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Original Articles

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Descriptive Analysis of Dexmedetomidine's Utility in a Palliative Care Unit at the End of Life

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Abstract

Context: Pain and symptom management at the end of life (EoL) can pose unique challenges, particularly when symptoms are refractory to conventional methods. Dexmedetomidine, originally approved for sedation in ventilated patients, has been demonstrated to be beneficial in pain management and palliative care settings by functioning as an alpha-2 agonist.

Methods: A retrospective review of inpatient palliative care unit (IPU) records from January 2020 to December 2023 was conducted. Twenty-five adult patients receiving continuous dexmedetomidine for refractory pain at the EoL were identified. These patients were further evaluated for concurrent opioid, benzodiazepine, and chlorpromazine usage.

Results: Patients experienced predominantly cancer-related pain, and had a median infusion duration of 5 days. Dexmedetomidine's initial dosing differed between the intensive care unit (ICU) and IPU settings. There was a trend toward a decreased opioid requirement 24 hours after initiation. Patients transferred from the ICU showed a progressive increase in opioid use.

Conclusion: This study contributes to understanding dexmedetomidine's role in managing refractory symptoms at the EoL in the palliative care setting.

Keywords: benzodiazepines; delirium; dexmedetomidine; end of life; opioids; refractory pain and symptoms

Key Message

Dexmedetomidine is a useful medication for managing refractory symptoms at the end of life. In our study, we demonstrate a reduction in total opioid and benzodiazepine needs following initiation of dexmedetomidine infusion. Patients and families anecdotally experience a decrease in total suffering.

Background

Management of pain and nonpain symptoms at the end of life (EoL) presents unique challenges, especially when pain is complex and refractory to conventional opioid therapy. In such situations, coanalgesic medications become essential to alleviate suffering. Dexmedetomidine was originally approved for sedation in mechanically ventilated patients and has previously been shown to reduce pain and opioid requirements in postoperative surgical intensive care unit (SICU) patients.[1] It acts as an α–2 agonist—with primary analgesic effects and potentiation of opioid-induced analgesia from activation of the α–2 adrenergic receptor (AR) in the dorsal horn of the spinal cord with inhibition of substance P release.[2,3] It has several unique properties, including rapid onset of action (5–20 minutes), short elimination half-life (2 hours),[4] minimal respiratory depression,[1,5] and mild sedation resembling natural sleep—frequently allowing patients to

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maintain an ability to communicate while experiencing a sense of calm.[6] Because of these properties, there is a growing interest in the use of dexmedetomidine for pain and symptom management at the EoL.

Previous descriptive articles and pilot studies have examined the use of dexmedetomidine for refractory symptoms in palliative care patients outside the intensive care unit (ICU) setting, although all are of limited size. The use of dexmedetomidine has been described for refractory dyspnea at the EoL,[7] in the setting of terminal extubation,[8] for baclofen withdrawal,[9] as well as for symptoms, including delirium, opioid-induced hyperalgesia, and pain.[2,10] Three previous case series have reported the use of dexmedetomidine in patients receiving comfort-focused care in palliative care units, with the most common indication being refractory pain.[11–13] Dosing protocols are comparable, ranging from 0.2 mcg/kg/hour to at most 2 mcg/kg/hour, although only two institutions in a U.S. national survey reported institutional guidelines for dexmedetomidine use by palliative care teams outside the ICU.[14] Monitoring of adverse events varied among the case series, with two studies assessing vital signs, including blood pressure, heart rate, and respiratory rate.[12,13] Among the 29 patients in these studies, only 3 discontinued dexmedetomidine therapy due to intolerable side effects, consisting of 2 cases of hypotension and 1 case of dyspnea. One case series described the safe use and titration of dexmedetomidine outside the ICU without mandatory vital signs monitoring in patients receiving comfort-focused care at EoL.[11]

Our primary objective is to provide a descriptive analysis of dexmedetomidine's utility for patients receiving comfort-focused care, particularly for managing refractory symptoms at the EoL. We present data on the medication's usage in the inpatient palliative care unit (IPU) at our institution, where specialized care is administered by a multidisciplinary palliative team comprising physicians, pharmacists, nurse practitioners, social workers, and oncology nursing staff with additional training in palliative care. In accordance with our institutional guidelines,[10] we did not require vital sign monitoring, relying instead on nursing assessments that include pain evaluation and documentation of reassessment. Furthermore, we contextualize the use of dexmedetomidine alongside other commonly employed medications and medication classes for EoL care, such as opioids, benzodiazepines, and chlorpromazine.

