Continuous infusions of lorazepam, midazolam, and propofol for sedation of the critically ill surgery trauma patient: a prospective, randomized comparison

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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
The study compared continuous infusions of lorazepam, midazolam and propofol for the sedation of mechanically-ventilated, critically ill trauma or surgery patients.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The patient population comprised mechanically-ventilated surgery and trauma patients who required sedation. Their age ranged from 18 to 70 years. Patients were excluded if they:

- required neuromuscular blockade;
- had a known history of alcohol abuse;
- were allergic to the drugs under investigation, or to eggs, glycerol or soybeans;
- had a closed-head injury of more than grade 2;
- had renal failure requiring dialysis;
- were in a stupor or coma due to metabolic causes; or
- had pancreatitis.

Setting
The setting was secondary care. The study was conducted in South Carolina, USA.

Dates to which data relate
The dates during which the clinical and resource use data were gathered were not reported. The price year was not reported.

Source of effectiveness data
The effectiveness data were derived from a single study.
Link between effectiveness and cost data
The costing was carried out prospectively on the same sample as that used for the effectiveness study.

Study sample
No power calculations were reported. In addition, there was no explicit statement from the authors to indicate that the initial study sample was appropriate for the clinical question. Thirty-one patients, including 24 trauma patients, were recruited. The final sample (n=30) contained 10 patients in each of the lorazepam, midazolam and propofol groups. One patient was excluded because of a protocol violation.

Study design
The study was a randomised controlled trial performed in a single centre. The patients were randomly assigned to one of the three groups by a randomised block design, although no further details about the methods of recruitment or randomisation were reported. The study was an open-label trial and there was no blinding of assessment of outcome. The principal investigators made an assessment of the level of sedation.

The patients were followed-up until they no longer required sedation or for a maximum of 10 days. Some patients did not complete the study. Five patients failed to respond to the sedative agent to which they were assigned, and were switched to another agent. Of these, 3 did not respond to propofol adequately and 2 on midazolam became totally unresponsive and were removed from the study. In addition, 2 required paralysis (1 for lorazepam and 1 for midazolam).

Analysis of effectiveness
It was not stated whether the results were analysed in terms of intention to treat or treatment completers only. The level of sedation was assessed on a scale of 1 to 6 using the modified Ramsay Sedation Scale (see Other Publications of Related Interest). This was evaluated every 5 to 10 minutes by the two principal investigators. If the Ramsay score was less than 2, an additional sedative bolus was administered until the score was between 2 and 5. Once adequate sedation was achieved, further assessments were made every 6 hours for the first 48 hours and then every 8 hours for the duration of the study.

The primary outcome was the number of patients with adequate, under- or over-sedation. The time to sedation, the number of sedation failures, and the number of infusion bags in which drug precipitation occurred, were also recorded. There were no statistically-significant differences in the age or body weight of the patients. The groups of patients were similar in terms of the Acute Physiologic Assessment and Chronic Health Evaluation (APACHE II), the Injury Severity Score (ISS) and the length of time that the patients required sedation. The authors noted that those patients randomised to midazolam tended to be older, whilst those allocated to lorazepam had higher scores on the severity of illness measures (APACHE II and ISS).

Effectiveness results
The patients receiving midazolam were more often adequately sedated. These patients were adequately sedated for 79% of the time, compared with 68% for lorazepam-treated patients, (p<0.03) and 62% for propofol-treated patients, (p<0.01).

The patients receiving lorazepam were more frequently over-sedated These patients were over-sedated for 14% of the time, compared with 6% for midazolam-treated patients, (p<0.03) and 7% for propofol-treated patients, (p<0.02).

The patients receiving propofol were more often under-sedated. These patients were under-sedated for 31% of the time, compared with 18% for lorazepam-treated patients, (p<0.05) and 16% for midazolam-treated patients, (p<0.01).

There was no difference in the time to sedation for lorazepam (1.02 hours, standard deviation, SD=1.18), midazolam (1.09 hours SD=1.71), and propofol (0.61 hours, SD=0.51), (p<0.05). There was also no difference in the number of sedation failures for lorazepam (1), midazolam (1) and propofol (3), (p<0.09).
Drug losses due to precipitation in the infusion bags was highest for lorazepam (18% per bag or bottle dispensed), than for midazolam (0%) and propofol (0%), (p<0.02).

One patient receiving propofol developed a rash.

Transient hypotension, in response to fluid administration, occurred in one patient receiving midazolam and two patients receiving propofol.

Clinical conclusions
The authors concluded that there was no statistically-significant difference in efficacy between the three agents. However, this was in contradiction to the results, which showed that midazolam was statistically significantly the most titratable.

Measure of benefits used in the economic analysis
The authors concluded that, despite statistically-significant differences in some of the outcomes of interest, the three agents were equal in terms of efficacy. A cost-minimisation analysis was therefore carried out.

Direct costs
The perspective of the study was not stated, but appears to have been that of a hospital.

The direct cost of sedation was calculated as follows:

(drug acquisition cost multiplied by drug use per day) plus (cost of tubing multiplied by the number of infusion sets per day) plus (the number of minibags or glass bottles per day multiplied by their cost).

