Original Article

Dexmedetomidine Versus Midazolam for End-of-Life Sedation: The DREAMS Non-Blinded Randomized Clinical Trial

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Abstract

Context. End-of-life distress and delirium are common in palliative care inpatients, often requiring sedatives that diminish interaction. Current practices rely on clinical experience rather than evidence.

Objectives. To compare the sedative efficacy of subcutaneous dexmedetomidine versus midazolam in managing end-of-life distress while maintaining responsiveness, and to evaluate comparative effect on delirium in the terminal phase.

Methods. Single center randomized non-blinded clinical trial (ACTRN12621000052831) of palliative care inpatients in an Australian Local Health District admitted for end-of-life care. Patients received dexmedetomidine (0.5 μg/kg/h) or midazolam (0.25 mg/kg/day) via subcutaneous infusion for symptom management during the terminal phase. The primary outcome was responsiveness measured by mean Richmond Agitation Sedation Score-Palliative version (RASS-PAL) compared between treatment arms over the first 72 hours. Secondary outcomes included delirium severity (memorial delirium assessment score [MDAS]) and patient comfort (Patient Comfort Assessment [PCA]).

Results. Fifty two patients were randomized (median age 80 years [IQR 72−88]; 63% male) and included in the primary analysis. Mean RASS-PAL scores showed no significant difference between arms (dexmedetomidine vs. midazolam: day 1: −2.33 vs. −1.90; day 2: −2.44 vs. −2.86; day 3: −2.95 vs. −2.53; all $P > 0.05$). Dexmedetomidine showed superior early delirium severity scores (day 1 MDAS: 6.5 vs. 8.8, $P = 0.05$) which did not persist. Protocol withdrawal occurred earlier in the midazolam arm (5 vs. 0 patients on day 1, $P = 0.025$). Patient comfort scores remained mild (PCA < 3) in both arms.

Conclusion. Dexmedetomidine and midazolam can achieve sedative equivalence with similar RASS-PAL scores. Dexmedetomidine patients experienced lower initial delirium severity scores and fewer early withdrawals in secondary analysis. Current dosing guideline for midazolam may need revising. J Pain Symptom Manage 2025;70:459−469.

Key Words

Randomized controlled trials, delirium, conscious sedation, terminal care, hypnotics and sedatives

Introduction

Distress and delirium in the terminal phase are common in palliative care inpatients.[1,2] The presence of agitation, distress or delirium can be distressing to family members and staff, with symptom management focusing on alleviating apparent distress.[3] Management often requires sedative medications, to the point of decreased responsiveness and diminished ability for

Editorial Comment: David Hui, MD, MSc, FAAHPM. Senior Associate Editor.

This randomized trial highlighted how dexmedetomidine may be an alternate option to midazolam for proportional sedation in the palliative care unit. The findings should be interpreted with caution given the non-blinded nature and other limitations.

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Accepted for publication: 20 July 2025.

0885-3924/$ - see front matter
https://doi.org/10.1016/j.jpainsymman.2025.07.027

meaningful interaction,[4] referred to as palliative sedation. Recommended medications for palliative sedation are drawn from experience and best practice[3,5,6] without a robust evidence base, resulting in clinical uncertainty.

Benzodiazepines are the first-line agents for terminal delirium and end-of-life distress in palliative medicine[5,6] with antipsychotics and barbiturates used in refractory cases. The primary benzodiazepine prescribed in palliative care is midazolam, which has been used for this indication since 1988.[7,8] Suggested doses and their escalation are not based on robust evidence[9] but on case reports and expertise which contrasts to the critical care setting where evidence is more robust.[10,11] Midazolam, like other benzodiazepines, can potentially worsen delirium[12] and can cause paradoxical agitation,[13] which can be more distressing in the dying patient. A trial-validated approach to the use of midazolam and its efficacy at the end of life is not currently available.

Alpha-2 agonists are a novel class of sedatives, particularly injectable agent dexmedetomidine, which is used in critical care. Dexmedetomidine can promote natural sleep and provide a more rousable form of sedation in the critically ill, allowing interactivity and cooperation with staff and families[14] in both ICU and palliative care settings.[15] Dexmedetomidine infusions are associated with a reduction in delirium, potentially related to decreasing central catecholamines in the locus coeruleus,[14] and have analgesic potential.[14,15] A recent cohort study reported the use of dexmedetomidine for the treatment of terminal delirium,[16] showing a favorable response for both resolution of distressing symptoms and enhanced interactivity in a palliative care unit. Positive results for analgesia and anxiety have also been reported.[17] Importantly, these studies were not randomized and were both single arm trials without comparator groups; comparisons have only been done retrospectively.[18]

Midazolam and dexmedetomidine have been compared in randomized controlled trials in intensive care units.[19,20] There is a growing interest in dexmedetomidine in palliative care due to its benefits in providing more proportional sedation and reducing the incidence of observed delirium.[14-16,21,22]

The aim of this randomized controlled trial was to validate and compare the sedative effects of the alpha-2 agonist dexmedetomidine and the benzodiazepine midazolam when given by infusion to palliative care inpatients at the end-of-life, using targeted doses and validated tools.[23] The trial aimed to determine if either agent would result in better rousability while maintaining comfort in the terminal phase, with a hypothesized superiority for dexmedetomidine compared to midazolam for rousability.

Secondary outcomes included evaluation of delirium[24] severity and comfort as measured by families and carers,[25] to determine if either dexmedetomidine or midazolam were superior at alleviating distress from delirium or for family perception of patient comfort at the end-of-life.