Methods

A retrospective review of records from the IPU at a single large academic center was performed for the period January 2020–December 2023. Permission from the local Institutional Review Board was obtained (#809014). Inclusion criteria consisted of patients seen by the IPU palliative care team who received intravenous (IV) dexmedetomidine infusion in the IPU at the EoL (see Appendix for institutional guideline).[10] Parameters assessed included demographic data, hospital length of stay (LOS), primary medical service, pain descriptors, level of care at the time of dexmedetomidine infusion initiation (ICU vs. IPU), duration of dexmedetomidine infusion, dexmedetomidine dose (initial, maximum, and final dose before discontinuation), and presence of concurrent administration of chlorpromazine.

To evaluate the progressive effect of dexmedetomidine infusion across an entire admission, values for numerical pain score (NPS), Richmond Agitation Sedation Scale (RASS), and morphine equivalent daily dose (MEDD) were assessed at initiation of dexmedetomidine infusion, 24 hours after initiation, and at termination of infusion. This information was further stratified into dexmedetomidine infusions that were initiated in the IPU versus those initiated in the ICU. Similarly, dexmedetomidine dose, lorazepam equivalent dose (LED), and the presence of concurrent chlorpromazine administration were assessed across the continuum of a patient's admission. Statistical significance was predefined as $p < 0.05$ and all analyses for significance were generated using a Student's *t test*.

Most patients received either IV lorazepam or IV midazolam during their admission to the IPU. To standardize benzodiazepine dosing, we created a new variable, LED. Based on accepted conversions between other benzodiazepines and lorazepam, we applied a 1:1 conversion of lorazepam:midazolam for intravenous bolus doses and a 1:2 conversion for continuous intravenous infusion.[15]

Descriptive statistics were used to summarize patient demographic data. We further assessed information related to the patient's hospital course (diagnosis, LOS, discharge, and primary team). The patient's pain profile was categorized as neuropathic, nociceptive, or mixed.

Results

Twenty-five patients met the inclusion criteria. Median patient age was 63 (mean: 62) years with most patients characterized as male, White, and having a solid malignancy. Median LOS was 24 days (mean 28) and median days on dexmedetomidine infusion were 5 days (mean 11). There was a trend toward younger age in patients initiated on dexmedetomidine infusion in the IPU compared with those initiated in the ICU (59 vs. 72), but this did not reach significance ($p = 0.058$). Dexmedetomidine infusion was continued until time of death in all but one patient. This single patient had revoked hospice and ultimately was discharged alive. The majority of patients was cared for by the Internal Medicine service (69%) with the palliative care team comanaging symptoms. Pain was characterized as primarily cancer-related, mixed nociceptive/neuropathic, and acute-on-chronic (Table 1).

Median starting dose for dexmedetomidine infusion was 0.2 mcg/kg/hour, median maximal dose was 0.8 mcg/kg/hour, and terminal dose was 0.6 mcg/kg/hour. Dexmedetomidine infusion was started at a statistically significantly higher dose in the ICU compared with the IPU (0.36 mcg/kg/hour vs. 0.21 mcg/kg/hour, $p = 0.003$) (Table 2).

In all patient groups, there was a trend toward decreased MEDD 24 hours after initiation of dexmedetomidine infusion, although this effect disappeared at termination of infusion. For the subset of patients initiated on dexmedetomidine infusion in the ICU and subsequently transferred to the IPU, there was a progressive increase in MEDD. LED increased from initiation of dexmedetomidine infusion to termination (1 mg to 4 mg, $p = 0.028$). Chlorpromazine was initiated in five patients during dexmedetomidine infusion (Fig. 1).

Patients initiated on dexmedetomidine infusion had a median RASS of 0. Twenty-four hours after the initiation of dexmedetomidine, median RASS decreased to –1, and ultimately decreased to a nadir of –3 at the time of discontinuation of the infusion. For the subset of patients initiated on dexmedetomidine infusion in the IPU, mean RASS progressively decreased with time on the infusion (–0.4 to –2.6, $p = 0.0003$). Mean RASS at termination of infusion was higher for patients

