Economic evaluation of propofol for sedation of patients admitted to intensive care units

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
The use of propofol and midazolam for the sedation of patients admitted to the intensive care unit (ICU).

Type of intervention
Other: Anaesthesia.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients aged 18 years or more who required sedation with propofol or midazolam as a primary sedative agent when being mechanically ventilated in the ICU. The exclusion criteria were a known or suspected allergy to propofol or midazolam, suspected or known pregnancy, coma caused by cerebrovascular accident or of an unknown cause, and uncontrolled seizures.

Setting
The setting was a hospital ICU. The economic study was carried out in Canada.

Dates to which data relate
The effectiveness and resource use data were gathered from September 1994 to June 1995. The price year was 1997.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was conducted on the same sample of patients as that used in the effectiveness study.

Study sample
Power calculations were not conducted. A sample of 156 patients was identified at the study hospitals and enrolled in the study. However, the method used to select the sample was not described. There were 79 patients in the midazolam group and 77 in the propofol group. The authors reported that since there were 26 deaths (11 in the midazolam group versus 15 in the propofol group) and 11 sedation failures (4 in the midazolam group versus 7 in the propofol group, of whom 1 and 4, respectively, had died), 124 patients remained in the study. The mean age of the remaining patients was 59.8 years in the midazolam group and 60.3 years in the propofol group. The percentages of women were 45% (midazolam group) and 27% (propofol group), respectively. A further 25 patients had tracheal extubation while continuous sedation was ongoing and were therefore excluded from the study sample. Thus, the final group included 99
patients, 53 in the midazolam group and 46 in the propofol group.

**Study design**
This was a prospective, randomised clinical trial that was carried out at four centres across Canada. More specifically, the Queen Elizabeth II Health Sciences Centre (Halifax, Nova Scotia), Foothills Hospital (Calgary, Alberta), Ottawa General Hospital (Ottawa, Ontario), and Vancouver General Hospital (Vancouver, British Columbia). The methods of randomisation and outcome assessment were not reported. Patients were followed until discharged from the ICU. No loss to follow-up was reported.

**Analysis of effectiveness**
The analysis of the clinical study was conducted on the basis of treatment completers only since the outcomes were assessed in the final study sample of 99 patients. The outcome measures used were sedation status and the length of stay (LOS) in the ICU during three phases. Sedation status was defined as insufficient if the Ramsay score was below the target, adequate if the score was at the target, and excessive if the score was above the target. The three phases considered for LOS in the ICU were sedation preparation (phase I), sedation and extubation (phase II), and discharge planning (phase III). Mortality and sedation failure were also reported. Sedation failure was defined as the inability to achieve a target sedation level appropriate for the patient, according to the Ramsay score, because of the occurrence of a serious adverse reaction. The authors stated that the study groups were comparable in terms of age and baseline haemodynamic parameters, but there were more women in the midazolam group (45%) than in the propofol group (27%), (p=0.05).

**Effectiveness results**
The percentage of patients with insufficient sedation status was 8.1% in the midazolam group and 11.2% in the propofol group, (p=0.29).

The percentage of patients with adequate sedation status was 44% in the midazolam group and 60.2% in the propofol group, (p=0.01).

The percentage of patients with excessive sedation status was 18.4% in the midazolam group and 12% in the propofol group, (p=0.12).

The percentage of patients with undefined sedation status was 29.5% in the midazolam group and 16.6% in the propofol group, (p=0.01).

The LOS in the ICU for the midazolam group versus the propofol group was:

3 hours versus 2.7 hours in phase I, (p=0.81),

30.3 hours versus 21.5 hours in phase II, (p=0.08), and

26 hours versus 26.5 hours in phase III, (p=0.94).

The total ICU stay was 72.7 hours for the midazolam group versus 69.8 hours for the propofol group, (p=0.94).

Considering specific timeframes within each phase, statistically significant differences were achieved only for "termination to ready for extubation" in phase II, where the ICU stay was 7.1 hours for the midazolam group versus 2.5 hours for the propofol group, (p=0.001).

Mortality was 13.9% in the midazolam group versus 19.5% in the propofol group, (p=0.37).

Sedation failure was observed in 4 patients in the midazolam group versus 7 patients in the propofol group, (p=0.30).
Clinical conclusions
The effectiveness study showed that propofol was associated with a higher rate of patients achieving adequate sedation status in comparison with midazolam. The overall LOS was not significantly different between the groups.

Measure of benefits used in the economic analysis
The health outcomes were left disaggregated and no summary benefit measure was used in the economic analysis. In effect, a cost-consequences analysis was conducted.

