Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial

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.

CRD summary
The study assessed the costs and benefits of dexmedetomidine for sedation of adult medical and surgical intensive care unit patients who required mechanical ventilation for more than 24 hours. The authors concluded that compared with lorazepam, dexmedetomidine reduced duration of delirium and coma and increased time at the targeted level of sedation at no added cost. Reporting and methodology were satisfactory. The authors' conclusions appear appropriate but readers should take into account the limited generalisability and lack of uncertainty assessment.

Type of economic evaluation
Cost-effectiveness analysis

Study objective
To assess the costs and benefits associated with dexmedetomidine for the sedation of adult medical and surgical intensive care unit (ICU) patients requiring mechanical ventilation for more than 24 hours.

Interventions
The intervention was dexmedetomidine (0.15μg/kg/mL). The comparator was lorazepam (1mg/mL). Each drug was titrated by the bedside nurse to a maximum of 10mL/hour (1.5μg/kg per hour for dexmedetomidine or 10mg/hour for lorazepam) to achieve the sedation goal set by the patient's medical team using the Richmond Agitation Sedation Scale (RASS). The administered drug was infused as needed until extubation or 120 hours was reached. Beyond 120 hours patients were treated with lorazepam or midazolam according to each intensive care unit's usual protocol.

Location/setting
USA/in-patient

Methods
Analytical approach:
An economic evaluation based on a single trial. The study had a 12 month time horizon. The authors did not state the perspective but appeared adopt a health service perspective.

Effectiveness data:
Effectiveness data were based on a double-blind randomised controlled trial of 106 adult mechanically ventilated medical and surgical intensive care unit patients conducted between August 2004 and April 2006 at two tertiary care centres in USA (Vanderbilt University Medical Center and Washington Hospital Center). Participants were randomised to be sedated with either dexmedetomidine (52 patients) or lorazepam (51 patients) for up to 120 hours. Patients were followed for up to 12 months. Data were analysed using an intention-to-treat approach.

The primary measures of effectiveness were number of delirium-free or coma-free days and the percentage of days spent within the target level of sedation. Both measures were obtained directly for observational data from the trial. Delirium was measured using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Patients were monitored twice daily for delirium for 12 days or until hospital discharge. Patients were categorised as having delirium if they had a RSS score of -3 or greater and a positive CAM-ICU. Coma was defined as a RASS score of -4 or -5. Sedation level was measured using the RASS: a patient was defined as achieving the target level of sedation if they were within one RASS point of the sedation goal. Target sedation levels were defined both by the nurse and physician.
Monetary benefit and utility valuations:
Not applicable.

Measure of benefit:
The primary measures of benefit were increase in number of delirium-free or coma-free days and increase in percentage of days spent within the target level of sedation.

Cost data:
Direct costs were included in the analysis. These included the cost of hospital care (pharmacy, respiratory care, intensive care unit and hospital costs) and drug costs. Costs were obtained directly from Vanderbilt University Medical Center for the 90 patients who enrolled there (costs were unavailable for Washington Hospital Center patients). Hospital costs were based on the procedural-based cost accounting methodology used in the hospital department. Drug costs were calculated using the actual number of vials used for each patient multiplied by the actual cost to purchase and administer that drug to the patient. Costs were reported in 2006 US Dollars ($).

Analysis of uncertainty:
No analysis of uncertainty was conducted.

Results
From study days one to 12, patients treated with dexmedetomidine experienced a median of seven days with and interquartile range (IQR) of one to 10 delirium-free and coma-free days compared with three days (IQR one to six) for lorazepam patients (p=0.01). Eighty-seven per cent of patients treated with dexmedetomidine experienced delirium or coma at some point in the 12-day assessment period compared with 98% in the lorazepam group (p=0.03).

Patients treated with dexmedetomidine were at or within one RASS point of the nurse's stated sedation goal for a median of 80% (IQR 58% to 100%) of the time while on study drugs compared to 67% (IQR 48% to 83%) for those treated with Lorazepam (p=0.04). For the physician's goal, the associated results were 67% (IQR 50% to 85%) for dexmedetomidine patients and 55% (IQR 8% to 67%) for lorazepam patients (p=0.008).

The 28-day mortality in the dexmedetomidine group was 17% versus 27% in the lorazepam group (p=0.18). The 12-month time to death was 363 in the dexmedetomidine group versus 188 days in the lorazepam group (p=0.48).

Median drug costs were $4,675 in the dexmedetomidine group and $2,335 in the lorazepam group. In the dexmedetomidine group, median costs were $27,460 (IQR $15,710 to $46,430) for pharmacy, $3,530 (IQR $2,170 to $6,940) for respiratory care, $61,400 (IQR $37,300 to $108,200) for intensive care unit costs and $101,400 for hospital costs. In the Lorazepam group, median costs were $20,660 (IQR $9,840 to $42,270) for pharmacy, $2,920 (IQR $2,070 to $5,830) for respiratory care, $59,500 (IQR $35,900 to $83,000) for intensive care unit costs and $78,900 (IQR $44,000 to $124,600) for hospital costs. All p values were non-significant for the care costs.

Authors’ conclusions
The authors concluded that compared with lorazepam, dexmedetomidine reduced the duration of delirium and coma and increased time at the targeted level of sedation at no added cost of care.

CRD commentary
Interventions:
The interventions appeared appropriate and were described adequately. The choice of comparator was justified, Lorazepam was recommended by the Society of Critical Care Medicine’s clinical practice guidelines for sustained sedation of mechanically ventilated intensive care unit patients and appeared to be current practice. The authors indicated that there may be other available benzodiazepine and novel medications.

Effectiveness/benefits:
The effectiveness estimates were reported clearly. The methodology used to measure outcomes was reported clearly and appropriate. An appropriate method of randomisation was used in the trial so the risk of bias was minimised. Trial
methodology and participant characteristics were reported clearly. Given that the effectiveness outcomes were derived from a relatively small sample of patients from two tertiary American centres, it was likely that the effectiveness results would generalise only to similar centres treating patients with comparable demographics.

Benefit measures were appropriate for this study and were described appropriately but were specific to the study setting and population. A more generic measure such as quality-adjusted life-years (days) may have increased the generalisability of the study.

Costs:
The study perspective was not stated clearly; it appeared that the appropriate cost categories were included for a health care perspective. Costs were reported clearly but the specific items included in care costs were not reported. In particular it was unclear what costs were included in hospital costs. The methods used to derive costs appeared appropriate. Costs were derived directly from a single USA tertiary medical centre so it was likely that the cost results would generalise only to other USA tertiary centres with a similar demographic. The costs appeared to be adjusted appropriately for inflation and appropriately were not discounted due to the short time horizon.

Analysis and results:
Effectiveness and cost outcomes were presented only in a disaggregated format: there was no form of incremental analysis to assess the cost-effectiveness of dexmedetomidine so it was difficult to interpret the results and reach a conclusion about cost-effectiveness. There was no assessment of uncertainty and this precluded conclusions about the robustness of the results; this was a key limitation of the study.

The authors stated that they believed the trial patients to be representative of demographics expected at most busy intensive care units but noted that these data may not apply to trauma, neurological and burn intensive care units. The authors stated that the results were not applicable to sedatives other than lorazepam (such as propofol). Due to the small trial size and specificity of outcomes to the given setting it was likely that the results would generalise only to other American tertiary centres with similar demographics.

Concluding remarks:
Overall the level of reporting and methodology was satisfactory and the authors' conclusions appear appropriate but readers should take into account the limitations of the study.

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