Pain Ther (2023) 12:593–605
https://doi.org/10.1007/s40122-023-00485-2

BRIEF REPORT

Emergency Palliative Cancer Care: Dexmedetomidine Treatment Experiences—A Retrospective Brief Report on Nine Consecutive Cases

Erik Torbjørn Løhre · Augstein Svedahl · Gunnhild Jakobsen · Tora Skeidsvoll Solheim · Pål Klepstad · Morten Thronæs

Received: November 30, 2022 / Accepted: February 6, 2023 / Published online: February 18, 2023

ABSTRACT

Introduction: Dexmedetomidine, an alpha-2 adrenergic receptor agonist with potential opioid sparing properties, is utilized in palliative medicine, but the knowledge base for this practice is limited. We describe concomitant use of dexmedetomidine and opioids in an acute palliative care unit.

Methods: We included all hospitalized palliative cancer care patients treated with dexmedetomidine from January 2019 to January 2021. Demographics, opioid doses, dexmedetomidine indications and dosing, reported effects and adverse responses, as well as treatment lengths were recorded.

Results: Three women and six men aged 42–-66 years with metastatic cancer and Eastern Cooperative Oncology Group (ECOG) performance status I–IV used dexmedetomidine and opioids concomitantly. Indications for dexmedetomidine were pain (n = 7) and anxiety (n = 2). Dexmedetomidine was administered intravenously in two patients and subcutaneously in seven. All administrations were continuous infusions; initial doses ranged from 240 to 1344 μg/24 h with later doses from 240 to 2440 μg/24 h. Physicians reported relief from pain and anxiety, but two patients required neuraxial pain management during admission. At day 2 of dexmedetomidine treatment, the opioid dose was reduced in six out of nine patients. For all patients with available data at day 7, mean opioid dose was reduced to 74% of the initial dose. When excluding the two patients requiring neuraxial pain management, the corresponding number was 80%. Two patients had transient hypotension, but dexmedetomidine was well tolerated and in no cases withdrawn due to adverse effects. Mean

E. T. Løhre (✉) · G. Jakobsen · T. S. Solheim · M. Thronæs
Cancer Clinic, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
e-mail: erik.t.lohre@ntnu.no

E. T. Løhre · T. S. Solheim · M. Thronæs
Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology, Trondheim, Norway

A. Svedahl · P. Klepstad
Department of Anesthesiology and Intensive Care Medicine, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

G. Jakobsen
Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology, Trondheim, Norway

P. Klepstad
Department of Circulation and Medical Imaging, Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology, Trondheim, Norway

dexmedetomidine treatment length was 40 days.
Conclusions: Dexmedetomidine treatment decreased opioid consumption and was well tolerated in a retrospective study of nine palliative cancer care patients. It may represent a treatment option late in the disease trajectory.

Keywords: Dexmedetomidine; Palliative care; Cancer pain; Anxiety; Retrospective

Key Summary Points

Why carry out this study?

In some patients with advanced cancer, pain and anxiety are difficult symptoms to treat properly, both due to insufficient symptom relief and unwanted side effects from parenteral opioids and benzodiazepines.

We present retrospective data on the potential role of additional dexmedetomidine for these patients.

What was learned from the study?

Additional dexmedetomidine decreased opioid consumption and was well tolerated in a small retrospective study.

Symptom relief was reported. Due to study design and limited available data, the results must be interpreted with caution.

INTRODUCTION

Pain and anxiety are prevalent symptoms in patients with advanced cancer, and late in the disease trajectory patients also suffer from increased drowsiness [1, 2]. Opioids are the mainstay of analgesic therapy for moderate-to-severe cancer pain and benzodiazepines are used to treat anxiety [3, 4]. Both opioids and benzodiazepines increase the probability for drowsiness, which may limit adequate dose titration and result in suboptimal symptom management [5–7]. Consequently, there is a need for novel treatment options to alleviate refractory symptoms late in the course of cancer [8–11].

