Sedation in the intensive care unit: a systematic review
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Authors' objectives
To determine which form of sedation is associated with optimal sedation, the shortest time to extubation, and length of intensive care unit (ICU) stay.

Searching
Studies were identified by searching MEDLINE, EMBASE/Excerpta Medica and the Cochrane Library (1980 to June 1998, keywords provided); reviewing bibliographies of relevant articles; contacting authors and 18 pharmaceutical companies; handsearching six relevant journals (Anaesthesiology, Anaesthesia and Analgesia, Canadian Journal of Anaesthesia, British Journal of Anaesthesia, Anaesthesia and Intensive Care, and Anaesthesia) from 1980 to 1986; and searching personal files.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs). Studies in abstract form were excluded.

Specific interventions included in the review
Short-term (less than 24-hours) or long term (greater than 24-hours) sedation. Sedative agents were grouped into the following four categories: benzodiazepines (e.g. diazepam, midazolam, lorazepam), opiates (e.g. morphine, fentanyl), neuroleptics (haloperidol, methotrimeprazine) and anaesthetic agents (propofol and inhalational agents such as isoflurane). Studies had to include a comparison of at least two sedative drugs. Co-interventions included anaesthesia, analgesia, neuromuscular blockade and weaning strategy. The relative effectiveness of the anaesthetic agent propofol, and the benzodiazepine midazolam, were compared in 20 of 32 clinical trials. Other agents included the benzodiazepine lorazepam; the opiates alfentanil, pethidine, papaveretum, fentanyl, morphine, and lytic solution (pethidine, promethazine, and dihydroergotamine); and the anaesthetic agents isoflurane and ketamine.

Participants included in the review
Mechanically ventilated adult patients requiring short-term or longer-term sedation. Studies of people undergoing withdrawal of life support were excluded. Participants in the included studies were cardiac surgery patients, other surgical patients, trauma patients, medical patients or mixed ICU patients.

Outcomes assessed in the review
Quality of sedation. A variety of scoring systems were to used to assess the quality of sedation including the Ramsay score, the modified Ramsay score, Cook and Palma modified Glasgow Coma Scales. Other outcomes included time to extubation and length of stay in ICU.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
Selected publications were critically appraised using seven validity criteria which included percentage follow-up, blinding, intention to treat, baseline data provided (e.g. age, weight, hepatic function, renal function, and lung function), standardised interventions, specific dosing schedules and outcomes. Data were extracted in duplicate and disagreements were resolved by consensus.

Data extraction
Data were extracted in duplicate and disagreements were resolved by consensus. Data on study/patient population, length of sedation, sedation score target level, sedatives, mean dosage, mean percentage time at sedation target levels, mean time to extubation, mean length of ventilation and mean ICU length of stay were extracted into tables.

Methods of synthesis
How were the studies combined?
The studies were too clinically heterogeneous to permit statistical pooling so a narrative summary was provided.

How were differences between studies investigated?
The study results were analysed separately for short- and longer-term sedation, cardiac surgery patients and other ICU patients, and by the different agents being compared.

Results of the review
32 studies with a total of 2453 patients randomised to treatment. Short term sedation was evaluated in twenty studies and sedation of longer than 24 hours was evaluated in fourteen studies (two studies evaluated both short and long term sedation). Sixteen studies evaluated the outcome of time to extubation, and six studies reported data on length of stay in ICU.

Assessment of Validity:
Masking of allocation to treatment was not documented in any trial. Blinding health care workers was conducted in 5 (16%) of 32 trials. Standardised co-interventions that could affect the outcomes of time to extubation and length of ventilation or ICU stay were variably reported (weaning strategy, 3 (9%) of 32 trials; anaesthesia for postoperative patients, 7 (78%) of 9; use of analgesia, 7 (22%) of 32; and neuromuscular blockers, 13 (41%) of 32 trials). Intention-to-treat analysis was used in 26 (81%) of 32 trials.

Short-term (<= 24 h) sedation (number of studies = 20):
In cardiac patients, pethidine (meperidine) and alfentanil led to similar sedation quality and time to extubation in one RCT. Propofol was better than midazolam for improving sedation quality in two of seven RCTs and for shortening the time to extubation in five of eight RCTs. Propofol shortened the duration of ventilation in one of seven RCTs. Length of ICU stay was similar in the propofol and midazolam groups in two RCTs. In surgical patients or mixed patients in the ICU, propofol was better than midazolam for improving sedation quality in three of six RCTs and for shortening the time to extubation in three of three RCTs. Midazolam and lorazepam did not differ for sedation quality in one RCT. Isoflurane was better than midazolam for improving sedation quality and shortening time to extubation in one RCT. Propofol and lytic solution (pethidine, promethazine, and dihydroergotamine) had a similar sedation quality, but propofol led to a shorter time to extubation.

Longer-term (> 24 h) sedation (number of studies = 14):
In surgical patients or patients in the ICU, propofol and midazolam had a similar sedation quality in three of six RCTs. Sedation quality was better in the midazolam group in one RCT and in the propofol group in two RCTs. Time to extubation was shorter in the propofol group than in the midazolam group in three of four RCTs. Length of stay in the ICU was similar for the propofol and midazolam groups in one RCT. Midazolam and lorazepam had a similar sedation quality in one RCT. Time to extubation was shorter with isoflurane than with midazolam, but sedation quality and length of ICU stay were similar between groups (one RCT). Alfentanil and propofol led to better sedation quality, shorter time to extubation, and shorter length of ICU stay than did morphine plus midazolam (one RCT).

Authors’ conclusions
Considering the widespread use of sedation for critically ill patients, more large, high-quality, randomised controlled trials of the effectiveness of different agents for short-term and long-term sedation are warranted.
CRD commentary
This is a good quality review with a clear objective and selection criteria. The search strategy was good, but only published studies were included, which could have resulted in publication bias, although they did attempt to locate unpublished data by contacting authors and companies. The authors do not state if there were any language restrictions. Validity of the trials was assessed, and data extraction was performed independently by two reviewers. The review is of relevance to those working in ICU and the conclusions appear to follow on from the results.

Implications of the review for practice and research
Practice: Propofol appears to offer some advantage in the setting where rapid waking of the patient is desired, but more study is required to determine whether the increased cost and potential to cause hypotension are outweighed by this benefit.

Research: Considering the widespread use of sedation for critically ill patients, more large, high-quality, randomised controlled trials of the effectiveness of different agents for short-term and long-term sedation are warranted. More economic evaluations are warranted in this field, given the diverse purchasing costs of different agents and their variable and incompletely evaluated effect of economic outcomes, such as duration of mechanical ventilation and duration of ICU stay.

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