Systematic Review and Meta-Analysis

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Comparison between remifentanil and other opioids in adult critically ill patients

A systematic review and meta-analysis

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Abstract

Background and aims: To identify the efficacy and safety of remifentanil when compared with other opioids in adult critically ill patients.

Methods: We searched for studies in the Cochrane Library, MEDLINE, and EMBASE that had been published up to May 31st, 2019. Randomized clinical trials using remifentanil comparing with other opioids for analgesia were included. Two reviewers independently applied eligibility criteria, assessed quality, and extracted data. Duration of mechanical ventilation was the primary outcome, and secondary outcomes included weaning time, intensive care unit (ICU), length of stay (LOS), hospital LOS, mortality, side effects, and costs.

Results: Fifteen studies with 1233 patients were included. Remifentanil was associated with a significant reduction in the duration of mechanical ventilation in the adult ICU patients when compared with other opioids ($P = .01$). Remifentanil also reduced the weaning time ($P = .02$) and the ICU LOS when compared with other opioids ($P = .01$). There was no difference in the hospital LOS ($P = .15$), side effects ($P = .39$), and mortality ($P = .79$) between remifentanil and other opioids, what's more, remifentanil increased the costs of anesthesia ($P < .001$) but did not increase cost of hospitalization ($P = .30$) when comparing with other opioids.

Conclusions: Remifentanil reduced the duration of mechanical ventilation, weaning time, and ICU LOS when compared with other opioids in adult critically ill patients. Higher quality RCTs are necessary to prove our findings.

PROSPERO registration number: CRD42016041438.

Abbreviations: CI = confidence interval, GRADE = Grading of Recommendations, Assessment, Development, and Evaluation, ICU = intensive care unit, IV = inverse variance, LOS = length of stay, M-H = Mantel-Haenszel, RR = risk ratio, SMD = standard mean differences.

Keywords: intensive care unit, meta-analysis, opioids, remifentanil

1. Introduction

Pain is very common among patients admitted to an intensive care unit (ICU) whether at rest or during standard care procedures.[1,2] Analgesia is often required for ICU patients to relieve pain, improve comfort, reduce stress, and facilitate procedures. Currently, opioids, such as morphine, fentanyl, sufentanil, and remifentanil, are commonly used for pain management in the ICU.[3] However, the accumulation of opioids leads to numerous side effects, such as nausea, vomiting, ileus, hemodynamic instability, respiratory depression, and prolongs the duration of mechanical ventilation and ICU length of stay (LOS).[4]

Remifentanil, a 4-anilidopiperidine derivative of fentanyl, is an ultra-short-acting μ-opioid receptor agonist. It has a rapid onset of action (1 minute) and a rapid offset of action following discontinuation (3–10 minutes) irrespective of the duration of infusion. Its property of organ-independent metabolism makes the pharmacokinetics of remifentanil unaffected by the renal and live dysfunction which is very common in critically ill patients.[4] Therefore, we hypothesized that remifentanil could be a better analgesic than other opioids in critically ill patients.

The results of an early meta-analysis showed that remifentanil was associated with reduced weaning time, but not associated with a reduction in mechanical ventilation duration, ICU LOS, or mortality. Furthermore, in this meta-analysis, remifentanil was not only compared with other opioid, but also with sedative

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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agent.[5] Another recent meta-analysis found that remifentanil as compared with other opioids was associated with decreased duration of mechanical ventilation, time to extubation, and the length of ICU stay. However, the subjects of this meta-analysis were patients under the treatment of mechanical ventilation and included many post-surgery patients. In 5 of their included studies, remifentanil and other opioids were only used during the operation (not used in the ICU), and some of them were carried out in the anesthesia recovery room, not the ICU.[6] Therefore, this meta-analysis may not represent the value of remifentanil in critically ill ICU patients. On the other hand, recent studies indicated that remifentanil as compared with other opioids was associated with a higher incidence of side effects, such as opioid-induced hyperalgesia.[7,8]

Therefore, we conducted this systematic review and meta-analysis to identify the efficacy and safety of remifentanil when compared with other opioids in adult critically ill patients.

2. Study aim

We aim to assess the effects of remifentanil on the duration of mechanical ventilation, weaning time, ICU LOS, hospital LOS, cost, and mortality in critically ill patients; and aim to assess the side effects of remifentanil as well.

3. Method

This study is a review and meta-analysis. So ethical approval is not necessary.

This systematic review is performed in accordance with the methods recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline.[9] We registered this systematic review and meta-analysis on PROSPERO international prospective register of systematic reviews (https://www.crd.york.ac.uk/prospero/) on February 11, 2018, the registration number CRD42016041438.

