased when remifentanil was co-administered with sevoflurane during intraoperative period [SMD (95% CI) -1.21 (-1.81, -0.61), $P < 0.001$, $I^2 = 89\%$] as compared with the use of placebo.

Conclusion: This meta-analysis showed that the use of remifentanil attenuated hemodynamic fluctuation during tracheal intubation and decreased emergence agitation under sevoflurane anesthesia in children.

Keywords: Pediatrics, Anesthesia, Intubation, Blood Pressure, Heart Rate, Postoperative Complications.

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LIST OF ABBREVIATIONS

RCT, randomized controlled trial; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; EA, emergence agitation; PACU, postanesthesia care unit; PONV, postoperative nausea and vomiting; RR, risk ratio; OR, odds ratio; CI, confidence interval; Std, Standardized; SD, standard deviation; SMD, standardized mean difference; BP, blood pressure; HR, heart rate; RFTN, remifentanil; M-H, Mantel-Haeszel; IV, inverse variance

INTRODUCTION

Sevoflurane is commonly used in general anesthesia or sedation for surgical procedures and non-invasive interventions in children because it has several advantages for reducing airway irritation and facilitating anesthetic induction and recovery.[1] However, the single use of sevoflurane is likely to be insufficient to attenuate any noxious stimuli caused by tracheal intubation, thereby causing hemodynamic instability. Moreover, sevoflurane may cause postoperative temporary behavioral disturbance such as emergence agitation (EA) in children.[2, 3] Therefore, additional drugs can be used as the adjuvant to compensate for the limitations of sevoflurane.[1, 4, 5]

As well as in the total intravenous anesthesia, remifentanil can be used in the inhalational anesthesia to reduce the requirements of inhalational anesthetic agents and to improve hemodynamic stability.[6] Remifentanil is also used as an adjuvant to sevoflurane anesthesia in children, and shows various effects on several perioperative outcomes.[1, 7, 8] However, the efficacy and clinical benefits of using remifentanil combined with sevoflurane have not yet been systematically investigated in children.[9]

Therefore, we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) to examine the effects of remifentanil on the induction and the recovery of sevoflurane anesthesia in children.

METHODS

This systematic review and meta-analysis was conducted according to the recommendations of the Cochrane collaboration[10] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[11, 12] The protocol was developed based on the guideline of PRISMA protocol[13, 14] and registered at PROSPERO (registration number, CRD42015025129).

Study eligibility

We included published and unpublished RCTs, quasi-RCTs, and trials with a randomized cross-over design comparing perioperative intravenous remifentanil with placebo in children younger than 18 years undergoing any surgeries or procedures with general anesthesia or sedation via inhalation of sevoflurane (Table 1). If the study included both adults and children, only the data for children were used.

There was no limitation in types of remifentanil administration (bolus or continuous infusion). used airway devices (endotracheal tubes, supraglottic airways or facial mask), .premedication, anesthetic induction agents, neuromuscular blocking agents, nitrous oxide; and date, regions or the languages of publication. The trials involving non-intravenous administration of remifentanil were excluded.

Outcomes

Because this systematic review aimed to investigate the effects of remifentanil on the induction and the recovery profiles of sevoflurane anesthesia, we determined two primary outcomes regarding anesthetic induction and recovery respectively, which was most frequently reported in relevant studies found in a preliminary search: hemodynamic changes during tracheal intubation and the incidence of EA during recovery. Several outcomes involving the anesthetic induction and the recovery were also determined as secondary outcomes: the parameters related to the recovery duration including the time taken for extubation, and the length of stay in the

postanesthesia care unit (PACU); severity of the postoperative pain; and withdrawal movements induced by an intravenous rocuronium injection during induction. Moreover, any adverse events such as postoperative nausea and vomiting (PONV), coughing and respiratory depression observed in the perioperative period were checked.

Study selection

We developed the search strategy for MEDLINE using medical subject headings and text words such as ‘sevoflurane’, ‘remifentanil’, and ‘pediatric’, and combined it with the Cochrane Highly Sensitive Search Strategy[10] to identify RCTs, quasi RCTs, and cross-over trials. We adapted this strategy to other electronic databases adequately. We searched MEDLINE (PubMed; since 1946, Appendix 1); EMBASE (since 1947); Cochrane library (CENTRAL; since 1898); CINHAL (the Cumulative Index to Nursing and Allied Health Literature; since 1960); Web of Science (since 1990); Google Scholar; LILACS (The Latin-American and Caribbean System on Health Sciences Information; since 1982); IMSEAR (Index Medicus for the South-East Asia Region) (since 1990); IndMED (since 1986); and KoreaMed (since 1996). The search was conducted on May, 2014, and updated on November, 2015. The retrieved citations were imported to EndNote (Thomson Reuters, PA, USA) and duplications were automatically and manually removed by comparing their authors, titles, and publication date.

Two reviewers independently screened titles and abstracts according to the study eligibility criteria and attempted to obtain full-text of the retrieved studies. When the full-text was not obtained, we attempted to contact the authors of reviewed studies to receive the full-text; if unsuccessful, data were extracted only from the abstract. The two reviewers then independently reviewed the full-texts and selected eligible studies.

References of the selected studies and other related review articles were also checked to retrieve additional studies. Moreover, we searched proceedings of relevant medical conferences such as The American, European, and Korean Society of Anesthesiologists. We also searched ClinicalTrials (https://clinicaltrials.gov) to check protocols of relevant ongoing clinical trials.