Dexmedetomidine is a potent and selective alpha-2 adrenergic receptor agonist, first approved in the US in 1999, and now in clinical use in more than 70 countries [11, 12]. Dexmedetomidine is used as a sedative, anxiolytic, and analgesic-sparing drug [13, 14]. The sedative response is unique and, by reducing central sympathetic activity, makes the patient stay arousable and able to communicate [15–17]. The anxiolytic and analgesic-sparing qualities are mediated through adrenoreceptors located in the central nervous system [13, 16]. With reduced doses of opioids and benzodiazepines, dexmedetomidine might contribute to less therapy-induced drowsiness and a decreased delirium occurrence [5, 6, 18]. In addition, dexmedetomidine's presumed neuroprotective and anti-inflammatory attributes can represent a potential for delirium management [16, 17, 19]. Moreover, while opioids and benzodiazepines may reduce respiratory rates, dexmedetomidine does not exert this respiratory depressant effect [20].

Evidence from randomized controlled trials and a Cochrane review showed that extended use of dexmedetomidine is feasible and beneficial in intensive care, with reduced duration of mechanical ventilation and length of stay [16, 21, 22]. The short onset of action (15 min after IV administration) and the short terminal half-life (2–2.5 h) make the drug easy to monitor and titrate [23]. Dexmedetomidine is also rapidly absorbed after subcutaneous administration and usually well tolerated, with bradycardia and fever as the most relevant potential adverse effects [11, 23–25].

A decade ago, a review article outlined the possibilities for the use of dexmedetomidine in palliative care patients [23]. However, the evidence base for its use in this group of patients is still limited [26]. For adults, case reports described symptom relief in patients with severe cancer pain and anxiety, and anecdotal papers reported positive effects on various symptoms like delirium, dyspnea, vomiting, and depression [8–10, 27–31]. In terminally ill children, a

recent systematic review, based on retrospective evidence, found dexmedetomidine for pain control to be significantly associated with improved quality of life [32].

For more than 20 years, dexmedetomidine has proven useful in anesthesia. For patients with advanced cancer and complex symptomatology, the drug may constitute a novel pharmacological approach for improved palliative care. With the aim of describing effects, safety, and tolerability, we reviewed the charts of adult cancer patients consecutively treated with dexmedetomidine in an acute palliative care unit (APCU). We addressed the following research questions:

1. Which indications were decisive for initiating dexmedetomidine treatment?
2. What effects and side effects were registered and when?
3. For how long was dexmedetomidine used, and was it continued after hospital discharge?

METHODS

Study Design

The APCU, Cancer Clinic, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway, has 12 beds and approximately 600 admissions a year, and is an ESMO designated center of integrated oncology and palliative care. The admitted patients consist of adult cancer patients with incurable disease and symptom burden warranting hospitalization. Previous research demonstrated that mean symptom scores at admission for worst pain intensity, anxiety, and drowsiness were 5.2, 3.0, and 5.2 (numeric rating scale (NRS) 0–10), respectively [33]. Patients with hematological, gynecological, and pulmonary cancer are only admitted to the APCU when in need of neuraxial pain management. The current study is an in-house cohort study including all patients consecutively treated with continuous administration of dexmedetomidine between January 1, 2019 and January 1, 2021. Treatment was initiated if insufficient symptom relief, and/or unacceptable side effects with the use of standard interventions. Dexmedetomidine treatment was started and monitored by anesthesiologists. The study participants were identified retrospectively.

The Intervention

Dexmedetomidine was used as an add-on to regular medication for management of refractory symptoms. The starting dose depended on clinical judgement and patient weight, but set no lower than 240 μg/24 h (equivalent to 0.2 μg/kg/h for a patient weighing 50 kg). Evaluations were conducted every 8 h for the first 24 h, thereafter daily. Dexmedetomidine dose adjustments and dose adjustments of the regular medication for symptom management were made based on patient reports and physician-evaluated symptom relief and side effects.

Data Collection and Assessments

Data on patient demographics, metastatic status, Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities, and pre-intervention symptom management were collected by chart review [34]. Physician-reported information on dexmedetomidine indications, dosing, effects and side effects, and treatment length were also collected from the patients' medical records. Opioid dose at the introduction of dexmedetomidine was defined as 100% and further opioid doses calculated as percentages of that dose. Vital parameters, including blood pressure, heart rate, and oxygen saturation were measured every 8 h for the first 24 h, then daily until day seven of treatment. After that, follow-up was performed as in routine care. Body temperature was measured if hyperthermia was suspected. Tolerability and safety were assessed in accordance with the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 [35].

Statistical Analysis

Descriptive analyses were used to summarize clinical quantitative data. Means or medians

were used as descriptors of central tendencies, and range as descriptor of dispersion. Statistical analysis was performed using SPSS statistical software (Version 27.0).