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Table 1. Demographics of Patients Receiving Dexmedetomidine for Pain in the Inpatient Palliative Unit

	n (%)	Median (mean, StDev)
Age	—	63 (62, 14.3)
Sex		
Female	11 (44)	—
Male	14 (56)	—
Race/ethnicity		
Asian	2 (7.7)	—
Other	1 (3.8%)	—
White	16 (61.5)	—
Diagnosis		
Heme m alignancy	2 (7.7)	
Nononcologic	3 (11.5)	
Solid m alignancy	20 (76.9)	
Length of stay	—	25 (28.1, 22.7)
D/C status		
Alive	1 (4)	—
Dead	24 (96)	—
Discharging team		
Bone marrow transplant	2 (7.7)	—
Medicine	18 (69.2)	—
Surgery	5 (19.2)	—
Pain type		
Cancer-related	23 (88.5)	—
Nononcologic	2 (7.7)	—
Pain character		
Neuropathic	5 (19.2)	—
Nociceptive	8 (30.8)	—
Mixed	10 (38.5)	—
Unknown	2 (7.7)	—
Pain timing		
Acute	5 (19.2)	—
Chronic	2 (7.7)	—
Acute-on-chronic	18 (69.2)	—

D/C, discharge; SD, standard deviation.

Table 2. Dosing of Symptom-Targeting Medications over Patient Course in Relation to Day of Dexmedetomidine Administration

Dexmedetomidine administration day	*Median (mean, StDev)*	P (D^0 vs. D^x)
Dexmedetomidine dose (mcg/kg/hr)		
D^0	0.2 (0.21, 0.08)	
D^{+1}	0.6 (0.64, 0.42)	
D^X	0.8 (0.58, 0.43)	**0.0000074***
Lorazepam equivalent dosing (mg/d)		
D^0	1 (1.99, 4.03)	
D^{+1}	0.5 (2.43, 6.65)	
D^X	4 (5.75, 5.82)	**0.0072497***
Morphine equivalent dose (mg/d)		
D^0	441 (629, 627)	
D^{+1}	240 (595, 720)	
D^X	378 (566, 507)	0.8788698

D^0, day of dexmedetomidine initiation; D^{+1}, first 24 hours following dexmedetomidine initiation; D^x, 24 hours before discontinuation of dexmedetomidine; d, day.
*Significance of bold, statistical significance ($P < 0.05$).

initiated in the ICU versus the IPU (–4.5 vs. –2.6, $p = 0.016$) (Fig. 2).

There were no statistically significant associations between dexmedetomidine infusion duration and NPS, although this was confounded by missing NPS scores as patients approached death (consistent with institutional nursing practice).

Discussion

Our study demonstrates the effective use of dexmedetomidine infusion in treating symptoms at the EoL. It is important to note that these are patients with refractory pain (Mean MEDD: 371 mg at initiation of dexmedetomidine infusion) for whom all other analgesic options have been exhausted. Our IPU team treats patients experiencing cancer pain at the EoL and it is reflected in our patient demographic profile. There was a trend toward younger age in those patients initiated on infusion in the IPU that is perhaps reflective of EoL patients in that setting being younger, experiencing more complex courses of treatment for their cancer, and having a higher need for specialized palliative services. The average age of the patients in our study (62 years) was similar to other case series evaluating dexmedetomidine in a palliative care unit (49 + 13.3 and 42–66).[12,13] Most patients' pain was characterized in the medical record as nociceptive, neuropathic, and acute-on-chronic, consistent with cancer-related pain.[16] The mixed characteristics of this pain necessitate multimodal approaches to pain control.

Patterns of dexmedetomidine use significantly differed in those patients initiated in the ICU, as opposed to the IPU. Patients were initiated on dexmedetomidine infusion at rates 70% higher in the ICU setting compared with those initiated on dexmedetomidine in the IPU (mean 0.36 mcg/kg/hour vs. 0.21 mcg/kg/hour, $p = 0.003$). This likely reflects the greater familiarity with and frequency of use of dexmedetomidine in the ICU.[17] In addition, higher ICU nursing-to-patient ratios, as well as nurse-driven bedside titration protocols and more readily available options to treat potential cardiovascular side effects, likely contribute to a greater willingness to initiate and maintain higher doses.[18–21] Further studies evaluating dexmedetomidine use in the ICU versus IPU settings are needed.

