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관상동맥우회술의 마취에서

레미펜타닐과 펜타닐의 비교

: 무작위배정비교임상시험의 메타분석

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박 선 경

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Comparisons between the Uses of Remifentanil and Fentanyl in Coronary Artery Bypass Graft : A Meta-Analysis of Randomized Controlled Trials

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Comparisons between the Uses of Remifentanil and Fentanyl in Coronary Artery Bypass Graft : A Meta-Analysis of Randomized Controlled Trials

by Sun-Kyung Park

(Directed by Jeong-Hwa Seo, M.D., Ph.D.)

A thesis submitted to the Department of Clinical Medical Sciences in partial fulfillment of the requirement of 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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Abstract

Comparisons between the Uses of Remifentanil and Fentanyl in Coronary Artery Bypass Graft : A Meta-Analysis of Randomized Controlled Trials

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Objectives: The objective of this meta-analysis was to evaluate whether remifentanil could reduce postoperative recovery time and improve intraoperative hemodynamic stability in patients undergoing coronary artery bypass graft (CABG).

Search methods: We extensively searched randomized controlled trials comparing remifentanil with fentanyl in patients undergoing CABG until May 2015 using the electronic databases such as MEDLINE, CINAHL, EMBASE, CENTRAL of Cochrane Library, Web of Science, and KoreaMed.

Selection criteria: We included randomized controlled trials (RCTs) comparing remifentanil with fentanyl for adult patients undergoing CABG.

Data collection and analysis: Two review authors independently assessed study quality and extracted the data. Continuous variables were presented as standardized mean differences (SMDs) with 95% confidence intervals (CIs) and dichotomous variables as risk ratios (RRs) with 95% CIs. Assessments for statistical heterogeneity and publication bias, and sensitivity analyses were performed.

Results: Our meta-analysis showed that remifentanil was associated with reduced postoperative mechanical ventilation time compared with fentanyl [SMD (95% CI) -0.46 (-0.88, -0.05), $P = 0.03$, $I^2 = 91\%$, n = 1309 in 9 RCTs] but there were no significant differences in the lengths of intensive care unit and hospital stay. Although intraoperative heart rate and cardiac index were comparable between the remifentanil and fentanyl arms, mean blood pressure was significantly lower at tracheal intubation [SMD (95% CI) -0.35 (-0.62, -0.08), $P = 0.010$, $I^2 = 61\%$, n = 709 in 9 RCTs] and at the sternotomy [SMD (95% CI) -0.53 (-0.69, -0.36), $P < 0.00001$, $I^2 = 0\%$, n = 593 in 7 RCTs]. The incidence of postoperative hypotension was also higher in the use of remifentanil [RR (95% CI) 2.25 (1.47, 3.42), $P = 0.0002$, $I^2 = 9\%$, n = 912 in 3 RCTs]. The incidences of postoperative atrial fibrillation, myocardial ischemia, and nausea or vomiting were comparable between the two arms.

Conclusions: Our meta-analysis showed that the use of remifentanil decreased postoperative mechanical ventilation time in patients undergoing CABG as compared with fentanyl. However, because the use remifentanil may have a higher risk of lower blood pressure, care should be taken to avoid the inadvertent hypotension during the perioperative period of CABG.

Keywords: remifentanil; coronary artery bypass; fentanyl; meta-analysis; Respiration, Artificial, Intensive Care Units, Length of Stay, Arterial Pressure

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Introduction

Coronary artery bypass graft (CABG) is the mainstay of treatment for severe coronary artery diseases.[1] In the anesthesia for CABG, maintaining hemodynamic stability is strongly required because the patients undergoing CABG have a high risk of postoperative major adverse cardiac and cerebrovascular events.[2] Moreover, endocrine stress reactions induced by inflammation may increase postoperative morbidity and mortality,[3] thus attenuation of neurohumoral responses is crucial for anesthesia of CABG.[4]

Fentanyl is one of most common opioids used for anesthetic maintenance and postoperative analgesia of cardiac surgery.[5] Fentanyl is used as an adjuvant for intravenous or inhalational anesthesia, reducing hormonal and metabolic responses to perioperative stress. However, its use for the long perioperative period of cardiac surgery may prolong the duration of postoperative recovery.[6]

Remifentanil is an ultra-short-acting opioid metabolized by plasma cholinesterases, thus, it has characteristics of rapid onset and short duration compared with other opioids.[4] Titrating the dose of remifentanil is relatively ease, so it seems beneficial to maintain intraoperative hemodynamic stability and to shorten recovery period after CABG.[4] However, remifentanil may cause some adverse events such as intraoperative hypotension[7] or postoperative hyperalgesia,[8] thus usefulness of remifentanil in anesthesia of CABG seems to be controversial.

Therefore, we performed this systematic review and meta-analysis of randomized controlled trials (RCTs) to extensively investigate whether remifentanil has a benefit in reducing postoperative recovery time and maintaining intraoperative hemodynamic stability in patients undergoing CABG compared with fentanyl.

Methods

This systematic review and meta-analysis was performed depending on a pre-specified protocol that outlined the aim, search strategy, eligibility criteria, data extraction strategy, and statistical analysis. The protocol was registered in PROSPERO (Registration number, CRD42015025268). The reporting of this review was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement.[9]

Selection Criteria

We included any RCTs comparing the uses of remifentanil and fentanyl in adult patients undergoing CABG. We included both off-pump CABG and on-pump CABG. We did not restrict kind of other anesthetic drugs (inhalational or intravenous) and type (bolus or continuous) or timing (anesthetic induction, maintenance, and recovery) of study drug administration.

Search Strategy

We searched RCTs comparing the uses of remifentanil and fentanyl during the perioperative period of CABG until May 2015 using electronic databases of MEDLINE, CINAHL, EMBASE, CENTRAL of Cochrane Library, Web of Science, and KoreaMed using several keywords such as CABG, remifentanil, and fentanyl. We also searched additional electronic databases including IndMED, LILACS, IMSEAR, WPRIM, IMEMR, SciELO. Moreover, we searched ClinicalTrials for ongoing clinical trials, and proceedings of relevant anesthetic conferences such as

American Society of Anesthesiologists, European Society of Anaesthesiology, Korean Society of Anesthesiologists, and Korean Society of Cardiothoracic and vascular Anesthesiologists from 2000 to 2015. In addition, we performed backward snowballing by scanning of references of retrieved articles. We did not restrict language, date, or location of publications.

Study Selection

Two investigators independently examined titles and abstracts of the retrieved articles according to the selection criteria. Differences in the selection between the two investigators were resolved by discussion or consultation to another investigator.

Data extraction

Two investigators extracted data regarding patients characteristics, study design, anesthetic and surgical managements, and clinical outcomes. The primary endpoint was the duration of postoperative mechanical ventilation. Secondary endpoints were lengths of intensive care unit (ICU) and hospital stay, intraoperative mean arterial blood pressure (MBP), heart rate (HR), cardiac index (CI) in various time points. We also extracted any data with regard to perioperative adverse events such as hypotension, arrhythmia, myocardial ischemia, and nausea or vomiting.

