A lack of evidence of superiority of propofol versus midazolam for sedation in mechanically ventilated critically ill patients: a qualitative and quantitative systematic review

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Authors' objectives
To assess the efficacy and harm of propofol versus midazolam in mechanically-ventilated, critically-ill patients.

Searching
The following sources were searched for full reports published in peer-reviewed journals in any language: MEDLINE (via PubMed and Knowledge Finder) from 1966 to June 1999; Excerpta Medica from 1984 to January 1999; and the Cochrane Library (Issue 1, 1999). The search was conducted using the following free text and MeSH terms, either alone or in combination: 'propofol', 'midazolam', 'critically ill', 'critical care', 'intensive care' and 'random'. The bibliographies of identified studies and reviews were also examined.

Abstracts from scientific meetings, studies of animals, and review articles were excluded. The manufacturers of propofol and midazolam were not contacted. The authors of the primary studies were contacted for clarification of ambiguous data, but no responses were received.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible.

Specific interventions included in the review
Comparisons of propofol with midazolam were eligible. The average maintenance dose, where stated, was between 0.6 and 3 mg/kg/hour for propofol, and between 0.012 and 0.3 mg/kg/hour for midazolam. Concomitant analgesic drugs included morphine (10 trials reported doses ranging from 0.005 to 0.046 mg/kg/hour) and various other opioids. Three studies did not use opioids.

Participants included in the review
Critically-ill mechanically-ventilated adult patients in the intensive care unit (ICU) were eligible. The average age of the patients in each trial ranged from 37 to 69 years. Most of the patients were surgical, medical or trauma patients, and all were intubated and ventilated. The most common exclusion criteria in the individual studies were hepatic pathology, gross obesity, renal failure, neurological pathology and haemodynamic instability.

Outcomes assessed in the review
The inclusion criteria were not defined in terms of the outcomes. The following primary outcomes were assessed:

the efficacy of sedation, estimated as the percentage of time adequately sedated over the total time sedated, with the definition of adequate sedation taken from the original study;

the weaning time from mechanical ventilation, defined as the delay from the end of drug administration to extubation;

adverse drug reactions, including hypertriglyceridaemia and arterial hypotension;

the length of ICU stay;

mortality; and

cost estimations.

A clinically relevant hypertriglyceride level was defined as at least a doubling of the normal values as reported in the
individual trial. Arterial hypotension was defined as a systolic blood-pressure of less than 90 mmHg, or the need for an intervention. The depth of sedation was assessed in sixteen trials using the Ramsay scale.

How were decisions on the relevance of primary studies made?
One author screened the abstracts of the identified reports. Studies that clearly met the inclusion criteria were read by all the authors independently. Consensus was reached by discussion.

Assessment of study quality
Validity was assessed using the 5-point, 3-item Oxford scale of Jadad et al. (see Other Publications of Related Interest). The criteria used to assess validity were proper randomisation, double-blinding, and the reporting of withdrawals. Validity was assessed and scored by all five authors independently, and consensus was reached by discussion.

Data extraction
Two investigators independently extracted the data, and the other investigators checked it. The following information was extracted: the inclusion and exclusion criteria for the patients; the number of included and analysed patients; the patients' characteristics; indication for sedation; baseline level of sedation; definition of target sedation; duration of sedation; regimens of propofol and midazolam; concomitant analgesia; and sponsorship. Data from the crossover RCT were reported as if they had come from a parallel group trial, and the data were used assuming the lack of any carryover effect. An intention to treat analysis could not be performed because most of the trials only reported the number of analysed patients.

Methods of synthesis
How were the studies combined?
The weighted mean differences (WMD) and 95% confidence intervals (CIs) were calculated for the continuous data. The pooled relative risk (RR), 95% CI and the number-needed-to-treat (NNT) were calculated for dichotomous data. This was carried out using a fixed-effect model where the data were homogeneous (p>0.1), and a random-effects model for non-homogeneous data. The data were weighted by the size of the trial.

How were differences between studies investigated?
The trials were arbitrarily separated into short-term (36 hours or less) and long-term (at least 54 hours) sedation studies. The data on weaning time were analysed according to these groups.

Results of the review
Twenty-seven RCTs (1,624 patients) were included. One RCT used a crossover design, whilst all the others were parallel group studies.