There was a progressive decline in RASS appreciated as dexmedetomidine infusion proceeded (Fig. 2). However, this is confounded by the expected decrease in level of consciousness in the terminal dying phase.[22] Further studies are necessary to compare RASS in patients receiving dexmedetomidine infusion to a control group. Note that we identified a deeper RASS at termination of dexmedetomidine infusion in those patients initiated on infusion in the ICU compared with the IPU. This may be attributable to the fact that ICU patients are more likely to be admitted with an acute comorbid or superimposed disease processes that may affect lucidity or hasten death.[23,24]

MEDD results for patients initiated on dexmedetomidine infusion in the IPU demonstrated a U-shaped pattern, with a decrease in median MEDD 24-hours after initiation. MEDD subsequently increased at the time of dexmedetomidine termination, which correlated to death in most cases. This is likely reflective of a greater and more liberal use of opioids at the EoL as well as variability in nursing practice in the

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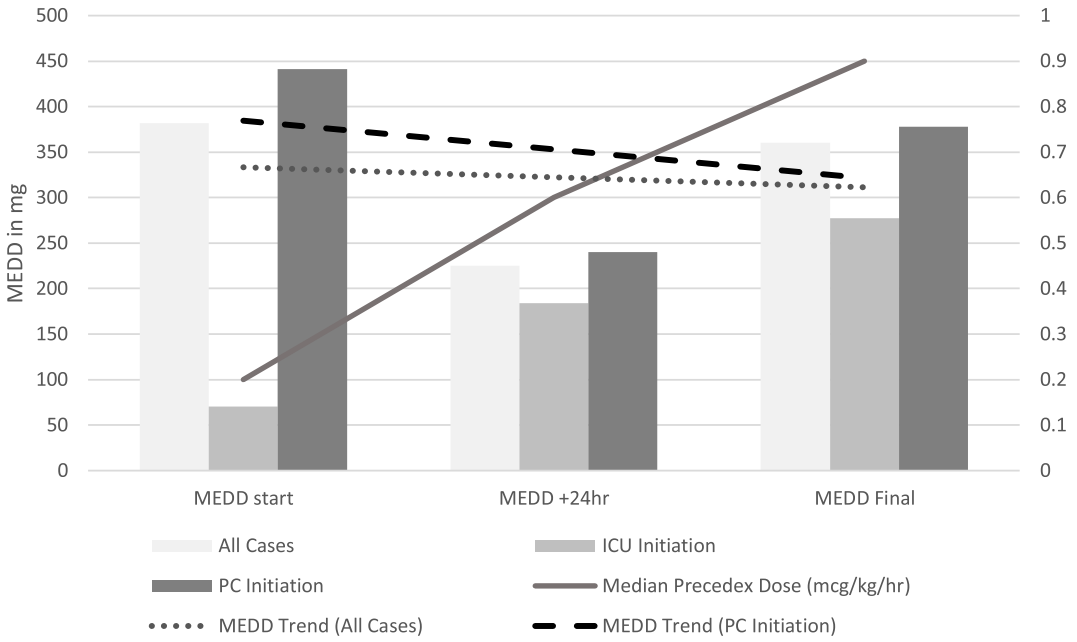

FIG. 1. Opioid trend and dexmedetomidine dosing in relation to the day of dexmedetomidine administration. hr, hour; ICU, intensive care unit; kg, kilogram; mcg, microgram; mg, milligram; MEDD, morphine equivalent daily dose; PC, palliative care.

management of symptoms in nonverbal patients,[25–27] and does not necessarily detract from the significance of the reduction in MEDD at 24 hours. It is important to note that in patients initiated on dexmedetomidine in the IPU, the final MEDD did not exceed the baseline MEDD, suggesting that dexmedetomidine is opioid-sparing in patients at the EoL through unique activity at α2-AR receptors. In the subset of patients initiated on dexmedetomidine in the ICU, there was a progressive increase in MEDD. It is important to note that these patients in the ICU had a much lower starting MEDD (45 mg vs. 441 mg) and is more likely suggestive of convergence in opioid prescribing practice once transferred to the IPU. Other cases of patients receiving dexmedetomidine in a palliative care unit have similarly described decreases in pain and delirium.[11–13]

Most patients were receiving minimal benzodiazepines at the onset of dexmedetomidine infusion. This is consistent with our clinical experience, which finds that patients best suited to

