Critical Care

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# Could remifentanil reduce duration of mechanical ventilation in comparison with other opioids for mechanically ventilated patients? A systematic review and meta-analysis

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## Abstract

**Background:** Sedation and analgesia are commonly required to relieve anxiety and pain in mechanically ventilated patients. Fentanyl and morphine are the most frequently used opioids. Remifentanil is a selective μ-opioid receptor that is metabolized by unspecific esterases and eliminated independently of liver or renal function. Remifentanil has a rapid onset and offset and a short context-sensitive half-life regardless of the duration of infusion, which may lead to reductions in weaning and extubation. We aimed to compare the efficacy and safety of remifentanil to that of other opioids in mechanically ventilated patients.

**Methods:** We conducted a search to identify relevant randomized controlled studies (RCTs) in the PubMed, Embase, Cochrane Library and SinoMed databases that had been published up to 31 December 2016. The results were analysed using weighted mean differences (WMDs) and 95% confidence intervals (CIs).

**Results:** Twenty-three RCTs with 1905 patients were included. Remifentanil was associated with reductions in the duration of mechanical ventilation (mean difference -1.46; 95% CI -2.44 to -0.49), time to extubation after sedation cessation (mean difference -1.02; 95% CI -1.59 to -0.46), and ICU-LOS (mean difference -0.10; 95% CI -0.16 to -0.03). No significant differences were identified in hospital-LOS (mean difference -0.05; 95% CI -0.25 to 0.15), costs (mean difference -709.71; 95% CI -1590.98 to 171.55; $I^2$ 88%), mortality (mean difference -0.64; 95% CI -1.33 to 0.06; $I^2$ 87%) or agitation (mean difference -0.71; 95% CI -1.80 to 0.37; $I^2$ 93%).

**Conclusions:** Remifentanil seems to be associated with reductions in the duration of mechanical ventilation, time to extubation after cessation of sedation, and ICU-LOS. No significant differences were identified between remifentanil and other opioids in terms of hospital-LOS, costs, mortality or agitation.

**Keywords:** Analgesia, Remifentanil, Mechanical ventilation, Meta-analysis, Systematic review, Critical care

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## Background

Pain and anxiety are among the worst experiences for the critically ill, especially those on mechanical ventilation. Mechanically ventilated patients generally require a combination of analgesia and sedation to improve compliance with mechanical ventilation, adaption to endotracheal tubes, and pain relief [1]. Propofol and midazolam have been identified as the hypnotic drugs most commonly used for sedation in the intensive care unit (ICU), and among sedatives, shorter elimination half-lives are associated with shorter awakening times, resulting in reductions in time to weaning and time to extubation [2]. Opioids are commonly used in the ICU for analgesia, and the accumulation of opioid agents may cause respiratory depression, thus leading to prolongation of time to weaning and extubation.

Studies have found the most frequently used opioids to be fentanyl (30–35%), morphine (15–33%), and sufentanil (25–40%), the specific proportions of which differ in the results of different surveys, with remifentanil being less commonly used (10%) [3, 4]. However, the use of opioids may not be ideal in mechanically ventilated critically ill patients. The renal metabolism of morphine results in accumulation of morphine-6-glucuronide in patients with renal impairment. In addition, common adverse effects of morphine include histamine release, pruritus, and constipation [5]. Fentanyl, alfentanil and sufentanil undergo hepatic metabolism, and continuous infusion results in accumulation and prolongation of effect [5]. Those pharmacodynamic and pharmacokinetic profiles have disadvantages in terms of rapid weaning and extubation.

Similar to fentanyl, alfentanil, and sufentanil, remifentanil is a potent, selective 4-anilidopiperidine μ-opioid analgesic. However, unlike fentanyl and other opioids, remifentanil is completely metabolized by unspecific esterases in a manner that is independent of liver or renal function [5, 6]. Since unspecific esterases have been found to be widely distributed in living human cells, there are no ICU disease states or types of organ failure that would lead to reduced breakdown of remifentanil. The major breakdown product of remifentanil is remifentanil acid (RA), which has a potency of only 1/300 to 1/4600 that of remifentanil, has poor brain penetration and is unlikely to cause respiratory failure [6, 7]. Remifentanil has a highly predictable onset and offset effect, a terminal half-life of approximately 10 to 20 minutes, and a context-sensitive half-life of 3 to 4 minutes [6, 8]. The unique pharmacokinetics of remifentanil may lead to reductions in time to weaning and extubation and, accordingly, may be associated with reductions in mechanical ventilation time, length of ICU stay (ICU-LOS), and costs.

Several randomized controlled studies (RCTs) and cohort studies have been conducted to compare the efficacy and safety of remifentanil with those of other opioids. Mechanical ventilation time and extubation time are commonly evaluated indicators. Taking Dahaba et al.'s study [1] as an example, 40 mechanically ventilated patients who were assigned an analgesia protocol involving the administration of either remifentanil or morphine; these analgesics were initiated at the minimum dose and titrated up to an optimal level of sedation, with midazolam serving as a rescue treatment. The results of this study showed that remifentanil was associated with significant reductions in mean duration of mechanical ventilation and extubation time. The same outcome measures have been assessed in several RCTs). The results of a meta-analysis [9] showed that remifentanil was associated with reduced time to extubation after sedation cessation, but no significant difference was identified between remifentanil and other opioids in terms of mechanical ventilation duration. However, another meta-analysis [10] showed that remifentanil was associated with a significantly reduction in the duration of mechanical ventilation. The results of a cost-consequence analysis performed by Al et al. [11] suggested that remifentanil was associated with significantly decreased ICU costs, whereas the results of Engoren et al.'s study [12] showed that higher opioid and anaesthetic costs but lower hospital costs were identified in remifentanil group relative to the fentanyl group. The results of these economic analyses were complex. On the one hand, reductions in ventilation time, ICU-LOS and length of stay in hospital (hospital-LOS) were associated with a reduction in overall cost, but shorter-acting anaesthetics were more expensive. On the other hand, morphine withdrawal-associated immunosuppression and remifentanil discontinuation were identified as independent risk factors for ICU-acquired infections, and excessive analgesia was associated with nosocomial pneumonia delirium and psychological disorders, which increases the complexity of the evaluation of remifentanil [13]. Several studies have been conducted since the meta-analysis was performed in 2009 [10], which showed that remifentanil was associated with reduced time to extubation after sedation cessation and indicated the presence of no significant differences between remifentanil and other opioids in terms of mortality, duration of mechanical ventilation, ICU-LOS, and risk of agitation. Therefore, we conducted this study with the intention of updating these data and re-evaluating the efficacy and safety of remifentanil in mechanically ventilated patients relative to the safety and efficacy of other opioids.

## Methods

### Search strategy and selection criteria

Four electronic databases were searched (PubMed, Embase, Cochrane Library and SinoMed)) to identify

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studies published from 2001 until December 2016. A search strategy was developed for PubMed (Additional file 1: Appendix 1) and the other databases. Our research was limited to RCTs, and no language restriction was applied. The reference lists of relevant articles were also reviewed. We contacted the authors of the studies if additional data were required for the predefined outcomes. Non-English language articles were translated before further analysis.

Studies were included if they met the following criteria: (1) the study population consisted of adults (mean age ≥18 years old) undergoing mechanical ventilation; (2) the study design was an RCT; (3) remifentanil or a remifentanil/sedative combination was used for analgesia and sedation; and (4) the outcomes included at least one of the following measures: duration of mechanical ventilation, time to extubation after cessation of sedation, ICU-LOS, hospital-LOS, costs, proportion of patients with agitation, delirium, nausea/vomiting, or mortality.