Methods

Trial Design

The DREAMS (Dexmedetomidine for the Relief of End-of-life Agitation and for optiMized Sedation) trial was a randomized controlled non-blinded single-center study and was prospectively registered on the Australia New Zealand Clinical Trials Registry (ACTRN12621000052831). This trial was designed to compare the efficacy of dexmedetomidine versus midazolam for the management of end-of-life distress, whilst maximizing potential interactivity using proportional sedation[26]—defined as the use of medications titrated to relieve refractory symptoms without requiring deep sedation - and reducing delirium during the terminal phase. The trial was conducted following CONSORT guidelines for reporting randomized controlled trials. The protocol is presented in Supplement 1 and the statistical analysis plan in Supplement 2. The protocol has been published.[27]

Recruitment to the trial began in May 2021 and was completed in November of 2023. The trial was approved by the joint Illawarra Shoalhaven Local Health District / University of Wollongong Human Ethics Committee (ETH2020/1943). Patients provided pre-emptive written informed consent and were aware that their participation would begin at the beginning of their terminal phase if distress or delirium were present.

Patient Population

English-speaking adults (aged 18 years and above) admitted to hospital under the specialist palliative care team within a regional Australian Local Health District were eligible for inclusion if they were admitted for end-of-life care, had capacity to consent, were accepting of potentially more proportional sedation during their dying phase, and provided pre-emptive written consent.

Patients were excluded if they had known severe cardiac failure defined as known left ventricular ejection fraction of <20% on echocardiograph within the past 12 months and a history of cardiac failure, or if prior consent was not obtained due to factors including pre-existing delirium, rapid deterioration, or inappropriate goals of admission.

Randomization and Sample Size

Patients were randomly assigned in a 1:1 ratio to receive dexmedetomidine Y or midazolam using an

online tool with a block size of 6.[28] During the study, clinicians, nursing staff and patients were unblinded to the treatment arm post-randomization, due to resource limitations.

Previous research assessing dexmedetomidine for agitation and delirium at the end-of-life, which included a 22-patient cohort study, showed a 100% initial response, with a 59% rate of dose escalation.[16] This informed the investigators' approach to determining sample size based on the following considerations. The Richmond Agitation Sedation Score (Palliative version, RASS-PAL)[23] was used to assess responsiveness and agitation in the cohort study.[16] For this study, a RASS-PAL of zero or below was considered acceptable, indicating patients who were calm, drowsy, or sedated, but not agitated. Although the RASS-PAL is an ordinal scale it has 10 defined levels and can be treated as a continuous variable;[29] based on pragmatic consensus amongst the investigator group a between-group difference of one point was selected as the minimally clinically relevant difference for the purposes of power calculation and interpretation. This one-point difference was deemed clinically meaningful as it represents a distinct change in sedation or agitation level that would be readily observable by clinicians and potentially impact patient comfort and family interaction; for example, a shift from mild agitation (+1) to normal alertness and calm (0), or from drowsy but easily roused (−1) to moderate sedation (−2). With a power of 80% and a 5% two-sided significance level, and assuming a standard deviation of 1.26, an independent sample t-test indicated that a total of 26 patients per arm were required.

Trial Intervention

Randomization was performed and trial assessments began when the senior medical officer clinically determined an eligible, symptomatic patient was entering the terminal phase, determined as death likely within seven days. Clinical signs considered reflective of impending terminal phase, included decreasing level of responsiveness, worsening symptoms, deteriorating oral intake, deteriorating swallow, fluctuating cognition, physical deterioration without reversible cause or physical deterioration where reversal was outside goals of care. Patients who were included in the trial were all suffering refractory distress requiring treatment with sedative medications at the end of life.[5,6] Refractory distress was defined as distress persisting despite optimal management of physical, psychological, or existential symptoms with standard therapies. Delirium was assessed clinically using DSM-IV criteria.[30]

At trial commencement, a subcutaneous infusion of either dexmedetomidine (0.5 μg/kg/h) or midazolam (0.25 mg/kg/day) was initiated using an indwelling subcutaneous cannula (Table 1). Breakthrough doses of either dexmedetomidine or midazolam, arm dependent, were also made available for ongoing symptoms of agitation as subcutaneous bolus injections. Breakthrough medications were available for other symptoms (including, pain, dyspnea, nausea and death rattle) at the treating clinician's discretion; a list of agents used across the trial is presented in Appendix 2. Doses of midazolam and dexmedetomidine were not modified for renal function but were for hepatic function based on modified end-stage liver disease (sodium, MELD-Na) score due to drug excretion changes.

Infusion doses of dexmedetomidine were calibrated to the lower range of critical care administration approved by regulatory authorities[31] and informed by our pilot trial results.[16] Midazolam infusion doses (0.25 mg/kg/day) were determined based on established palliative care guidelines[5,6] and anesthetic literature,[32] similar to proportional sedative doses.[26] Infusion doses were based on respective evidence bases, rather than equivalence between different molecules. Breakthrough doses were calculated on loading dose principles for dexmedetomidine (0.5 ug/kg[30,33]), while midazolam breakthrough doses (2.5−5 mg) reflect standard clinical practice in the institution where the study was conducted and international guidance.[34,35]

The intervention medication continued until death or withdrawal from study protocol which could occur due to inefficacy—defined as requiring excess breakthrough trial medication doses without other rationale (three or more doses per 24 hour period); poor control of symptoms per outcome tools (e.g., patient experiencing unacceptable agitation or delirium, being a RASS-PAL > 0 or an MDAS > 12)); or family request. Withdrawal from protocol was defined as voluntary cessation of study drug prior to death. Patients who died while receiving the study drug were considered to have remained on protocol at time of death.

