The effects of preanesthetic oral clonidine on total requirement of propofol for general anesthesia

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 preanaesthetic oral clonidine or diazepam, administered to patients prior to propofol, to induce anaesthesia in minor breast conserving surgery.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised female breast cancer patients of ASA physical status I or II, who were aged between 36 and 64 years and were undergoing minor breast conserving surgery. Patients were excluded from the analysis if they had hypertension, diabetes, organic heart disease, electrocardiograph abnormalities, renal or hepatic function disorders, or gastrointestinal disturbances.

Setting
The setting was secondary care. The economic analysis was conducted in Osaka, Japan.

Dates to which data relate
The dates during which the effectiveness and resource use data were collected do not appear to have been reported. The price year was not stated.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The cost data appear to have been collected prospectively using the same patient sample as in the effectiveness analysis.

Study sample
Power calculations do not appear to have been used to determine the sample size. The method used to select the sample was not specified. Breast conserving surgery patients were chosen as an example of a minor surgical procedure, which was appropriate for the study question. Eighty patients participated in the study, 20 in each of the four groups (75 microg clonidine, 150 microg clonidine, placebo, and 10 mg oral diazepam).
Study design
This was a randomised controlled trial carried out in a single centre. The patients were randomly assigned to one of the four groups using a computer-generated random numbers table. The duration of follow-up was until the end of the time spent in the postoperative recovery room. There was no loss to follow-up. The patients and anaesthesiologists were both blinded to grouping in the study.

Analysis of effectiveness
The analysis of effectiveness was conducted on an intention to treat basis. The primary clinical outcomes used in the analysis were the preoperative anxiety and sedation rates in patients, and the incidence of side effects such as bradycardia and hypotension. The anxiety and sedation levels were measured using a visual analogue scale with scores ranging from 0 (best) to 100 (worst). Both groups were shown to be similar at baseline analysis in terms of their clinical and demographic characteristics.

Effectiveness results
No incidence of bradycardia or hypotension was observed in either the clonidine or diazepam groups. Patients receiving either 150 microg clonidine, (p<0.001), or 10 mg diazepam, (p<0.05), had significantly lower rates of preoperative anxiety compared with the placebo group. The exact figures were not reported as the results were presented graphically. No significant differences in the preoperative sedation scores were observed.

Clinical conclusions
Low dosages of clonidine and diazepam are safe preanaesthetic medications, which can induce anxiolysis in patients, but do not appear to have any sedative actions.

Measure of benefits used in the economic analysis
Since the effectiveness analysis showed no difference in effectiveness between the four groups, the economic analysis was based on the difference in costs only (cost-minimisation analysis).

Direct costs
The quantities of resources used and the costs were reported separately. Only the direct costs associated with preanaesthetic medication and the use of propofol were included in the analysis. The costs were not discounted, which was appropriate given the very short duration of the study. The dates during which the resource data were collected, and the price years used, do not appear to have been provided. The unit costs for propofol appear to have been taken from a published US study (see Other Publications of Related Interest). The source of the cost data for the pre-anaesthetic medications does not appear to have been reported. The average cost data were reported in the economic analysis, but no price year was given.

Indirect Costs
The indirect costs were not included.

Currency
US dollars ($). The exchange rate was $1 = 140 Japanese yen. No dates for the currency conversion were provided.

Sensitivity analysis
No sensitivity analysis was conducted.

Estimated benefits used in the economic analysis
Not applicable due to the cost-minimisation approach adopted.

**Cost results**
The average total requirement for propofol was:

- for the 75 microg clonidine group, 719 (+/- 64) mg/kg (SEM 12.8 +/- 4.1);
- for the 150 microg clonidine group, 491 (+/- 39) mg/kg (SEM 9.0 +/- 2.3);
- for placebo, 841 (+/- 70) mg/kg (SEM 15.1 +/- 3.1); and
- for oral diazepam, 717 (+/- 499) mg/kg (SEM 13.5 +/- 4.0).

The level of propofol used in the 150 microg clonidine group was significantly lower than that in the placebo group, (p<0.01).