Studies in which remifentanil was not compared with another opioid or another opioid/sedative combination were excluded. Publications available only in abstract form or as meeting reports were excluded.

### Data extraction and quality assessment

Two reviewers (ZYB and WYH) independently extracted data from the published sources using a predesigned data extraction form. The following data were abstracted from each included study: the study ID, journal, year of publication, country, setting, centre, mean age, proportion of male subjects, disease severity, disease type, proportion of post-surgical patients, sample size, comparator, inclusion criteria, exclusion criteria, intervention and outcomes. Two reviewers independently rated the quality of the RCTs using the Modified Jadad scores [14], which are determined using a checklist designed to measure the quality of RCT reporting. The following elements are evaluated when calculating a Modified Jadad score: randomization (0–2), concealment of allocation (0–2), double blinding (0–2), and withdrawals and dropouts (0–1). The trials were rated based on what they reported, and the results of the quality assessment are described in the table describing the characteristics of included studies (Table 1).

Discordant opinions between the two reviewers were discussed until consensus was reached. If consensus could not be reached, a consulting group including two experts (XXM and DB) resolved the disagreements.

### Outcomes and statistical analysis

The primary outcome was duration of mechanical ventilation. The primary outcome was analysed in five subgroups: analgesia only; analgesia and sedation; and comparisons of remifentanil with fentanyl, morphine, and/or sufentanil. The secondary outcomes included (1) time to extubation after cessation of sedation; (2) ICU-LOS; (3) hospital-LOS; (4) costs; (5) mortality; and (6) agitation. Costs were measured in dollars, and other currencies converted into dollars according to the 2016 exchange rate. The costs were measured as overall costs, such as ICU or hospital costs. Maximum costs were preferentially used if a study reported more than one cost measure.

The pooled effects were analysed using weighted mean differences (WMDs) and 95% confidence intervals (CIs). The presence of statistically significant heterogeneity across trials was quantitatively assessed using the $I^2$ statistic. Inverse variance random-effects models were applied for the data analysis. Publication bias was evaluated using funnel plots when at least ten studies were included in this meta-analysis. A *p* value less than 0.05 was considered statistically significant. All statistical analyses were performed using Review Manager Version 5.3.

## Results

### Study selection

Overall, 585 potentially relevant articles were identified using the search strategy. After screening the titles/abstracts of the studies, 49 articles remained and were obtained in full-text form. Twenty-six studies failed to meet the previously described inclusion criteria; therefore, 23 studies were included in this meta-analysis. Of the included studies, 19 were published in English, two were published in French, one was published in Chinese, and one was published in Thai. No relevant unpublished studies were identified. Figure 1 presents the study selection process.

### Study characteristics and quality

A total of 1905 critically ill adult patients were included in the studies subjected to meta-analysis. The sample sizes of the 23 included studies ranged from 20 to 205 participants. Twenty-two studies compared remifentanil with another one or two opioids, and one study compared remifentanil/propofol with fentanyl/midazolam. Table 1 summarizes the basic characteristics of the included studies.

The results of the study quality assessment showed that five of the 23 RCTs were of high quality (Modified Jadad score 4–7), and the other 18 RCTs were of suboptimal quality (Modified Jadad score 0–4); these studies commonly lacked details regarding concealment of allocation and withdrawals and dropouts. Table 2 summarizes the quality of the included RCTs.

### Outcomes

The primary outcome, duration of mechanical ventilation, was reported in 18 RCTs. Remifentanil was

**Table 1** Characteristics of included studies

| Study ID | Journal | Year | Participants | Setting | Post-surgical patients | Interventions | Sedative | Aim | Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Al et al. [11] | *Critical Care* | 2010 | 205 mechanically ventilated medical and surgical patients; mean age 65; mean SAPS II 45 | ICU | 37–44% | Remifentanil group: remifentanil 0.4–45ug/kg/h, propofol as rescue treatment once remifentanil infusion > 12 ug/kg/h was needed; control group: analgesia was achieved by either morphine 1–0 mg/h or fentanyl 25–100 mg/h, either propofol 0.5–4 mg/kg/h or midazolam 0.01–0.2 mg/kg/h or lorazepam 0.01–0.1 mg/kg/h for sedation | Remifentanil group: propofol 65%; control group: propofol 46%, midazolam 81%, lorazepam 7% | SAS 3–4 | Time to extubation after cessation of sedation, duration of mechanical ventilation, ICU-LOS, costs |
| Rozendaal et al. [16] | *Intensive Critical Medicine* | 2009 | 205 mechanically ventilated medical and surgical patients; mean age 65; mean SAPS II 45 | ICU | 37–44% | Remifentanil group: remifentanil 0.4–45 ug/kg/h, propofol as rescue treatment once remifentanil infusion > 12 ug/kg/h was needed; control group: analgesia was achieved by either morphine 1–10 mg/h or fentanyl 25–100 mg/h, either propofol 0.5–4 mg/kg/h or midazolam 0.01–0.2 mg/kg/h or lorazepam 0.01–0.1 mg/kg/h for sedation | Remifentanil group: propofol 65%; control group: propofol 46%, midazolam 81%, lorazepam 7% | SAS 3–4 | Time to extubation after cessation of sedation, ICU-LOS, duration of mechanical ventilation |
| Spies et al. [13] | *Intensive Critical Medicine* | 2011 | 65 adult medical and surgical patients requiring mechanical ventilation for more than 24 h; mean age 63; mean APACHE II 25; mean SOPA 9 | ICU | 92–97% | Remifentanil group: remifentanil 0.1–0.4 ug/kg/min; fentanyl group: fentanyl 0.02–0.08 ug/kg/min; the study protocol did not allow any bolus application of either fentanyl or remifentanil | Remifentanil group: propofol, midazolam, lorazepam; fentanyl group: propofol, midazolam, lorazepam, proportion not mentioned | VAS ≤ 3 and/or BPS ≤ 6 | Duration of mechanical ventilation, ICU-LOS, hospital-LOS, delirium, reflux/vomiting |
| Lui et al. [20] | *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* | 2013 | 60 patients with mechanical ventilation for over 24 h after tumor operation; mean age 64; mean APACHE II 20 | ICU | 100% | Remifentanil group: remifentanil 0.05 ug/kg/h, titrated up with increment of 0.025 ug/kg/min; fentanyl group: fentanyl 0.5 ug/kg/h, titrated up with increment of 0.25 ug/kg/h; propofol as rescue treatment for remifentanil group once remifentanil infusion > 0.1 ug/kg/h and for fentanyl group once fentanyl infusion > 1 ug/kg/h | Remifentanil group: propofol 26%; fentanyl group: propofol 63% | Ramsay 2–3 | Duration of mechanical ventilation, ICU-LOS, costs |

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**Table 1** Characteristics of included studies *(Continued)*

