Propofol or midazolam for sedation and early extubation following cardiac surgery
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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
Midazolam and propofol for postoperative sedation and early extubation following cardiac surgery.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Patients undergoing cardiac surgery. The inclusion criteria were all adult ASA physical status II-III patients aged 18-70 years undergoing elective first time coronary artery bypass graft surgery (CABG), single-valve replacement, or correction of arterial septal defect.

Setting
Institution. The study was carried out in Montreal, Canada.

Dates to which data relate
There was no mention of the dates during which data were collected, and no prices were specified.

Source of effectiveness data
The evaluation of the sedation profile of midazolam and propofol for early extubation following cardiac surgery was derived from a single randomised study.

Link between effectiveness and cost data
Costing was undertaken on the same patient sample as that used in the effectiveness study.

Study sample
Following Institutional Review and Bioethics Committee approval, written informed consent was obtained from 47 patients (20 in the midazolam group and 21 in the propofol group) undergoing cardiac surgery. 6 patients were excluded: 3 because of excessive postoperative bleeding, 2 because of hemodynamic instability, and 1 operation was Cancelled preoperatively by the surgeon. Power calculations were carried out to achieve a power of 80% with a value of alpha=0.05.

Study design
The study was a randomised double-blind study. Patients were randomised in blocks of four if they successfully weaned from cardiopulmonary bypass (CPB) with cardiac index > 2.0 L.min⁻¹.m⁻². To maintain a double-blind protocol, each patient received 2 infusions simultaneously at an identical rate determined by the pharmacist who prepared the study medications. Patients in the propofol group received an infusion of propofol plus an infusion of normal saline (placebo) whereas patients randomised to the midazolam group received an infusion of midazolam plus an infusion of intralipid solution (placebo). All drugs or placebo were prepared in identical bags. Appropriate dilution of propofol and midazolam was made to obtain comparable infusion rates. The follow-up period was 16 hours after cessation.

**Analysis of effectiveness**
The analysis of the study was based on treatment completers only. The primary health outcomes used in the analysis were the efficacy of postoperative sedation and early extubation as indicated by duration of operation and of CPB, discharge time, level of sedation, preoperative morphine dose and blood loss. The groups were shown to be comparable in terms of age, sex, weight, height, and type and duration of operation.

**Effectiveness results**
The duration of operation (minutes) and duration of CPB (minutes) for the midazolam group were 191.2 (+/- 34.0) and 72.2 (+/-24.6) respectively, and for the propofol group, were 184.0 (+/- 32.5) and 63.5 (+/- 16.8), respectively.

ICU and hospital discharge time (days) for the midazolam group were 3.9 (+/- 1.7) and 7.8 (+/- 2.7) respectively and for the propofol group, were 3.7 (+/- 1.7) and 7.2 (+/- 1.7) respectively.

The average infusion rate of midazolam was 0.25 (+/- 0.02 micrograms.kg⁻¹.min⁻¹), range: 0.23 - 0.48 while that of propofol was 10.6 (+/- 2.9micrograms.kg⁻¹.min⁻¹), range: 7.1 - 32.4. In the midazolam group, 65.4% of the sedation time was spent at the desired level against 67% in the propofol group (not significant). The average total dose of morphine during the first 4 hours after surgery was 4.9 (+/- 3.9mg) for midazolam and 3.9 (+/-2.5mg) for propofol (not significant). In the midazolam group, 40% of the patients received nitroprusside and 70% received nitroglycerine against 33% and 67% in the propofol group (not significant). Blood loss (ml) for the first 3 hours was 367.6 (+/- 225.1) for midazolam and 345.8 (+/- 243.8) for propofol and total blood loss was 885.0 (+/- 652.2) and 890.3 (+/- 656.1) respectively.

**Clinical conclusions**
No differences were found between the two groups for the time spent at each level of sedation, number of infusion rate adjustments, amount of analgesic and vasoactive drugs, times to awakening and extubation. No patient required tracheal reintubation.

**Measure of benefits used in the economic analysis**
The primary health outcomes used in the analysis were decreased mortality and morbidity. The indicators used were duration of operation and of CPB, discharge time, level of sedation, preoperative morphine dose and blood loss.

**Direct costs**
Infusion costs were calculated as the product of the mean total study drug multiplied by acquisition cost, and the range of infusion costs was calculated as the product of the range of total study drug administration multiplied by acquisition cost.

**Statistical analysis of costs**
Statistical analysis was performed using t-test for normally distributed numerical data. Chi-square and Fisher's exact test were used for nominal data. A P<0.01 was applied to costs. Mean and standard deviations were also used in the analysis.
Sensitivity analysis
Sensitivity analysis was carried out.

Estimated benefits used in the economic analysis
The level of sedation was easily controlled in both groups. There was no difference in the time to weaning and tracheal extubation following termination of sedation (midazolam 91.5 (+/- 59 mins.) versus propofol 87.5 (+/- 65 mins.), (P=NS)). During the infusion and the subsequent 16 hours after cessation, there were no differences in hemodynamic variables. Patients emerged from anaesthesia within a mean of 1.5 hours after completion of surgery and were easily maintained at the required sedation level with either drug.

Cost results
The mean infusion cost of propofol was higher (Can$9.37 per 200mg) than the cost of midazolam (Can$6.12 per 10mg vial). The acquisition cost (Can$ mg(-1)) for midazolam was 0.612 and for propofol was 0.048. The mean infusion cost (Can$) for the respective groups were 2.82 (+/- 0.61, range: 1.76 - 3.67) and 8.49 (+/- 2.03, range: 4.80 - 14.40).

Synthesis of costs and benefits
Costs and benefits were not combined. At the current rate for CABG in Canada of Can$20,000 the use of propofol would have added 0.03% to the overall cost. However, this difference will not impact on the hospital budget.

Authors' conclusions
Midazolam and propofol are safe and effective sedative agents permitting early extubation in the selected cardiac patient population but propofol costs were higher.

CRD COMMENTARY - Selection of comparators
The reason for the choice of comparator was clear.

Validity of estimate of measure of benefit
The indicators used to measure the primary health outcomes in the analysis would appear to be valid. The generalisability of the results would appear to be valid for low risk patients undergoing uncomplicated cardiac surgery.

Validity of estimate of costs
Although the method for calculating the infusion cost and the range of infusion costs were specified, the cost methodology was not substantial. No prices were specified. The authors could have done a more detailed cost analysis in comparing the two groups.

Other issues
Overall the study seemed sound. Power calculations showed that the sample size was adequate to detect the required difference at p=0.05. The authors did seem to achieve their objective of evaluating the sedation profile of midazolam and propofol for early extubation following cardiac surgery. Also, the issue of generalisability was addressed and good comparisons with other studies were made.

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