3.1. Search strategy

We searched 3 electronic databases including Cochrane Library, MEDLINE, and EMBASE databases for reports of studies that included databases from their inception to May 31th, 2019. Our search strategy used appropriate medical subject headings and keywords. The search strategy is in the appendix (see Supplement Content, which illustrates the search strategy, http://links.lww.com/MD2/A477). We also manually checked clinical trials.gov and the references of the relevant studies to identify other potentially trials or unpublished reports. Two reviewers (SY and HZ) completed the research of this systematic review independently. A consensus of all the authors was made to resolve the inconsistency of the literature review.

3.2. Study selection

Eligible studies were those that matched the following criteria:

1. Type of study: randomized controlled trial;
2. Human study;
3. Population: adult patients (age $\geq$ 18 years) admitted to the ICU;
4. Intervention: remifentanil used for analgesia management;
5. Predefined outcomes: duration of mechanical ventilation, weaning time (from the beginning to the end of the mechanical ventilation weaning procedure), ICU LOS, hospital LOS, side effects (nausea/vomiting, hemodynamic instability, and delirium), mortality, and costs.

The study with the most recent publication date was included in the review if there were more than 1 eligible trial from 1 team with the same subjects.

Studies that met any of the following criteria were excluded from the analysis: a study not set in an ICU (remifentanil was not administrated in ICU); a study that remifentanil was compared with non-opioid drugs; a study was in neither English nor Chinese language.

The primary outcome was the duration of mechanical ventilation. The second outcomes were weaning time, ICU LOS, hospital LOS, side effects (nausea/vomiting, hemodynamic instability, and delirium), mortality, and costs.

3.3. Data extraction

Two reviewers (SY and HZ) reviewed the titles, abstracts, and all full-text articles according to a standard data extraction form independently. We resolved disagreements through discussion with a third author (HW). The data extracted in the analysis were as follows: the study ID (combined the first author's name with publication year), country, selected population, size, site, intervention, and outcome. We also checked the additional files and contacted the authors for more details if necessary.

3.4. Quality assessment and publication bias

Two reviewers independently explored the quality of selected RCTs using the Cochrane Collaboration Risk of Bias tool by RevMan 5.3 software.[10] This tool considers 7 different domains: adequacy of sequence generation, allocation sequence concealment, blinding of participants and caregivers, blinding for outcome assessment, incomplete outcome data, selective outcome reporting, and the presence of other potential sources of bias not accounted for in the other 6 domains. Each domain was categorized as low, unclear, or high risk of bias. Two reviewers (SY and HZ) made judgments independently. In cases of disagreement, a resolution was first attempted by discussion and then by consulting a third author (HW) for arbitration.

We assessed the possibility of publication bias by using funnel plots which were implemented in RevMan 5.3 software (Cochrane Library, London, UK). We also used egger's regression test to measure funnel plot asymmetry using Stata 12.0 software (StataCorp LP, Texas).[11]

3.5. Grading the quality of the evidence

We used the methodology of the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group to assess the quality of the evidence for all the outcomes by Stata 12.0 software. This tool included 4 domains: risk of bias, inconsistency, indirection imprecision, and publication bias. The quality of evidence was classified as very low, low, medium, and high.

3.6. Statistical analysis

We used RevMan 5.3 software (Cochrane Library, London, UK) to perform the statistical analysis. We analyzed pooled effects by calculating risk ratio (RR) with 95% confidence intervals (95% CI) for dichotomous variables and standard mean differences

(SMD) with 95% CI for continuous variables. Mantel-Haenszel (M-H) and inverse variance (IV) methods were applied for dichotomous variables and continuous variables, respectively.

We assess the heterogeneity of the trials using the I^2 statistic as implemented in RevMan5.3 software. I^2 values of 25% to 50% indicated low, 50% to 75% indicated moderate, and >75% indicated high heterogeneity. Heterogeneity was significant when $I^2 > 50\%$ and $P < .1$. The analyses were performed using random-effects models.[12] The results were expressed using P values. A P values less than .05 was considered statistically significant.

4. Results

4.1. Study identification and selection

Our search strategy identified 13,897 relevant citations, while 13,892 from electronic selection and 5 from other references. We assessed 11,176 articles after the removal of duplicates. We screened titles and abstracts to identify potentially eligible studies and retrieved 41 manuscripts for full-text review. Twenty-six of those studies were excluded: 4 studies were not in English or Chinese,[13–16] 12 did not include the relevant outcomes for systematic review,[17–28] 5 were not set in the ICU,[29–33] 3 studies using remifentanil versus non-opioid for sedation,[34–36] and 2 studies are not RCTs.[37,38] In total, 15 studies[39–53] were eligible and included in this systemic review, which ultimately included 1233 subjects. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the selection of studies is shown in Figure 1.