Monitoring

Patients were monitored for side effects whilst on trial, including local and systemic reactions to both medications, which were reported to the trial monitoring committee (site pharmacist and independent physician) as required. Adverse events were recorded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.[36] Cardiac monitoring, including heart rate and blood pressure, was not specifically undertaken in this trial for either arm after consultation with the ethics committee. This decision was based on several factors: our prior pilot study showed no significant cardiovascular effects with subcutaneous dexmedetomidine in the terminal population,[16] pharmacokinetic testing demonstrates attenuated cardiovascular effects with subcutaneous administration;[37] the dose administered was lower than doses associated with significant cardiovascular effects in critical care;[33] and additional monitoring for patients in the terminal

Table 1
Tools and Medications Utilised in the Trial

Trial Drug	Infusion Dose	Breakthrough Dose	Modifications
Dexmedetomidine	0.5 mcg/kg/hour, rounded UP to nearest 10 mcg	**0.5 mcg/kg**, rounded UP to nearest 10mcg, every 2 hours as required	Increase breakthrough interval based on MELD-Na[a]
Midazolam	0.25 mg/kg/day, rounded UP to nearest mg	**2.5–5 mg**, every 2 hours as required	
Trial Tool	*Trial Use*	*Scoring*	*Incorporates*
RASS-PAL[23] Performed by nurses and doctors 3x daily	Measurement of consciousness and agitation	Score from **−5 to +4** Significant agitation: 2+ Mild agitation: 1 Normal: 0 Mild Sedation: −1 to −3 Deeper Sedation: −4 to −5	Testing of awareness and sedation as well as degree of agitation, ranging from not rousable to combative
MDAS[24] Performed by doctors 1x daily	Measurement of delirium	Score from **0–30** Scores <7 = no delirium Scores 7–12 = mild delirium Scores >13 = moderate to severe delirium	Testing of alertness, executive function, attention, psychomotor activation, hallucinations and delusions
PCA[25] Performed by patient or family/carers 1x daily	Measurement of comfort	Score from **0–10** Mild symptoms: 0–3, Moderate symptoms: 4–6 Severe symptoms: 7–10 =	Severity of discomfort, ranging from completely comfortable to worst possible discomfort.

[a]Breakthrough intervals were increased to 3 hourly if MELD-Na (modified end-stage liver disease (sodium version) score from 10 to 19, and to 4 hourly if 20–29.
Abbreviations: RASS-PAL = richmond agitation sedation score (Palliative); MDAS = memorial delirium assessment score; PCA = patient comfort assessment.

phase is not typically performed in our center due to emphasis on comfort, and the lack of impact on management.

Outcomes and Metrics

The primary endpoint of the trial was defined as the mean daily RASS-PAL (Table 1). The RASS-PAL is a palliative version of the well-validated Richmond Agitation Sedation Score, the RASS,[29] modified to be less invasive during the dying phase.[23] A RASS-PAL was performed at regular intervals after infusion start by nursing or medical staff (minimum three times daily) to assess level of responsiveness and agitation. The mean daily RASS-PAL was calculated by averaging all measurements taken during the 24-hour period prior to infusion reload (typically around 11am). The primary outcome was the comparison of mean RASS-PAL scores between treatment arms. If the time gap was not precisely 24 hours, the mean RASS-PAL assessments between infusions were performed.

Secondary endpoints included the mean daily memorial delirium assessment score (MDAS) and patient comfort assessment (PCA) (Table 1). The MDAS is a validated tool, designed to assess and track delirium, particularly in cancer patients.[24] It allows for proportional pro-rata completion, enabling an mean delirium score to be calculated even if patients are unable to respond to all ten components of assessment.[24,38] For patients who were unresponsive, MDAS items that were observable rather than interactive were utilized to produce a pro-rated score, including awareness, attention, perceptual disturbance, delusion, psychomotor activity. MDAS was first completed on randomization and repeated daily by the medical officer, to track delirium severity.

The PCA is a validated tool that enables both families and nurses to assess patient comfort and express specific concerns.[25] The tool consists of a scale rating from 0 to 10 based on the level of discomfort felt by the patient from absent (0) to severe (10), as well as specific concerns identified and comments as applicable. Families were asked to complete a PCA daily (patients were asked if rousable), as they felt able, to provide a measurement of perceived comfort levels; this study focused on the 10-point symptom intensity scale. Observations of symptom severity and presence of symptoms were documented in the electronic health record (EHR) and/or on paper forms prior to EHR integration.

The principal investigator (BT) trained the health care professionals in implementing the protocol, use of the rating scales, and patient consent processes. Recorded education sessions were available to reduce inter-assessor variability.

Statistical Analysis

Comparisons were made according to treatment group. Patients who had consented but did not meet the inclusion criteria were not randomized and were excluded from analysis. If a patient or family member withdrew consent during treatment, data collected up until that point was included in this analysis.

Two-sided t-tests with an alpha-level of significance of 5% were performed between arms, using the daily mean of scores, for the RASS-PAL, the MDAS and the PCA. Inter-arm assessments were performed for

variance across metrics. Kaplan-Meier curves were created for withdrawal rates off protocol, and rates of death on trial for between-arm comparisons.

All participants randomized were included in the analysis according to the intention-to-treat principle, with data analyzed only for the duration that patients remained on protocol-directed treatment. Post-withdrawal outcomes were not included in this primary analysis. Most of the analysis focuses on the first 72 hours ("the analysis period") of the trial due to patient attrition resulting in a lack of robust sample size beyond that analysis period.