Assessment of risk of bias

We assessed the quality of each study by using the Cochrane Collaboration’s risk of bias tool with seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting, and other bias. Each domain was graded with high, low or unclear risks. If the studies have domains of high risk of bias, sensitivity analyses were conducted to evaluate the effects of the study on the pooled results.

Data synthesis and analysis

Data synthesis and analysis were performed using RevMan 5.3 (Cochrane Collaboration, Oxford, UK). Dichotomous outcomes were presented as risk ratios (RR) with 95% confidence intervals (CIs) and continuous outcomes as standardized mean differences (SMDs) with 95% CIs. Considering the potential heterogeneity among the included studies, data were combined using the random-effects model. Statistical heterogeneity was assessed using the I^2 statistic and chi-squared test. Sensitivity analysis was conducted to the studies with high risk of bias or poor quality of data. Publication bias was evaluated with funnel plots and Egger's test.[10] Statistical significance was determined with two-tailed *P*-value = 0.05 for the null-hypothesis testing and with *P*-value = 0.10 for heterogeneity testing.

Results

Search results

We retrieved 2428 articles via the literature search and excluded 1153 duplications, and 1220 articles because they were not eligible by reviewing titles and abstracts. Afterward, we checked full-texts of 55 eligible studies and 49 studies were excluded by various reasons (Fig.1). Further searching and screening for proceedings of anesthesia conferences yielded additional 9 studies, thus 15 RCTs were finally included in our analysis (Fig. 1).

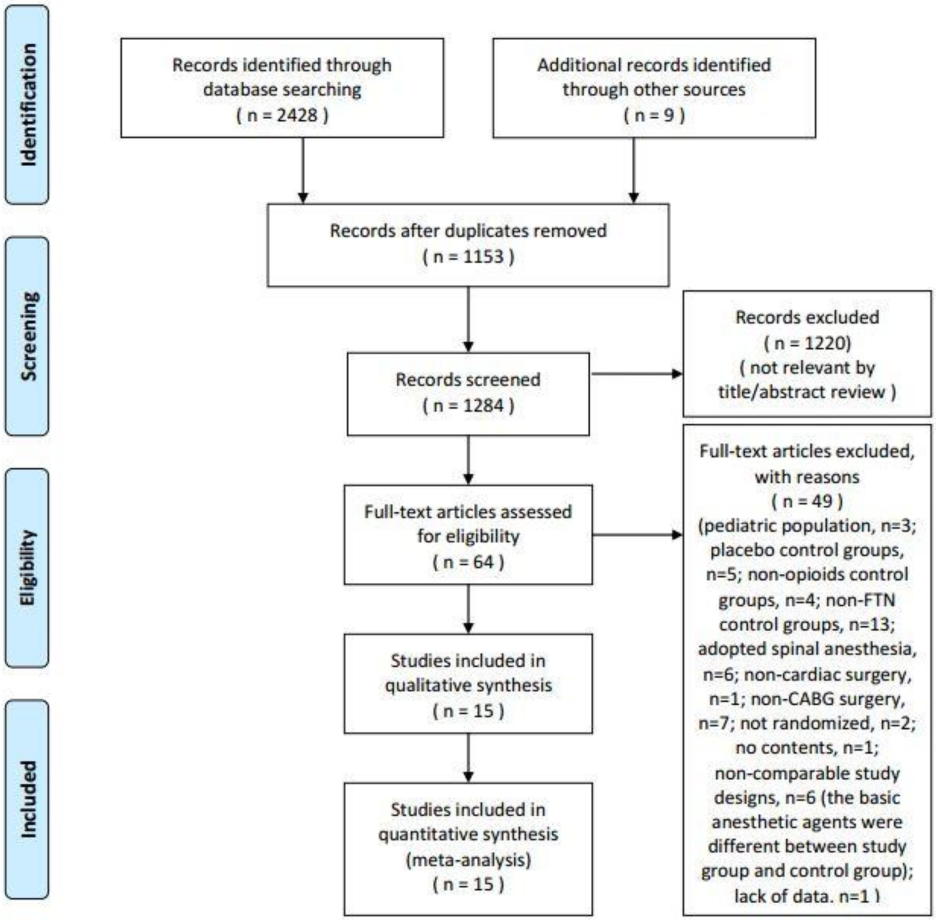

Figure 1.Flow diagram of study selection.

Characteristics of included studies

The 15 included studies randomized 1635 patients into the remifentanil arm (n = 776) and the fentanyl arm (n = 859). Five studies clearly described the type of surgery as off-pump CABG[11 12] or on-pump CABG,[3 13 14] but ten studies[15-24] reported only CABG without describing its specific type. Dose and administration type of remifentanil and fentanyl were various among the included studies (Table 1).

Table 1. Characteristics of included randomized controlled trials.

Study ID	Interventions (No. of patients)	Drug dosage	Period of study drug administration	Age (years)	Type of surgery	Premedication (route)	Induction drugs	Maintenance drugs
Askin 2013	Remi (20)	Remi 1 ug/kg + 0.1-1 ug/kg/min	Induction~end of surgery	52±12	OPCAB	diazepam 10 mg (oral), morphine 0.1-0.15 mg/kg (IM)	midazolam 0.1-0.15 mg/kg	Midazolam maintenance infusion 0.4-1 µg/kg/min
	FTN (20)	FTN 10-15 mcg/kg + 0.1-1 ug/kg/min		58±15				
Bedirli 2007	Remi (25)	Remi 3mcg/kg + 1mcg/kg/min	Before intubation~ maintenance	63±10	on pump CABG	ranitidine 150mg*2(oral), diazepam 10mg(oral), morphine 5mg(IM)	midazolam 0.15mg/kg	Not described
	FTN (25)	FTN 10mcg/kg + 5mcg/kg/h		59±12				
cheng 2001	Remi (150)	Remi 1mcg/kg/min and titrated	before intubation~ continued until patients were settled in ICU	63±10	on pump CABG	midazolam 1-3mg(IV), morphine 0.05mg/kg(IV)	PPF 0.5mg/kg + 10mg bolus every 10s until LOC	(after intubation~at the end of CPB) isoflurene end-tidal conc. 0.5% + (from rewarming~) PPF initial rate of 2 mg/kg/h and titrated
	FTN (154)	FTN 10mcg/kg		63±10				
Gurbet 2004	Remi (25)	Remi 0.05mcg/kg/min, 0.5mcg/kg bolus	from immediately after the completion of the surgery	58.2±2.6	OPCAB	morphine 0.1mg/kg (IM)	TPT 3mg/kg fentanyl 5mcg/kg	2% SEVO in 40% oxygen
	FTN (25)	FTN 1mcg/kg/h, 10mcg bolus		60.5±2.3				
Howie 2001	Remi (150)	Remi 1mcg/kg + 1mcg/kg/min	Induction ~ at ICU	63±10	elective CABG	midazolam 1-3mg (IV), morphine	PPF 0.5mg/kg + additional	Isoflurane at a concentration of