4.1.1. Characteristics of included studies. The characteristics of individual studies included in this systematic review are presented in Table 1. We included 15 RCTs in this review. The other opioids compared with remifentanil included: 3 studies

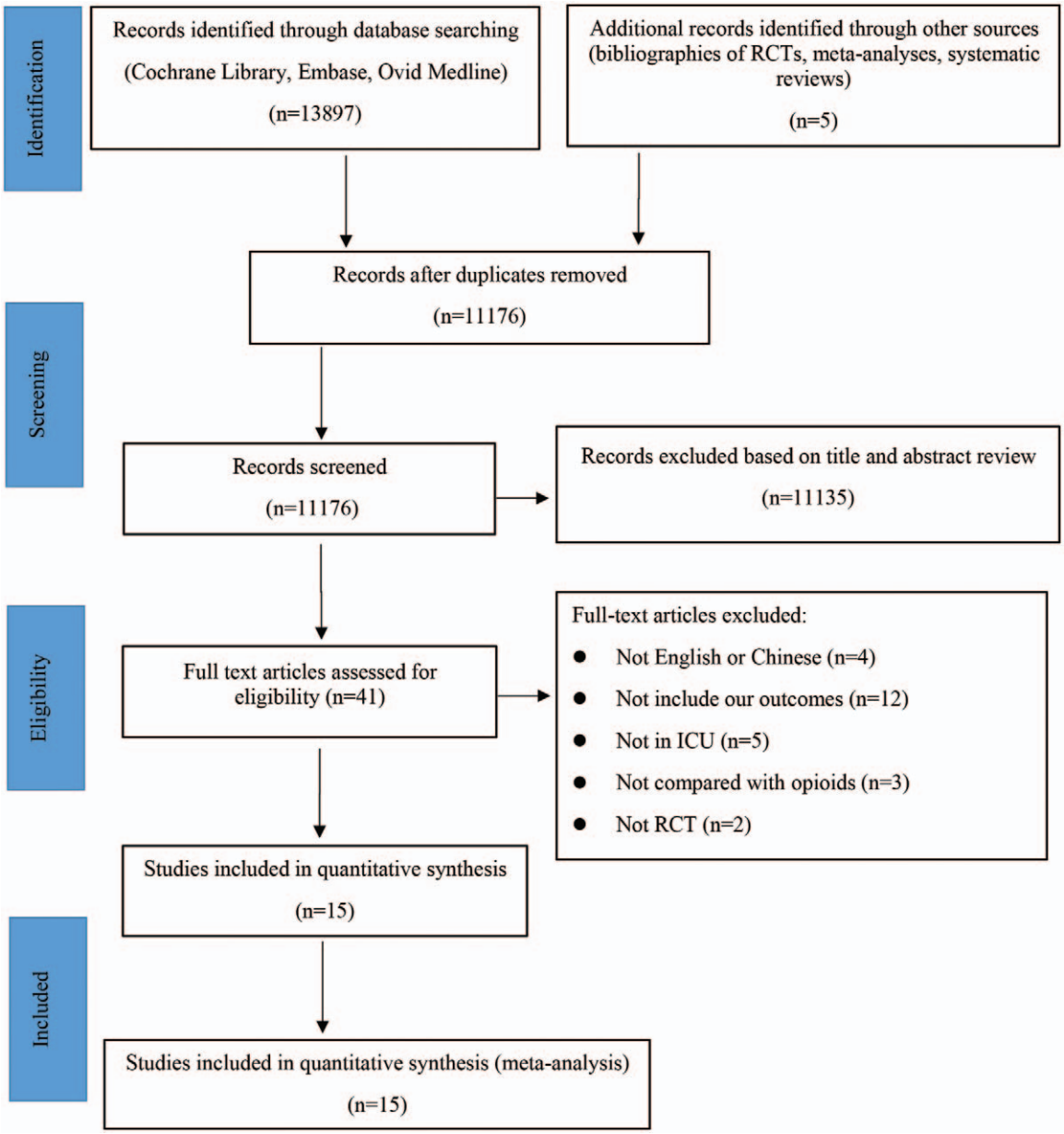

Figure 1. Flow chart showing the selection of studies in this meta-analysis.

Table 1

Main characteristics of the 17 studies included in the systemic review and meta-analysis.