All analyses were performed using Prism, version 10 (GraphPad), and Excel, version 16 (Microsoft).

Results

Trial Flow and Participants

Between May 2021 and November 2023, a total of 659 patients were admitted under a palliative care medical specialist within the Australian Local Health District. Patients were assessed for inclusion by medical staff considering eligibility criteria. Of those admitted, 60 patients were approached to consider participation; 59 provided informed consent and one declined. Fifty-two of the consented patients were subsequently randomized and included in the analysis; 26 received dexmedetomidine (DXM) and 26 received midazolam (MDZ) (Fig. 1).

Baseline characteristics were similar in both arms (Table 2), with predominantly male patients (DXM 65% and MDZ 61%) and a similar mean age (DXM 80.1 and MDZ 79.5 years). Amongst patients randomized, 92% had cancer as a primary diagnosis, comprising 88% of the dexmedetomidine arm and 96% of the midazolam arm. The median 24-hour infusion dose was 805 mcg (range 540−1330mcg, IQR = 200mcg) for dexmedetomidine and 18 mg (range 11−26 mg, IQR = 3.75 mg) for midazolam. As would be expected in a study in a terminal population, the rate of attrition due to death was high in both arms (Table 3). This rate was initially higher in the midazolam arm but equalized rapidly (Fig. 2). Less than half of participants remained alive in either arm by day 4. Both arms displayed a high rate of withdrawal from protocol, with 9 patients in the dexmedetomidine arm and 8 in the midazolam arm withdrawing during the 72-hour analysis period. On day one, more patients withdrew from protocol in the midazolam arm (5/26, 19%) compared to the dexmedetomidine arm (0/26, 0.0%) (Fisher's exact test, $P = 0.025$), which was statistically significant, which was not sustained on day two (MDZ 2/13, 15%, DZM 7/16, 44%, $P = 0.21$) or day three (MDZ = 1/9, 11%, DXM = 2/10, 20%, $P = 0.57$. By the end of the 72-hour analysis period, 15% ($n = 4$) of midazolam patients remained on protocol, whilst 23% ($n = 6$) of dexmedetomidine patients remained on protocol.

Protocol failure was observed in both arms but occurred earlier in the midazolam arm (Table 3). For patients on midazolam, the EHR recorded 100% of patients as uncomfortable at withdrawal, compared to 55% (4/9) of patients on dexmedetomidine. The most consistent rationale for withdrawal for dexmedetomidine patients without protocol failure was desire for deeper sedation. Patients who withdrew were treated with escalated doses and medications at the treating clinician's discretion, in line with guidelines[5,6] and clinical judgement.

Primary Outcome

For the primary outcome of rousability, there was no significant difference in the mean RASS-PAL between arms over the analysis period (Table 3). The averaged RASS-PAL ranged from −2 to −3, indicating light to moderate sedation. Within both treatment arms, there was variability observed in RASS-PAL during the first 24 hours. Variability was more pronounced and sustained into the second day with dexmedetomidine, which also exhibited less agitation compared to the midazolam arm (Fig. 3).

Secondary Outcomes

For the secondary outcome of delirium, MDAS categories of absent (<7), mild (7−12) and moderate-severe (13+) were utilized[24] (Table 1). Prior to initiation of trial medication (day 0), more than 50% of patients in both arms experienced moderate-severe delirium (Table 3). On day 1, both arms showed significantly decreased MDAS scores compared to day 0 (DXM $P = 0.004$, MDZ $P = 0.002$). On day 1, patients on dexmedetomidine experienced a statistically significant reduction in delirium severity compared to midazolam patients (MDAS 6.5 vs. 8.8, $P = 0.05$, Table 3). This difference was not sustained into day 2. No patients rebounded into the moderate-severe delirium band after starting study medications (Table 3). The significant decrease in MDAS scores were maintained for the entire analysis period for both arms, though midazolam arm scores increased on day 3, when very low patient numbers ($n = 4$) remained on treatment (Table 3).

During the analysis period, fewer patients in either treatment arm experienced no delirium compared to mild delirium (MDAS <7 versus 7-12) (Table 3). The prevalence of delirium varied between 62 and 100%, depending on treatment arm (Table 3). Pro-rata scoring of the MDAS was required for most patients at initiation (DXM=65% vs. MDZ=69%), reflecting high proportions of moderate-severe delirium at terminal phase.