	FTN (154)	FTN 10mcg/kg + normal saline infusion		63±10		0.05mg/kg (IV)	bolus of 10mg of PPF iv were given every 30s until LOC	0.5% end-tidal
Knapik 2006	Remi (20)	Remi 0.5mcg/kg/min -> 0.25 μg/kg/min	before intubation ~ during operation	57.2±6.1	CABG	midazolam (oral)	etomidate 0.2mg/kg + 1% isoflurane	isoflurane initial concentration of 1%, then adjusted within the range of 0.6% to 1.5%
	FTN (20)	FTN 5μg/kg -> 2.5mcg/kg/h		54.4±8.1				
Maddali 2006	Remi (58)	(intraop) Remi 1mcg/kg/min + (postop) FTN bolus 1mcg/kg	after induction of anesthesia ~ on transfer to the PCSU, discontinued	57.3±7.6	CABG	midazolam 0.15mg/kg(oral)	TPT 1-1.5mg/kg + midazolam 0.05-0.1mg/kg + FTN 1-3mcg/kg	PPF 2-5 mg/kg/hr
	FTN (59)	(intraop) FTN 0.025-0.15mcg/kg/min + (postop) FTN 0.25-1.5mcg/kg/hr	after induction of anesthesia ~ until meet weaning criteria	57.8±8.9				
	FTN + postop diclofenac (59)	(intraop) FTN bolus 2mcg/kg (total < 20 mcg/kg) + (postop) diclofenac 75mg * 2 times	On transfer to the PCSU, and repeated after 12 hours	53.4±8.6				
Mekis 2004	Remi (27)	1. Remi 0.5mcg/kg/min-> (after intubation) 0.3 μg/kg/min	during induction	61.3±8.7	CABG	midazolam 10mg(oral)	midazolam 2mg + pofol 6mg/kg/h	PPF 4.5 mg/kg/h
	FTN (27)	2. FTN 5mcg/kg		60.5±9.9				

Mollhoff 2001	Remi (172)	1. Remi placebo loding + Remi 1mcg/kg/min	before intubation~until meet weaning criteria	62±8.8	Elective CABG	diazepam 10mg(oral) + Midazolam 0.05 mg/kg (IV)	midazolam 0.05mg/kg + PPF 0.5mg/kg + PPF infusion 3mg/kg/h	PPF maintenance infusion 3mg/kg/h
	FTN (149)	2. FTN 15mcg/kg loading + placebo infusion + FTN bolus 2mcg/kg, if needed		63±8.4				
myles 2002	Remi (29)	Remi 0.83 ug/kg/min	Induction~end of surgery	64±7.5	Elective CABG	temazepam 10mg(oral) + morphine 5mg(IM)	PPF 8 mg/kg/h	PPF infusion 5 mg/kg/h, then dosage adjustements were standardized by porpofol
	low dose FTN (24)	(induction) FTN 8 ug/kg + (before sternotomy) FTN 4 ug/kg + saline placebo infusion	induction, and before sternotomy	61±10				
	high dose FTN (24)	(induction) FTN 16 ug/kg + (before sternotomy)FTN 8 ug/kg + saline placebo infusion	induction, and before sternotomy	62±7.6				
Nasiri 2010	Remi (24)	1. Remi 5 mcg/kg	during induction	66±5.7	CABG	Not reported	Not reported	not described
	FTN (17)	2. FTN 8 mcg/kg		65±4.8				
	routine FTN (23)	3. routine FTN		65.7±6				
von Dossow 2008	Remi (15)	Remi 0.3–0.6 µg/kg/min	after induction~until 2hr after ICU arrival	66±5.9	elective CABG	flunitrazepam 1-2mg(oral), midazolam 0.07-0.1mg/kg(oral)	midazolam 1-4mg, fentanyl 4-7mcg/kg, etomidate 0.15-0.3mg/kg	SEVO 1.0 – 2.0 vol%
	FTN (18)	FTN 5–7 µg/kg/h	after induction~end of surgery	65±8.9				

wang 1999	Remi (20)	Remi 0.5mcg/kg + 0.025mcg/kg/min + SEVO 5%->3%	during induction	61±8	elective CABG	lorazepam 2-4mg/kg	SEVO 5%->3%	sevo 2%
	FTN (20)	FTN 10.5mcg/kg + etomidate 0.2mg/kg + isoflurane 1%		60±9			etomidate 0.2mg/kg + 1% isoflurane	isoflurane 1%
Winterhalter 2008	Remi (21)	(induction) FTN 8mcg/kg + (intaop) Remi 0.25 mcg/kg/min + (at sternotomy) remi bolus 0.3mcg/kg	after induction~ during surgery	63±10	elective on-pump CABG	midazolam(oral)	PPF 10mg/kg/h + FTN 8mg/kg	SEVO end-tidal concentration of 1–2% (stopped during CPB) + (During CPB) PPF infusion 3–5 mg/kg/h
	FTN (21)	(induction) FTN 8mcg/kg + (intraop) FTN 4 mcg/kg bolus every 30 min		64±7				
Zeydanoglu 2005	Remi (20)	Remi 1mcg/kg -> 0.1-0.4mcg/kg/min	induction~during maintenance	55.15±6.96	CABG	Not reported	etomidate	SEVO
	FTN (20)	FTN 7-10mcg/kg -> 1-2mcg/kg/min		61.45±7				

Data of patient age are shown as mean ± SD.

Remi = remifentanil, FTN=fentanyl, CABG=coronary artery bypass graft, OPCAB=off-pump CABG, intraop=intraoperative, postop=postoperative, SEVO=sevoflurane, PPF=propofol, TPT=thiopental, CPB=cardiopulmonary bypass, LOC=loss of consciousness

Assessment of risk of bias

Risk of bias evaluation revealed that methodological quality of included trials was relatively moderate (Fig 2; Fig 3). We could not assess the risk of bias in two RCTs[21 24] owing to the lack of data regarding the methodological detail. Thirteen studies[3 11-20 22 23] were evaluated as low risk of bias in most of the domains (Fig 2).

Sensitivity Analysis

A sensitivity analysis excluding four studies[17 21 23 24] that had unclear blinding risk showed no significant difference in the summary effect size with overlapping 95% CIs. Another sensitivity analysis excluding two studies[21 24] that had the unknown risk of bias also showed a similar treatment effect with overlapping 95% CIs. Therefore, the inclusion of these studies did not bias the pooled results significantly.