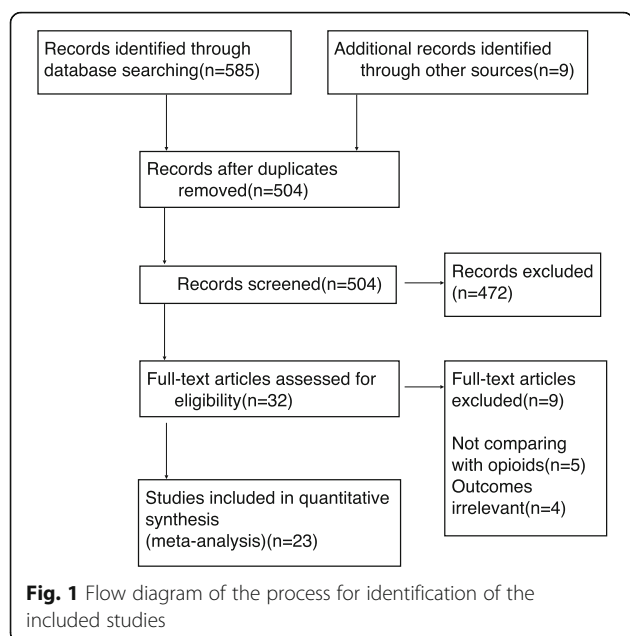| Study | Journal | Year | Population | Setting | % | Drug regimen | Rescue/co-sedation | Target | Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Khanykin et al. [36] | *The Heart Surgery Forum* | 2013 | 71 mechanically ventilated postoperative patients; mean age 64 | ICU | 100% | Remifentanil group: remifentanil 0.2–0.5 ug/kg/min as required after termination of bypass, remifentanil 0.1–0.2 ug/kg/min for postoperative pain; low-dose fentanyl group: fentanyl 3–4ug/kg as required after termination of bypass, morphine 2.5–5 mg for postoperative pain | None | NR | ICU-LOS, hospital LOS, extubation time |
| Bhavsar et al. [21] | *Anesthesia* | 2016 | 60 mechanically ventilated postoperative patients; mean age 68 | ICU | 100% | Remifentanil group: remifentanil 0.4–0.6 ug/kg/min during surgery, remifentanil 0.1ug/kg/min after surgery; sufentanil group: sufentanil 1–2ug/kg within 1–2 minutes, total dose of sufentanil 3–3.5ug/kg before cardiopulmonary bypass | None | VAS 3–4 | Duration of mechanical ventilation, ICU-LOS, hospital-LOS |
| Engoren et al. [12] | *Anesthesia & Analgesia* | 2001 | 90 adult patients undergoing cardiac surgery; mean age 60 | ICU | 100% | Remifentanil group: remifentanil infusion at 0.5–1 ug/kg/min,then maintained 0.05–1 ug/kg/min; fentanyl group: fentanyl 7–10 ug/kg for the induction and additional doses of 1–2 ug/kg as needed for intense stimulus; sufentanil group: sufentanil 1–4 ug/kg for the induction and 0.1–0.3 ug/kg as needed for intense stimulus | None | NR | Duration of mechanical ventilation, ICU-LOS, hospital LOS, costs |
| Muellejans et al. [22] | *Critical Care* | 2006 | 80 adult patients undergoing elective cardiac surgery; mean age 66; mean SAPS II 33 | ICU | 100% | Remifentanil group: remifentanil 6–60 ug/kg/h; fentanyl/midazolam group: fentanyl 1–2 ug/kg/h, midazolam 0.02–0.04 mg/kg/h; propofol as rescue treatment for remifentanil group and midazolam ± fentanyl for fentanyl/midazolam group | None | VAS < 4 | Delirium, time to extubation after cessation of sedation, duration of mechanical ventilation, ICU-LOS, costs |
| Muellejans et al. [23] | *Critical Care* | 2004 | 152 mechanically ventilated medical or surgical patients; mean age 60; mean SAPS II 28 | ICU | 92–95% | Remifentanil group: remifentanil 9–12 ug/kg/h fentanyl group: fentanyl 1–2 ug/kg/h; propofol as rescue treatment for both groups | Remifentanil group: propofol 35%; fentanyl group: propofol 40% | SAS 4 | Proportion required rescue sedation, nausea/vomiting, time to extubation after cessation of sedation |
| Karabinis et al. [24] | *Critical Care* | 2004 | 161 mechanical ventilated elective or emergency neurosurgical patients; mean age 47 | neuro-ICU | 25–49% | Remifentanil group: remifentanil 9-18 ug/kg/h; fentanyl group: fentanyl 0.1–7.9 ug/kg/min; morphine group: 0–6.8 mg/kg/min; propofol as rescue treatment for remifentanil group and all patients changed to midazolam infusion on day 3 | Remifentanil group: propofol 90%, midazolam 36%; fentanyl group: propofol 100%, midazolam 30%; morphine group: propofol 93%, midazolam 30% | SAS < 4 | Mortality, time to extubation after cessation of sedation, duration of mechanical ventilation |

**Table 1** Characteristics of included studies *(Continued)*

| Study | Journal | Year | Population | Setting | % | Intervention | Concurrent sedation | Sedation target | Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Baillard et al. [25] | Annales Françaises d'Anesthésie et de Réanimation | 2005 | 41 mechanically ventilated medical and trauma patients; mean age | ICU | 29% | Remifentanil group: remifentanil 10 ug/kg/h and titrated; sufentanil group: sufentanil 0.125 ug/kg/h and titrated; current midazolam for both groups at 0.1 mg/kg/h | Both of remifentanil and sufentanil group: midazolam 100% | Ramsay 4 | Mortality, time to extubation after cessation of sedation, ICU-LOS |
| Dahaba et al. [1] | Anesthesiology | 2004 | 40 mechanically ventilated patients after orthopedic or general surgery; mean age 58; mean SAPS II 23 | ICU | 100% | Remifentanil group: remifentanil 9–12 ug/kg/h morphine group: morphine 0.04–0.06 mg/kg/h; routine current midazolam 0.03 mg/kg/h for both groups as rescue treatment | Remifentanil group: midazolam 30%; morphine group: 45% | SAS 4 | Proportion of patients with agitation, nausea/vomiting, mortality, time to extubation after cessation of sedation, duration of mechanical ventilation, ICU-LOS |
| Breen et al. [26] | Critical Care | 2005 | 105 mechanically ventilated 3–10days) patients; mean age 54; mean SAPS II 43 | ICU | 8–13% | Remifentanil group: remifentanil 6–18 ug/kg/h; fentanil or morphine group: standard clinical protocol for the unit; midazolam 2 mg bolus as rescue treatment for both groups | Remifentanil group: midazolam 74%; fentanyl group: midazolam 62%; morphine group: midazolam 23% | SAS 3–4 | Nausea/vomiting, mortality, time to extubation after cessation of sedation; duration of mechanical ventilation, ICU-LOS |
| Belhadj Amor et al. [27] | Annales Françaises d'Anesthésie et de Réanimation | 2007 | 19 mechanically ventilated patients with renal impairment (creatinine clearance <50 ml/min); mean age 60; mean APACHE II 37 | ICU | 0 | Remifentanil group: remifentanil 6 ug/kg/h, titrated up by increment of 100 ug/h; fentanyl group: fentanyl 1.5 ug/kg/h, titrated up with increment of 25 ug/h; routine concurrent midazolam infusion for both groups at 0.1 mg/kg/h | Remifentanil group: midazolam 78%; fentanyl group: midazolam 95% | Ramsay 3-4 | Proportion of patients with agitation, time to extubation after cessation of sedation, ICU-LOS |
| Carrer et al. [28] | Minerva Anestesiologica | 2007 | 100 mechanically ventilated postsurgical patients; mean age 69; mean SAPS II 26 | ICU | 100% | Remifentanil group: remifentanil 6 ug/kg/h and titrated; morphine group: morphine 0.03–0.04 mg/kg/h and titrated; concurrent morphine for both groups at 0.01 mg/kg/h, diazepam 0.1 mg/kg as rescue treatment | Remifentanil group: diazepam 28%; morphine group: diazepam 60% | Ramsay 3 | Proportion of patients achieving optimal level of sedation without rescue therapy, nausea/vomiting, duration of mechanical ventilation, ICU-LOS |
| Gerlach et al. [29] | Journal of Cardiothoracic & Vascular Anesthesia | 2002 | 26 mechanically ventilated postsurgical patients; mean age 64 | ICU | 100% | Remifentanil group: remifentanil 0.15–0.3 ug/kg/min; sufentanil group: sufentanil 0.5–1 ug/kg/h | Both of remifentanil and sufentanil groups: propofol, proportion not mentioned | Self-reported no pain | Duration of mechanical ventilation, nausea/vomiting, time to extubation after cessation of sedation |
| Guggenberger et al. [30] | European Journal of Anaesthesiology | 2006 | 59 mechanically ventilated postsurgical patients; mean age 67 | ICU | 100% | Remifentanil group: remifentanil 0.5–1 ug/kg/min; sufentanil group: 30–40 ng/kg/min | Both of remifentanil and sufentanil groups: propofol, proportion not mentioned | VAS < 4 | Duration of mechanical ventilation, hospital-LOS, time to extubation after cessation of sedation, ICU-LOS |
| Knapik et al. [31] | Medical Science Monitor | 2006 | 40 mechanically ventilated postsurgical patients; mean age 56 | ICU | 100% | Remifentanil group: remifentanil 0.25–0.5 ug/kg/min; fentanyl group: fentanyl 2.5 ug/kg/h | None | VAS < 4 | Duration of mechanical ventilation, hospital-LOS |
| | | 2006 | | ICU | 100% | | | VAS < 4 | |