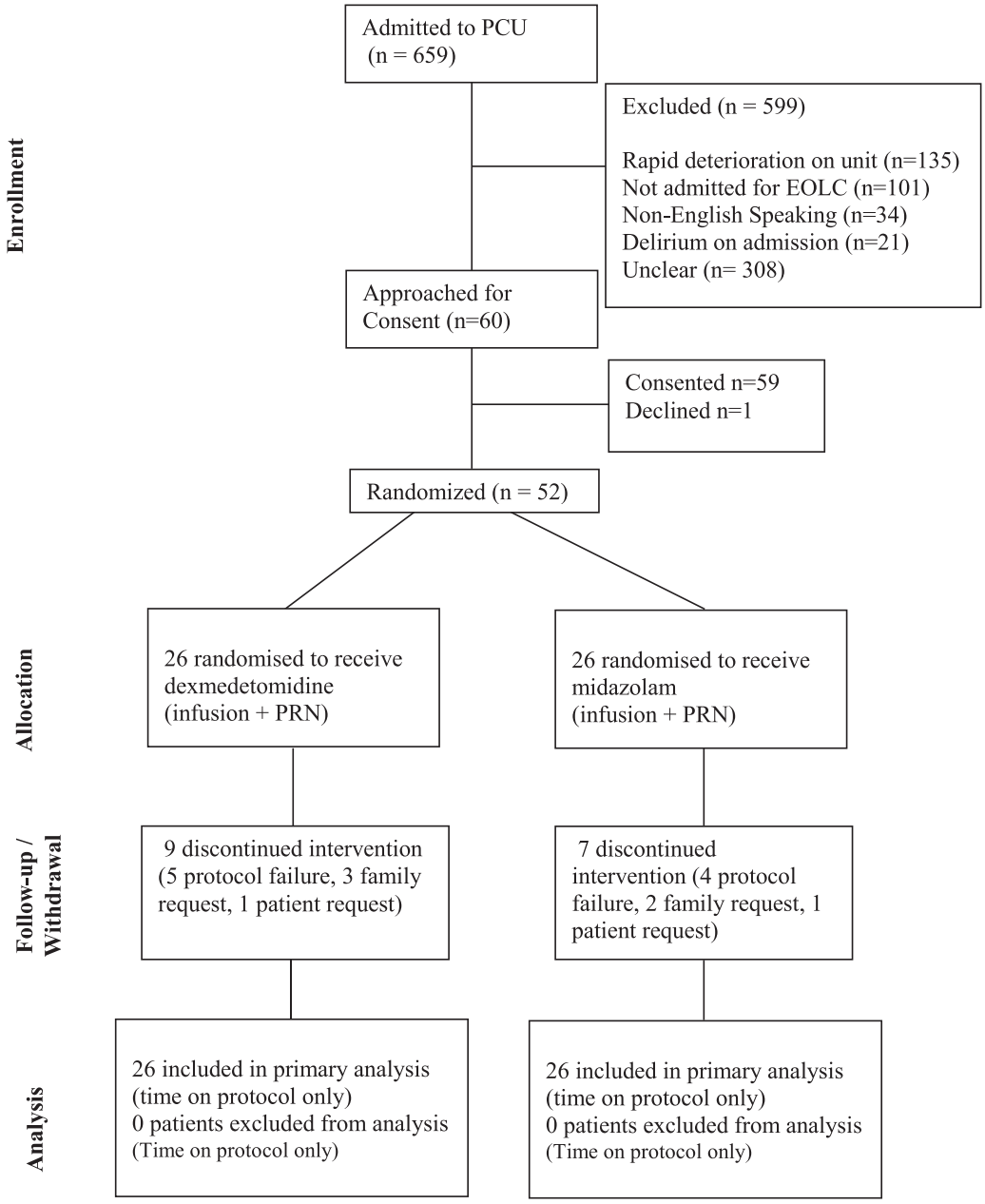

Fig. 1. Study Flow of the dexmedetomidine for relief of end-of-life agitation and optiMised sedation (DREAMS) study during the analysis period.

PCA scores were primarily completed by families, with an overall completion rate of 75% (124/166). Completion rate was higher in the dexmedetomidine arm (DXM 82/100, 82% vs. MDZ 42/66 64%, chi-square $P = 0.008$). Daily mean PCA scores remained below 3 (mild or no symptoms) in both arms for the analysis period. There was no significant day-to-day difference between treatment arms. However, a statistically significant improvement in patient comfort was observed within the dexmedetomidine arm on day three compared to day two, with the mean PCA decreasing from 2.71 (day two) to 0.91 (day three) ($P = 0.03$, Table 3). This was not observed in the midazolam arm, where the mean PCA remained between 2 and 3 (Table 3).

Opioid infusion doses were similar between the treatment arms throughout the analyzed period, increasing by 55% in the dexmedetomidine arm and 83% in the midazolam arm from the initial doses, with no significant difference between arms (Table 3). No relationship was observed between changing opioid doses and delirium severity.

During the trial phase one patient suffered an adverse outcome associated with excess breakthrough dexmedetomidine dosing which was reported to the monitoring committee, the specific adverse outcome

Table 2
Demographics and Baselines

No. (%) of Patients		
Characteristic	Dexmedetomidine Arm ($n = 26$)	Midazolam Arm ($n = 26$)
Sex		
Male	17 (65%)	16 (61%)
Female	9 (35%)	10 (39%)
Age (years, mean + SD)	80.1 (9.3)	78.5 (8.8)
Weight (kg, mean + SD)	68.1 ± 15.5	68.7 ± 13.6
Primary diagnosis, No./total%		
Cancer		
Lung	5, (19%)	6, (23%)
Gastrointestinal	5, (19%)	9, (35%)
Genitourinary	9, (35%)	7, (26%)
Breast	2, (8%)	1, (4%)
Other	2, (8%)	2, (8%)
Non-cancer	3, (12%)	1, (4%)
MELD-Na (category/total%)		
<10	13, (50%)	7, (27%)
10–19	11, (42%)	18, (69%)
20–29	2, (8%)	1, (4%)

was excessive somnolence of 12 hours with the patient returned to interactivity without other side effects; basic clinical assessment showed a regular pulse with normally perfused peripheries. The other predominant side effect noted in both arms was dry mouth requiring oral saliva substitute (presence 100% both arms), however given other medications and terminal phase of patients this was difficult to determine if this was a result of the study medications. No other adverse effects were reported in either arm.