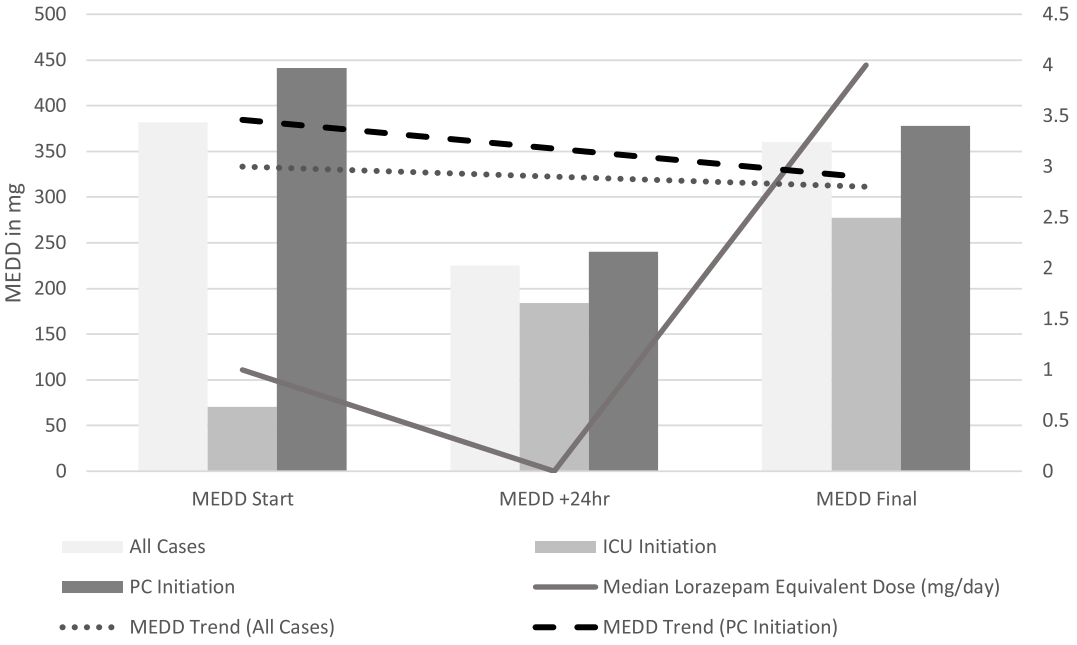

FIG. 2. Individual RASS compared with the time course of dexmedetomidine administration. RASS, Richmond Agitation Sedation Scale.

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dexmedetomidine as a coanalgesic tend to be those with a strong desire to preserve their lucidity. However, as patients progressed toward termination of the dexmedetomidine infusion (and in most cases, death), there was an increase in LED (2.0 mg to 5.8 mg, $p = 0.03$). Other studies have similarly shown concomitant use of midazolam in patients receiving dexmedetomidine at the EoL for comanagement of delirium or agitation.[12,13] This finding might be the inverse of cases where severe, refractory EoL delirium has been palliated by stopping benzodiazepines and initiating dexmedetomidine.[11] Further research can investigate if there is a benzodiazepine-sparing effect of dexmedetomidine in the subset of patients requiring high doses of benzodiazepines before initiation of dexmedetomidine infusion. It is important to note that 5 of the patients received chlorpromazine in addition to benzodiazepines and dexmedetomidine infusion. Our IPU generally utilizes chlorpromazine as a cosedative in terminal delirium and is suggestive of the refractory symptoms in the patient population studied here.

The general sense of suffering experienced in the room at the three evaluation points is a critical, missing data point in this study, which is a "suffering index." In our clinical practice, the consideration and initiation of dexmedetomidine is reserved for patients with truly refractory pain, often displaying elements of total pain,[28] and frequently with co-occurring delirium with profound collective suffering experienced by the patient and their family. With initiation and titration of dexmedetomidine, we anecdotally see a decrease in this total quantity of suffering. We find this to be true whether the patient can verbalize the total suffering aspects of their pain. In future studies, we hope to find an objective measure of the calm and wellbeing our patients experience when receiving dexmedetomidine infusions at the EoL. It is these unique qualities of dexmedetomidine—to bring about a sense of lucid calm, improved analgesia, and reduced agitation, without impacting respiratory drive[4]—that make it a powerful addition to the palliative care toolbox.

Limitations

This was a retrospective review of patient charts from a single center and is thus prone to selection bias and may not be representative of the general population. Objective documentation of dexmedetomidine's clinical effects and side effect profile were difficult to locate, which may have biased our results. We only examined adjunct medication (MEDD, LED) administration patterns at the onset of dexmedetomidine infusion, 24 hours after initiation of infusion, and at discontinuation of infusion. We suspect that increasing the sampling rate for medications used across an IPU admission would offer more granularity, and potentially uncover more association between variables. It is important to note that there is an inherent continuation bias in those patients initiated on dexmedetomidine infusion in the ICU before palliative evaluation; see Figure 1 and Figure 3 for differences in patients initiated on dexmedetomidine infusion in the ICU versus IPU. There were two missing data points for the characterization of patients' pain, as listed in Table 1. As per institutional guidelines, many objective scoring tools (such as NPS and RASS) are not used as patients approach the EoL. As a result, NPS was not assessed in most cases as patients approached the EoL and ultimately required the exclusion of NPS data from analysis.