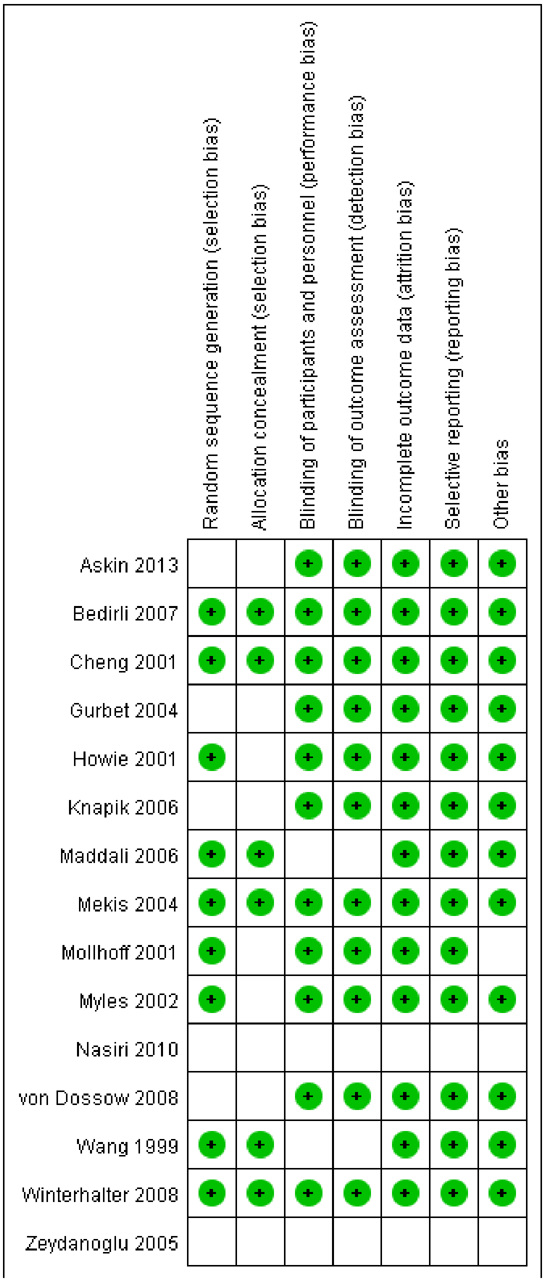

Figure 2. Risk of bias summary. The green mark and blank mean low and unclear risk of bias, respectively.

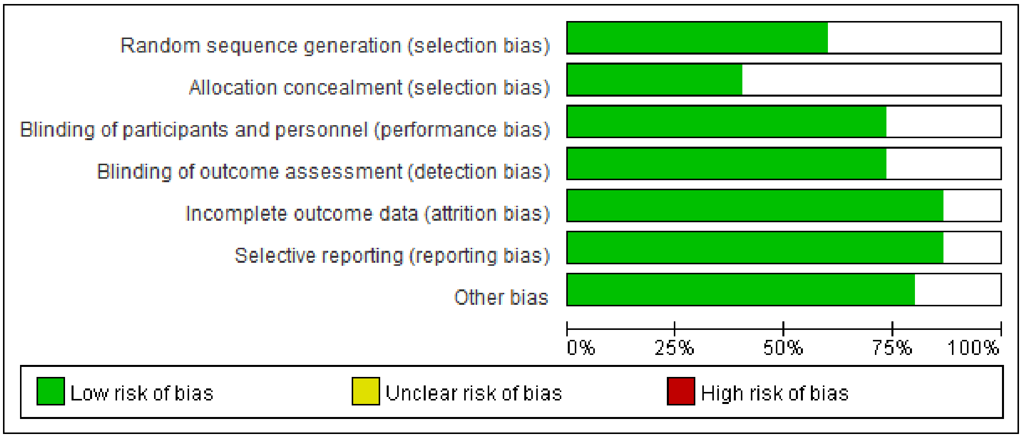

Figure 3. Risk of bias graph showing the proportion of the judgment of the risk of bias in each domain.

Quantitative Data Synthesis

Postoperative recovery times

A meta-analysis of 9 RCTs showed that the use of remifentanil was associated with a significant reduction in the duration of mechanical ventilation [SMD (95% CI) -0.46 (-0.88, -0.05), P = 0.03, I^2 = 91%, n = 1309 in 9 RCTs] (Fig 4).[3 11 14 15 17 19 20 22 24]

However, no difference was found in the length of ICU stay [SMD (95% CI) -0.09 (-0.32, 0.14), P = 0.45, I^2 = 72%, n = 1359 in 10 RCTs] (Fig 6, Fig 7)[3 11 13-15 17 19 20 22 24] and hospital stay [SMD (95% CI) -0.01 (-0.19, 0.17)], P = 0.92, I^2 = 47%, n = 1056 in 6 RCTs] (Fig 5, Fig 6).[3 13-15 19 20]

Intraoperative vital signs

Our meta-analyses showed that the use of remifentanil was associated with lower MBP after tracheal intubation [SMD (95% CI) -0.35 (-0.62, -0.08), P = 0.010, I^2 = 61%, n = 709 in 9 RCTs][11 13 15 16 18 20 21 23 24] and sternotomy [SMD (95% CI) -0.53 (-0.69, -0.36), $P < 0.00001$, I^2 = 0%, n = 593 in 7 RCTs][3 11 13 15 16 20 24] as compared with fentanyl (Fig. 7). There were no significant difference in MBP at surgical incision, chest closure, and end of surgery (Fig.7).

There was no evidence of differences in heart rate between remifentanil and fentanyl at tracheal intubation,[3 11 13 15 16 18-21 23 24] at surgical incision,[11 15 16 19 24] at sternotomy,[3 11 13 15 16 19 20 24] at chest closure,[11 13 15 16 19 20] and at the end of surgery (Fig.8).[3 11 13 15 16 19 20 24]

In addition, there was no evidence of differences in intraoperative cardiac index at several time points between remifentanil and fentanyl (Fig 9). No differences were noted at tracheal intubation,[13 16 20] at sternotomy,[13 16 20] at chest closure,[16 20] and at the end of surgery.[13 16]

Postoperative adverse events

Six studies[11 12 14 15 19 20] reported various adverse events. A meta-analysis of three studies[14 15 19] showed higher incidence of postoperative hypotension, which was defined as systolic blood pressure lower than 80 mmHg for more than 1 s, in the remifentanil arm as compared with the fentanyl arm [RR (95% CI) 2.25 (1.47, 3.42), P = 0.0002, I^2 = 9%, n = 912 in 3 RCTs)] (Fig 10).[14 15 19] There were no significant differences in the incidences of other adverse events such as atrial fibrillation,[11 14 19] myocardial ischemia[14 19 20] and nausea or vomiting (Fig.10).[11 12 14 19]