				Intervention		Outcomes						
Study ID	Size	Patients	Setting	Remifentanil group	Control group	Intubation time	Weaning time	ICU LOS	Hospital LOS	Side effects	Mortality	Costs
Bhavsar 2016	60	Post-cardiac surgery	CICU	Remifentanil	Sufentanil	Yes	NR	Yes	NR	NR	NR	NR
Breen 2005	105	Other post-surgery	ICU	Remifentanil	Morphine or fentanyl	NR	NR	NR	NR	Yes	Yes	NR
Carrer 2007	100	Other post-surgery	ICU	Remifentanil	Morphine	Yes	NR	Yes	NR	Yes	NR	NR
Dahaba 2004	40	Other post-surgery	ICU	Remifentanil	Morphine	Yes	NR	Yes	NR	Yes	NR	NR
Engoren 2001a	62	Post-cardiac surgery	ICU	Remifentanil	Fentanyl	Yes	NR	Yes	Yes	NR	NR	Yes
Engoren 2001b	57	Post-cardiac surgery	ICU	Remifentanil	Sufentanil	yes	NR	Yes	yes	NR	NR	Yes
Guggenberger 2006	50	Post-cardiac surgery	SICU	Remifentanil	Sufentanil	Yes	NR	Yes	Yes	NR	NR	NR
Karabinis 2004a	69	Other post-surgery	ICU	Remifentanil	Fentanyl	Yes	Yes	NR	NR	NR	NR	NR
Karabinis 2004b	75	Other post-surgery	ICU	Remifentanil	Morphine	Yes	Yes	NR	NR	NR	NR	NR
Khanykin 2013	64	Post-cardiac surgery	ICU	Remifentanil	Fentanyl	Yes	NR	Yes	Yes	NR	NR	NR
Lee 2014	96	Medical critically ill patients	ICU	Remifentanil	Morphine	Yes	Yes	Yes	NR	NR	Yes	NR
Liu 2013	60	Other post-surgery	ICU	Remifentanil	Fentanyl	Yes	NR	Yes	NR	Yes	NR	Yes
Liu 2017	70	Medical critically ill patients	ICU	Remifentanil + midazolam	Fentanyl	Yes	Yes	Yes	NR	NR	Yes	NR
Maddail 2006	117	Post-cardiac surgery	PCSU	Remifentanil	Fentanyl	Yes	NR	Yes	NR	NR	NR	NR
Muellejans 2004	152	Post-cardiac surgery	ICU	Remifentanil	Fentanyl	NR	Yes	Yes	NR	Yes	NR	NR
Muellejans 2006	72	Post-cardiac surgery	ICU	Remifentanil	Fentanyl	Yes	Yes	Yes	NR	Yes	NR	NR
Spies 2011	60	Medical critically ill patient	ICU	Remifentanil	Fentanyl	Yes	NR	Yes	Yes	YES	NR	NR

CICU = cardiac intensive care unit; ICU = intensive care unit; LOS = length of stay; NR = not reported; PCSU = post-cardiac surgical unit; SICU = surgical intensive care unit.

with sufentanil,[39,43,44] 10 studies with fentanyl,[40,43,45,46,48–53] and 5 studies with morphine.[40–42,45,47] The population of included studies consisted of surgical patients (including post-cardiac surgery[39,43,44,46,50–52] and other surgical patients[40–42,45,48]) and medical critically ill patients admitted to the ICU.[47,49,53] Four studies were multi-center,[40,45,47,51] and the other studies were single-center. Two studies were performed in multi-countries,[40,51] 1 in America,[43] 1 in Austria,[42] 2 in Denmark,[39,46] 2 in China,[48,49] 1 in Korea,[47] 3 in Germany,[44,52,53] 1 in Greece,[45] 1 in Italy,[41] and 1 in Oman.[50]

4.2. Risk of bias assessment

For all RCTs included in this meta-analysis, most of the domains were evaluated as having low risk of bias (allocation sequence concealment, blinding for outcome assessment, incomplete outcome data, and selective outcome reporting of domains). The results of the study quality assessment were summarized in Figure 2.

Funnel plots were visually inspected and did not demonstrate evidence of publication bias in the duration of mechanical ventilation (see Supplement Content, which illustrates funnel plots of the duration of mechanical ventilation, http://links.lww.com/MD2/A474) and the ICU LOS (see Supplement Content, which illustrates funnel plots of the ICU LOS, http://links.lww.com/MD2/A473). The Egger regression test showed that the tests of asymmetry were not significant for main endpoints, including: the duration of mechanical ventilation ($t=-1.56$; 95% CI −8.81 to 1.41; $P=.14$); weaning time ($t=-0.35$; 95% CI −9.01 to 7.00; $P=.745$); ICU LOS ($t=-1.75$; 95% CI −9.71 to 1.06; $P=.11$); side effects: nausea/vomiting ($t=0.49$; 95% CI −2.29 to 3.12; $P=.657$), hypotension ($t=1.69$; 95% CI −2.41 to 5.54; $P=.233$), and dysrhythmia ($t=-0.15$; 95% CI −5.447 to 5.07; $P=.892$); mortality ($t=1.03$; 95% CI −14.47 to 17.01; $P=.49$). However, the test of hospital LOS was asymmetry ($t=-4.38$; 95% CI −36.41 to −5.78; $P=.02$) (see Supplement Content, which illustrates Egger regression test of the hospital LOS, http://links.lww.com/MD2/A472).