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**Table 1** Characteristics of included studies (Continued)

| Study | Journal | Year | Patients | Setting | % | Intervention | Sedation groups | Target | Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Maddali et al. [32] | Journal of Clinical Anesthesia | | 180 mechanically ventilated postsurgical patients; mean age 55 | | | Remifentanil group: remifentanil 1 ug/kg/min; fentanyl group: 0.025–0.15 ug/kg/min; diclofenac group: propofol 2–5 mg/kg/h | Both of remifentanil and fentanyl groups: propofol 100% | | Duration of mechanical ventilation, time to extubation after cessation of sedation, ICU-LOS |
| Myles et al. [19] | Anesthesia and Analgesia | 2002 | 87 mechanically ventilated postsurgical patients; mean age 62 | ICU | 100% | Remifentanil group: remifentanil 0.83 ug/kg/min; small dose fentanyl group: fentanyl bolus, small dose, at 12 ug/kg; moderate dose fentanyl group: fentanyl bolus, moderate dose, at 24 ug/kg | All of remifentanil, small dose fentanyl and moderate dose fentanyl groups: propofol 100% | NR | Duration of mechanical ventilation, hospital-LOS, costs |
| Winterhalter et al. [33] | European Journal of Anaesthesiology | 2008 | 42 mechanically ventilated postsurgical adult patients; mean age 63 | ICU | 100% | Remifentanil group: remifentanil 0.25 ug/kg/min; fentanyl group: fentanyl bolus 4 ug/kg every 30 min | Both of remifentanil and fentanyl groups: propofol 100% | VAS < 4 | Duration of mechanical ventilation, hospital-LOS, time to extubation after cessation of sedation |
| Bedirli et al. [34] | Journal of Anesthesia | 2007 | 50 mechanically ventilated postsurgical patients; mean age 61 | ICU | 100% | Remifentanil group: remifentanil 1ug/kg/min; fentanyl group: fentanyl 5 ug/kg/h | None | NR | Hospital-LOS;ICU-LOS |
| Chinachoti et al. [35] | Medical Association of Thailand | 2002 | 152 mechanically ventilated patients with normal renal function or mild renal impairment; mean age 59; mean SAPS II 26 | ICU | NR | Remifentanil group: 9–60 ug/kg/h; morphine group:0.045–0.3 mg/kg/h | Both of remifentanil and morphine groups: midazolam | SAS 4 | Time to extubation after cessation of sedation, duration of mechanical ventilation |

APACHE Acute Physiology and Chronic Health Evaluation, BPS Behavioural Pain Scale, ICU intensive care unit, ICU-LOS intensive care unit length of stay, NR not recorded, SAPS Simplified Acute Physiology Score, SAS Sedation Agitation Scale, SOPA Survey of Pain Attitudes, VAS Visual Analog Scale

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**Fig. 1** Flow diagram of the process for identification of the included studies

associated with a reduction in the duration of mechanical ventilation (mean difference -1.46; 95% CI -2.44 to -0.49; $I^2$ 89%. Fig. 2a).

As for the secondary outcomes, remifentanil was associated with reductions in time to extubation after sedation cessation (mean difference -1.02; 95% CI -1.59 to -0.46; $I^2$ 96%. Fig. 3a) and ICU-LOS (mean difference -0.10; 95% CI -0.16 to -0.03; $I^2$ 85%. Fig. 3b). No significant differences in hospital-LOS (mean difference -0.05; 95% CI -0.25 to 0.15; $I^2$ 88%. Additional file 2: Figure S2a), costs (mean difference -709.71; 95% CI -1590.98 to 171.55; $I^2$ 88%. Additional file 2: Figure S2b), mortality (mean difference -0.64; 95% CI -1.33 to 0.06; $I^2$ 87%. Additional file 2: Figure S2c) and agitation (mean difference -0.71; 95% CI -1.80 to 0.37; $I^2$ 93%. Additional file 2: Figure S2d) were identified. Table 3 summarizes the data for and analyses of outcome measures.

As for the subgroup analyses, remifentanil was associated with a reduction in mechanical ventilation duration in the subgroup of studies in which both analgesia and sedation were administered (mean difference -2.99; 95% CI -5.09 to -0.89; $I^2$ 84%. Additional file 3: Figure S1a) and the subgroup of studies in which remifentanil

**Table 2** Quality assessment of included RCTs

| Study ID | Randomization | Concealment of allocation | Double blinding | Withdraws and dropouts | Modified Jadad score | Quality assessment |
|---|---|---|---|---|---|---|
| Al et al. [11] | 2 | 0 | 0 | 0 | 2 | Low |
| Rozendaal et al. [16] | 2 | 0 | 0 | 0 | 2 | Low |
| Spies et al. [13] | 2 | 2 | 2 | 1 | 7 | High |
| Liu et al. [20] | 2 | 0 | 0 | 0 | 2 | Low |
| Khanykin et al. [36] | 2 | 0 | 0 | 1 | 3 | Low |
| Bhavsar et al. [21] | 2 | 0 | 0 | 0 | 2 | Low |
| Engoren et al. [12] | 2 | 0 | 0 | 0 | 2 | Low |
| Muellejans et al. [22] | 1 | 0 | 0 | 1 | 2 | Low |
| Muellejans et al. [23] | 1 | 0 | 1 | 1 | 3 | Low |
| Karabinis et al. [24] | 1 | 0 | 0 | 0 | 1 | Low |
| Baillard et al. [25] | 2 | 0 | 1 | 0 | 3 | Low |
| Dahaba et al. [1] | 2 | 2 | 2 | 1 | 7 | High |
| Breen et al. [26] | 1 | 0 | 0 | 0 | 1 | Low |
| Belhadj Amor et al. [27] | 2 | 0 | 2 | 0 | 4 | Low |
| Carrer et al. [28] | 1 | 0 | 0 | 0 | 1 | Low |
| Gerlach et al. [29] | 2 | 2 | 0 | 0 | 4 | High |
| Guggenherger et al. [30] | 2 | 0 | 0 | 1 | 3 | Low |
| Knapik et al. [31] | 1 | 0 | 0 | 0 | 1 | Low |
| Maddali et al. [32] | 2 | 0 | 0 | 1 | 3 | Low |
| Myles et al. [19] | 2 | 0 | 2 | 1 | 5 | High |
| Winterhalter et al. [33] | 2 | 2 | 2 | 0 | 6 | High |
| Bedirli et al. [34] | 2 | 0 | 0 | 0 | 2 | Low |
| Chinachoti et al. [35] | 2 | 0 | 1 | 0 | 3 | Low |

