Dexmedetomidine for end of life sedation: retrospective cohort comparison study

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Received 5 March 2023
Accepted 12 June 2023

To cite: Thomas B, Barclay G, Barbato M. *BMJ Supportive & Palliative Care* Epub ahead of print: [please include Day Month Year]. doi:10.1136/spcare-2023-004252

ABSTRACT

Objectives Infused sedatives are often utilised to alleviate distress at the end of life. Which sedative best achieves this is unknown. This study compares breakthrough medication requirements of patients treated with the novel agent dexmedetomidine compared with patients treated with standard-care sedatives.

Methods A retrospective cross-cohort comparison. Two studies of patients at the end of life under sedation at the same palliative care unit, one utilising novel sedatives, and the other standard care were compared. Breakthrough medication requirements were compared using paired t-tests, including opioids, benzodiazepines and anticholinergics. Changes in background infusions were compared.

Results The dexmedetomidine cohort required less breakthrough interventions per day compared with the standard care group, the reduction was significant (2.2 vs 3.9, p=0.003). There was a significant difference in benzodiazepine requirements, with the dexmedetomidine cohort requiring fewer doses per day than the standard care cohort (1.1 vs 0.6, p=0.03). Anticholinergics were more commonly utilised in the standard care cohort but there was no significant difference (p=0.22). Opioid requirements were similar across cohorts with comparable rates of breakthrough use and infusion increases.

Conclusions This study demonstrates a reduction in breakthrough medication requirements, particularly benzodiazepines, for patients sedated with dexmedetomidine at end of life.

WHAT IS ALREADY KNOWN ON THIS TOPIC?

⇒ Sedation may be required to alleviate distress in patients nearing death, however which sedative is best suited for this purpose is unknown.

WHAT THIS STUDY ADDS?

⇒ Patients sedated with dexmedetomidine required less breakthrough medications at end of life, particularly benzodiazepines.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY?

⇒ The study highlights the potential benefits of dexmedetomidine at the end of life.

INTRODUCTION

Patients near the end of life (EOL) may suffer from multiple distressing symptoms, including pain, nausea, agitation, confusion and distress. When patients are distressed with refractory symptoms, sedation may be prescribed to alleviate their distress.[1] Standard sedatives used in palliative medicine may include continuous infusions of benzodiazepines (midazolam, clonazepam); if refractory, sedatives may be escalated to broad-spectrum antipsychotics (levomepromazine) or barbiturates (phenobarbital). Midazolam is the first-line sedative utilised in Australia.[2] This is in accordance with the EAPC framework for EOL sedation[3] which has been endorsed by the Australian and New Zealand Society of Palliative Medicine.[2]

Other symptoms may be treated with opioids (pain and dyspnoea), anticholinergics (secretory breathing) or neuroleptics (nausea and agitation), with considerable variation.[4 5] The evidence for EOL sedatives is not robust, with usage predicated on consensus and guidelines. Small-scale observational studies and retrospective analysis have been performed, but there is minimal evidence for actual efficacy, especially for midazolam at the EOL. Despite this, midazolam is the preferred agent in Australia[2] and listed in Europe,[2] with dose recommendations given without robust evidence.[6]

Recent studies have focused on alpha-2 receptor agonists like clonidine[7] and dexmedetomidine[8] for EOL symptoms,

with developing interest.[9 10] There are currently no published randomised control trials comparing sedatives at EOL; There is currently a head-to-head study of midazolam and dexmedetomidine that is recruiting.[11]

This paper analyses two EOL patient cohorts from a single palliative care unit (PCU), one group sedated with dexmedetomidine,[8] the other sedated with the treating clinician's choice of medications.[12] Both of these studies were undertaken by authors of this paper at differing times, with two authors involved in each study. There can be significant challenges in completing comparative research in palliative medicine, including recruitment, ethical approval and appropriate selection. The availability of these two similar cohorts in the same setting therefore provides a valuable opportunity to assess whether any difference can be seen in breakthrough medication usage for symptoms, to further direct research and optimise EOL care.