4.2.1. Primary outcome

4.2.1.1. Duration of mechanical ventilation. Sixteen studies focus on mechanical ventilation time; they all showed that remifentanil significantly reduced the duration of mechanical ventilation. Fourteen of them were included in the meta-analysis.[39–50,52,53] One study was excluded because of the impossibility of data extraction.[40] Pooled analysis of 13 studies[39,41–50,52,53] showed that remifentanil was associated with a significant reduction in the duration of mechanical ventilation when compared with other opioids (SMD −0.23; 95% CI −0.41 to −0.06; $P=.01$; IV random; heterogeneity $I^2=50\%$, $P=.01$) (Fig. 3).

4.2.2. Second outcomes

4.2.2.1. Weaning time. Five studies[45,47,49,51,52] that recruited 487 subjects observed weaning time. Remifentanil was associated with a significantly shorter time when compared with the other opioids (SMD −0.21; 95% CI −0.40 to −0.03; $P=.02$; IV random; heterogeneity $I^2=11\%$, $P=.34$) (see Supplement Content, which illustrates remifentanil decrease the weaning time, http://links.lww.com/MD2/A479).

4.2.2.2. ICU length of stay. Fourteen studies[39–44,46–53] observed the ICU LOS. Thirteen studies[39,41–44,46–53] that recruited 1034 patients were included in the meta-analysis. Breen's study was excluded because of the impossibility of data extraction.[40] Remifentanil was associated with a reduction in the ICU LOS when compared with the other opioids (SMD −0.33; 95% CI −0.60 to −0.07; $P=.01$; IV random; heterogeneity $I^2=77\%$, $P<.01$) (Fig. 4).

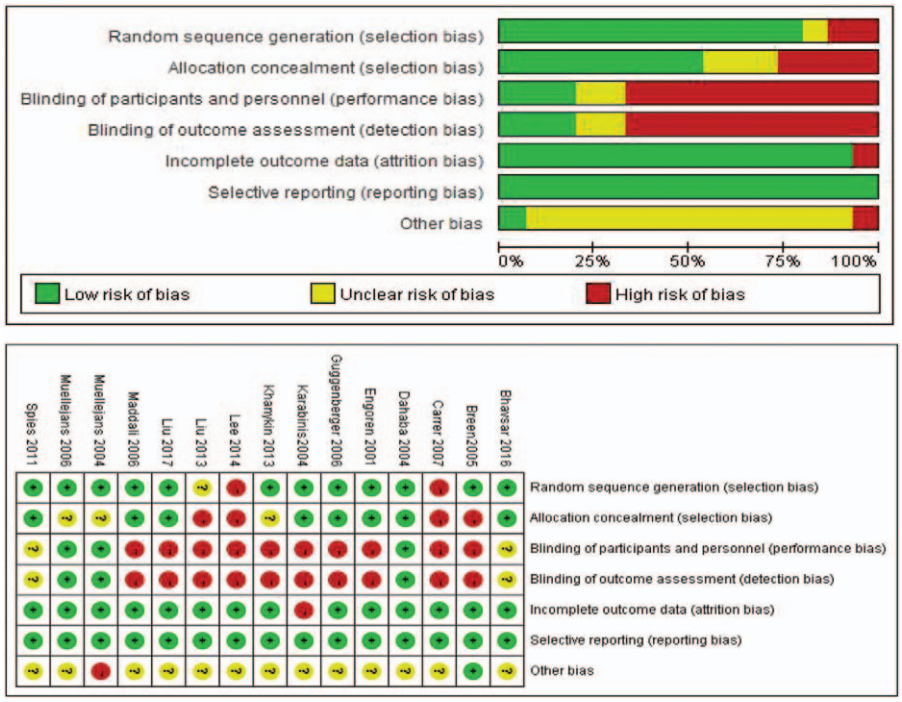

Figure 2. Methodological quality trials using the Cochrane risk of bias tool. Symbols show low risk of bias (+), unclear risk of bias (?), or high risk of bias (−). Overall risk of bias using the Cochrane risk of bias tool.

4.2.2.3. Hospital LOS. Four studies[43,44,46,53] that recruited 264 patients found that there was no significant difference in the hospital LOS between remifentanil and other opioids (SMD −0.31; 95% CI −0.74 to 0.12; $P=.15$; IV random; heterogeneity $I^2=70\%$, $P=.009$) (see Supplement Content, which illustrates no difference in the hospital LOS, http://links.lww.com/MD2/A475).