Study or Subgroup	Remifentanil Mean	Remifentanil SD	Remifentanil Total	Fentanyl Mean	Fentanyl SD	Fentanyl Total	Weight	Std. Mean Difference IV, Random, 95% CI
Zeydanoglu 2005	279.5	19.16	20	421.25	17.8	20	3.7%	-7.51 [-9.35, -5.67]
Askin 2013	390	192	20	618	222	20	10.3%	-1.08 [-1.74, -0.41]
Winterhalter 2008	240	182	21	418	212	21	10.5%	-0.88 [-1.52, -0.25]
von Dossow 2008	405	246.7	15	450	263	18	10.1%	-0.17 [-0.86, 0.51]
Myles 2002	438	348	29	486	340.8	48	12.0%	-0.14 [-0.60, 0.32]
Cheng 2001	216	912	150	222	444	154	13.5%	-0.01 [-0.23, 0.22]
Howie 2001	216	918	150	222	444	154	13.5%	-0.01 [-0.23, 0.22]
Mollhoff 2001	306	726	145	252	300	148	13.5%	0.10 [-0.13, 0.33]
Maddali 2006	647	273	58	542	315.8	118	13.0%	0.35 [0.03, 0.66]
Total (95% CI)			**608**			**701**	**100.0%**	**-0.46 [-0.88, -0.05]**

Heterogeneity: Tau² = 0.32; Chi² = 86.83, df = 8 (P < 0.00001); I² = 91%
Test for overall effect: Z = 2.18 (P = 0.03)

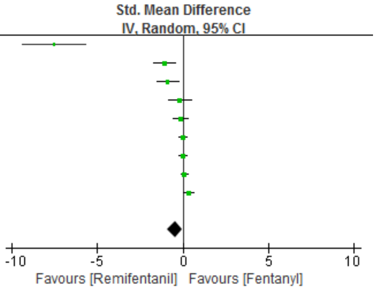

Figure 4. A forest plot for the duration of mechanical ventilation.

Study or Subgroup	Remifentanil Mean	Remifentanil SD	Remifentanil Total	Fentanyl Mean	Fentanyl SD	Fentanyl Total	Weight	Std. Mean Difference IV, Random, 95% CI
Zeydanoglu 2005	33.15	4.04	20	39.65	4.13	20	6.3%	-1.56 [-2.28, -0.84]
von Dossow 2008	49	14.1	15	75	51.9	18	6.5%	-0.64 [-1.35, 0.06]
Bedirli 2007	40.8	28.8	25	50.4	26.4	25	8.3%	-0.34 [-0.90, 0.22]
Maddali 2006	60	31.2	58	62.4	39.6	118	12.4%	-0.06 [-0.38, 0.25]
Howie 2001	16.8	40.8	150	19.2	45.6	154	14.0%	-0.06 [-0.28, 0.17]
Winterhalter 2008	21	3.8	21	21	1.3	21	7.7%	0.00 [-0.60, 0.60]
Myles 2002	23	14.1	29	22.5	12.6	48	9.8%	0.04 [-0.42, 0.50]
Cheng 2001	26.4	45.6	150	24	40.8	154	14.0%	0.06 [-0.17, 0.28]
Mollhoff 2001	26.4	40.8	145	21.6	24	148	13.9%	0.14 [-0.09, 0.37]
Askin 2013	20.7	6.5	20	14.6	6.7	20	7.0%	0.91 [0.25, 1.56]
Total (95% CI)			**633**			**726**	**100.0%**	**-0.09 [-0.32, 0.14]**

Heterogeneity: Tau² = 0.09; Chi² = 32.27, df = 9 (P = 0.0002); I² = 72%
Test for overall effect: Z = 0.75 (P = 0.45)

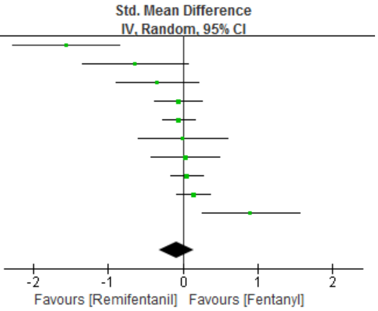

Figure 5. A forest plot for the length of ICU stay.

Study or Subgroup	Remifentanil Mean	Remifentanil SD	Remifentanil Total	Fentanyl Mean	Fentanyl SD	Fentanyl Total	Weight	Std. Mean Difference IV, Random, 95% CI
Myles 2002	4.9	2.1	29	5.9	2.2	48	11.1%	-0.46 [-0.92, 0.01]
Winterhalter 2008	9	2	21	10	2.3	21	7.3%	-0.46 [-1.07, 0.16]
Cheng 2001	5	10	150	4.9	7.6	154	24.7%	0.01 [-0.21, 0.24]
Howie 2001	4.4	10.2	150	4	3.2	154	24.7%	0.05 [-0.17, 0.28]
Mollhoff 2001	6.9	6.8	139	6.1	14.5	140	23.9%	0.07 [-0.16, 0.31]
Bedirli 2007	8.8	2.9	25	7.4	2.6	25	8.3%	0.50 [-0.06, 1.06]
Total (95% CI)			**514**			**542**	**100.0%**	**-0.01 [-0.19, 0.17]**

Heterogeneity: Tau² = 0.02; Chi² = 9.36, df = 5 (P = 0.10); I² = 47%
Test for overall effect: Z = 0.10 (P = 0.92)

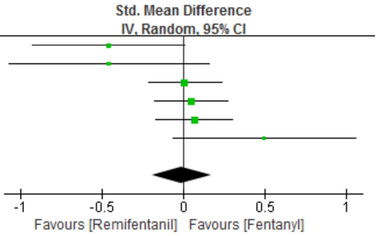

Figure 6. A forest plot for the length of hospital stay.