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| Study or Subgroup | remifentanil Mean | SD | Total | other opioid Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Breen 2005 | 94 | 13.9 | 57 | 147.6 | 159.1 | 48 | 0.0% | -53.60 [-98.75, -8.45] |
| Carrer 2007 | 17 | 6 | 50 | 18 | 4 | 50 | 6.8% | -1.00 [-3.00, 1.00] |
| Chinachoti 2002 | 15.7 | 9.7 | 74 | 14.4 | 7.5 | 78 | 5.4% | 1.30 [-1.47, 4.07] |
| Claudia 2011 | 136 | 28.5 | 28 | 162 | 33.6 | 32 | 0.4% | -26.00 [-41.72, -10.28] |
| Dahaba 2004 | 14.1 | 2.8 | 20 | 18 | 3.3 | 20 | 7.0% | -3.90 [-5.80, -2.00] |
| Gerlach 2002 | 4.7 | 5.3 | 13 | 7.5 | 4.3 | 13 | 4.0% | -2.80 [-6.51, 0.91] |
| Guggenherger 2006 | 5.4 | 1.7 | 25 | 6.2 | 2.3 | 33 | 8.5% | -0.80 [-1.92, 0.32] |
| Karabinis 2004 | 46.8 | 29 | 84 | 40.7 | 34.1 | 40 | 0.6% | 6.10 [-6.15, 18.35] |
| Karabinis 2004 | 46.8 | 29 | 84 | 35.2 | 29.5 | 37 | 0.7% | 11.60 [0.25, 22.95] |
| Knapik 2006 | 4.2 | 4.7 | 20 | 5.7 | 3.9 | 20 | 5.6% | -1.50 [-4.18, 1.18] |
| Maddali 2006 | 10.7 | 4.5 | 58 | 10.8 | 5.8 | 59 | 7.0% | -0.10 [-1.98, 1.78] |
| Milo 2001 | 3.9 | 1.07 | 29 | 2.78 | 1.21 | 33 | 9.2% | 1.12 [0.55, 1.69] |
| Milo 2001 | 3.9 | 1.07 | 29 | 4.75 | 0.68 | 28 | 9.3% | -0.85 [-1.31, -0.39] |
| Muellejans 2004 | 20.6 | 5.2 | 40 | 24.2 | 6.9 | 39 | 5.5% | -3.60 [-6.30, -0.90] |
| Muellejans 2006 | 18.5 | 2.5 | 39 | 18.5 | 2.2 | 33 | 8.5% | 0.00 [-1.09, 1.09] |
| Myles 2002 | 9.4 | 5.7 | 29 | 20.9 | 9.1 | 55 | 4.8% | -11.50 [-14.68, -8.32] |
| Rajesh 2016 | 5.18 | 0.53 | 30 | 4.35 | 0.66 | 30 | 9.4% | 0.83 [0.53, 1.13] |
| Rozendaal 2009 | 93.6 | 312.7 | 96 | 122.4 | 410.8 | 109 | 0.0% | -28.80 [-128.10, 70.50] |
| Wang 2013 | 73.6 | 26.7 | 30 | 94.9 | 37.3 | 30 | 0.3% | -21.30 [-37.71, -4.89] |
| Winterhalter 2008 | 4 | 3 | 20 | 6.9 | 3.5 | 21 | 6.8% | -2.90 [-4.89, -0.91] |
| **Total (95% CI)** | | | 855 | | | 800 | 100.0% | -1.46 [-2.44, -0.49] |

Heterogeneity: Tau² = 2.62; Chi² = 170.50, df = 19 (P < 0.00001); I² = 89%
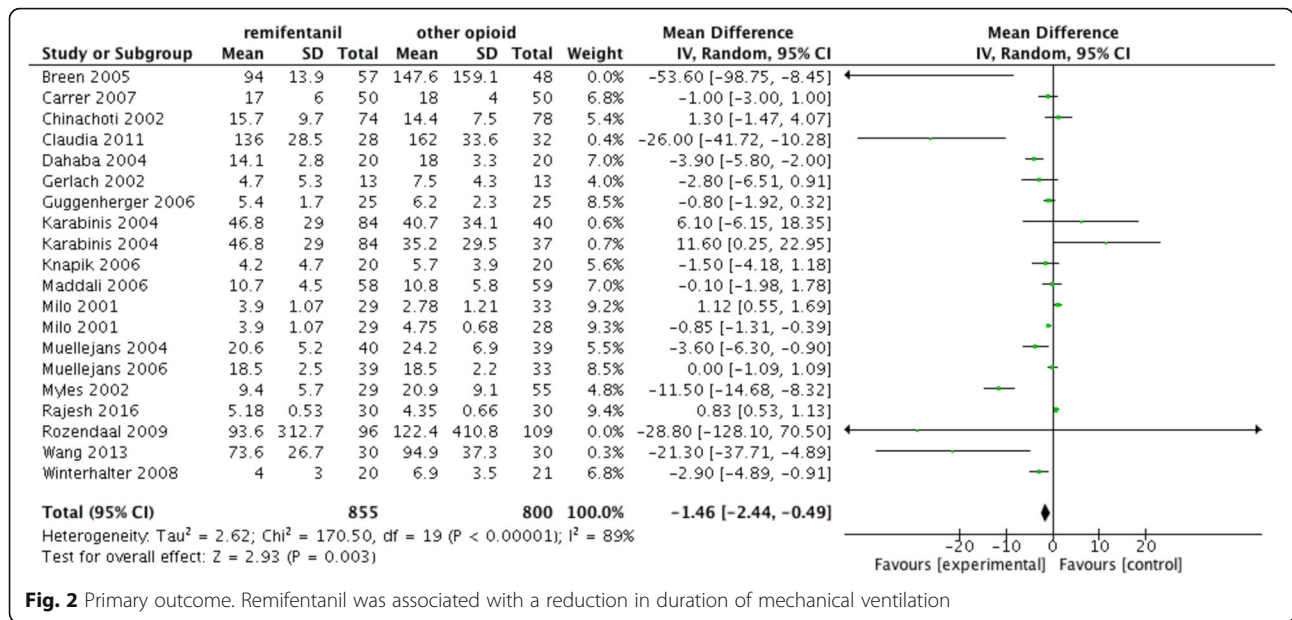Test for overall effect: Z = 2.93 (P = 0.003)

