

Alpha-2 agonists for sedation of mechanically ventilated adults in intensive care units: a systematic review

Moira Cruickshank,¹ Lorna Henderson,¹
Graeme MacLennan,¹ Cynthia Fraser,¹
Marion Campbell,¹ Bronagh Blackwood,²
Anthony Gordon³ and Miriam Brazzelli^{1*}

¹Health Services Research Unit, University of Aberdeen, Aberdeen, UK

²Centre for Infection and Immunity, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, UK

³Faculty of Medicine, Department of Surgery and Cancer, Charing Cross Hospital, Imperial College London, London, UK

*Corresponding author

Declared competing interests of authors: Moira Cruickshank, Lorna Henderson, Graeme MacLennan, Cynthia Fraser, Marion Campbell and Miriam Brazzelli's institution received funding from the UK Department of Health to undertake this work. Anthony Gordon has received research support and speaker fees from Orion Pharmaceuticals [a manufacturer of dexmedetomidine (Dexdor[®], Orion Corporation)] outside the submitted work. He also declares research support and/or personal/speaker fees from Tenax Therapeutics Inc., from HCA International and from Ferring Pharmaceuticals Inc., and former membership of the Baxter Healthcare Advisory Board (1-day meeting, 10 September 2012) in relation to previous research projects. Marion Campbell declares former membership of the National Institute for Health Research Health Services and Delivery Research Researcher-led Board (2009–15).

Published March 2016

DOI: 10.3310/hta20250

Scientific summary

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Health Technology Assessment 2016; Vol. 20: No. 25

DOI: 10.3310/hta20250

NIHR Journals Library www.journalslibrary.nihr.ac.uk

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Background

Sedation is a key component of the care of critically ill patients who may need invasive or uncomfortable procedures, such as mechanical ventilation (MV). In the intensive care unit (ICU), indications for sedation include pain control, to allow use of distressing procedures and minimise patient discomfort, to provide protection from stressful and harmful stimuli, reduction and control of agitation, and to enable nocturnal sleep and induce amnesia.

Evidence from randomised controlled trials (RCTs) and current clinical guidelines support the use of minimum possible sedation levels to achieve the desired effects, while preserving patient comfort and safety. Indeed, the recent trend has been towards lighter levels of sedation, with only a minority of patients requiring continuous deep sedation. Optimal sedation level varies widely between patients, depending on their clinical condition and treatment requirements. Prevalence of anxiety and agitation in critically ill patients undergoing MV has been reported to be > 70%. Therefore, assessment and monitoring of sedation level should be routinely performed in ICUs. Usually, sedation level is measured by means of scoring sedation scales. The most commonly used scales are the Richmond Agitation–Sedation Scale and the Ramsay Sedation Scale.

Often, sedation requirements are not optimally managed, and oversedation or undersedation may occur with important deleterious effects, such as cardiorespiratory depression, prolonged MV, hypertension and tachycardia. The recent *Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit* [pain, agitation and delirium (PAD) guidelines] recommend routine monitoring of the depth of sedation to address suboptimal sedation levels, use of sedation protocols and light target sedation levels using either daily sedation interruptions or titration of sedatives.

These guidelines also stress the importance of routine assessment of pain with provision of adequate analgesia to all critically ill patients and routine monitoring of delirium. Pain is the main stressor reported by patients and the most common memory patients have of their ICU stay. Delirium may occur in up to 80% of mechanically ventilated ICU patients and is associated with higher mortality, longer MV and hospital stay, and increased risk of cognitive impairment.

A variety of sedative agents are available for the management of critically ill patients in ICUs. The choice of sedative or analgesic agents to achieve appropriate levels of sedation and pain relief can be quite challenging and must take account of the pharmacological properties of the different drugs as well as the individual patient's characteristics and needs. In the UK, the most commonly used drugs are propofol (Diprivan®, AstraZeneca), benzodiazepines [midazolam (Hypnovel®, Roche) and lorazepam (Ativan®, Pfizer)] and alpha-2 adrenergic receptor agonists [dexmedetomidine (Dexdor®, Orion Corporation) and clonidine (Catapres®, Boehringer Ingelheim)]. A shift from benzodiazepines to propofol has been recently observed in ICU practice. The PAD guidelines suggest that use of non-benzodiazepines (propofol or dexmedetomidine) may improve clinical outcomes over benzodiazepine-based sedation strategies (midazolam or lorazepam).