Discussion

This non-blinded randomized controlled trial has demonstrated that both midazolam and dexmedetomidine are effective at providing relief from distress and delirium at the end-of-life, when delivered by subcutaneous infusion with breakthrough dosing. When testing for interactivity and responsiveness, as measured by mean RASS-PAL, neither agent was superior during the first 72 hours. Given the RASS-PAL ranges, both agents achieved a comfortable level of sedation with potential interactivity at doses chosen. Observed variability in RASS-PAL scores between treatment arms suggests that a continuous monitoring methodology may better detect differences in responsiveness, rather than averaged daily scores. Some patients were observed to have RASS scores below −3, indicating a deeper sedation despite proportional dosing. These lower scores are likely to reflect the natural progression of the dying phase with decrease in consciousness independent of medication effect, or potentially differing effects of similar medication dosing due to individualized patient factors resulting in variable sedation levels.[39]

Delirium severity improved in both arms during the terminal phase, with dexmedetomidine demonstrating a statistically superior benefit for the first 24 hours on

Table 3
Dexmedetomidine (DXM) and Midazolam (MDZ) Assessments and Metrics Performed on Trial for First 3 Days With Significance Between Arms Where Assessed

	Day 0		Day 1		Day 2		Day 3	
	DXM	MDZ	DXM	MDZ	DXM	MDZ	DXM	MDZ
Patients on protocol[a] (n, %)	26 (100%)	26 (100%)	23 (88%)	15 (58%)	12 (46%)	10 (38%)	6 (23%)	4 (15%)
Patients off protocol (n, %)	-	-	**0**	5 (19%)	7 (27%)	7 (27%)	9 (35%)	8 (31%)
Patients died (n, %)	-	-	3 (12%)	6 (23%)	7 (27%)	9 (35%)	11 (42%)	14 (54%)
Withdrawals from protocol								
Protocol failure	-	-	0	2	2	1	3	1
Family request	-	-	0	2	3	0	0	0
Patient request	-	-	0	1	1	0	0	0
RASS-PAL (mean)	−0.04	−0.42	−2.33	−1.9	−2.44	−2.86	−2.95	−2.53
Significance	$P = 0.393$		$P = 0.389$		$P = 0.4945$		$P = 0.6153$	
RASS-PAL 1+ (n, %)	10 (38.46%)	10 (38.46%)		1 (3.7%)	1 (4.55%)	2 (12.50%)	1(8.33%)	
RASS-PAL 0 (n, %)	5 (19.23%)	5 (19.23%)	2 (7.69%)	4 (14.81%)	3 (13.64%)	-	1(8.33%)	4 (44.44%)
RASS −1 to −3 (n, %)	11 (42.31%)	9 (34.62%)	16 (61.54%)	18 (66.67%)	10 (45.45%)	4 (25.00%)	3 (25.00%)	2 (22.22%)
RASS below −3 (n, %)	-	2 (7.69%)	8 (30.77%)	4 (14.81%)	8 (36.36%)	10 (62.50%)	7 (58.33%)	3 (33.33%)
MDAS (mean)	12.42	12.73	6.52	8.7	7.31	7.09	6.13	8.5
Significance (between arms)	$P = 0.844$		***P = 0.049***		$P = 0.828$		$P = 0.220$	
Significance from Day 0	-	***P = 0.0004***	***P = 0.002***	***P = 0.006***	***P = 0.0002***	***P = 0.02***	$P = 0.06$	
MDAS < 7 (absent) (n,%)	6 (23%)	2 (8%)	8 (35%)	5 (28%)	5 (33%)	4 (36%)	3 (38%)	-
MDAS 7–12 (mild) (n, %)	6 (23%)	10 (38%)	15 (65%)	13 (72%)	10 (67%)	7 (64%)	5 (62%)	4 (100%)
MDAS > 13 (mod-sev) (n, %)	14 (54%)	14 (58%)	-	-	-	-	-	-
PCA (mean)			2.58	2.54	2.71	2.33	0.92	2.19
Opioid Infusions (% increase from baseline)	-	-	18%	37%	38%	42%	55%	83%
Significance	-	-	$P = 0.15$		$P = 0.94$		$P = 0.51$	

[a]On protocol status was determined at time of medical assessment, once daily, which may result in slight count differences between % on protocol and daily MDAS/RASS PAL figures, as patients could be withdrawn at any time.