Quality assessment and data collection

Quality assessment of studies and data collection were independently conducted by two authors. The quality of each study was assessed using the Cochrane collaboration's risk of bias tool based on the seven domains: sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias); and other potential bias. The risk of bias was graded as 'high', 'low', or 'unclear' in each domain.

Data were extracted using a standardized data collection form regarding participants; intervention and comparison groups; primary and secondary outcomes; type of surgery; and anesthetic management. For data only presented in a graphical form, the two authors independently extrapolated the numerical data using an image processing program (Image J 1.49; NIH, Bethesda, MD, USA), then averaged them. If we did not obtain necessary data in the full-text, we attempted to contact the authors of the studies to ask for these information. If there were any disagreements in selecting studies, assessing risk of bias, and collecting data, they were resolved by consensus of the two authors or by discussion with the third author. If the attempts were unsuccessful, abstracts of the studies or imputed data recommended by the Cochrane Collaboration were used.

Data synthesis

Data was synthesized using the Review Manager software (version 5.3; The Cochrane Collaboration, Oxford, UK). When a meta-analysis was feasible, the random-effects models were applied for all relevant outcomes because substantial heterogeneity was expected among the included studies owing to differences in anesthetic and surgical managements.

Dichotomous data were presented as number of patients involving the event and that of total patients, were synthesized by the Mantel-Haenszel method[15] and presented as risk ratios

(RRs) or Peto odds ratios (ORs) with 95% confidence intervals (CIs). Continuous data were shown as mean, standard deviation (SD), and number of total patients; were synthesized by the inverse variance method and presented as standardized mean differences (SMDs) with 95% CIs. If the presented data were either inappropriate for a meta-analysis or missing data, they were imputed to appropriate types of variables according to the methods of the Cochrane Collaboration.[10] If one study had more than one intervention or comparison groups, the data were appropriately combined into the remifentanil or control arms, then included in the meta-analysis. The significance level was 0.05 for all analyses.

Heterogeneity

Statistical heterogeneity among the studies was assessed using Chi^2 test and I^2 statistic.[16] Substantial heterogeneity was suggested when the I^2 value was > 50% and the *P* value of Chi^2 test > 0.10. If substantial heterogeneity was found, potential factors explaining the heterogeneity were explored by predetermined subgroup analysis, including following criteria: anesthetic induction agents, dose or type of remifentanil administration, use of premedication, nitrous oxide or neuromuscular blocking agent, the types of surgery, and patient age. When a pooled analysis was not possible, the results of each study were reported separately.

Sensitivity analysis

Sensitivity analysis were performed to check the robustness of overall effects by excluding each study one by one. It was performed according to the predetermined protocol with regard to studies with low quality, imputed data, and multiple intervention arms.

Publication bias

Publication bias was assessed using the funnel plot and Egger's test. If the funnel plot was visually asymmetric and the *P* value of the Egger's test was < 0.10, publication bias was suspected.

Table 1. Inclusion criteria and the outcomes for meta-analysis.

Types of study	Randomized controlled trials No region or language restriction
Types of participant	Children, 0-18 years undergoing sevoflurane anesthesia Exclusion: Non-intravenous administration of remifentanil
Types of intervention	Intravenous administration of remifentanil or placebo during general anesthesia
Types of outcome	Primary outcomes 1. Change in vital signs during intubation (mean blood pressure, systolic blood pressure, and heart rate) 2. Incidence of emergence agitation Secondary outcomes 1. Extubation time 2. Length of stay in postanesthesia care unit 3. Incidence of postoperative nausea or vomiting 4. Severity of postoperative pain 5. Incidence of withdrawal movements associated with rocuronium injections

RESULTS

Search results

Among 1920 citations identified by the search strategy, 13 published RCTs were finally included in qualitative and quantitative analysis (Figure 1). In the 13 RCTs (n=1237, aged 1-11 years), 705 children received remifentanil and 532 children received placebo during sevoflurane anesthesia. Timing and type of remifentanil administration, the uses of induction drugs, neuromuscular blocking agents, nitrous oxide, premedication, and type of surgery were various among the included studies (Table 2).

Twelve RCTs[17-28] involved various types of surgeries under general anesthesia with tracheal intubation, and one RCT involved diagnostic bronchoscopy under sedation (Table 2).[29] Premedication was performed only in five RCTs by using midazolam,[28, 29] atropine,[17] glycopyrrolate[21] and ketamine (Table 2).[26, 28] Nitrous oxide was used in seven studies (Table 2).[17, 21, 23-26, 29] Because five RCTs had two[21, 24, 26] or three[20, 30] remifentanil arms involving different doses, they were combined into a single arm to include meta-analyses (Table 2).[19-21, 24, 31, 32]

Assessment of risk of bias

We assessed risk of bias of included RCTs using a tool recommended by the Cochrane Collaboration (Figure 2 and 3).[10] Two studies (14.2%)[27, 29] had high risk of bias in blinding of participants and one study (7.1%)[27] had high risk of bias in personnel and blinding of outcome assessment.

