Sedation in the intensive care unit with remifentanil/propofol versus midazolam/fentanyl: a randomised, open-label, pharmacoeconomic trial

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
This article compared an analgesia-based sedation regimen with remifentanil and propofol versus a conventional regimen with midazolam and fentanyl in patients requiring postoperative mechanical ventilation in the intensive care unit (ICU) following cardiac surgery. Remifentanil was administered at 6 to 12 microg/kg per hour, or up to a maximum of 60 microg/kg per hour. Propofol supplementation, where required, was given at 0.3 to 1.0 mg/kg per hour, or up to a maximum of 4 mg/kg per hour. The conventional midazolam/fentanyl regimen comprised an initial dose of fentanyl of 1 to 2 microg/kg, followed by a dose of 1 to 2 microg/kg per hour (or up to a maximum of 7 microg/kg per hour) plus an initial dose of 0.03 to 0.2 mg/kg midazolam.

Type of intervention
Palliative care.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients aged 18 to 75 years who had undergone elective coronary artery and/or heart valve surgery, were intubated and were expected to require mechanical ventilation for 12 to 72 hours. Patients were excluded from the study if one of the following conditions was given or expected to become applicable: pre-existing impaired central nervous system function, weight greater than 120 kg, use of neuromuscular blocking agents in the ICU, epidural anaesthesia, ASA (American Society of Anaesthesiologists) IV and V. Also excluded were patients with a history of allergy to the study medication or of opioid abuse, patients who required analgesia and sedation beyond 72 hours, patients who required a tracheotomy, and pregnant or lactating women.

Setting
A secondary care provider provided the interventions in an inpatient setting. The study was conducted in a single hospital in Germany.

Dates to which data relate
The authors did not state the dates during which the data were collected. The price year was 2003.

Link between effectiveness and cost data
The costing was undertaken prospectively on the same sample that provided the effectiveness data.

Study sample
The authors reported that the total sample size should have guaranteed a global power of at least 80% for a standardised
Effect size of 0.7. In total, 80 patients were enrolled in the study, of which 72 could be evaluated (modified intention to treat population). Of these, 8 patients (7 in the midazolam-fentanyl and 1 in the remifentanil-propofol group) had to be excluded during the study because of mechanical ventilation for longer than 72 hours (3 patients), reintubation (4 patients) and because they were only randomised and did not receive the study medication on account of postoperative bleeding (1 patient). The 7 treated patients were excluded because the primary efficacy measure could not be assessed because of a lack of essential data. Therefore, a total of 39 patients were analysed for the remifentanil-propofol group and 33 patients for the midazolam-fentanyl group.

Study design
This was a randomised, single-centre, open-label, parallel-group clinical study. The patients were randomised on a 1:1 basis. No further details of the randomisation method were reported. Double blinding was judged to be impractical on account of the different dosing algorithms and physical characteristics of the drugs used. No patients were lost to follow-up.

Analysis of effectiveness
ICU entry was the starting point. The efficacy of the two regimens was assessed through measurement of several time points throughout the treatment period:

- time from arrival on ICU to weaning;
- weaning time (calculated as the time interval from start of weaning to extubation);
- time from arrival on ICU to extubation;
- time from extubation to eligible ICU discharge;
- time from arrival on ICU to eligible ICU discharge (primary endpoint of the study); and
- time from arrival on ICU to actual ICU discharge.

The number of patients with adverse events was also reported (any adverse event, any drug-related adverse event, any serious adverse event, any drug-related serious adverse event). The analysis was conducted on an intention to treat basis. No adjustments for baseline characteristics were reported.

Effectiveness results
The difference between the groups in the mean time (measured in hours) from arrival on ICU to weaning was not statistically significant.

All other time differences measured between the groups were statistically significant.

For instance, the mean time from arrival on ICU to eligible ICU discharge was 46.1 (± 22.0) hours for the remifentanil-propofol group and 62.4 (± 27.2) hours for the midazolam-fentanyl group, (p<0.05).

In terms of adverse events, the only statistically significant difference was the number of patients with any drug-related adverse event. This was 9 in the remifentanil-propofol group (n=40) and 2 in the midazolam-fentanyl group (n=39), (p<0.05).

Clinical conclusions
Analgesia and sedation with remifentanil and propofol can facilitate a higher turnover of patients, by reducing time on mechanical ventilation and by shortening the overall length of ICU stay, compared with a conventional regimen comprising midazolam and fentanyl.
Modelling
A decision analytic model representing the study was constructed to simulate the results gained with a different remifentanil-propofol regimen and to explore the robustness of the results in terms of modelling parameter variations.