**Fig. 2** Primary outcome. Remifentanil was associated with a reduction in duration of mechanical ventilation

**a**

| Study or Subgroup | remifentanil Mean | SD | Total | other opioid Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Amor 2007 | 24.67 | 16.33 | 9 | 48 | 21.33 | 10 | 0.1% | -23.33 [-40.32, -6.34] |
| Baillard 2005 | 22 | 54 | 21 | 96 | 72 | 20 | 0.0% | -74.00 [-113.10, -34.90] |
| Boris 2013 | 3.25 | 0.63 | 33 | 4 | 0.66 | 31 | 17.8% | -0.75 [-1.07, -0.43] |
| Dahaba 2004 | 0.28 | 0.1 | 20 | 1.22 | 0.12 | 20 | 18.8% | -0.94 [-1.01, -0.87] |
| Gerlach 2002 | 4.7 | 5.3 | 13 | 7.5 | 4.31 | 13 | 2.1% | -2.80 [-6.51, 0.91] |
| Guggenherger 2006 | 0.83 | 0.12 | 13 | 0.83 | 0.16 | 13 | 18.7% | 0.00 [-0.11, 0.11] |
| Maddali 2006 | 4.05 | 3.66 | 58 | 4.08 | 3.76 | 59 | 9.1% | -0.03 [-1.37, 1.31] |
| Maddali 2006 | 4.05 | 3.66 | 58 | 7.18 | 3.83 | 59 | 9.0% | -3.13 [-4.49, -1.77] |
| Muellejans 2004 | 1.1 | 2.8 | 77 | 1.3 | 0.9 | 75 | 15.0% | -0.20 [-0.86, 0.46] |
| Muellejans 2006 | 2.2 | 4.3 | 39 | 5.7 | 6.6 | 33 | 3.7% | -3.50 [-6.13, -0.87] |
| Winterhalter 2008 | 4 | 3.03 | 21 | 6.96 | 3.53 | 21 | 5.7% | -2.96 [-4.95, -0.97] |
| **Total (95% CI)** | | | 362 | | | 354 | 100.0% | -1.02 [-1.59, -0.46] |

Heterogeneity: Tau² = 0.44; Chi² = 252.40, df = 10 (P < 0.00001); I² = 96%
Test for overall effect: Z = 3.54 (P = 0.0004)

**b**

| Study or Subgroup | remifentanil Mean | SD | Total | other opioid Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Amor 2007 | 15 | 13 | 9 | 17 | 11 | 10 | 0.0% | -2.00 [-12.89, 8.89] |
| Baillard 2005 | 26 | 18.5 | 21 | 19 | 11.5 | 20 | 0.0% | 7.00 [-2.38, 16.38] |
| Berdirli 2007 | 1.7 | 1.2 | 25 | 2.1 | 1.1 | 25 | 0.9% | -0.40 [-1.04, 0.24] |
| Boris 2013 | 0.91 | 0.03 | 33 | 0.95 | 0.02 | 31 | 17.7% | -0.04 [-0.05, -0.03] |
| Breen 2005 | 7.8 | 18.7 | 57 | 8.7 | 19.7 | 48 | 0.0% | -0.90 [-8.29, 6.49] |
| Carrer 2007 | 2.3 | 2.3 | 50 | 2.3 | 2.5 | 50 | 0.4% | 0.00 [-0.94, 0.94] |
| Claudia 2011 | 23 | 4.5 | 28 | 26 | 4.5 | 32 | 0.1% | -3.00 [-5.28, -0.72] |
| Dahaba 2004 | 0.86 | 0.15 | 20 | 1.74 | 0.36 | 20 | 7.7% | -0.88 [-1.05, -0.71] |
| Guggenherger 2006 | 0.83 | 0.12 | 13 | 0.83 | 0.16 | 13 | 11.7% | 0.00 [-0.11, 0.11] |
| Maddali 2006 | 2.5 | 1.3 | 58 | 2.6 | 1.8 | 59 | 1.2% | -0.10 [-0.67, 0.47] |
| Maddali 2006 | 2.5 | 1.3 | 58 | 2.6 | 1.5 | 59 | 1.4% | -0.10 [-0.61, 0.41] |
| Milo 2001 | 0.78 | 0.16 | 29 | 0.82 | 0.08 | 28 | 15.0% | -0.04 [-0.11, 0.03] |
| Muellejans 2004 | 1.7 | 1.68 | 77 | 1.65 | 1.69 | 74 | 1.3% | 0.05 [-0.49, 0.59] |
| Muellejans 2006 | 2.1 | 0.9 | 40 | 2.7 | 28.9 | 39 | 0.0% | -0.60 [-9.67, 8.47] |
| Myles 2002 | 0.95 | 0.2 | 29 | 0.95 | 0.12 | 24 | 13.3% | 0.00 [-0.09, 0.09] |
| Myles 2002 | 0.96 | 0.2 | 29 | 0.95 | 0.22 | 24 | 11.3% | 0.01 [-0.10, 0.12] |
| Rajesh 2016 | 0.84 | 0.04 | 30 | 0.88 | 0.04 | 30 | 17.5% | -0.04 [-0.06, -0.02] |
| Rozendaal 2009 | 5.9 | 10.4 | 96 | 2.7 | 2.3 | 60 | 0.1% | 3.20 [1.04, 5.36] |
| Wang 2013 | 5.2 | 1.5 | 30 | 6.2 | 2.1 | 30 | 0.5% | -1.00 [-1.92, -0.08] |
| **Total (95% CI)** | | | 732 | | | 676 | 100.0% | -0.10 [-0.16, -0.03] |

Heterogeneity: Tau² = 0.01; Chi² = 117.75, df = 18 (P < 0.00001); I² = 85%
Test for overall effect: Z = 3.00 (P = 0.003)

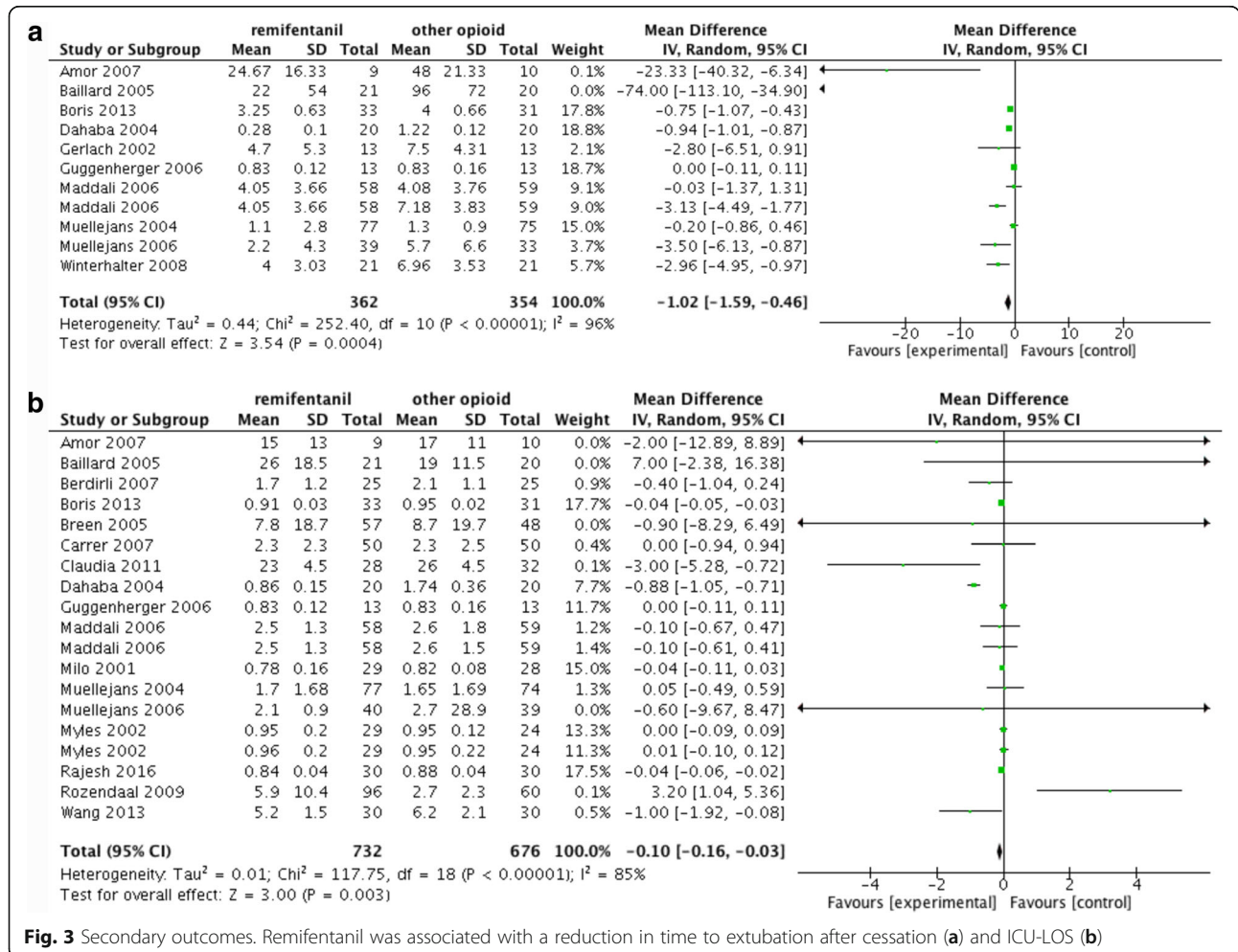**Fig. 3** Secondary outcomes. Remifentanil was associated with a reduction in time to extubation after cessation (**a**) and ICU-LOS (**b**)