METHOD

Datasets from two studies were extracted; both were conducted in a 15-bed PCU at the Port Kembla Hospital, NSW, Australia. The first study[12] was conducted from 2013 to 2015; the second study[8] from 2018 to 2020. Both involved research into EOL patients and were approved by the University of Wollongong Human Research Ethics Committee.

Study 1 aimed to increase the body of knowledge around bispectral index (BIS) monitoring at the EOL, as well as assessing sedation and comfort in unresponsive palliative care patients through use of family and nursing completed scores and comparison with bispectral data. It also assessed the impact of breakthrough medications on unresponsiveness based on bispectral readings post administration of breakthroughs, in comparison with the RASS (Richmond Agitation Sedation Scale). Study 2 aimed to assess the impact of the dexmedetomidine for the treatment of terminal delirium for EOL patients, utilising the Memorial Delirium Assessment Scale, RASS-PAL and the Nursing Delirium Screening Scale to monitor presence and progression of delirium for patients treated with a continuous subcutaneous infusion of dexmedetomidine. Both studies were small pilot studies, with recruitment limited by lack of resources.

All data analysed were related to treatment received for patients during their terminal phase for patients with a clinically diagnosed terminal delirium—34 patients in study 1, 22 patients in study 2.

Data including background medications, breakthrough doses, symptom burden at EOL were extracted and matched. The patients in study 1 were given sedative medications consistent with standard of care at the PCU as infusions, while the patients in study 2 were given the novel sedative dexmedetomidine as their sedative infusion. Indications for all other medications, including background infusions and breakthrough doses were comparable across both time periods and were in line with standard of-care.[4]

Statistical analysis was performed with both descriptive statistics and t-tests to detect differences, if any, between arms.

RESULTS

Sixty-six patients were included in this analysis, 34 from study 1 and 22 from study 2. All patients included were in their terminal phase. There was variability between studies as to breakthrough requirement, with statistically significantly less daily overall required doses in study 2 compared with study 1, and less requirement for benzodiazepine interventions in study 2. Variability between opioid use for pain, opioid use for dyspnoea and anticholinergic use was seen across both studies, however not to the level of statistical significance. Opioid infusions were present in all patients in both studies, as were sedative infusions with variability of medications in study 1. No patients in study 2 required infused anticholinergics. All patients were prescribed regular opioids and sedatives, as well as breakthrough doses of benzodiazepines and opioids for their full treatment episode. Breakthrough doses were given based on clinical assessment of need made at the time of delivery. For full details and breakdown, please refer to table 1.

DISCUSSION

This study is the first to compare the novel sedative dexmedetomidine with standard palliative care sedatives for patients with terminal delirium. Breakthrough medications are often required when symptoms are not controlled by background treatments, including opioids for pain or dyspnoea, anticholinergics for uncontrolled secretions, or benzodiazepines for agitation or distress.[4 9]

Dexmedetomidine appears to show favourability for agitation when comparing these cohorts by the surrogate marker of breakthrough medications, with significantly less benzodiazepines required. This may reflect mechanistic differences in managing terminal delirium between alpha-2 agonists and benzodiazepines; alpha-2 agonists like dexmedetomidine may reduce delirium while standard medications used in palliative care are aimed at suppressing symptoms of delirium.[8 9]

Patients sedated with dexmedetomidine required fewer daily breakthrough medications than patients given standard sedatives. This is a blunt measurement but may reflect the properties of dexmedetomidine as an analgesic, anxiolytic, sedative, antiemetic and relaxant.[9 10] Dexmedetomidine administration leads to a reduction in release of substance P in the dorsal horn of the spinal cord, promoting analgesia and potentially leading to a reduction in opioid consumption. This is drawn from the anaesthetic and intensive