4.2.2.4. Side effects. Seven studies (589 patients) observed the side effects and showed that there was no significant difference between remifentanil and other opioids (RR 1.16; 95% CI 0.83–1.63; $P=.750$; M-H random; heterogeneity $I^2=0\%$, $P=.390$) (see Supplement Content, which illustrates no difference in the side effects, http://links.lww.com/MD2/A478). Subgroup analyses were similar: 5 studies (457 patients)[40–42,48,51] observed nausea/vomiting (RR 1.01; 95% CI 0.58–1.76; $P=.69$; M-H random; heterogeneity $I^2=0\%$, $P=.96$); 4 studies (324 patients)[42,48,51,52] observed hemodynamic instability: hypotension (RR 1.85; 95% CI 0.87–3.92; $P=.11$; M-H random; heterogeneity $I^2=0\%$, $P=.41$), and dysrhythmia (RR 1.43; 95% CI 0.55–3.73; $P=.47$; M-H random; heterogeneity $I^2=0\%$, $P=.71$); 2 studies (132 patients)[52,53] observed delirium (RR

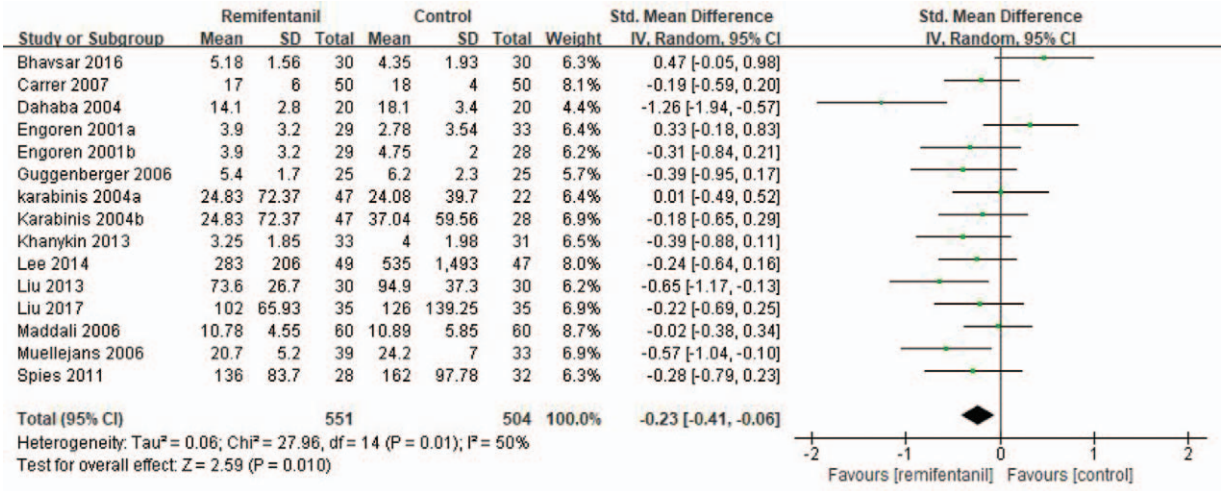

Figure 3. Forest plot comparing the duration of mechanical ventilation (h) between remifentanil and other opioids. CI: confidence interval; IV: inverse variance.

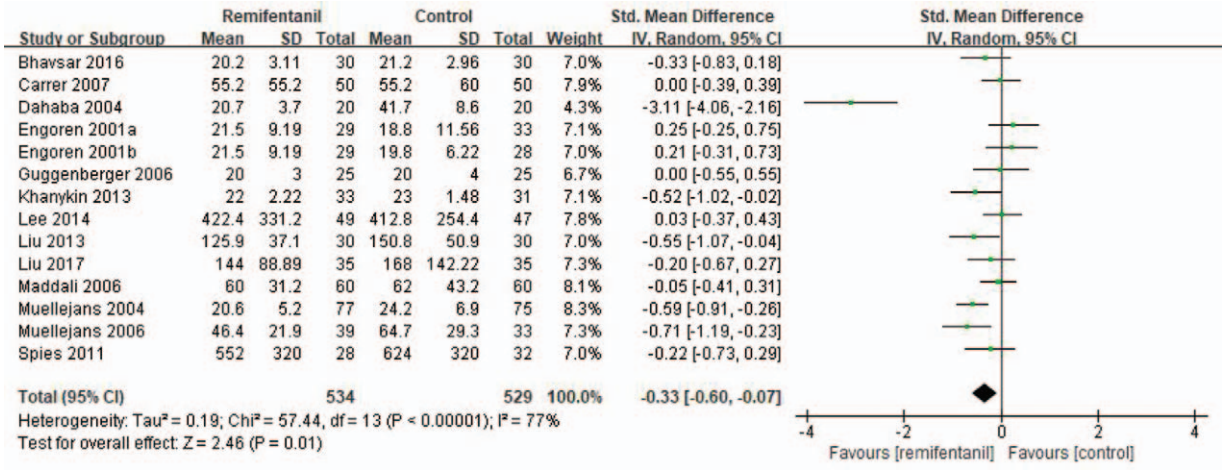

Figure 4. Forest plot comparing the ICU length of stay (h) between remifentanil and other opioids. CI = confidence interval; IV = inverse variance.