There is limited analysis of dexmedetomidine's adverse effects that can be performed in our present data set. Patients receiving dexmedetomidine in our IPU were necessarily receiving comfort-focused care. This change in care delivery frequently includes orders to minimize or exclude vital sign measurement. Similarly, as can be appreciated by the patients' profoundly depressed RASS, patients are not able to provide an NPS or further descriptors of infusion side effects. That said, there were no appreciable episodes of patient discomfort or intolerance that resulted in infusion termination. In the absence of objective adverse effect data, oral morphine equivalent (OME) and RASS data can infer the overall effect and tolerance of the dexmedetomidine infusion, but they are limited tools.

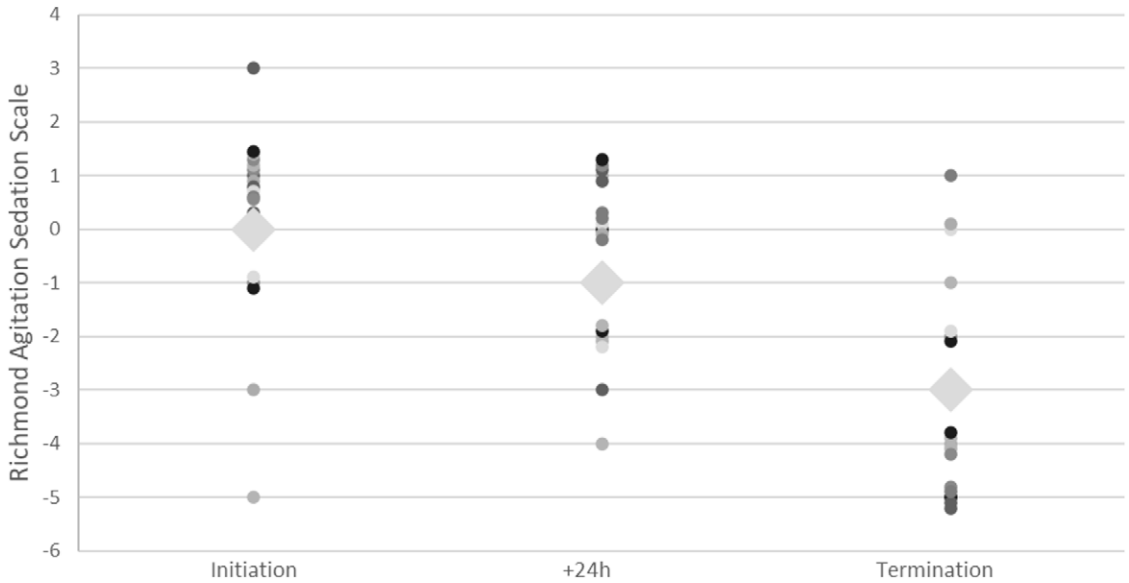

FIG. 3. Opioid trend and benzodiazepine dosing in relation to the day of dexmedetomidine administration.

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Place in Therapy

Dexmedetomidine's utility is evident for patients approaching the EoL, particularly those assessed by an interprofessional palliative team as having opioid-refractory and complex total pain.[29] It is most useful in cases where patients wish to remain lucid for some period of time. We have considered moving its use "up-stream," to those with a do-not-attempt-resuscitation but full care status. The use of dexmedetomidine in this patient population currently has significant barriers to implementation, including the risk of dexmedetomidine withdrawal.[30] and the lack of guidelines for the nonICU management of cardiovascular side effects.[3,21,31] Until we receive more guidance on these barriers to implementation, we support the use of dexmedetomidine at the EoL only.

Conclusion

This study contributes to understanding the role of dexmedetomidine in managing refractory symptoms in the palliative care setting at the EoL. Our study demonstrates an initial marked decrease in MEDD and an ultimate lower MEDD at termination of dexmedetomidine infusion than the patient's baseline MEDD. RASS values declined as the patient's course progressed, which is typical at the EoL. The need for escalating benzodiazepine dosing in most patients, as well as some patients needing adjuvant chlorpromazine for agitation and proportionate sedation, suggests that these patients were experiencing refractory symptoms in multiple domains. Further studies assessing the impact of dexmedetomidine when coadministered with other commonly used medications at the EoL, such as opioids, benzodiazepines, and chlorpromazine, will be important.

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