Ethics

The retrospective chart review was approved by the Regional Committee for Medical and Health Research Ethics (reference number 2021/258166). The study was conducted in accordance with the Declaration of Helsinki [36].

RESULTS

Patient Demographics

During the 2-year study period, nine patients used dexmedetomidine as an add-on to the regular medical management of refractory symptoms provided at the APCU. Six were men and mean age was 54 years (range, 42–66 years). All had metastatic disease (one patient with lymph node metastases only) and median ECOG performance status was III (range, I–IV).

Table 1 Patient demographics

Characteristics	*n* (range)
Gender	
Female	3
Male	6
Age (years), mean	54 (42–66)
Weight (kg), mean	75 (50–89)
Metastatic cancer	9
ECOG performance status, median	III (I–IV)
Comorbidity	
Cardiovascular disease	3
Liver disease	1
Chronic obstructive pulmonary disease	1

Further information on patient demographics is shown in Table 1.

Pre-intervention Symptom Management

Prior to the introduction of dexmedetomidine, all patients were administered continuous parenteral opioid infusions via syringe drivers. Three patients received opioids intravenously, the remaining six subcutaneously. Maximum parenteral opioid dose was hydromorphone 850 mg/24 h, and two patients used more than one opioid. Additionally, one patient already underwent neuraxial pain management. Two patients experienced severe anxiety despite parenteral midazolam (68 and 13 mg/24 h, respectively), when dexmedetomidine was introduced. Details on pre-dexmedetomidine symptom management are delineated in Table 2.

Indications for Use

For seven patients, pain was decisive for the introduction of dexmedetomidine and for two, anxiety. The two patients with difficult-to-treat anxiety also suffered from pain and depression, respectively. Four patients experienced unacceptable side effects from pre-dexmedetomidine symptom management, of which drowsiness was the most common.

Dexmedetomidine Administration and Dosing

All patients had continuous infusions of dexmedetomidine. Starting doses ranged from 240 to 1344 µg/24 h, and continued doses ranged from 240 to 2440 µg/24 h. Mean maintenance dose at day 7 was 977 µg/24 h. The specifics are described in Table 3 and illustrated in Fig. 1. The two patients with severe anxiety received the drug intravenously. In line with expressed wishes, for one patient the infusion rate was decreased when suitable or increased for comfort care. The other seven patients were given dexmedetomidine subcutaneously.

Table 2 Pre-intervention symptom management

Administration and drugs			*n*	Dose range
Intrathecal				
	Local anesthetic			
		Bupivacaine	1	180[a]
Intravenous				
	Opioid			
		Hydromorphone	3	260–850[a]
	Benzodiazepine			
		Midazolam	3	2–68[a]
		Diazepam	1	35[a]
	Corticosteroid			
		Dexamethasone	3	16[a]
	Peripherally acting analgesic			
		Paracetamol	2	4000[a]
	Anesthetic			
		Ketamine	1	120[a]
		Esketamine	2	25–30[a]
Subcutaneous				
	Opioid			
		Hydromorphone	3	18–280[a]
		Morphine	1	105[a]
		Oxycodone	2	290–365[a]
	Benzodiazepine			
		Midazolam	6	2–13[a]
	Anesthetic			
		Ketamine	1	90[a]
		Esketamine	3	25–75[a]
Transdermal				
	Opioid			
		Fentanyl	2	1200–12000[b]
Oral				
	Opioid			
		Methadone	1	15[a]

Table 2 continued

Administration and drugs		*n*	Dose range
Benzodiazepine			
	Oxazepam	2	10–15[a]
Cortocosteroid			
	Dexamethasone	5	4–16[a]
Peripherally acting analgesic			
	Paracetamol	4	3000–4000[a]
Antiepileptic			
	Gabapentin	2	900[a]
	Pregabalin	1	225[a]
Antidepressant			
	Mirtazapine	1	30[a]
	Escitalopram	1	15[a]

[a]mg/24 h
[b]μg/24 h

Registered Effects

With no systematic NRS registrations available, effect evaluations are based on chart reviews. The two patients with severe anxiety experienced symptom relief with acceptable side effects, but also midazolam doses were increased during the first week of dexmedetomidine treatment (Table 3). They were able to communicate with both staff and next of kin. Among the seven other patients started on dexmedetomidine, pain relief was observed in five. For two patients, initiating neuraxial pain management was necessary to achieve sufficient pain relief during the primary hospital stay. One of these patients required additional propofol sedation, and for the other, dexmedetomidine was withdrawn due to pain relief from intrathecal pain management.