Change in hemodynamics during tracheal intubation

Four studies (n= 356)[19, 22, 24, 32] reported mean blood pressure and three studies (n= 178)[20, 28, 33] reported systolic blood pressure before and after tracheal intubation. The pooled effect size

showed that the change in blood pressure during intubation was significantly smaller in the remifentanil arm than in the placebo arm [SMD (95% CI) -1.33 (-1.89, -0.77), $P < 0.001$, I^2 = 87%; Figure 4]. Seven studies (n=534)[19, 20, 22, 24, 28, 32, 33] reported the heart rate before and after intubation. The change in heart rate was also significantly smaller in the remifentanil arm than in the placebo arm [SMD (95% CI) -1.21 (-1.81, -0.61), $P < 0.001$, I^2 = 89%; Figure 5]. The pooled effect sizes of blood pressure and heart rate were consistent in the subgroup analyses regarding the use of neuromuscular blocking agents and premedication. However, when remifentanil was administered via a continuous infusion, the change of heart rate during intubation was similar between the renifentanil and placebo arms.

Incidence of emergence agitation

There were five studies[17, 18, 34-36] that have dichotomous data for the incidence of EA. Three studies[17, 34, 36] clarified the definition of EA as a state of scoring more than 10 in pediatric anesthesia emergence delirium scale. One study[35] defined EA as frequency of agitation during recovery but another study[18] had no definition of EA. The meta-analysis showed that the incidence of EA was significantly lower in the remifentanil arm than in the placebo arm [SMD (95% CI) -1.21 (-1.81, -0.61), $P < 0.001$, I^2 = 89%; Figure 6]. The subgroup analyses according to the use of premedication, nitrous oxide, and the definition of EA showed consistent pooled results.

Secondary outcomes

Extubation time (n = 312 in 4 studies; Figure 7)[17, 21, 33, 34] and the length of PACU stay (n = 272 in 4 studies; Figure 8)[20, 33, 34, 36] were not significantly different between the remifentanil and placebo arms. The incidence of PONV (n = 188 in 3 studies; Figure 9)[20, 33, 36] and severity of postoperative pain (n = 120 in 2 studies; Figure 10)[20, 21] were also comparable between both arms. The incidence of withdrawal movements (n = 130 in 2 studies; Figure 11)[22, 24] associated with rocuronium injection during anesthetic induction was significantly lower in the

remifentanil arm than in the placebo arm. The summary results of meta-analyses are presented in Table 3.

Table 2. Characteristics of the included studies.

Study ID	Interventions in each arm	Period of study drug administration	No in each arm	Age (yr)	Type of surgery	Premedication (route)	Induction drugs	Use of N_2O (%)
Dong 2010	1. RFTN 0.1 mcg/kg/min 2. Placebo	Induction and maintenance	30 30	3~7	Adenotonsillectomy	Atropine 0.01 mg/kg (intramuscular)	Propofol 2.5 mg/kg + fentanyl 3 mcg/kg	50%
Gouda 2004	1. RFTN 0.25 mcg/kg bolus 2. Placebo	End of surgery	20 20		Myringotomy	None	Not reported	0
He 2009	1. RFTN 1 mcg/kg bolus + 1 mcg/kg/min 2. RFTN 1 mcg/kg bolus + 2 mcg/kg/min 3. RFTN 1 mcg/kg bolus + 3 mcg/kg/min 4. Placebo	Induction and maintenance	30 30 37 33	3~8	Mixed	None	Sevoflurane 5%	0
Kim 2013	1. RFTN 0.3 mcg/kg/min 2. RFTN 0.6 mcg/kg/min 3. RFTN 0.9 mcg/kg/min 4. Placebo	Induction and maintenance	15 15 15 15	1~5	Adenotonsillectomy	None	Thiopental 5 mg/kg + fentanyl 1 mcg/kg	0
Kim H 2007	1. RFTN 0.1 mcg/kg/min 2. RFTN 0.1 mcg/kg/min + 0.05 mcg/kg/min postoperatively 3. Placebo	Induction and maintenance	30 30 30	3~7	Tonsillectomy	Glycopyrrolate 0.004 mg/kg (intramuscular)	Thiopental 5 mg/kg	50%
Kim J 2007	1. RFTN 1 mcg/kg bolus 2. Placebo	Induction	35 35	4~10	Mixed	None	Thiopental 5 mg/kg	0
Na 2013	1. RFTN 1mcg/kg bol + 0.25-0.5 mcg/kg/min 2. Placebo	Intuction and maintenance	42 42	2~6	Adenotonsillectomy	None	Thiopental 5 mg/kg	60%
Na 2014	1. RFTN 0.5 mcg/kg bolus after thiopental injection 2. RFTN 0.5mcg/kg bolus after rocuronium injection	Induction	30 30	3~10	Ophthalmic surgery	None	Thiopental 5 mg/kg	50%

	3. Placebo		30					
Oh	1. RFTN 1mcg/kg bolus + 0.25-0.5 mcg/kg/min	Induction and maintenance	39	6~11	Strabimus surgery	None	Propofol 2.5 mg/kg	50%
2010	2. Placebo		39					
Ozturk	1. RFTN 1mcg/kg bol + 0.15mcg/kg/min	Induction and maintenance	25	2~6	Diagnostic bronchoscopy	Midazolam 0.5 mg/kg (oral)	Sevoflurane 6-8% + atropine 10 mcg/kg	50%
2009	2. Placebo		25					
Park	1. RFTN 1 mcg/kg bolus	Induction	32	1~7	Mixed	Ketamine 1 mg/kg (intravenous)	Sevoflurane 8%	50%
2009	2. RFTN 2 mcg/kg bolus		32					
	3. Placebo		32					
Shen	1. RFTN 0.02-0.05 mcg/kg/min	Induction and maintenance	25	2~5	Cochlear implantation	None	Propofol 1 mg/kg + fentanyl 2 mcg/kg	0
2012	2. Placebo		25					
Weber	1. RFTN 1 mcg/kg bolus	Induction	20	1~9	Mixed	Ketamine 2.4 mg/kg & midazolam 0.4 mg/kg (oral)	Sevoflurane 8%	0
2003	2. Placebo		20					

RFTN, Remifentanil.

