Use of remifentanil as a sedative agent in critically ill adult patients: a meta-analysis
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CRD summary
The authors concluded that the available evidence did not support the use of remifentanil as a sedative agent in critically-ill adult patients. The authors’ conclusions reflected the evidence presented. Given a number of review weaknesses (small sample sizes, potential for publication bias, and poor quality of included trials), the reliability of the conclusions is uncertain.

Authors’ objectives
To assess the effectiveness of remifentanil as a sedative agent in critically-ill adult patients.

Searching
The Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and MEDLINE were searched (up to August 2009) with no language restrictions. Search terms were reported. Reference lists of related editorials, reviews and original articles were handsearched. The websites of the International Network of Agencies of Health Technology Assessment and International Society of Technology Assessment in Health Care were also searched.

Study selection
Randomised controlled trials (RCTs) that compared remifentanil with another opioid (sufentanil, alfentanil, fentanyl or morphine) or hypnotic or sedative agent (propofol or midazolam) in critically-ill adult patients (over 18 years) were eligible for inclusion.

The primary outcomes were risk of agitation during the use of study drug and duration of mechanical ventilation. Secondary outcomes included: hospital mortality; proportion of patients not requiring rescue sedative agent; time to extubation after cessation of sedation; and length of intensive care unit stay.

The included trials compared remifentanil with another opioid (sufentanil, fentanyl, morphine) or hypnotic agent (propofol, midazolam, lorazepam). Trial settings, sedation protocols and drug dosages were varied. Patient groups also varied, including: mechanically ventilated medical and surgical patients; ages; acute physiology and chronic health evaluation (APACHE II) scores; and simplified acute physiology (SAP II) scores. Over half of the patients treated with remifentanil were also treated with a rescue sedative agent in many of the trials. Most of the trials excluded patients with neurological disease. Daily interruption of sedative drug administration was used in only one trial.

Two reviewers independently assessed studies for inclusion; the authors did not state how any disagreement was resolved.

Assessment of study quality
Two authors independently assessed trial quality using individual components of the trial (allocation concealment, blinding, loss to follow-up, intention-to-treat analysis) and the composite Jadad score. There was no disagreement between the reviewers in the quality ratings.

Data extraction
Two reviewers independently extracted data to calculate the relative risk (RR) for categorical outcomes and mean differences for continuous outcomes, together with corresponding 95% confidence intervals (CIs). Data was extracted using a pre-designed data abstraction form. There was no disagreement between the reviewers in the data abstracted.

Methods of synthesis
Pooled relative risks, weighted-mean-differences (WMDs) and their 95% confidence intervals were calculated using the random-effects model. Statistical heterogeneity was assessed using the $X^2$ and $I^2$ tests.

Publication bias was assessed visually using a funnel plot; the ’trim and fill’ method was used to adjust for any potential
publication bias.

Results of the review
Eleven RCTs (1,067 patients) were included in the review. Four trials had adequate allocation concealment; six trials were double-blinded. The Jadad score of trials were varied, the median score (interquartile range) was 3 (1 to 4). The funnel plot suggested evidence for the presence of publication bias.

Remifentanil was associated with a reduction in the time to tracheal extubation after cessation of sedation (WMD -2.04 hours, 95% CI -0.39 to -3.69; I²=83.5%, eight RCTs).

Remifentanil was not associated with a significant reduction in mortality (four RCTs), use of rescue sedative agent (three RCTs), duration of mechanical ventilation (eight RCTs), length of intensive care unit stay (eight RCTs) and risk of sedative agitation (three RCTs) when compared with an alternative opioid or hypnotic agent.

Authors’ conclusions
The available evidence did not support the use of remifentanil as a sedative agent in critically-ill adult patients.

CRD commentary
The review question was clearly stated. Several relevant databases were searched without any language restrictions, so language bias was unlikely. Review processes were conducted in duplicate, minimising the risk of error and bias.

Trial quality was assessed using appropriate criteria and quality reported to be poor. Statistical methods used to combine data appeared appropriate; results of the meta-analysis were adequately reported. One trial (remifentanil group) was included twice in the meta-analysis. The authors acknowledged a number of limitations including: heterogeneity; potential conflict of interest by remifentanil manufacturing company (GlaxoSmithKline funded some of the primary trials); potential for publication bias; small sample sizes; and the poor quality of included trials. The conclusions reflected the results of the included trials.

Given a number of weaknesses (small sample sizes, potential for publication bias, and poor quality of included trials), the reliability of the conclusions is uncertain.

Implications of the review for practice and research
Practice: The authors stated that the current evidence does not support the routine use of remifentanil as a sedative agent in critically-ill adult patients.

Research: The authors stated that a large RCT (including daily interruption of sedative drug administration) is required to assess whether remifentanil, with or without another short acting hypnotic agent, is cost effective in critically-ill adult patients with multiple organ failure. The authors also noted that further studies are needed to investigate whether remifentanil is better than dexmedetomidine or whether a combination of remifentanil with dexmedetomidine is better than other sedative agents in the intensive care unit setting.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.