At day 2 of dexmedetomidine treatment, the opioid consumption was reduced in six out of nine patients (Table 3). One patient died at day 4 and one was discharged at day 6, but for the four remaining patients the systemic opioid dose at day 7 was lower than at the introduction of dexmedetomidine. For the seven patients with available data after 1 week of dexmedetomidine treatment, mean systemic opioid consumption was reduced by 26% (Fig. 1). When excluding the two patients started on neuraxial pain management during the first week of dexmedetomidine treatment, mean systemic opioid consumption was reduced by 20% (Fig. 1). When also excluding the one patient with severe anxiety, the corresponding number was 35% (Fig. 1). For one patient started on neuraxial pain management, the systemic opioid dose was increased approximately by 5% the following day, and for the other, decreased by 9% (Table 3).

Safety and Tolerability

Two patients experienced hypotension at day 1 of dexmedetomidine administration. One patient had a temporary drop in blood pressure

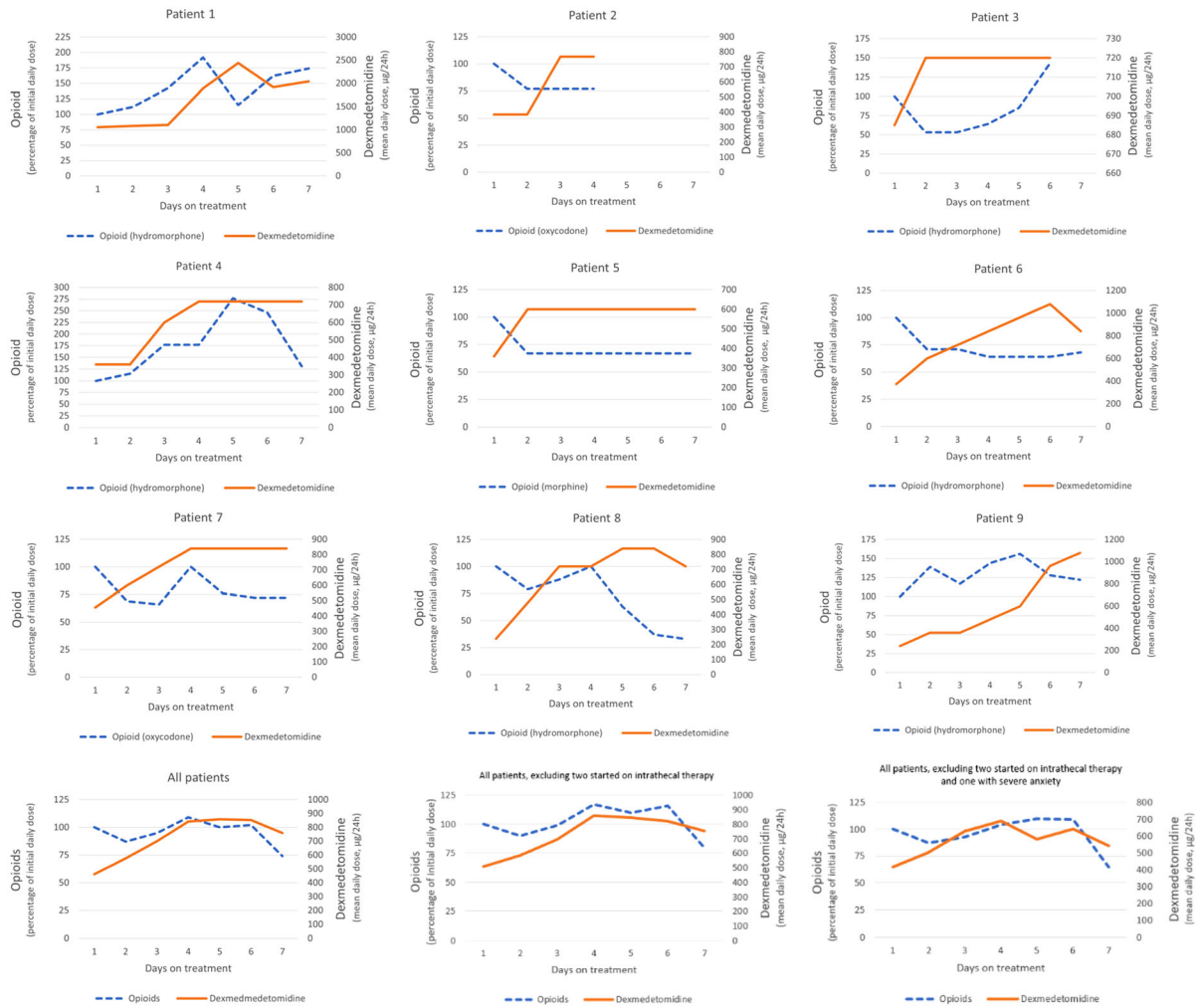

Fig. 1 Dosages during the first week of concomitant dexmedetomidine and opioid treatment. For opioids, indicated as percentages of the dose when dexmedetomidine was introduced. For patient No. 6, additional fentanyl and methadone dose reductions (Table 3) are not displayed

from 94/60 to 70/46 mmHg and intravascular fluid replenishment was indicated. The incident was classified as CTCAE grade 3. One patient had a temporary drop in blood pressure from systolic 100–110 to 92/56 mmHg, classified as a grade 2 reaction. For both patients, dexmedetomidine administration was continued without further hypotension. No incidents of drug-related hyperthermia, bradycardia, hypertension, respiratory depression, or agitation were reported. In addition, no treatment-related drug withdrawals occurred. The observed sedative responses did not limit continued use, even though the two patients with severe anxiety experienced drowsiness. For the patient who died after 4 days of dexmedetomidine use, imminent cancer-related death was expected prior to the administration of the drug.