Table 3. Summary results of the meta-analyses of each outcomes.

	No of studies	Participants	SMD or RR	95% CI	I^2 (%)	*P*-value of effect size
BP change during intubation	7	534	-14.43	-20.30, -8.56	89%	<0.00001
HR change during intubation	7	534	-19.21	-29.36, -9.06	93%	0.0002
Incidence of emergence agitation	5	284	0.51	0.31, 0.85	42%	0.01
Extubation time	4	312	0.95	-0.51, 2.41	70%	0.2
Length of PACU stay	4	272	-5.39	-11.71, 0.93	93%	0.09
PONV incidence	3	188	1.24	0.49, 3.12	4%	0.65
Severity of postoperative pain	2	120	1.26	-1.09, 3.61	94%	0.29
Withdrawal movements during rocuronium injection	2	130	0.26	0.16, 0.44	0%	<0.00001

BP, blood pressure; HR, heart rate; PACU, postanesthesia care unit; PONV, postoperative nausea and vomiting.

Figure 1. PRISMA diagram.

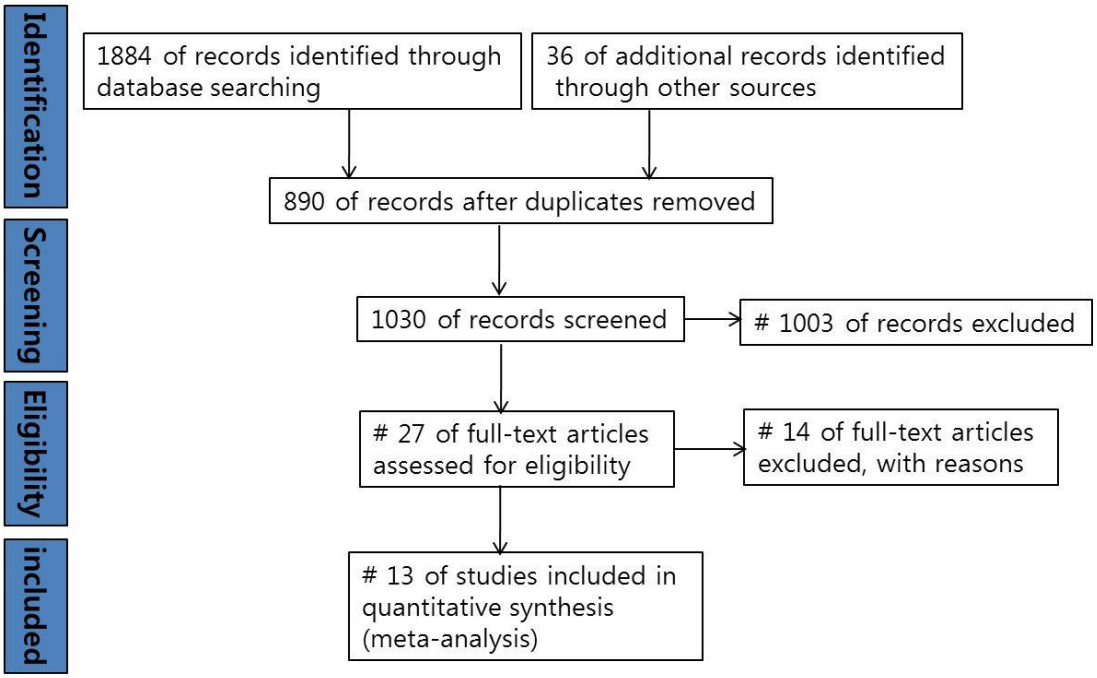


Figure 2. Methodological quality summary: reviewers' judgments about each methodological quality item for each included study. Green plus, red minus marks, and blnak means the low, high, and unclear risk of bias, respectively.