Study or Subgroup	Remifentanil Mean	Remifentanil SD	Remifentanil Total	Fentanyl Mean	Fentanyl SD	Fentanyl Total	Weight	Std. Mean Difference IV, Random, 95% CI
14.4.1 Tracheal intubation								
Knapik 2006	81.4	12.9	20	95.7	20	20	9.2%	-0.83 [-1.48, -0.18]
Bedirli 2007	61	9	25	71	15	25	10.3%	-0.80 [-1.37, -0.22]
Mekis 2004	73.3	15.9	27	86.2	20.5	27	10.8%	-0.69 [-1.24, -0.14]
Myles 2002	62	9	29	70	13.4	48	12.2%	-0.66 [-1.14, -0.19]
Nasiri 2010	77	16	24	89.4	23.7	40	11.4%	-0.58 [-1.10, -0.06]
Howie 2001	75.6	21.1	150	77.8	17.8	154	17.4%	-0.11 [-0.34, 0.11]
Askin 2013	93.3	33.3	20	93.3	33.2	20	9.6%	0.00 [-0.62, 0.62]
Wang 1999	79.9	17.1	20	77.1	14.2	20	9.6%	0.17 [-0.45, 0.80]
Zeydanoglu 2005	99.9	13.9	20	94.9	17	20	9.5%	0.32 [-0.31, 0.94]
Subtotal (95% CI)			**335**			**374**	**100.0%**	**-0.35 [-0.62, -0.08]**
Heterogeneity: Tau² = 0.09; Chi² = 20.27, df = 8 (P = 0.009); I² = 61%								
Test for overall effect: Z = 2.58 (P = 0.010)								
14.4.2 Surgical incision								
Howie 2001	80	13.3	150	95.6	17.8	154	30.5%	-0.99 [-1.23, -0.75]
Askin 2013	80	14	20	92	22	20	22.9%	-0.64 [-1.27, -0.00]
Knapik 2006	100	15.7	20	100	15.7	20	23.3%	0.00 [-0.62, 0.62]
Zeydanoglu 2005	89.9	17	20	89.9	17	20	23.3%	0.00 [-0.62, 0.62]
Subtotal (95% CI)			**210**			**214**	**100.0%**	**-0.45 [-1.02, 0.12]**
Heterogeneity: Tau² = 0.26; Chi² = 15.22, df = 3 (P = 0.002); I² = 80%								
Test for overall effect: Z = 1.55 (P = 0.12)								
14.4.3 Sternotomy								
Knapik 2006	92.9	11.4	20	101.4	15.7	20	6.7%	-0.61 [-1.24, 0.03]
Myles 2002	75	10	29	82	13	48	12.2%	-0.58 [-1.05, -0.11]
Howie 2001	75.6	13.3	150	84.4	17.8	154	51.5%	-0.56 [-0.79, -0.33]
Bedirli 2007	74	16	25	83	20	25	8.5%	-0.49 [-1.05, 0.07]
Askin 2013	86	14	20	94	19	20	6.8%	-0.47 [-1.10, 0.16]
Zeydanoglu 2005	99.9	17	20	107.4	17	20	6.9%	-0.43 [-1.06, 0.20]
Winterhalter 2008	76	12	21	80	11	21	7.3%	-0.34 [-0.95, 0.27]
Subtotal (95% CI)			**285**			**308**	**100.0%**	**-0.53 [-0.69, -0.36]**
Heterogeneity: Tau² = 0.00; Chi² = 0.67, df = 6 (P = 1.00); I² = 0%								
Test for overall effect: Z = 6.28 (P < 0.00001)								
14.4.4 Chest closure								
Myles 2002	66	9	29	71	8.5	48	25.5%	-0.57 [-1.04, -0.10]
Howie 2001	73.3	13.3	150	75.6	11.1	154	33.3%	-0.19 [-0.41, 0.04]
Knapik 2006	76.4	8.6	20	75.7	8.6	20	20.9%	0.08 [-0.54, 0.70]
Askin 2013	85	24.8	20	71.1	11.1	20	20.3%	0.71 [0.07, 1.35]
Subtotal (95% CI)			**219**			**242**	**100.0%**	**-0.05 [-0.48, 0.38]**
Heterogeneity: Tau² = 0.13; Chi² = 10.59, df = 3 (P = 0.01); I² = 72%								
Test for overall effect: Z = 0.22 (P = 0.83)								
14.4.5 End of surgery								
Bedirli 2007	68	11	25	75	12	25	15.6%	-0.60 [-1.17, -0.03]
Howie 2001	71.1	11.1	150	75.6	11.1	154	27.7%	-0.40 [-0.63, -0.18]
Winterhalter 2008	71	13	21	75	11	21	14.5%	-0.33 [-0.94, 0.28]
Knapik 2006	76.4	8.6	20	75.7	6.4	20	14.2%	0.09 [-0.53, 0.71]
Askin 2013	85	24.8	20	80	16.8	20	14.1%	0.23 [-0.39, 0.85]
Zeydanoglu 2005	82.5	5.8	20	78.7	11.2	20	14.0%	0.42 [-0.21, 1.04]
Subtotal (95% CI)			**256**			**260**	**100.0%**	**-0.15 [-0.46, 0.16]**
Heterogeneity: Tau² = 0.08; Chi² = 11.07, df = 5 (P = 0.05); I² = 55%								
Test for overall effect: Z = 0.94 (P = 0.35)								

Test for subgroup differences: Chi² = 7.51, df = 4 (P = 0.11), I² = 46.7%

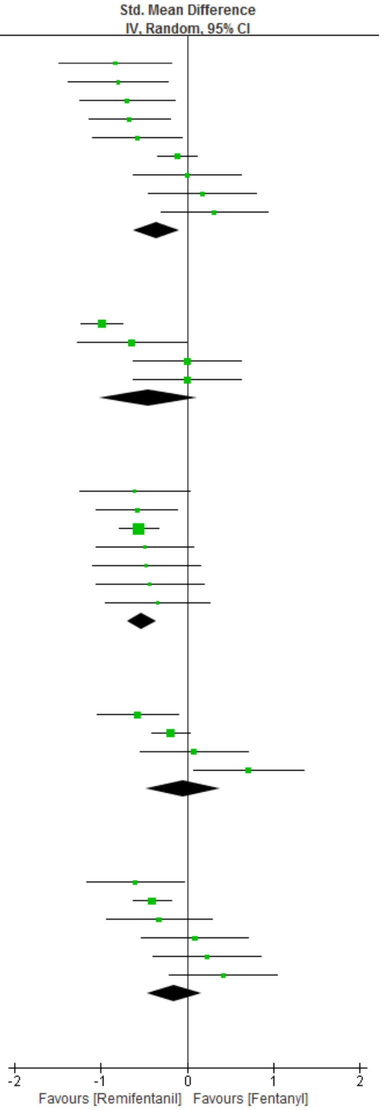

Figure 7. Forest plots for mean blood pressure at tracheal intubation, surgical incision, sternotomy, chest closure, and the end of surgery.