Treatment Length and Place of Care

Mean treatment period was 40 days (range, 4–-114 days). Cumulative treatment observation period was 361 days. All but one patient continued dexmedetomidine until death. In the one exception, dexmedetomidine was discontinued after 18 days of treatment. For the

Table 3 Mean daily dexmedetomidine (DEX), opioid, and midazolam doses during the first week

Patient	Drugs and dosing	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1[a]	DEX, μg/24 h	1056	1082	1104	1892	2440	1920	2040
	(Daily dose range, μg/kg/h)[b]	0.3–1.0	0.4–0.6	0.3–1.1	0.4–0.8	0.5–0.8	1.0–1.7	0.5–2.0
	Hydromorphone, mg/24 h	260	290	370	500	300	410	450
	Midazolam, mg/24 h	68	72	90	100	68	72	100
2[a]	DEX, μg/24 h	384	384	768	768[c]			
	Oxycodone, mg/24 h	365	280	280	280			
	Midazolam, mg/24 h	13	13	80	180			
3	DEX, μg/24 h	685	720	720	720	720	720[d]	
	Hydromorphone, mg/24 h	850	450	450	540	720	1215	
4	DEX, μg/24 h	360	360	600	720	720	720	720
	Hydromorphone, mg/24 h	130	150	230	230	360	320	170
5	DEX, μg/24 h	360	600	600	600	600	600	600
	Morphine, mg/24 h	105	70	70	70	70	70	70
6	DEX, μg/24 h	373	600	720	840	960	1080[e]	840
	Hydromorphone, mg/24 h	280	200	200	180	180	180	190
	Methadone, mg/24 h	15	15	15	15	15	0	0
	Fentanyl, μg/24 h	12,000	9600	9600	7200	3600	0	0
7	DEX, μg/24 h	455	600	720	840	840	840	840
	Oxycodone, mg/24 h	290	200	190	290	220	210	210
8	DEX, μg/24 h	240	480	720	720	840	840[e]	720
	Hydromorphone, mg/24 h	600	475	525	600	380	220	200
	Fentanyl, μg/24 h	1200	1200	1200	1200	1200	1200	1200

Table 3 continued

Patient	Drugs and dosing	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
9	DEX, µg/24 h	240	360	360	480	600	960	1080
	Hydromorphone, mg/24 h	18	25	21	26	28	23	22

[a]Anxiety decisive for the introduction of dexmedetomidine
[b]Range indicated due to large dose variations
[c]Died at day 4
[d]Discharged at day six and further dosing unavailable
[e]Neuraxial pain management started

patients who continued dexmedetomidine until death, three died during the primary hospital stay, two were discharged to nursing homes, and three to home care.