The 2014 Intensive Care National Audit and Research Centre national survey conducted among 235 adult general ICUs in the UK showed that propofol was the most widely used sedative agent, with 88% of the units reporting it as their first choice of sedative agent. Although approximately one-third of the surveyed units (32%) reported frequent use of midazolam, only a small proportion (6%) reported that midazolam was their first choice of sedative agent. Less than 1% of the units reported use of lorazepam. Around one-third of ICUs (33%) reported frequent use of clonidine and 10% reported frequent use of dexmedetomidine.

The ideal sedation strategy for critically ill patients in ICUs should address pain, sedation and anxiety; have favourable kinetics and clinical effects; be easily titrated and monitored; have a tolerable side effect profile; and be affordable. None of the commonly used sedative agents fulfils all these criteria or has been shown to be clearly superior to the others.

Objectives

The purpose of this assessment was to review the evidence from existing RCTs on the effects of alpha-2 agonists compared with each other and compared with alternative sedative agents in intensive care practice, with the purpose of informing any future RCT.

The specific objectives of this assessment were (1) to assess the effects of sedation using dexmedetomidine compared with clonidine in mechanically ventilated adults admitted to ICUs; and (2) to assess the effects of sedation using dexmedetomidine or clonidine compared with other most commonly used sedative agents (i.e. propofol and benzodiazepines) in mechanically ventilated adults admitted to ICUs.

Methods

This assessment was conducted according to current methodological standards. Comprehensive literature searches were conducted to identify reports of RCTs assessing the effects of alpha-2 agonists, propofol and benzodiazepines for sedation in ICUs. We searched major electronic databases including MEDLINE without revisions, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Science Citation Index, Bioscience Information Service and the Cochrane Central Register of Controlled Trials, for publications from 1999 onwards. Reports of relevant evidence synthesis were sought from the Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects. The World Health Organization International Clinical Trials Registry Platform, *metaRegister* of Controlled Trials and ClinicalTrials.gov were searched for evidence of ongoing studies. Final searches were carried out between 12 and 15 November 2014. Evidence for clinical effectiveness was considered from fully published RCTs comparing dexmedetomidine with clonidine or dexmedetomidine or clonidine with propofol or benzodiazepines (i.e. midazolam or lorazepam).

The population considered was critically ill adults admitted to ICUs who required MV. Primary outcomes of interest were mortality, duration of MV, ventilator-free days, length of ICU stay, adverse events and unpleasant side effects. Secondary outcomes were duration of weaning, time spent in target sedation range, proportion of patients in target sedation range, extubation readiness, discharge readiness, length of hospital stay, quality of life and costs. Data were extracted by one reviewer and double-checked by a second reviewer. The Cochrane risk-of-bias tool was used to assess the risk of bias of the included RCTs. Random-effects meta-analyses were performed when suitable data were available.

Results

Eighteen trials, with a total of 2489 patients, were included in the clinical effectiveness review. One trial (70 patients) compared dexmedetomidine with clonidine; nine trials (1134 patients) compared dexmedetomidine with propofol; four trials (939 patients) compared dexmedetomidine with midazolam; one trial (118 patients) compared dexmedetomidine with propofol and midazolam (three treatment arms); two trials (122 patients) compared dexmedetomidine with standard care (i.e. propofol and/or midazolam); and one trial (106 participants) compared dexmedetomidine with lorazepam. Overall, four trials were judged to be at low risk of bias, seven were judged to be at high risk of bias and the remaining seven trials did not provide sufficient information on which to base a judgement. Clinical heterogeneity among trials was mainly because of patient population (i.e. patients admitted to ICUs following elective surgery and general ICU patients), comparator interventions, dosage of sedative agents, outcome measures and units of measurements, and timing of follow-up assessments. Follow-up was short term (24 to 72 hours) in most trials.