Direct costs
Discounting was not relevant since the costs were incurred during a short time. The unit costs and the quantities of resources used were presented separately for some items. The health services included in the economic evaluation were physician visits, nursing time, other health care professional contacts, diagnostic tests and medications (including wastage). All health care professional visits were recorded according to specialty and type of visit. The cost/resource boundary of the study was unclear. Resource use was estimated in the basis of actual, individualised, prospectively gathered data derived from the sample of patients who were included in the effectiveness analysis. The costs were derived from the St. Paul's Hospital Cost Model, the details of which had been published elsewhere. All the costs were presented in 1997 values.

Statistical analysis of costs
Statistical tests were used to test the statistical significance of differences in the estimated costs. The type of tests used was not reported.

Indirect Costs
The indirect costs were not considered.

Currency
Canadian dollars ($).

Sensitivity analysis
Two types of sensitivity analyses were conducted. The first assessed the impact of variability in the cost data on the cost-advantage associated with propofol. The second analysis assumed equal time from extubation to ICU discharge for the two groups. The comparison of the total costs was then assessed using an analysis of covariance, which also permitted the impact of some cost components to be assessed.

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

Cost results
The median costs of stay in the ICU were Can$5,718 for propofol and Can$5,950 for midazolam, (p=0.94).

The median costs of sedation were Can$86.02 for propofol and Can$40.42 for midazolam, (p=0.08).

The median total costs were Can$5,765 for propofol and Can$5,998 for midazolam, (p=0.94), with a saving of Can$233 per patient.

The sensitivity analysis showed that using the 25th and 75th percentiles of total costs, the cost-difference ranged from an extra cost of Can$114 to a saving of Can$2,709 per patient with propofol.
The second sensitivity analysis showed that not only was extubation time 4.2 times (95% confidence interval, CI: 2.3 - 7.5) shorter with propofol than with midazolam, but also that extubation time was positively associated with the duration of sedation, \( p=0.05 \).

In addition, propofol costs were 3.6 times (95% CI: 2.4 - 5.3) higher than midazolam and sedative costs were positively associated with the duration of sedation.

Under the assumptions made in the second sensitivity analysis, the cost-saving associated with propofol was Can$403. This varied between Can$244 and Can$570 per patient when both the daily costs of the ICU and extubation reduction times were varied within +/- 30%.

The analysis also suggested that cost-savings with propofol increased with a longer duration of sedation.

**Synthesis of costs and benefits**
Not relevant since a cost-consequences approach was taken.

**Authors' conclusions**
Propofol was associated with a better sedation profile than midazolam patients. However, this did not translate into lower costs or lower stay in the intensive care (ICU).

**CRD COMMENTARY - Selection of comparators**
The authors did not provide a justification for the choice of the comparators. It was unclear whether midazolam was considered as the standard diagnostic approach. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The basis of the analysis of effectiveness was a randomised trial, which was appropriate for the study question. No information on the methods of randomisation, sample selection and outcome assessment was provided. The patients were not followed after ICU discharge. The choice of a short follow-up appears to have been appropriate since relevant outcomes were incurred over a short timeframe. The study was carried out in several centres, which enhances the transferability of the results to other settings. However, there were some limitations to the validity of the study. First, there was no justification for the choice of sample size. Second, the analysis of the clinical study was conducted on the basis of treatment completers only. Third, there was little information on the baseline characteristics of the patient sample. As the method of sample selection was not reported, it was unclear whether the patient sample was representative of the study population. The authors noted that the lack of masking was a potential limitation of the analysis, although blinding was quite unfeasible.

**Validity of estimate of measure of benefit**
No summary benefit measure was used in the analysis because a cost-consequences analysis was conducted.

**Validity of estimate of costs**
The perspective of the study was unclear. Therefore, it is not possible to assess whether all the relevant categories of costs were included in the analysis. Some unit costs and some data about resource consumption were provided. The price year was given, which will facilitate reflation exercises in other settings. The source of costs referred to a model that had been published elsewhere, and consequently, few details were provided. Resource consumption was prospectively assessed. Although the costs came from a single centre, extensive sensitivity analyses were conducted to assess the robustness of cost-savings associated with propofol. The authors noted that the potential economic advantage of propofol depended on optimal discharge criteria, which were a key issue in the analysis. It was also acknowledged that not all diagnostic tests and medications administered in the ICU were recorded.
Other issues
The authors compared their findings with those from a published study, which they identified as the only published analysis to compare propofol with midazolam. The authors observed that similar results were obtained despite some differences between the two analyses. The issue of the generalisability of the study results to other settings was not addressed. Only limited sensitivity analyses were conducted. The study involved critically ill patients admitted to the ICU and this was reflected in the conclusions of the analysis. The authors acknowledged that further limitations of the study were the absence of a quality of life measure from the patients’ point of view, and the absence of a measurement of adverse events.

Implications of the study
The study results suggested that propofol has no impact on ICU stay or costs since the shorter time gained from early extubation is counterbalanced by the prolonged time waiting for ICU discharge. Future studies should assess the reasons for such discharge delay.

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Other publications of related interest


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