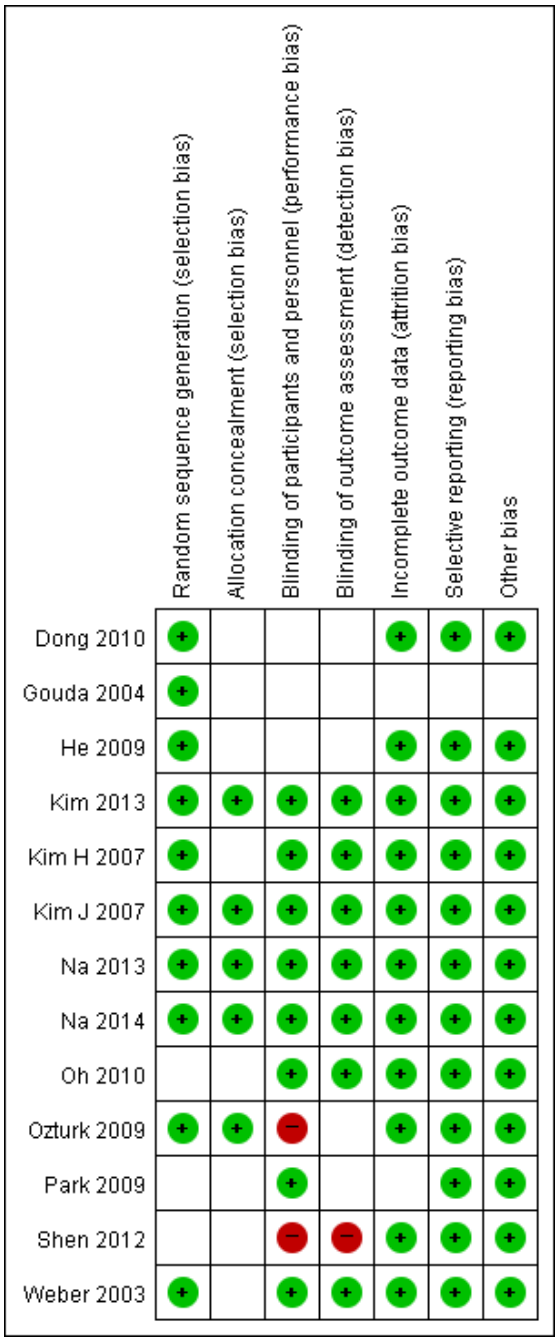


Figure 3. Methodological quality graph: reviewers' judgments about each methodological quality item presented as percentages across all included studies.

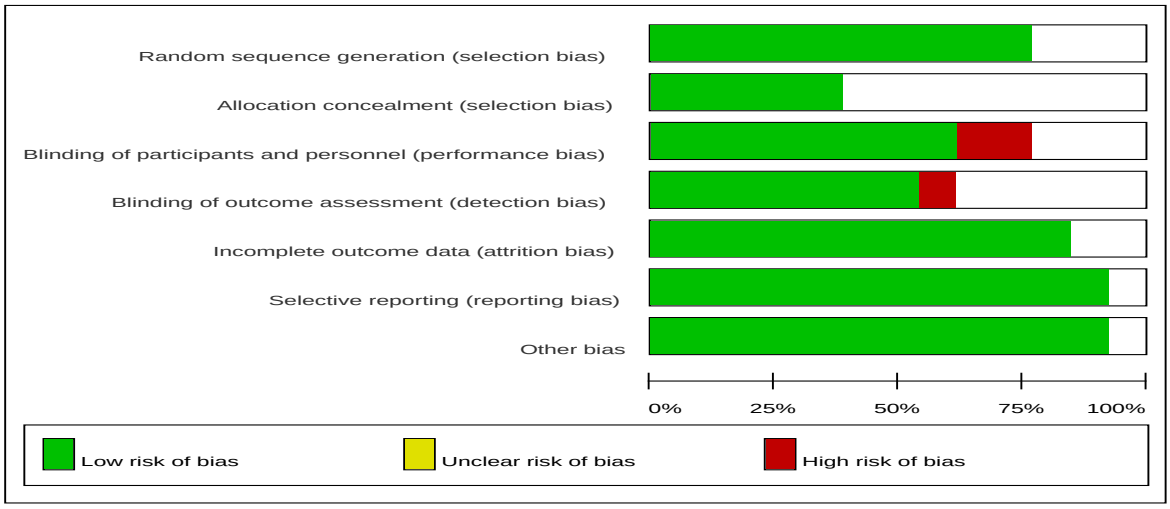
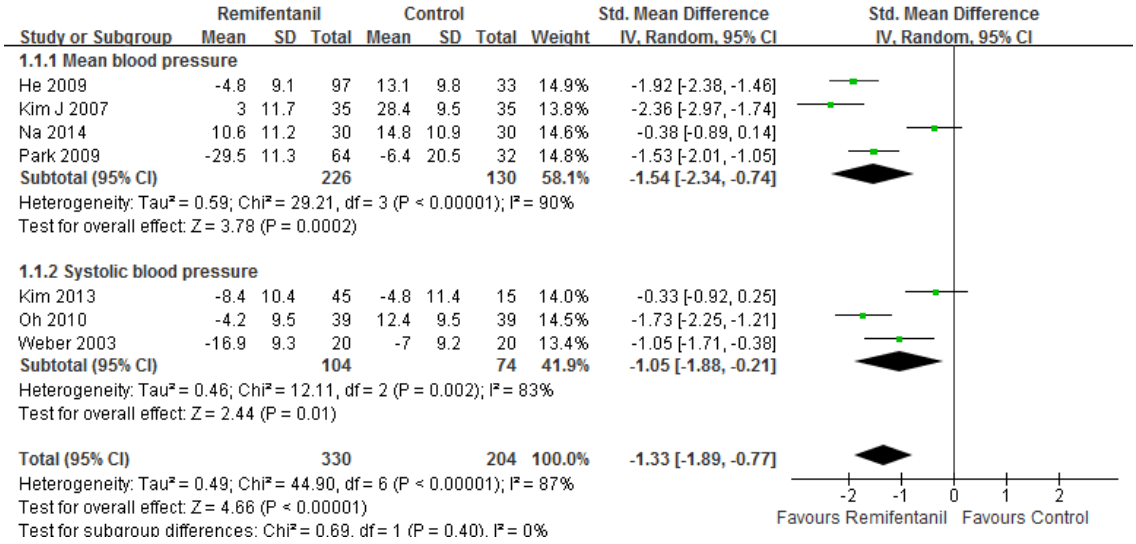
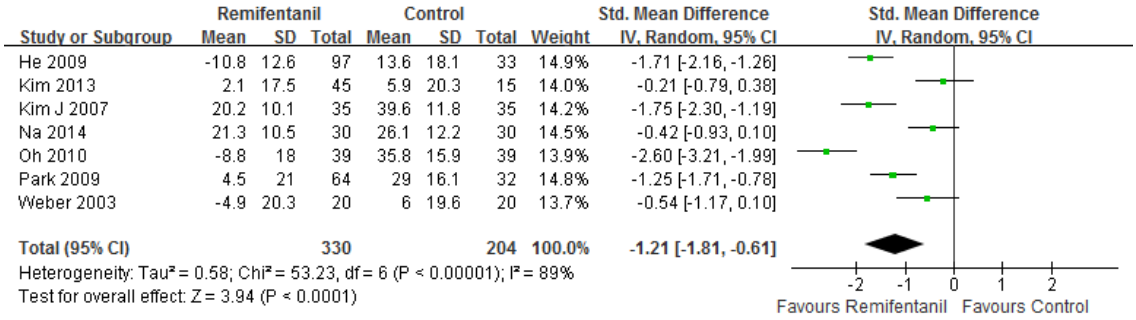