0.93; 95% CI 0.47–1.81; $P = .82$; M-H random; heterogeneity $I^2 = 15\%$, $P = .28$).

4.2.2.5. Mortality. Three studies[40,47,49] observed mortality. Pool analysis showed that there was no difference between remifentanil and other opioids (RR 0.92; 95% CI 0.51–1.66; $P = .79$; M-H random; heterogeneity $I^2 = 0\%$, $P = .82$) (see Supplement Content, which illustrates no difference in the mortality, http://links.lww.com/MD2/A476).

4.2.2.6. Costs. Two studies observed the costs.[43,48] Liu et al observed 60 patients after tumor operation showed that remifentanil increased the cost of ICU than fentanyl.[48] Engoren et al[43] compared remifentanil with fentanyl and sufentanil for 90 patients undergoing cardiac surgery. They found that remifentanil increased the costs of anesthesia ($P < .001$) but did not increase costs of hospital ($P = .3$) when comparing with other opioids.

4.3. GRADE quality evidence

The GRADE quality evidence was assessed with GRAD Epro software, and the results were as follows: for comparison of remifentanil with other opioids, the quality of evidence on the duration of mechanical ventilation was thought to be moderate; the quality of evidence on the duration of mechanical ventilation and weaning time were thought to be moderate; the ICU LOS, the incidence of side effects (nausea/vomiting, hypotension, dysrhythmia, and delirium), and mortality were thought to be low; the hospital LOS was thought to be very low (Table 2). The main reason for these results was that the heterogeneity was high ($I^2 > 50\%$). Other reasons for the demotion of the studies included: other types of bias (referred to as commercial interference), the lack of blinding, inconsistency, and imprecision.

5. Discussion

The main finding of our systematic review and meta-analysis was that remifentanil significantly reduced the duration of mechanical ventilation when compared with other opioids in adult critically ill patients. We also found the following: remifentanil significantly reduced the weaning time and ICU LOS; there was no significant difference in the hospital LOS, side effects, and mortality between remifentanil and other opioids.

Remifentanil is a fentanyl relative u-receptor agonist, and it is mainly combined with α-1-acid glycoprotein, which reaches rapidly blood–brain balance in 1 minute resulting in rapid onset and offset. In addition, remifentanil is different from other fentanyl analogues because it is hydrolyzed by nonspecific esterase in plasma and tissues, which is independent of liver and kidney.[4–6] Therefore, it is easy to explain why remifentanil could reduce the duration of mechanical ventilation, the weaning time, and the ICU LOS in comparison with other opioids in critically ill patients which usually have a prolonged use of opioid and with organ dysfunction. Our meta-analysis included both surgical patients and medical patients, which may well represent the adult critically ill patients. For another, remifentanil was all used in the ICU in our included RCTs. These were partially different from another meta-analysis: they mainly included short-term post-surgery patients; some of their included studies were carried out during the operation and in the anesthesia recovery room, not the ICU.[6]

Our meta-analysis found that there were no significant differences in hospital LOS and mortality between remifentanil and other opioids. However, we only included 3 to 4 studies for hospital LOS and mortality. These results were similar to the other 2 meta-analyses.[4,5] Hospital LOS and mortality are affected by many reasons which mainly may be the severity of diseases rather than the selection of analgesic therapy.

We also found that there was no significant difference in side effects between remifentanil and other opioids. The results were similar in the subgroup analyses of nauseous/vomiting, hypotension, dysrhythmia, and delirium. But these results were all assessed in small samples. And all the included studies did not observe the opioid-induced hyperalgesia which is the most unique side effect of remifentanil when compared with other opioids. Opioid-induced hyperalgesia has been well illustrated in the post-operative patients[7,8] and also should be paid more attention in the future studies of remifentanil in critically ill patients.

In our review, only 2 studies observed the costs. One found remifentanil increase cost of anesthesia while did not increase cost

Table 2

Quality of evidence of the studies that compared remifentanil with other opioids that were included in the meta-analysis, according to Grades of Recommendation, Assessment, Development, and Evaluation (GRADE).