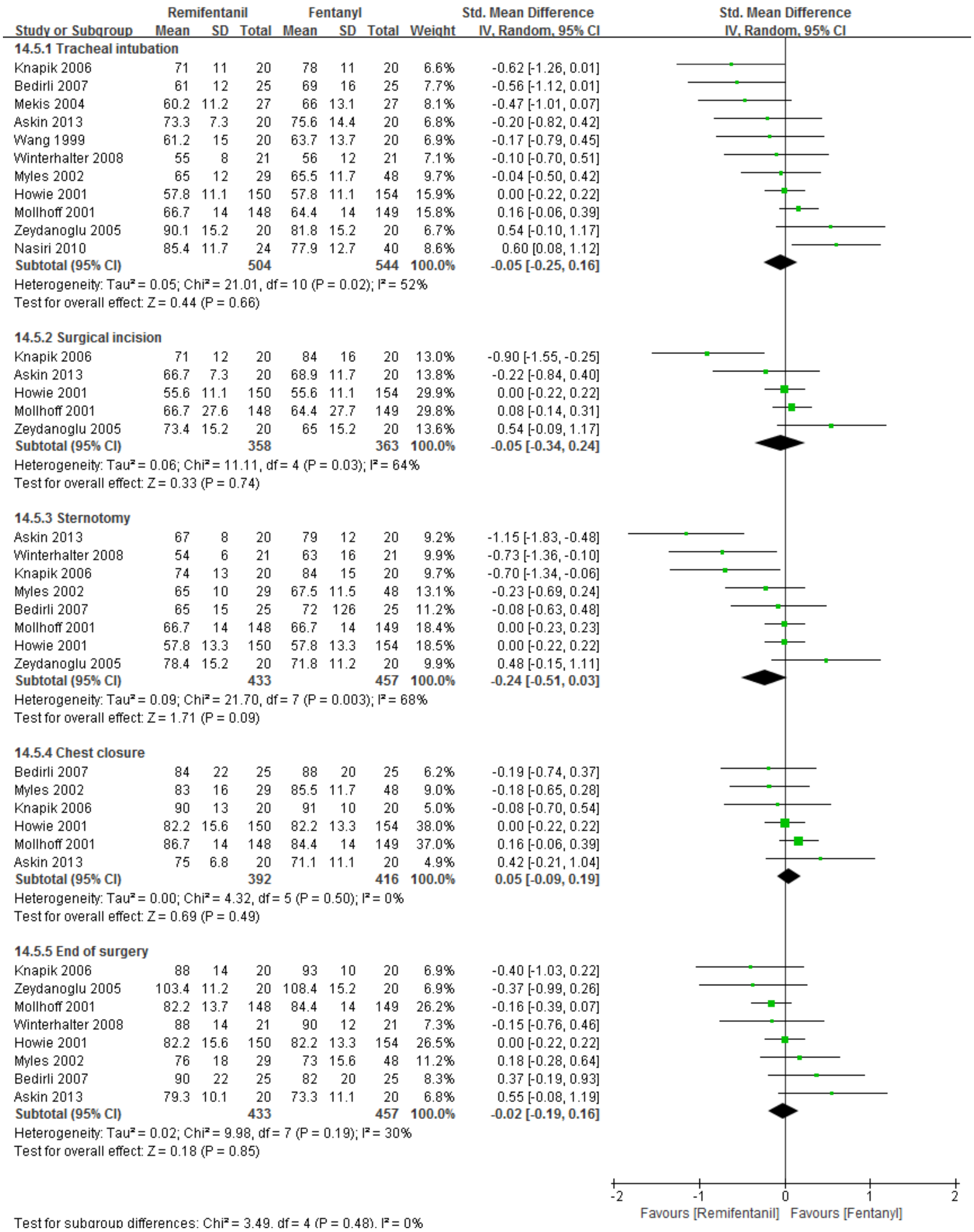

Figure 8. Forest plots for heart rate at tracheal intubation, surgical incision, sternotomy, chest closure, and the end of surgery.

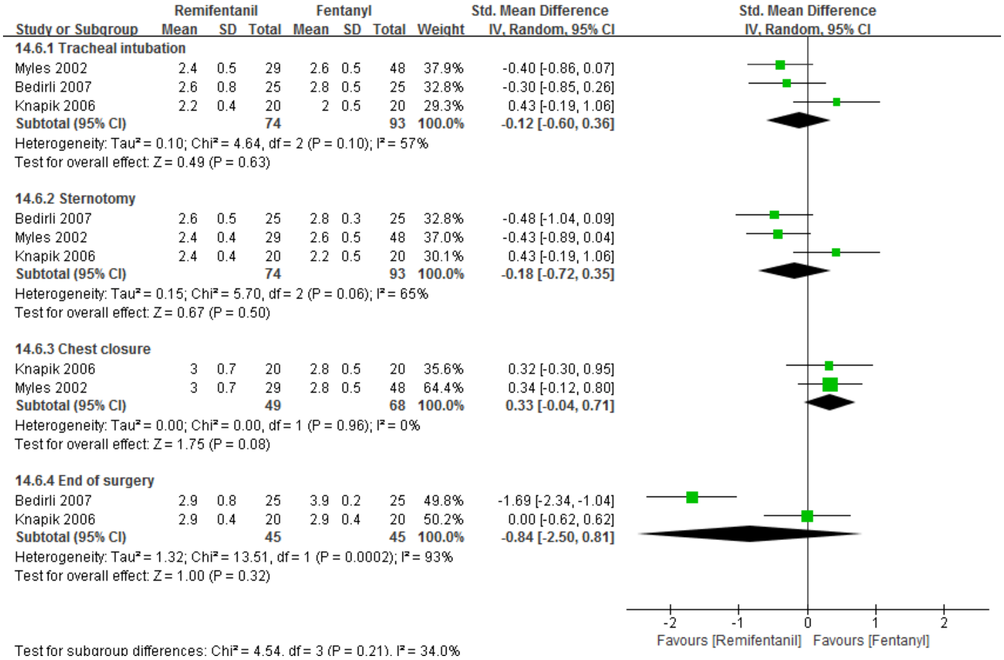

Figure 9. Forest plots for cardiac index at tracheal intubation, sternotomy, chest closure, and the end of surgery.

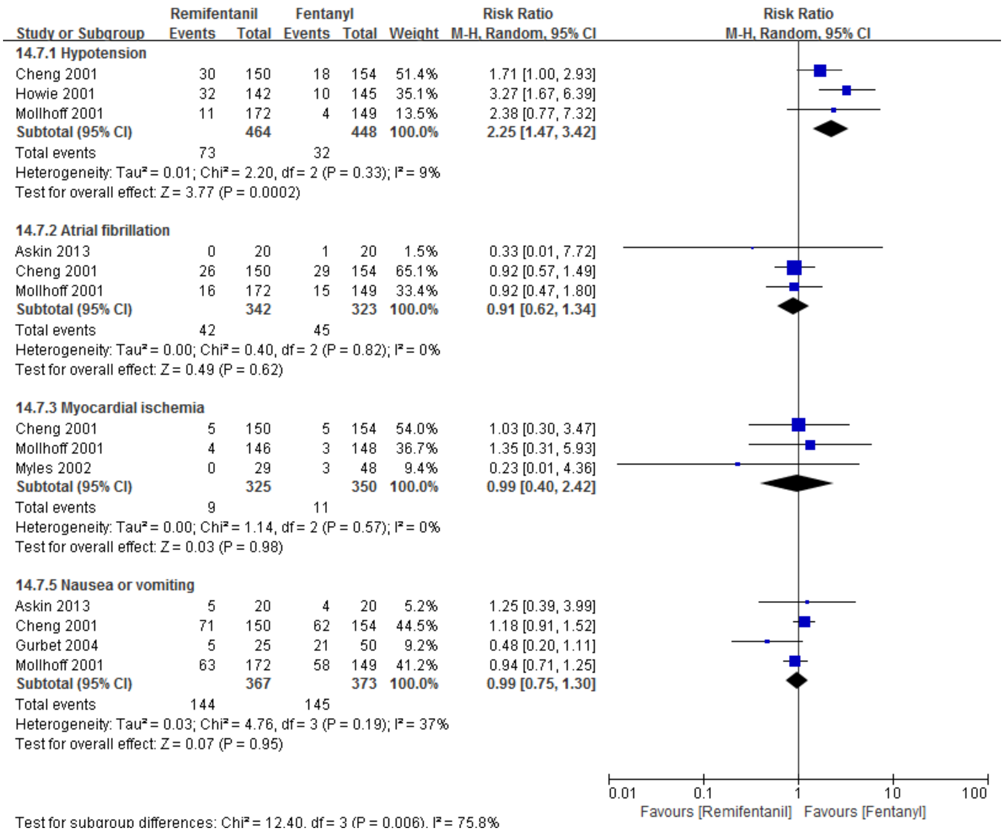

Figure 10. Forest plots for postoperative adverse events such as hypotension, atrial fibrillation, myocardial ischemia, and nausea or vomiting.