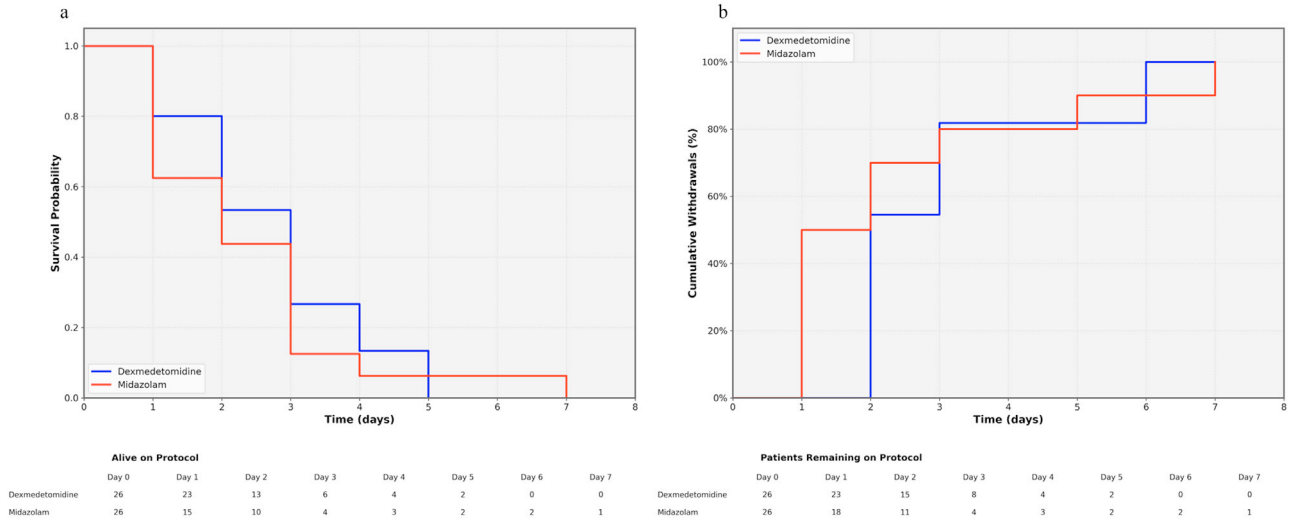

Fig. 2. (a) Deaths on protocol. (b) Withdrawal from protocol, excluding deaths.

the mean MDAS, however this should be cautiously interpreted pending confirmation from larger studies, especially given the prevalence of delirium in participants. This advantage did not persist, possibly reflecting tolerance to dexmedetomidine.[40] Prior research demonstrated that relatively rapid titration was needed in terminal delirium to maintain symptom control,[16] suggesting dose escalation may have shown a between-arm difference. In ICU, dexmedetomidine does demonstrate superior delirium control compared to midazolam in critically ill patients,[19] presumably due to decreased catecholamines in the locus coeruleus.[14,15] This study provides preliminary evidence that this advantage may extend to palliative care, albeit with potentially rapid tolerance impacting ability to determine significance.

Withdrawal rates in the dexmedetomidine arm aligned with titration timeframes observed in our previous study,[16] with withdrawals commencing on day two. This trial's limitation to single protocol doses of dexmedetomidine or midazolam without permitted increases likely led to earlier protocol withdrawal, and the ability to escalate doses may have led to longer protocol adherence and better symptom control.

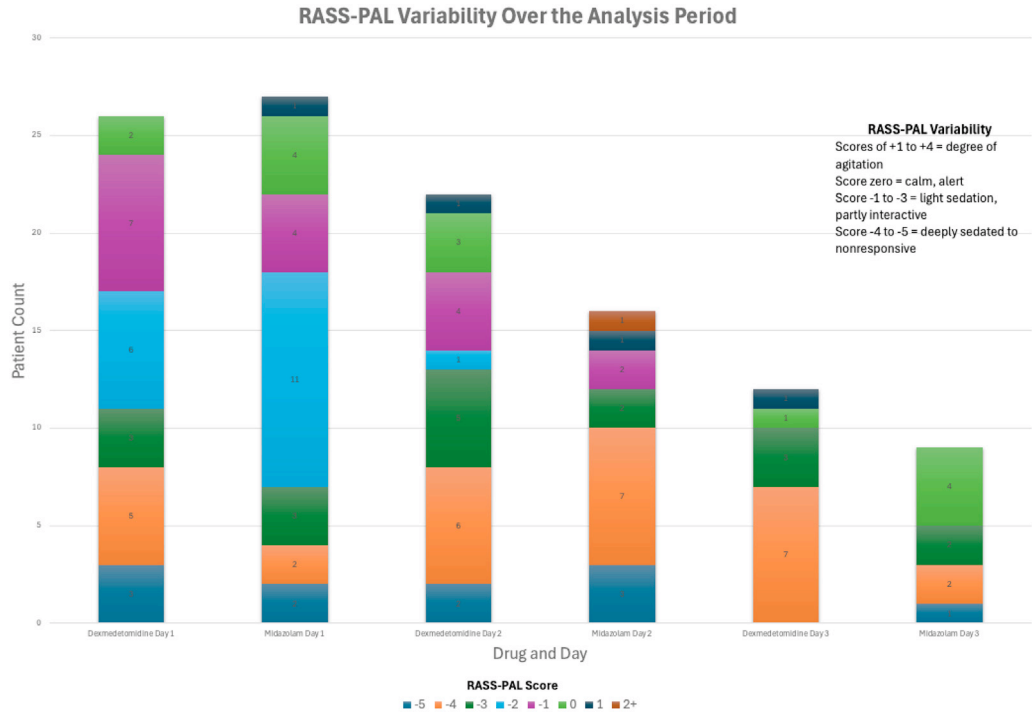

Fig. 3. RASS PAL Variability.

Patients in the dexmedetomidine arm were rated by families and carers as experiencing a fall in symptom severity as infusions continued by PCA, whereas midazolam patients remained mildly symptomatic throughout the analysis period. This could indicate a preference for dexmedetomidine by families that merits further qualitative exploration. Families and carers rated patients in both arms as comfortable, with average scores within the mildly symptomatic range,[25] which is reassuring given potential for family distress with poor perception of symptom control.[41] This finding offers reassurance to clinicians considering either midazolam or dexmedetomidine. The rate of withdrawal and the relatively small sample size make it difficult to draw robust conclusions; the lack of robust numbers of patient-completed forms due to deterioration into the dying phase similarly constrained the sample size. It is interesting that all patients on the dexmedetomidine arm when withdrawn were rated as comfortable, and a desire for deeper sedation was expressed. This may speak to a more lighter sedative experience on dexmedetomidine despite inconsistent RASS-PAL findings, as well as potentially mismatched expectations.