	Certainty assessment						No. of patients			
Outcome	Study design (No. of study)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Events	Placebo	Effect (95%CI)	Certainty
Ventilation time	RCT (15)	Serious*	Serious	Not serious	Not serious	None	551	504	SMD −0.23 (−0.41 to −0.06)	⊕⊕⊕◯ MODERATE
ICU LOS	RCT (14)	Serious*	Serious†	Not serious	Not serious	None	534	529	SMD −0.33 (−0.60 to −0.07)	⊕⊕◯◯ LOW
Hospital LOS	RCT (5)	Very serious‡	Serious†	Not serious	Not serious	None	144	149	SMD −0.31 (0.74–0.12)	⊕◯◯◯ VERY LOW
Weaning time	RCT (6)	Serious§	Not serious	Not serious	Not serious	None	294	240	SMD −0.21 (−0.4 to −0.03)	⊕⊕⊕◯ MODERATE
Mortality	RCT (3)	Serious‖	Not serious	Not serious	Serious¶	None	19/141	19/130	RR 0.92 (0.51–1.66)	⊕⊕◯◯ LOW
Nauseous/vomiting	RCT (5)	Serious#	Not serious	Not serious	Serious¶	None	24/234	22/223	RR 1.01 (0.58–1.76)	⊕⊕◯◯ LOW
Hypotension	RCT (4)	Serious**	Not serious	Not serious	Serious¶	None	20/166	9/158	RR 1.85 (0.87–3.92)	⊕⊕◯◯ LOW
Dysrhythmia	RCT (4)	Serious††	Not serious	Not serious	Serious¶	None	10/146	6/131	RR 1.43 (0.55–3.73)	⊕⊕◯◯ LOW
Delirium	RCT (2)	Serious‡‡	Not serious	Not serious	Serious¶	None	15/67	16/65	RR 0.93 (0.47–1.81)	⊕⊕◯◯ LOW

CI = confidence interval; ICU = intensive care unit; LOS = length of stay; No. = number; RCT = randomized controlled trial; RR = risk ratio; SMD = standardized mean difference.

* Nearly a third of studies' selection bias is high risk or unclear; almost two-third of studies' blinding of participants and caregivers and blinding for outcome assessment are high risk or unclear.

† $I^2 > 50\%$.

‡ One study's allocation sequence concealment is unclear; 4 studies' blinding of participants and caregivers and blinding for outcome assessment are high risk, and one is unclear.

§ Half of studies' selection bias are high risk; two-third of studies' blinding of participants and caregivers and blinding for outcome assessment are high risk.

‖ Two studies' adequacy of allocation sequence concealment is high risk and 1 study's sequence generation is high risk. Three studies' blinding of participants and caregivers and blinding for outcome assessment are high risk.

¶ Insufficient sample size.

One study's sequence generation is unclear and 1 is high risk, 3 studies' adequacy of allocation sequence concealment is high risk, and 1 is unclear. Three studies' blinding of participants and caregivers and blinding for outcome assessment are high risk.

** One study's sequence generation is unclear, 1 study's adequacy of allocation sequence concealment is high risk, and 2 are unclear. One study's blinding of participants and caregivers and blinding for outcome assessment is high risk.

†† One study's sequence generation is unclear, 2 studies' adequacy of allocation sequence concealment is high risk, and 1 is unclear. Two studies' blinding of participants and caregivers and blinding for outcome assessment are high risk.

‡‡ One study's adequacy of allocation sequence concealment is unclear. One study's blinding of participants and caregivers and blinding for outcome assessment is high risk.

of hospital,[43] another found that remifentanil increase cost of ICU.[48] Remifentanil has unique pharmacokinetics and pharmacodynamics profiles but is expensive when compared to other traditional opioids such as morphine and fentanyl. When we apply this analgesic, we must consider its cost, especially in the anesthesia procedure and ICU. Many studies[43,44,46,53] showed that remifentanil decrease mechanical ventilation time and hospital LOS. Further studies are needed to explore the cost-effectiveness of different analgesics.

There were several limitations in our meta-analysis:

1) the studies of this meta-analysis were small size, but the quality of each study was high;
2) the population of included studies was heterogeneous, and consisted of surgical and medical patients;
3) the type of the other opioids for the included studies were heterogeneous, which included morphine, fentanyl, and sufentanil;
4) the heterogeneities were high in some of the analyses, such as ICU LOS, and hospital LOS.

However, we analyzed the outcomes in subgroups classified by surgical and medical patients to reduce clinical heterogeneity. We also selected a random-effects model rather than a fixed-effects model to address the observed heterogeneity. Therefore, large, well-designed randomized controlled trials are necessary for the future.

6. Conclusions

In conclusion, remifentanil reduced the duration of mechanical ventilation, weaning time, and ICU LOS when compared with other opioids in adult critically ill patients. Large-scale randomized controlled trials are necessary to confirm our findings and to further evaluate the safety and cost of remifentanil in critically ill patients.

Author contributions

Shuguang Yang helped conceive the idea for the meta-analysis, search the literature, collect the data, perform the statistical analysis, create the figures/tables, and draft the manuscript. Huiying Zhao helped conceive the idea for the meta-analysis, design the study, participate in the literature search, collect the data, interpret the results, and draft the manuscript. Huixia Wang helped search the literature, analyze the data, create the figures, and revise the manuscript. Hua Zhang helped perform the statistical analysis and revise the manuscript. Youzhong An helped design the study and revise the statistical analysis and the manuscript. All authors read and approved the final manuscript for publication.

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