The separate quantities were only given for the duration of sedation. No unit costs were given. The costs were not discounted because they were incurred over a short time period. The mean initial and maintenance dose of each sedative agent was obtained from the patients' records and was reported. The source of the unit cost data was unclear. The dates during which the data were collected, and the price year, were not reported.

Statistical analysis of costs
The total costs were treated in a deterministic manner. The authors reported mean values for the sedation cost per patient day. These were compared using an analysis of variance with Bonferroni post hoc analysis.

Indirect Costs
The indirect costs were not calculated.

Currency
US dollars ($). The exchange rate was not reported.

Sensitivity analysis
No sensitivity analysis was carried out.

Estimated benefits used in the economic analysis
See 'Effectiveness Results' section.
**Cost results**
The cost of sedation per patient day was significantly greater for midazolam ($182, SD=98) and for propofol ($273, SD=200), than for lorazepam ($48, SD=76), (p<0.005).

The total cost per drug was $1,280 for lorazepam, $3,882 for midazolam, and $12,687 for propofol.

Eighteen per cent of the total cost for lorazepam was incurred due to precipitation of the drug in the infusion bag or bottle.

The authors calculated that the hospital would have saved a total of $14,280 or $8,808 if all the patients had received lorazepam or midazolam.

No currency conversions were reported.

**Synthesis of costs and benefits**
No synthesis of costs and effects was conducted.

**Authors' conclusions**
The authors' concluded that there was no statistically-significant difference in efficacy between lorazepam, midazolam and propofol. Lorazepam was the cheapest, and therefore preferred, option for the sedation of mechanically-ventilated trauma or surgical patients.

**CRD Commentary**
Selection of comparator:
This paper described the impact of three approaches to sedating a mechanically-ventilated patient in intensive care. The authors chose to compare the two benzodiazepines, lorazepam and midazolam, with propofol. It was unclear as to whether these three management strategies reflected current clinical practice.

Validity of estimate of effectiveness:
The selection of the Modified Ramsay Sedation Score seems to have been an appropriate way to assess the efficacy of the three alternative approaches. However, the assessments were made in a non-blinded manner by the study's investigators. This could have biased the results. A further limitation was that the study did not include a power calculation. The authors' conclusion that there was 'no statistical' difference in clinical efficacy could, therefore, have been due to a lack of power, as a result of the small sample size, rather than actual statistical equivalence. Further, it is questionable whether the results actually showed statistical equivalence given the size of the p-values reported. There were also trends towards differences between the groups at baseline, which could have influenced the results. It was unclear whether there was sufficient power to determine whether these differences were statistically significant.

The authors did not estimate an overall measure of benefit because they assumed that all three approaches were equivalent in terms of clinical outcome. However, more patients in the lorazepam group were over-sedated than in the other two approaches, and there were problems with the chemical stability of the drug infusion. If the authors' conclusions thatlorazepam, midazolam and propofol are statistically equivalent are accepted, it is questionable, given the study's findings, whether these three agents are actually clinically equivalent in terms of their impact on patient health gain. This question could have been addressed by careful selection of an appropriate measure of patient benefit.

Validity of estimate of benefit:
There was no summary measure of benefit. See comments in the 'Validity of estimate of effectiveness' section.

Validity of estimate of cost:
The cost of sedating patients with lorazepam, midazolam or propofol, apparently included the cost of drug wastage due to poor stability. The authors seems to have included only drug acquisition and given set costs. The cost of lorazepam losses, on account of precipitation, may have been higher had the additional costs of preparation and personnel time been included. More seriously, the study did not give a complete breakdown of the quantities and unit costs used to calculate the total cost, thus making it impossible to generalise to other settings.

Other issues:

The authors discussed their results in the context of other research. However, they did not present a complete set of cost results, and their conclusions did not match the results in terms of efficacy. Also, they did not discuss generalisability or carry out a sensitivity analysis.

Implications of the study
The authors suggested that it was difficult to select the most appropriate sedative on account of their different pharmacokinetic and pharmacodynamic characteristics. However, they highlighted that it was a choice made daily by the critical care team. The authors concluded that lorazepam was the preferred agent since it was equivalent to midazolam and propofol in term of efficacy, but was less expensive. You should consider the authors' recommendation in view of the data presented, and the internal validity of the study.

Source of funding
Supported in part by the Department of Pharmacy, Medical University of South Carolina, USA.

Bibliographic details

PubMedID
10579264

Other publications of related interest

Comment In: Critical Care Medicine 1999;27:2584.

Indexing Status
Subject indexing assigned by NLM

MeSH
Adolescent; Adult; Aged; Conscious Sedation /economics /methods; Costs and Cost Analysis; Critical Illness; Drug Costs; Female; Follow-Up Studies; Humans; Hypnotics and Sedatives /administration & dosage /adverse effects /economics; Infusions, Intravenous; Intensive Care Units; Lorazepam /administration & dosage /adverse effects /economics; Male; Midazolam /administration & dosage /adverse effects /economics; Middle Aged; Propofol /administration & dosage /adverse effects /economics; Prospective Studies; Respiration, Artificial; Safety; Treatment Outcome; Wounds and Injuries /surgery

AccessionNumber
21999002168

Date bibliographic record published
31/03/2002

**Date abstract record published**

31/03/2002