Figure 4. Forest plot for the change in blood pressure during tracheal intubation.



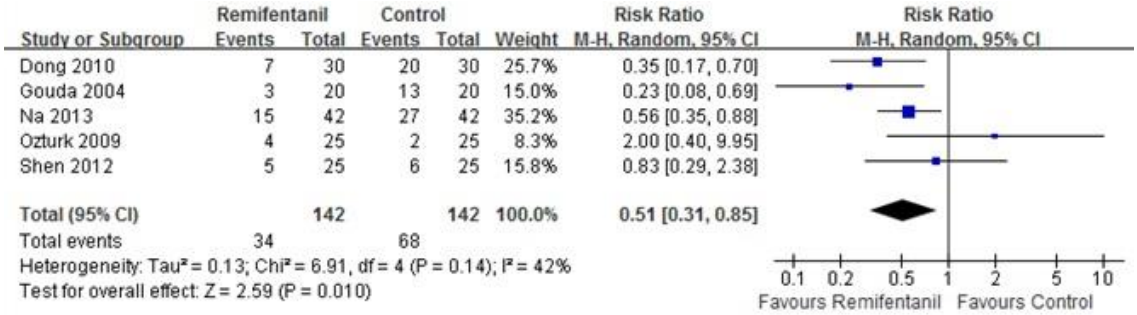
Std., standardized; SD, standard deviation; Cl, confidence interval; IV, inverse variance.

Figure 5. Forest plot for the change in heart rate during tracheal intubation.



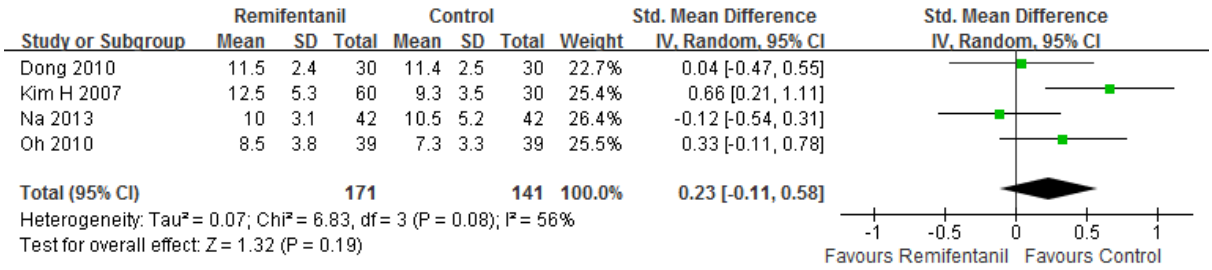
Std., standardized; SD, standard deviation; Cl, confidence interval; IV, inverse variance.

Figure 6. Forest plot for the incidence of emergence agitation.



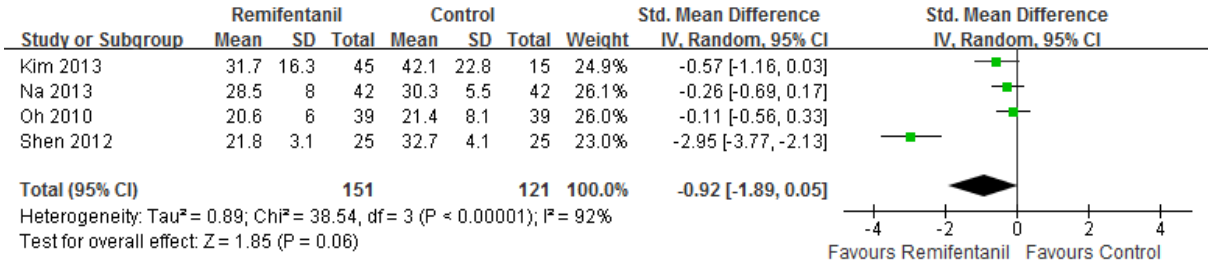
Cl, confidence interval; M-H, Mantel-Haeszel.

Figure 7. Forest plot for the extubation time.