The mean costs (+/- standard deviation) of premedicants and propofol for the patients were:

- $45.5 (+/- 14.3) in the 75 microg clonidine group,
- $33.5 (+/- 10.4) in the 150 microg clonidine group,
- $55.0 (+/- 16.8) in the placebo group, and
- $50.5 (+/- 19.6) in the oral diazepam group.

The costs for the 150 microg clonidine group were significantly lower than those for the placebo group, (p<0.01). Adverse events were not reported, and were thus not included in the economic analysis.

**Synthesis of costs and benefits**
Not applicable

**Authors’ conclusions**
Clonidine was shown to reduce the level of propofol required, and therefore, it also reduced the costs of anaesthesia without leading to adverse events. Diazepam, on the other hand, did not lead to a reduction in the use of propofol. In addition, it was noted that much higher rates of diazepam would be required, which would not be appropriate for minor surgical procedures and may delay postoperative recovery. The results suggest that the use of clonidine as a premedicant is appropriate when using propofol.

**CRD COMMENTARY - Selection of comparators**
The authors justified their choice of the comparator, oral diazepam, on the grounds that it has been shown to interact with propofol. However, it was noted that another study had shown that the administration of benzodiazepine had little effect on the requirements for propofol, which might suggest that this may not have been an ideal comparator for use in the analysis. However, a comparison with placebo was also provided, allowing the natural performance of the premedicants to be assessed. You should consider whether either of these comparators is appropriate in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness estimates used in the clinical analysis are likely to be valid, because they were obtained from a randomised controlled trial. The patients in all four groups were shown to be comparable at baseline analysis, and the study sample appears to have been representative of the study population. However, given that the analysis focused on
women, it would have been interesting to have seen if the impact of premedicants on patient anxiety may have been influenced by gender, by selecting a patient sample that included men. The study sample used in the analysis was not determined using power calculations. Thus, the sample size may have been insufficient to detect significant differences in groups other than the 150 microg clonidine group.

**Validity of estimate of measure of benefit**
As the clinical analysis demonstrated that there was no difference in clinical outcomes, other than in the intermediate outcome (preoperative patient anxiety rates), the economic analysis was based on the difference in the costs only. Future evaluations may wish to assess the value to the patients of reduced anxiety associated with such preoperative medicants.

**Validity of estimate of costs**
Very little cost data were provided in this study, although it should be borne in mind that the paper has not been written primarily as an economic evaluation. Only the costs of preoperative medicants and propofol were included in the analysis. The analysis does not appear to have included other key direct costs, such as the staff time involved in administering medication and anaesthesia, and postoperative recovery. Further, it is unclear whether other medications used, such as fentanyl and vecuronium, were included, although no significant difference in the use of fentanyl was reported. The analysis could also have included the wider costs to others in society, including patients, arising from recovery times. The dates during which the resource data were collected were not provided, although the costs and the resources used were reported separately. In addition, the price years do not appear to have been reported, nor the source of the unit cost data for premedicants.

**Other issues**
The authors did not consider the issue of the generalisability of the study’s findings. They did, however, refer to other studies in the literature which have focused on the performance of propofol and premedicants. The authors do not appear to have reported any limitations in their study.

**Implications of the study**
The authors indicate that by using clonidine as a premedicant, the costs of anaesthesia using propofol will be reduced.

**Source of funding**
None stated.

**Bibliographic details**

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**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM
MeSH
Administration, Oral; Adult; Anesthesia, General; Anesthetics, Inhalation /administration & dosage; Anesthetics, Intravenous /administration & dosage /economics; Anti-Anxiety Agents /administration & dosage /therapeutic use; Anxiety /prevention & control; Breast Neoplasms /surgery; Clonidine /administration & dosage /therapeutic use; Diazepam /administration & dosage /therapeutic use; Double-Blind Method; Drug Costs; Female; Fentanyl /administration & dosage; Hemodynamics /drug effects; Humans; Infusions, Intravenous; Intubation, Intratracheal; Lymph Node Excision; Mastectomy, Segmental; Middle Aged; Nitrous Oxide /administration & dosage; Oxygen /administration & dosage; Placebos; Preanesthetic Medication; Propofol /administration & dosage /economics

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