Table 1 Patient demographics and results

	Study 1	Study 2	
Demographics			
Mean age in years	71 (41–97)	73 (40–93)	
Female/male	15/25	7/15	
Mean length of stay in days	29.8 (3–95)	32.1 (8–76)	
Mean duration of sedative administration (survival) in days	3.6 (1–14)	3.5 (0.7–9.3)	
Results	**Study 1**	**Study 2**	**Significance**
Breakthrough medications			
Average daily breakthrough doses, combined	3.9	**2.2***	P=0.003
Patients requiring benzodiazepine breakthroughs	76% (26/34)	86% (19/22)	
Benzodiazepine doses (per day, mean)	1.1	**0.6***	P=0.03
Patients requiring anticholinergic breakthroughs	59% (20/34)	23% (5/22)	
Anticholinergic doses (per day, mean)	1.33	0.90	P=0.20
Patients requiring opioid breakthroughs, dyspnoea	47%	23%	
Dyspnoea opioid doses (per day, mean)	1.22	0.63	P=0.08
Patients requiring opioid breakthroughs, pain	44%	68%	
Pain opioid doses (per day, mean)	1.02	1.39	P=0.26
Infused medications	**Study 1**	**Study 2**	
Opioid infusion, subcutaneous	100%	100%	
Patients requiring opioid infusion increase	56% (19/34)	63% (14/22)	
Opioid infusion dose change (average)	1.33 (+33%)	1.40 (+40%)	P=0.65
Anticholinergic infusion, subcutaneous	100%	0%	
Sedative infusion, subcutaneous	100%	100%	
Midazolam (M)	100%		
Clonazepam (C)	18%		
Phenobarbital (P)	9%		
Combination MCP	37%		
Dexmedetomidine		100%	

care literature and has yet not been observed in the palliative population[10]; this may be a basis for future research.

Anticholinergics are commonly used at the EOL. There has been some controversy in their use, but recent randomised controlled trials have shown efficacy without worsening side effects in the management of terminal secretions.[13 14] Although not statistically significant, there was less anticholinergic breakthrough requirement in the dexmedetomidine study, and less infusional requirement, which may be due to the action of dexmedetomidine in decreasing salivation via alpha-2 receptor stimulation in the parotid glands. While conclusions about the distress this may alleviate cannot be drawn here, it is known that terminal secretions are a common cause of family and carer anguish and due to the evidence of minimal harms[14] this decrease could be a positive in favour of dexmedetomidine if borne out in larger studies.

Conducting research with terminal patients remains challenging with ethical issues often considered difficult to surmount.[15] Utilising existing data to answer new questions can help overcome this, the complexity around research in this vulnerable populations remains. Better quality evidence such as randomised clinical trials, focusing on similar questions, would provide more robust answers to the question of sedative equivalence, and some of the authors are currently undertaking one such study[11] to help expand this knowledge base.

LIMITATIONS AND STRENGTHS

There are several limitations to this analysis. Although the two studies were conducted at the same PCU with similar standards of care present, the potential for confounding effects due to differing clinicians and study times is present. There was also a difference between datasets, as study 2 specifically included patients with terminal delirium, while study 1 was focused on BIS monitoring. It is difficult to know whether this would have impacted any analysis performed, and points to the limitations of retrospective cohort comparisons. Difference in sample size may also lead to skewed interpretation, with two small cohorts to draw from. Use of surrogate measures may lead to over or underestimation of symptom burden.

Strengths of this study include a relative lack of bias due to retrospective data analysis and the ability to incorporate data from two studies in a challenging population, namely patients at EOL, to better analyse

cares in this vulnerable group, with consistent medical and nursing practice in the same centre minimising clinical differences.

CONCLUSION

Similar levels of comfort, as determined by breakthrough medication requirements, were observed for patients sedated with dexmedetomidine or standard care at the EOL. Dexmedetomidine patients potentially required less breakthrough interventions, which may prove a fertile avenue for ongoing study. Opioid sparing and difference in analgesic requirements, seen with the use of dexmedetomidine in other settings, were not observed.

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Contributors MB was the primary investigator for study 1, BT was the primary investigator for study 2, GB was a coinvestigator for both. MB and BT respectively extracted data from individual sets. BT performed the primary analysis and prepared the manuscript. GB and MB edited the manuscript. All authors had input into the final version.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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