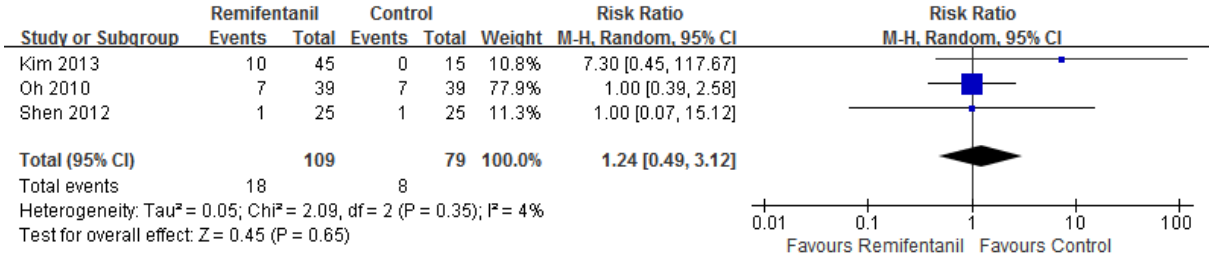
Std Std., standardized; SD, standard deviation; Cl, confidence interval; IV, inverse variance.

Figure 8. Forest plot for the length of stay in postanesthetic care unit.



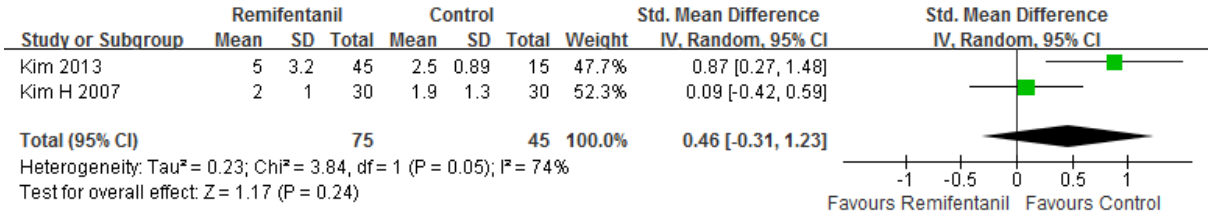
Std., standardized; SD, standard deviation; Cl, confidence interval; IV, inverse variance.

Figure 9. Forest plot for the incidence of postoperative nausea and vomiting.



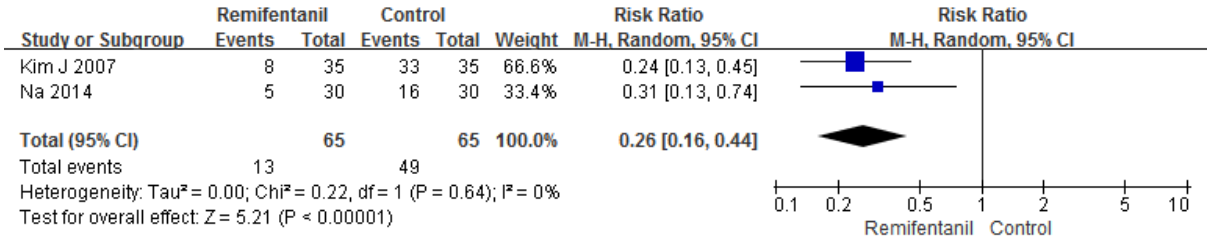
Cl, confidence interval; M-H, Mantel-Haeszel.

Figure 10. Forest plot for the severity of postoperative pain.



Std., standardized; SD, standard deviation; Cl, confidence interval; IV, inverse variance.

Figure 11. Forest plot for the incidence of withdrawal movements associated with the rocuronium injections.



Cl, confidence interval; M-H, Mantel-Haeszel.

DISCUSSION

Our meta-analysis provided the evidence that intravenous administration of remifentanil combined with sevoflurane anesthesia significantly decreased changes in the blood pressure and heart rate during tracheal intubation. Moreover, the postoperative EA occurred less frequently in the remifentanl arm than in the placebo arm. In addition, the use of remifentanil did not significantly prolong extubation time and the length of PACU stay compared to the placebo arm.

Although sevoflurane is known to be effective for induction of general anesthesia in children due to its minimal airway irritation and rapid induction time,[1] its single use may be insufficient to block noxious stimuli induced by tracheal intubation.[37-39] In our meta-analysis, the use of remifentanil combined with sevoflurane during induction period significantly attenuated hemodynamic fluctuation during tracheal intubation. However, in a subgroup analysis, the continuous infusion of remifentanil without a loading dose did not decrease the change in heart rate during intubation. Because the pharmacokinetic characteristics of remifentanil in children have not been completely investigated yet, remifentanil was not used via target-controlled infusion. Therefore, only a continous infusion of remifentanil for a few minutes before tracheal intubation without any loading dose seemed to be insufficient to exert an effective analgesic effect.

Several previous studies showed that propofol, dexmedetomidine, clonidine, fentanyl, and ketamine reduced the occurrence of postoperative EA in children.[2] In our meta-analysis, the use of remifentanil during sevoflurane anesthesia significantly reduced the incidence of postoperative EA.[17, 18, 34-36] As the quality of anesthesia and intraoperative pain control are known to be the major determinants of EA,[38, 39] remifentanil would reduce the incidence of EA by improving the anesthetic quality and attenuating postoperative surgical pain. Although the definition of EA was different among the included studies, the subgroup analysis according to the definition of EA showed comparable results.[17, 23, 27] The EA is known to occur more frequently in preschool children aged 4-6 years,[40, 41] and in our meta-analysis, the children aged

2-7 years were included. Therefore, the use of remifentanil combined with sevoflurane seems to be effective in children with high risk of EA.