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**Table 3** Data and analyses of outcome measures

| Outcome | Studies | Participants | Effect estimate | Heterogeneity ($I^2$) | Measure |
|---|---|---|---|---|---|
| Duration of mechanical ventilation (Fig. 1) | 18 | 1655 | -1.46 [-2.44] | 89% | Hour |
| Subgroup of analgesia only (Additional file 3: Figure S1a) | 4 | 291 | 0.14 [-0.79] | 91% | Hour |
| Subgroup of analgesia and sedation (Additional file 3: Figure S1b) | 14 | 1364 | -2.99 [-5.09] | 84% | Hour |
| Subgroup of remifentanil comparing with fentanyl (Additional file 3: Figure S1c) | 8 | 624 | -3.85 [-7.39] | 93% | Hour |
| Subgroup of remifentanil comparing with morphine (Additional file 3: Figure S1d) | 4 | 416 | -0.98 [-3.81] | 74% | Hour |
| Subgroup of remifentanil comparing with remifentanil (Additional file 3: Figure S1e) | 5 | 233 | -0.58 [-1.78] | 91% | Hour |
| Time to extubation after cessation of sedation (Fig. 2) | 10 | 716 | -0.68 [-0.74] | 96% | Hour |
| ICU-LOS (Fig. 2) | 17 | 1408 | -0.04 [-0.05] | 85% | Day |
| Hospital-LOS (Additional file 2: Figure S2a) | 9 | 507 | -0.05 [-0.25] | 88% | Day |
| Costs (Additional file 2: Figure S2b) | 4 | 437 | 943.54 [-1122.69] | 90% | Dollar |
| Mortality (Additional file 2: Fig. S2c) | 10 | 260 | -0.64 [-1.33] | 87% | Person |
| Agitation (Additional file 2: Fig S2d) | 3 | 184 | -0.71 [-1.80] | 93% | Person |
| Delirium (Additional file 2: Figure S2e) | 4 | 323 | 1.01 [0.63] | 0 | Person |

and fentanyl were compared (mean difference -3.85; 95% CI -7.39 to -0.31; $I^2$ 93%. Additional file 3: Figure S1c). No significant differences were identified in the subgroup of studies in which only analgesia was administered (mean difference 0.14; 95% CI -0.79 to 1.07; $I^2$ 91%. Additional file 3: Figure S1a), the subgroup of studies in which remifentanil and morphine were compared (mean difference -0.98; 95% CI -3.81 to 1.85; $I^2$ 74%. Additional file 3: Figure S1d), and the subgroup of studies in which remifentanil and sufentanil were compared (mean difference -0.58; 95% CI -1.78 to 0.62; $I^2$ 91%. Additional file 3: Figure S1e).

### Assessment of publication biases
Biases in the publication of the three outcome measures (duration of mechanical ventilation, time to extubation after cessation of sedation, and ICU-LOS) were evaluated using funnel plots. The funnel plots depicted in Fig. 4 were generally asymmetrical, which indicated the presence of publication bias. The points representing the evaluated studies in the three funnel plots were concentrated at the top showed that the studies had high precision and large sample sizes.

### Discussion
The results of this meta-analysis suggested that the use of remifentanil was associated with a reduction in the duration of mechanical ventilation when compared with other opioids, findings that were supported by the results of subgroup of studies in which analgesia and sedation were administered and subgroup of studies in which remifentanil was compared with fentanyl; however, the subgroups of studies in which analgesia alone

was administered and studies in which remifentanil was compared with morphine or sufentanil indicated the presence of no differences. Remifentanil was associated with reductions in time to extubation after sedation cessation and ICU-LOS but not reductions in hospital-LOS or costs.

The finding that remifentanil was found to reduce the duration of mechanical ventilation, time to extubation after sedation cessation, and ICU-LOS may be highly related to the unique pharmacokinetics and pharmacodynamics of remifentanil, namely, its rapid onset and offset, context-sensitive half-life that is hardly affected by the duration of infusion, and elimination that is independent of liver or renal function [14, 15]. In the subgroups, the results of the studies comparing remifentanil with fentanyl showed a maximal mean difference of 3.85 hours. As a selective μ-opioid receptor agonist [16, 17], remifentanil was similar to fentanyl in potency but different in pharmacokinetics. This result may indicate that remifentanil may be used as a substitute for fentanyl in some circumstances, especially in cases in which patients have developed kidney injuries or in which intermittent interruption of sedation and analgesia is needed to assess altered mental status. However, these results should be interpreted with caution for a few reasons. First, the mean differences between remifentanil and other opioids were only 1.5 hours for mechanical ventilation duration, 1 hour for time to extubation after sedation cessation, and 0.1 day for IC-LOS, which suggested that only miniscule differences may be identified in clinical practice. However, the potential benefits of remifentanil might be more apparent when used in patients with significant organ failure [6, 14], a