Discussion

Although pharmacokinetic elimination of remifentanil is more rapid than that of fentanyl,[25-29] there has been controversy in clinical benefits in reducing recovery time after CABG.[3 11 17 19 24] This systematic review and meta-analysis of 15 RCTs comparing the uses of remifentanil and fentanyl in patients undergoing CABG provided the evidence that remifentanil had advantage in shortening the duration of mechanical ventilation as compared with fentanyl. The aims of fast-track cardiac anesthesia via early extubation are decreased length of intensive care unit (ICU) and hospital stay, improved postoperative prognosis, and subsequent cost reduction of medical cost[30-34] and fast-track anesthesia in cardiac surgery is known to be safe and cost-effective.[30 35-37] However, in our meta-analysis, there were no significant differences in lengths of ICU and hospital stay. Therefore, the use of remifentanil may affect only immediate postoperative period, but not have long-term effects.

Because continuous infusion rate or target effect-site concentration of remifentanil are easily controlled and its response is prompt, remifentanil seems to be effective for maintaining intraoperative hemodynamic stability. In our meta-analysis, HR and CI were comparable between the uses of remifentanil and fentanyl during the anesthesia for CABG. However, lower MBP was shown at tracheal intubation and sternotomy in the use of remifentanil than that of fentanyl. The incidence of postoperative hypotension was also higher in the remifentanil arm than the fentanyl arm. Generally, the patients undergoing CABG have marginal cardiac reserve,[25] so their hemodynamic responses to administration of opioids are vulnerable.[2] Therefore, remifentanil should be carefully titrated to avoid inadvertent hypotension during the perioperative period.

Advantages of remifentanil with short-acting characteristics should be balanced with increased risk of postoperative pain, which may increase the risk of myocardial ischemic events. Thus, postoperative pain was our major concerns. However, unfortunately, no studies included in our meta-analysis reported outcomes regarding postoperative pain, so we could not evaluate it. Nevertheless, we showed that there was no significant difference in the incidence of postoperative myocardial ischemia between the uses of remifentanil and fentanyl. Moreover, there were no significant differences in other adverse events, such as atrial fibrillation and nausea or vomiting. Therefore, remifentanil seems to be safely used for perioperative period of CABG.

There were some limitations in our study. Although the use of intraoperative cardiopulmonary bypass is an influential factor for perioperative outcomes, only five studies[3 11-14] clearly reported on- or off-pump CABG, thus we could not categorize the analysis according to the type of CABG. Moreover, moderate heterogeneity was found because of various type of anesthetic agents or timing of study drug administration. However, the effect sizes were unchanged in the relevant subgroup analyses. In addition, although several studies had unclear risk of bias, the pooled effect sizes were robust in the sensitive analysis. In addition, we could not guarantee whether equipotent doses of remifentanil and fentanyl were used in each study. However, our meta-analysis included only randomized trials, thus potential bias may be minimized in pooling each effect size of each study.

Conclusion

This meta-analysis provided the evidence that the use of remifentanil significantly decreased the duration of mechanical ventilation after CABG as compared with the use of fentanyl. Moreover, there was no difference in the incidence of postoperative myocardial ischemia between the uses of remifentanil and fentanyl. However, the patients undergoing CABG have poor cardiac reserve and remifentanil seems to be more associated lower blood pressure during the perioperative period, therefore care should be taken in the use of remifentanil to avoid inadvertent perioperative hypotension.

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국문 초록

목적: 본 메타 분석은 관상동맥우회술을 받는 성인 환자에서 레미펜타닐을 사용하였을 때의 수술 후 회복 기간, 수술 중 혈역학적 안정성 및 수술 후 합병증의 발생률을 펜타닐을 사용한 경우와 비교함으로써 레미펜타닐이 펜타닐에 비해 임상적인 이득이 있는지 알아보고자 하였다.

방법: 관상동맥우회술을 받는 성인 환자를 대상으로 레미펜타닐과 펜타닐을 비교한 무작위 대조군 연구를 찾기 위해서 MEDLINE, CINAHL, EMBASE, CENTRAL of Cochrane Library, Web of Science 및 KoreaMed 등의 전자 데이터베이스를 검색하였으며 2015년 5월까지의 연구들을 포함시켰다. 2명의 저자가 독립적으로 무작위 대조군 연구들의 방법론적 품질을 평가하였으며 자료를 추출하였다.

결과: 레미펜타닐의 사용은 펜타닐의 사용과 비교하여 수술 후 인공환기

시간의 감소와 유의한 연관성이 있었다(표준화 평균차 -0.46, 95% 신뢰구간 -0.88 to -0.05, P = 0.03) 레미펜타닐은 수술 중 맥박수와 심박출량계수에는 영향을 미치지 않았으나 기관내삽관 시(표준화 평균차 -0.35, 95% 신뢰구간 -0.62 to -0.08, P = 0.010) 흉골절개술 시(표준화 평균차 -0.53, 95% 신뢰구간 -0.69 to -0.36, P < 0.00001) 평균동맥압을 펜타닐에 비해 유의하게 많이 감소시켰다. 또한 레미펜타닐의 사용 시 펜타닐에 비해 수술 후 저혈압의 발생 빈도가 유의하게 높았다. (상대위험비 2.25, 95% 신뢰구간 1.47 to 3.42, P = 0.0002). 심방세동, 심근허혈, 수술 후 오심, 구토 등의 부작용은 레미텐타닐과 펜타닐의 사용에서 유의한 차이가 없었다.

결론: 관상동맥우회술을 받는 환자에서 레미펜타닐의 사용은 펜타닐에 비해서 수술 후 기계적 조절환기의 지속기간을 줄여 준다는 이점이 있다. 한편, 레미펜타닐을 사용한 경우에 펜타닐에 비해서 기관내삽관 시와 흉골절개술 시의 평균동맥압이 낮았으며, 수술 후 저혈압의 발생률이 높았으므로 사용에 주의가 필요하다.

주요어: 레미펜타닐, 펜타닐, 관상동맥우회술, 메타 분석, 인공 환기, 재원

기간, 평균 동맥압

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