When examining protocol adherence, the study observed better control of distress with dexmedetomidine, with a faster rate of withdrawal in the midazolam arm. This implies the protocol dosing of midazolam may be insufficient to treat end-of-life distress in a sizeable subgroup of patients. Despite family perceptions recorded on the PCA indicating otherwise, staff EHR documentation described discomfort for all midazolam patients withdrawn from the midazolam protocol at time of discontinuation. This could be due to rapid development of tolerance to midazolam,[42] however it is important to note that the timeframes were less than expected. Importantly, the protocolized doses of midazolam were consistent with guidelines[5,6,9] for initiating midazolam in the terminal phase. Given that these doses have never been previously tested in an RCT in palliative medicine but developed by consensus,[7,43,44] there is an implication that the consensus may need to be amended with higher doses of midazolam utilized up-front.

Performing an RCT in terminal patients can be challenging,[45] however only one patient approached for this study declined to participate, implying that patients remain interested in participating in research even at the end-of-life.[46] Maintaining appropriate safeguards for these vulnerable populations remains essential.[47]

Limitations

This study was conducted across limited sites due in part to COVID-19-related relocations and closures, potentially affecting generalizability. Attrition from death and withdrawal as the trial progressed meant the sample size calculated for adequate power was not sustained throughout the trial, a common challenge in terminal care research. Future multi-site studies with larger patient populations could help address these limitations. The combination of small size and restricted sites, coupled with limited funding precluded the ability to blind the trial, introducing potential bias that could be addressed in a future adequately funded trial. These sample size constraints, combined with multiple secondary comparisons, may increase risks of Type I and Type II error, with caution needed in interpretation of results.

This trial was designed as a single-step trial, without titration doses in either arm, due to the intent to test interactive potential between dexmedetomidine and midazolam using proportional dosing, without leaving patients with uncontrolled symptoms in the terminal phase. The lack of titration doses potentially led to more rapid withdrawal from protocol than if escalation doses were available and may not reflect standard practice.

The diagnosis of refractory distress was determined by clinical judgment without specific criteria on a per-symptom basis, which may have introduced selection bias. The original study protocol relied on expert clinical assessment rather than strict definition to ascertain the suitability of sedatives for the alleviation of distressing symptoms, which reflects real-world palliative care practice. The absence of explicit assessment criteria could have introduced unintentional variability in the patient group. The predominance of a cancer diagnosis in this study may limit its generalizability, particularly given the high occurrence of delirium in terminal cancer patients.[24,38] Pro-rata scoring of the MDAS potentially impacted delirium assessment quality, which underscores limitations in delirium severity measurement in critically ill patients. The limited specificity of the MDAS in this population and the lack of specific tools suggest the need for more refined assessment instruments in this vulnerable group.[38] We note that baseline PCA assessments were not collected as part of the protocol design, limiting pre-post comparisons. Future studies should consider baseline comfort measurements where feasible.

While the RASS-PAL, our primary measure of awareness and rousability, did not show a significant difference between arms, we did observe some individual variability day-to-day that may reflect the limitations of using a discrete assessment tool for a continuous variable like consciousness, particularly using an assessment like the RASS-PAL that was performed pragmatically by nursing staff during clinical shifts rather than on a set timing schedule. It is also notable that the RASS-PAL is designed as an ordinal scale – albeit utilized in an interval fashion[29]—which

potentially further limits its utility in this space. The selection of a 1-point difference as the minimally clinically important difference for the RASS-PAL, while based on pragmatic consensus, does lack empirical validation in this population. This may further limit the interpretability of our findings and highlights the need for validated outcome measures in this space. Future research may benefit from continuous monitoring rather than static tool averages, such as the use of Bispectral index monitoring, which has been previously well tolerated when utilized in palliative care research[39] and may assist in capturing more granular differences between end-of-life sedatives. This would particularly assist when tools are impractical to administer with high frequency, as in this study, with most tools being completed only once daily.

Conclusions

Dexmedetomidine and midazolam can both provide relief from distress at the end-of-life, without necessitating deeper sedation. Our study suggests that patients treated with midazolam are more likely to require earlier dose escalation. Current guidance for starting doses of end-of-life sedatives may need revision.

Both dexmedetomidine and midazolam can reduce delirium in the terminal phase. Dexmedetomidine providing better early control, as well as potentially improving family perception of comfort. Optimal dosing remains unclear. Better tools and monitoring for delirium and awareness in dying patients are needed.

Author Contributions

BT designed the initial protocol, GB, WS-L, Camilla Chan, Zivai Nangati provided protocol feedback, BT, GB, WS-L recruited and assessed patients, BT wrote the initial draft and with KM and JM re-drafted the manuscript, all authors revised it critically and approved of the final version.

Disclosures and Acknowledgments

The authors acknowledge and thank the medical staff (Dr Zivai Nangati, Dr Camilla Chan, Dr Ronald Wai, Dr Helen Yourlo, Dr Mingshu Cai, Dr Michelle Petersen, Dr Lara Eldering, Dr Georgia Simmins, Dr Alison Apel, Dr Patrick Loui, Dr Nadia Shahzadi), the chief pharmacist of Port Kembla Hospital (Dr Phillip Spendley), and all of the nursing staff of Port Kembla and Bulli for their support and invaluable contributions. We are also deeply grateful to the patients and their relatives who were willing to participate in this challenging study. The author(s) declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article. The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: This study was supported by an Early Career Researcher Grant awarded to Dr Thomas by the Illawarra Shoalhaven Local Health District. The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; nor the decision to submit the manuscript for publication.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jpainsymman.2025.07.027.

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