The methodological design of the trials was often poor, as was the quality of the data reporting. The median Oxford validity score was 2 (range: 1 to 4). The primary studies exhibited several methodological problems: only one trial attempted to blind the study drugs; 40% of the studies did not mention the number of, and reasons for withdrawals; most trials had fewer than 50 patients; and few trials reported a baseline measurement of sedation.

Ten RCTs were sponsored by the manufacturers of the two drugs being studied.

Efficacy of sedation (19 RCTs).

The event scatter suggested that propofol was more efficacious than midazolam. The efficacy ranged from 54 to 97% with propofol, and from 26 to 95% with midazolam.

Duration of adequate sedation (9 RCTs, 615 patients).

The duration of adequate sedation was significantly greater with propofol than with midazolam; the WMD was 2.9 hours (95% CI: 0.2, 5.6, p=0.04).
Weaning time (12 RCTs, 633 patients).

Short-term sedation (9 RCTs): the weaning time was less with propofol than with midazolam. The average weaning time ranged from 0.8 to 4.3 hours after sedation with propofol, and from 1.5 to 7.2 hours after sedation with midazolam; the WMD was 2.2 hours (95% CI: 0.8, 3.7).

Long-term sedation (3 RCTs, 156 patients): there was a lack of evidence of difference in weaning times. The 3 RCTs favoured propofol with WMDs of 1, 13.1 and 35.8 hours, respectively.

Length of ICU stay (4 RCTs): no meaningful conclusions could be made.

Adverse drug reactions.

The specific adverse reactions, i.e. arterial hypotension and hypertriglyceridaemia, were reported significantly more often with propofol than with midazolam.

Arterial hypotension (7 RCTs): the pooled RR was 2.5 (95% CI: 1.3, 4.5) and the NNT was 12 (95% CI: 8, 33).

Hypertriglyceridaemia (4 RCTs): the pooled RR was 12.1 (95% CI: 2.9, 49.7) and the NNT was 6 (95% CI: 4, 10).

Mortality (8 RCTs): there was no significant difference between the intervention groups; the RR was 0.8 (95% CI: 0.5, 1.3).

Cost information
The costs were estimated in five reports. Three reports concluded that propofol was more cost-effective, whilst two concluded that midazolam was more cost-effective.

Authors' conclusions
Effective and adequate sedation in critically-ill patients undergoing mechanical ventilation is possible with both propofol and midazolam. The duration of effective sedation was longer with propofol, compared with midazolam. In post-operative patients who were sedated for less than 36 hours, weaning was faster with propofol.

CRD commentary
The aims were stated and the inclusion criteria were defined in terms of the study design, participants and interventions. Several relevant databases were searched, no language restrictions were applied, and the methods used to select the studies were described. The lack of an attempt to locate unpublished material raises the possibility of publication bias. Studies were restricted to RCTs and validity was formally assessed. The relevant data were extracted and presented in tabular format. The methods used to extract the data and assess validity were described. The data were pooled in a meta-analysis. However, results from an assessment of statistical heterogeneity were not reported, though comments were made on the clinical heterogeneity among the trials.

The authors discussed the methodological problems of the primary studies and the following limitations of the review. There was large variability in the use of different weaning protocols and extubation criteria, and in the definitions of target sedation. There was a lack of reporting of ICU stay, costs and mortality in the primary studies. Sixty per cent of the studies were either supported by the manufacturer of the drug, or published in a sponsored supplement of a peer-reviewed journal. Most of the data were taken from studies of short-term sedation in post-operative patients and, therefore, may not be applicable to long-term sedation in other patient groups. The evidence presented supports the authors' conclusions.

Implications of the review for practice and research
Practice: The authors state that effective and adequate sedation in critically-ill patients undergoing mechanical ventilation is possible with both propofol and midazolam.
Research: The authors state that further research should be directed to high-risk, long-term sedated ICU patients and should include ICU stay, costs and mortality.

**Funding**
Swiss National Research Foundation, PROSPER grant number 3233-05193997.

**Bibliographic details**

**PubMedID**
11273936

**Original Paper URL**
http://www.anesthesia-analgesia.org

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Critical Care; Critical Illness /therapy; Humans; Hypnotics and Sedatives /adverse effects /therapeutic use; Midazolam /adverse effects /therapeutic use; Propofol /adverse effects /therapeutic use; Randomized Controlled Trials as Topic; Respiration, Artificial; Time Factors; Ventilator Weaning

**AccessionNumber**
12001000934

**Date bibliographic record published**
30/06/2002

**Date abstract record published**
30/06/2002

**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.