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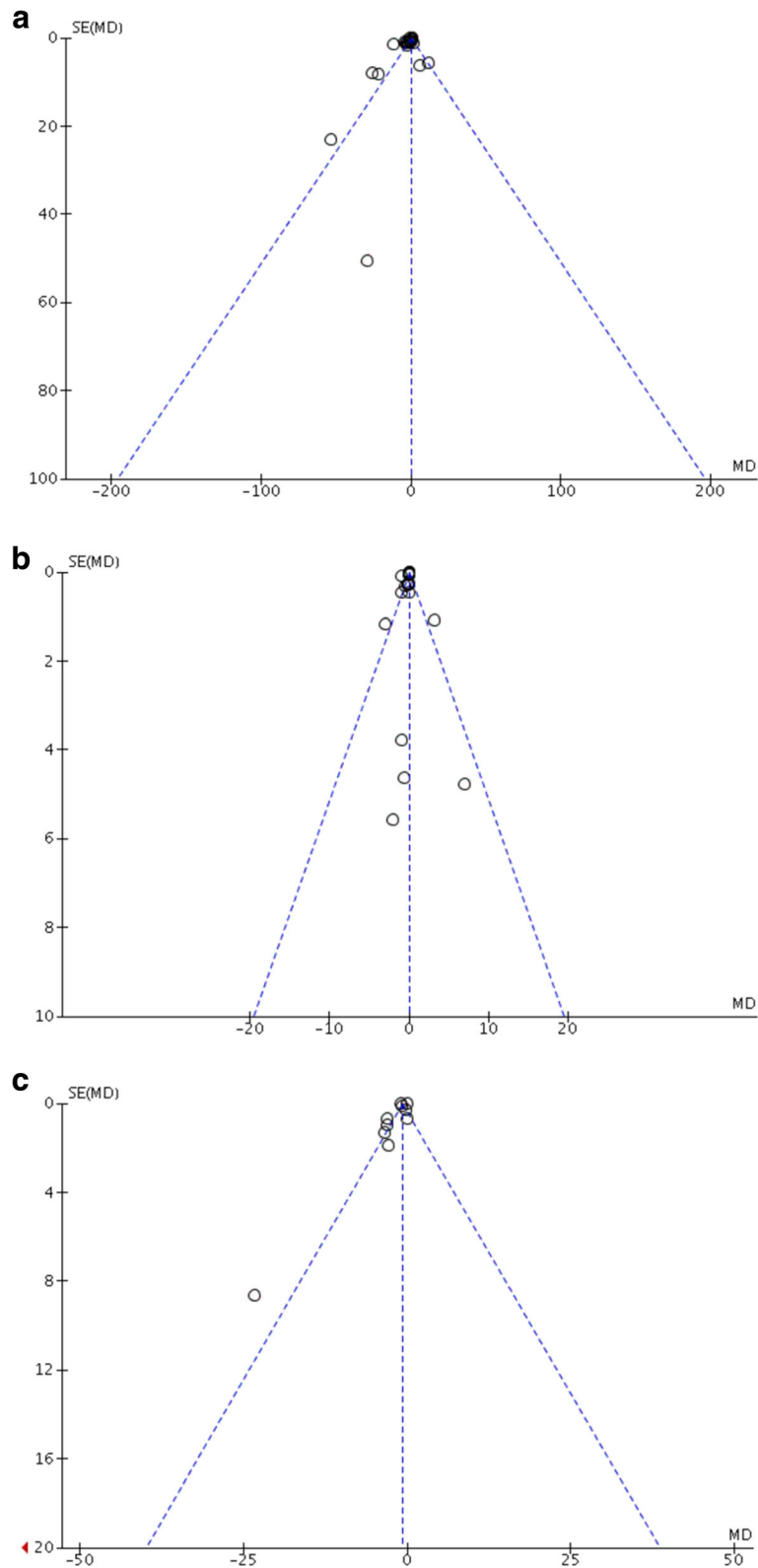


**Fig. 4** Funnel plots. Funnel plots were generally asymmetrical. The *hollow dots* and *dotted line* indicate individual studies and 95% confidence intervals, respectively. **a** Funnel plot of duration of mechanical ventilation. **b** Funnel plot of ICU-LOS. **c** Funnel plot of time to extubation after cessation of sedation

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hypothesis that more studies should explore. Moreover, neurologic assessment is essential for neurosurgical and neurotrauma patients; thus, the association between remifentanil and rapid and predictable awakening may be more meaningful in these patients, even though the difference between remifentanil and other opioids were less than 1 hour [5]. Second, high levels of heterogeneity were identified for all of the outcomes. There were remarkable differences across the included RCTs in terms of type of disease, analgesic agents and sedation protocols. We analysed the outcomes in subgroups classified by the use of different control groups and sedation protocols to reduce clinical heterogeneity; however, the statistical homogeneity was still obvious ($I^2 > 70\%$, considered as high heterogeneity). In addition, we selected a random-effects model rather than fixed-effects model to address the observed heterogeneity. Third, the funnel plots suggested the presence of publication bias in the three evaluated outcomes, which may be because the pharmaceutical companies that manufactured remifentanil funded some of the included studies.

Remifentanil was not associated with a reduction of hospital-LOS, costs, mortality, of agitation, and no differences were observed in the subgroups of studies in which only analgesia was administered and subgroup of studies in which remifentanil was compared with morphine or sufentanil, which may be because remifentanil and other opioids are similar in most regards; however, these results should be interpreted with caution for a few reasons. First, these outcome measures were assessed in small samples, and high homogeneity was observed. The mortality rate was low and not statistically powered to assess certain clinical outcomes [18]. Second, the combination of sedatives and analgesics made the estimation of the effect of opioids more difficult. Moreover, the sedation protocols and agents differed from study to study. Third, hospital-LOS and costs may be mainly affected by the severity of diseases rather than the selection of analgesia agents. In addition, anaesthetic costs accounted for only a small fraction of the overall costs. Costs were highly variable, with 95% CI ranging from -1590.98 to 171.55 dollars. Only four RCTs included assessments of costs [11, 12, 19, 20]. The types of diseases that patients were affected by in the four studies varied considerably, and the mean Acute Physiology and Chronic Health Evaluation II (APACHE II) score varied from 20.1 to 46, suggesting the presence of large variations in cost. Further cost-effectiveness studies are needed to explore the association between analgesic agents and cost.

The strengths of our meta-analysis include the structured search strategy, retrieval of all identified studies and large sample size. Taking the measurement of mechanical ventilation duration as an example, we included 18 RCTs in the comparisons, while the previous meta-analysis only included four RCTs [9] and we believe that our results might be more convincing than the results of the previous meta-analysis due to the inclusion of a larger sample size of patients.

There are limitations to our meta-analysis. First, the choice of hypnotic differed widely from one study to another, and the analysis of the effects of hypnotic choice was, thus, more difficult to perform. Second, both clinical and statistical heterogeneities were high. In addition, most of the included RCTs (78%) were of suboptimal quality. Third, we were unable to exclude publication bias, and negative studies may be missing, potentially resulting in overestimation of the effect sizes.

Taken together, remifentanil seems to be associated with reductions in the duration of mechanical ventilation, time to extubation after sedation cessation, and ICU-LOS. No significant differences were identified between remifentanil and other opioids in terms of hospital-LOS, costs, mortality or agitation.

## Conclusions

Remifentanil seems to be associated with reductions in the duration of mechanical ventilation and time to extubation after sedation cessation. Additional studies are needed to further evaluate the efficacy and safety of remifentanil and the association between the use of remifentanil and cost in critically ill patients, especially patients undergoing long-term mechanical ventilation.

## Additional files

**Additional file 1:** Appendix 1: PubMed search strategy. (PDF 18 kb)

**Additional file 2: Figure S2.** Secondary outcomes. There was no significant difference in hospital-LOS (a), costs (b), mortality (c) and agitation (d) in comparison with remifentanil and other opioids. (PDF 92 kb)

**Additional file 3: Figure S1.** Subgroup analyses. Remifentanil was associated with a reduction in duration of mechanical ventilation in subgroups of analgesia and sedation (b) and remifentanil comparing with fentanyl (c). There was no significant difference in subgroups of analgesia only (a), morphine (d), and sufentanil (e). (PDF 112 kb)

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to conception, design, data interpretation, manuscript revision for critical intellectual content, and supervision of the study. All authors read and approved the manuscript.

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