Our meta-analyses showed that the extubation time and the length of PACU stay were comparable between the remifentanil and the placebo arms. The incidence of PONV was also similar between both arms. Remifentanil is an ultra-short-acting opioid, thus it may not affect the duration of recovery or postoperative nauseous symptoms after discontinuation of its administration. Previous studies reported that intraoperative administration of remifentanil was associated with postoperative hyperalgesia.[42, 43] However, our meta-analysis provided no evidence that intraoperative use of remifentanil increased pain severity after sevoflurane anesthesia. The pain produced by intravenous administration of rocuronium is a discomforting factor during anesthetic induction. Our study showed that remifentanil administration during anesthetic induction significantly decreased withdrawal movements caused by rocuronium injection, thus remifentanil is likely to have some advantages in smooth anesthetic induction.

There were some limitations in our meta-analysis. Statistical heterogeneity was moderate in some combined results, probably because the dose, period, or methods of remifentanil administration were various in each study. However, the number of studies in each meta-analysis was small, thus performing subgroup-analyses to clarify the reasons of the heterogeneity was impractical. Moreover, because we could not obtain the relevant data for meta-analyses in some included studies, we imputed the data and used in the analysis, which could possibly bias the results. However, the pooled effect sizes were consistent in the sensitive analyses. In addition, although two studies[27, 29] had high risk of bias in blinding of participants or investigators, the sensitive analysis excluding the two studies showed minimal effects on the pooled results.

In conclusion, our meta-analysis provided the evidence that the use of remifentanil attenuated hemodynamic fluctuation during tracheal intubation in children undergoing sevoflurane anesthesia. Moreover, remifentanil decreased the incidence of EA without the prolongation of recovery time. Therefore, remifentanil could be effectively and safely used for anesthetic induction and maintenance with sevoflurane in children.

APPENDICIES

Appendix 1. MEDLINE via PubMed search strategy.

1. Pediatrics[mh] OR Infant[mh] OR Child[mh] OR Adolescent[mh]
2. pediatric*[tiab] OR paediatric*[tiab] OR neonate*[tiab] OR Infant*[tiab] OR infancy[tiab] OR Child*[tiab] OR Adolescen*[tiab] OR Teen*[tiab] OR young*[tiab] OR Youth*[tiab] OR baby[tiab] OR babies[tiab] OR kid[tiab] OR kids[tiab] OR toddler*[tiab] OR juvenile[tiab]
3. 1 OR 2
4. remifentanil[supplementary concept]
5. remifentan*[tiab] OR ultiva[tiab]
6. 4 OR 5
7. 3 AND 6
8. (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])
9. 7 AND 8

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국문 초록

서론: 세보플루란은 현재 소아 마취에 가장 많이 사용되는 흡입마취제이다. 하지만 세보플루란의 단독 사용은 기관삽관 등의 유해한 자극을 충분히 억제하지 못하고 수술 후 각성흥분을 호발한다고 알려져 있다. 따라서 본 메타분석 연구에서는 소아에서 세보플루란을 이용한 마취 시 레미펜타닐을 추가로 사용하는 것이 마취 유도 및 회복의 질을 향상시킬 수 있는지 알아보고자 하였다.

방법: 세보플루란을 이용하여 전신마취 또는 진정을 받는 18 세 이하의 소아 중에서 레미펜타닐을 정주받거나 받지 않는 무작위배정비교임상연구를 대상으로 문헌검색을 하였다. 두 명의 저자가 독립적으로 메타분석에 포함된 연구와 연구에서 추출된 자료의 질을 평가하였다.
모든 자료에서 확률효과모형 (Random-effects model)이 사용되었고 명목변수는 비교위험도 (risk ratio), 연속변수는 표준화된 평균차 (standardized mean difference, SMD)와 95% 신뢰구간 (confidence interval, CI)으로 제시하였다. 주요 결과는 기관삽관 전후의 혈역학적 반응, 회복시의 각성흥분의 빈도로 하였다.

결과: 1920 개의 연구를 검토한 결과 13 개의 연구와 1237 명의 소아가 메타분석에 포함되었다. 술 중 레미펜타닐을 사용한 군에서 대조군에 비해서 기관삽관 전후의 혈압변화 [표준화된 평균차 (95% 신뢰구간) -1.33 (-1.89, -0.77), $P < 0.001$] 와 심박수 [표준화된 평균차 (95% 신뢰구간) -1.21 (-1.81, -0.61), $P < 0.001$] 변화가 유의하게 줄어들었다. 또한 술 중 레미펜타닐을 사용한 군에서 회복시의 각성흥분의 빈도도 유의하게 줄어들었다 [표준화된 평균차 (95% 신뢰구간) -1.21 (-1.81, -0.61), $P < 0.001$].

결론: 이 메타분석을 통해서 소아에서 세보플루란을 이용한 마취를 시행할 때 레미펜타닐을 추가로 사용하는 것이 마취유도시 기관삽관 전후의 혈역학적 변화를 줄여주고 수술 후 각성흥분 등 합병증의 빈도를 줄이거나 최소한 증가시키지 않는 것을 알 수 있었다.

주요어 : 소아, 마취, 기관삽관, 혈압, 심박수, 수술후합병증.

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