Both clonidine and dexmedetomidine produced effective sedation. However, target sedation, with less need for additional sedation, was achieved in more patients who received dexmedetomidine than in those who received clonidine. Haemodynamic parameters appeared to be more stable among patients treated with dexmedetomidine.

Compared with propofol or benzodiazepines (midazolam or lorazepam), dexmedetomidine had no significant effects on mortality [risk ratio (RR) 1.03, 95% confidence interval (CI) 0.85 to 1.24, $I^2 = 0\%$; $p = 0.78$]. Length of ICU stay (mean difference -1.26 days, 95% CI -1.96 to -0.55 days, $I^2 = 31\%$; $p = 0.0004$) and time to extubation (mean difference -1.85 days, 95% CI -2.61 to -1.09 days, $I^2 = 0\%$; $p < 0.00001$) were significantly shorter among patients who received dexmedetomidine than among those who received alternative sedative agents. The proportion of time spent in adequate sedation range was not significantly different between sedative interventions (mean difference 2.53, 95% CI -0.82 to 5.87, $I^2 = 0\%$; $p = 0.14$), but dexmedetomidine was associated with a higher risk of bradycardia (RR 1.88, 95% CI 1.28 to 2.77, $I^2 = 46\%$; $p = 0.001$). We did not find any difference between dexmedetomidine and alternative sedative agents with regard to other adverse events such as hypotension, hypertension and tachycardia. There was no clear evidence that dexmedetomidine could reduce the risk of delirium (RR 0.83, 95% CI 0.65 to 1.06, $I^2 = 60\%$; $p = 0.14$), but statistical heterogeneity was observed in the analysis. In general, patients treated with dexmedetomidine were reported to be more easily arousable, more co-operative and better able to communicate than those treated with alternative sedative agents.

Subgroup analyses according to type of comparator were generally consistent with those of the overall population.

Limitations

The majority of the included trials assessed the effects of dexmedetomidine compared with propofol or midazolam. Data on the effects of dexmedetomidine compared with clonidine were limited (one trial).

There was considerable clinical heterogeneity among included trials, and most were at high or unclear risk of bias. Few trials blinded outcome assessors.

There was substantial variation in the choice, definitions and measurements of outcome measures, especially measures of ventilator dependence.

Transformation/imputation of data was required to combine results from included trials, as units of measurements and methods for analysing results varied considerably between trials.

Subgroup analyses were performed according to the type of comparators, but subgroups were usually too small to provide reliable conclusions.

Conclusions

There is an indication that dexmedetomidine may have a better cardiovascular safety profile than clonidine, but evidence is limited. Length of stay in ICUs and time to extubation were significantly shorter among patients who received dexmedetomidine than among those who received other sedative agents other than clonidine. No difference was observed in time in target sedation range between dexmedetomidine and alternative sedative interventions.

Incidence of bradycardia was significantly higher for dexmedetomidine, but did not impact on mortality. There was no clear evidence that dexmedetomidine was superior to other sedative agents in reducing the risk of delirium. Considerable clinical heterogeneity between trials was observed, and the overall risk of bias was high or unclear.

Recommendations for future research

Large, well-designed clinical trials are needed to (1) evaluate the long-term effects of clonidine for sedation in ICUs; and (2) identify subgroups of patients who are more likely to benefit from dexmedetomidine. Main subgroups of interest would be patients who require short-term sedation after elective surgery and general critically ill patients who require long-term sedation.

Ideally, such trials would include relevant clinical outcomes sets, proper outcome definitions, validated instruments to assess level of sedation and incidence of events such as delirium and coma, longer follow-ups and a full economic evaluation. Relevant clinical outcomes from an ICU perspective would comprise MV, length of ICU stay and incidence of delirium, bradycardia and hypotension. Patient-relevant outcomes such as the patients' ability to communicate with health-care personnel and the patients' perspective of quality of sedation would also require consideration in future trials.

Study registration

This study is registered as PROSPERO CRD42014014101.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research. The Health Services Research Unit is core funded by the Chief Scientist Office of the Scottish Government Health and Social Care Directorates.

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.027

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index.

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Editorial contact: nhredit@southampton.ac.uk

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 13/73/01. The contractual start date was in October 2014. The draft report began editorial review in May 2015 and was accepted for publication in November 2015. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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