Measure of benefits used in the economic analysis
The authors did not derive a summary measure of effectiveness. In effect, a cost-consequences analysis was performed. See 'Analysis of Effectiveness' section for the outcome measures for the clinical study.

Direct costs
Drug costs (including all concomitant medication and wastage), costs of materials for analgo-sedation (only variable costs), and personnel costs in the ICU were considered. All other types of costs were assumed not to differ significantly between regimens. Resource use was derived from the study centre and from the study sample. The financial department of the study centre checked the unit costs to ensure that they represented realistic estimates. Discounting was not relevant as the time period considered was less than 1 year. The price year was 2003.

Statistical analysis of costs
Means, medians, and ranges for cost categories and total costs were reported. The Wilcoxon rank-sum test was used to test differences in the costs.

Indirect Costs
Productivity costs were not included in the analysis.

Currency
Euro (EUR).

Sensitivity analysis
The authors performed scenario analyses to estimate the costs under routine circumstances compared with those by study protocol. Univariate sensitivity analyses were also performed.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
Overall mean and median costs were, respectively, EUR 1,712 and EUR 1,558 (range: 1,058 to 3,647) for the remifentanil-propofol group and EUR 1,729 and EUR 1,604 (range: 821 to 3,337) for the midazolam-fentanyl group, (p not significant).

Differences in the material cost and non-study drugs cost were not statistically significant.

Study drugs, nursing staff and physician staff costs were statistically significantly different between the study groups.

The model-based sensitivity analyses showed that variation in nursing staff costs and study drug costs have a strong impact on the study cost results.

Synthesis of costs and benefits
The costs and benefits were not combined.
**Authors' conclusions**

Compared with midazolam-fentanyl, a remifentanil-based regimen for analgesia and sedation supplemented with propofol significantly reduced the time on mechanical ventilation and allowed earlier discharge from the intensive care unit (ICU), at equal overall costs.

**CRD COMMENTARY - Selection of comparators**

The authors explicitly stated the reasons for their choice of the comparator. Specifically, it was the most widely used regimen in German ICUs as well as being the cheapest alternative with respect to direct drug costs. You should decide if these reasons are equally relevant in your own setting.

**Validity of estimate of measure of effectiveness**

The analysis was based on a randomised controlled trial. However, the method of randomisation was not explicitly stated. Power calculations were performed to ensure that the size of the study sample was adequate. The study sample was representative of the study population. The male-to-female ratio in the remifentanil-propofol group was higher than in the control group, and the authors did not report any adjustment for this imbalance. The implication of this in relation to the study results is not clear. Double blinding was not possible in the study, but blinding of the researchers who collected and analysed the data was not reported. This would have contributed to the avoidance of potential bias. Overall, the internal validity of the study would seem to be reasonably good.

**Validity of estimate of measure of benefit**

The authors did not derive a summary measure of effectiveness. In effect, a cost-consequences analysis was performed.

**Validity of estimate of costs**

The authors did not state a perspective for the analysis. However, all cost categories relevant to the hospital perspective were considered. Some individual costs were omitted from the analysis, but these costs were likely to have been the same in both arms of the trial and their omission is unlikely to have had any effect on the study results or its conclusions. Prices and official tariffs were used as unit costs, which is reasonable given the perspective adopted. The resource quantities were not reported separately from the costs. However, since the unit costs were reported, the quantities could therefore be derived from the reported data. The costs were expressed in 2003 prices. Discounting was not conducted as it was not relevant given the time horizon of the analysis.

**Other issues**

The authors acknowledged that, as their study was conducted in a single German hospital, its results might not be directly transferable to other countries and settings. Moreover, the year in which the data were collected was not reported. This could present difficulties in terms of comparing the results of this study with those from other settings. The authors’ conclusions reflected the scope of the analysis. The authors were not selective in reporting the results.

**Implications of the study**

Remifentanil-based analgesia and sedation has been shown to be effective and well tolerated in postoperatively ventilated patients who had undergone cardiac surgery. Compared with a midazolam-fentanyl regimen, a remifentanil-propofol regimen may reduce the time on mechanical ventilation, shorten the ICU stay, and be cost-neutral or even lead to cost-savings in the short- to medium-term mechanically ventilated patients (depending on the setting and dosing algorithm).

**Source of funding**

Funded by GlaxoSmithKline GmbH and Co. KG, Munich, Germany.

**Bibliographic details**

Muellejans B, Matthey T, Scholpp J, Schill M. Sedation in the intensive care unit with remifentanil/propofol versus midazolam/fentanyl: a randomised, open-label, pharmacoeconomic trial. Critical Care 2006; 10(3)