DISCUSSION

Statement of Principal Findings

The study reports accumulated treatment experiences from the use of dexmedetomidine in palliative cancer care. We present results from all consecutively treated patients during a two-year period and provide cumulative data from almost one year of treatment. Both symptom management and reduced opioid doses were documented in the reviewed charts. Two patients experienced initial hypotension, but administered in close collaboration with anesthesiologists dexmedetomidine use was safe. No side effect-related drug withdrawals were registered. However, due to study design and sample size, no firm conclusions can be drawn.

Appraisal of Methods

Retrospective studies have several inherent limitations [37]. The collected data were retrieved from charts not designed for the research purpose and biases may affect the results. The treatment was started at a university hospital with immediate access to both anesthesiology and palliative care expertise. Hence, the findings may not be generalizable to other settings. In addition, the large systemic doses of medications for symptom management, even in patients with intrathecal infusions, indicate that the studied patients were highly selected. Furthermore, patient-reported outcome measures (PROMs) are advocated in palliative care research [38]. The current study did not provide systematic and standardized PROMs, which implies that the results should be interpreted with even more caution. Finally, in clinical practice, efforts are made to best balance positive responses and side effects. This fact may have influenced both dexmedetomidine and

opioid dosing, and the choice to initiate neuraxial pain management in two patients.

On the other hand, the current paper describes the largest consecutive series of adult patients with advanced cancer and refractory pain and anxiety treated with dexmedetomidine. The findings may serve as a basis for hypotheses in future better-designed studies.

Comparison with Previous Work

Published 20 years ago, the first report on the use of dexmedetomidine in palliative care depicted its applicability in dying cancer patients with pain, anxiety, and symptoms compatible with side effects from the ongoing symptom management [27]. A decade later, a case report described the drug as a safe adjuvant agent for analgesia in patients with intractable cancer pain [8]. In addition to dexmedetomidine's positive effects on pain and anxiety, its analgesic sparing properties are reported [9, 28, 39]. Recently, a narrative review on the use of dexmedetomidine in palliative care highlighted cancer pain and neuropsychiatric symptoms as potential relevant indications [25]. This is supported by our study, which also indicated beneficial treatment effects.

Already the first report concerning dexmedetomidine for symptom relief late in the palliative care trajectory described the use of continuous infusions [27]. While intravenous administration previously was preferred, the proven rapid and efficient absorption of subcutaneously administered dexmedetomidine made subcutaneous drug delivery a feasible alternative [8, 10, 11, 17]. In addition, dexmedetomidine is demonstrated visually compatible in admixtures with drugs like morphine, hydromorphone, haloperidol, and hyoscine butylbromide, and the drug is stable in bags intended for subcutaneous infusions [40, 41].

Many clinicians refrain from loading doses and start with a rather low dose such as dexmedetomidine 0.3 μg/kg/h [25]. Maintenance doses ranging from 0.2 to 1.0 μg/kg/h are suggested, even though the use of higher doses is described in specialized units [10, 25, 39]. In our study, the lowest dexmedetomidine starting dose was approximately 0.2 μg/kg/h and the highest maintenance dose 2.0 μg/kg/h (Table 3). For compliance with common palliative care prescription standards, the doses were described as milligrams per 24 h [3, 25].

In the literature, the symptom relief of adjuvant dexmedetomidine are both described by physician-reported observations and PROMs [8–10, 27–29, 39]. In case reports where PROMs were registered, treatment results for cancer pain varied widely [8, 9]. With pain scores of NRS 8 before dexmedetomidine treatment, the corresponding scores after treatment ranged from 0 to 6 (0–10) [8, 9]. These findings are consistent with our results, where five out of seven patients with severe cancer pain described pain relief. In a case report on successful treatment of cancer pain and depression with intrathecal administration of dexmedetomidine and morphine, also significantly reduced symptom scores for anxiety and drowsiness were reported [29]. These data are congruent with our observations of reduced anxiety and acceptable side effects. However, in our study, the effects of increased midazolam doses must be considered and may even cause the observed effect.

The use of dexmedetomidine is restricted and its application in palliative care is off label [25]. The treatment in our study was initiated and monitored by anesthesiologists. Previous papers have described the safe use of dexmedetomidine in palliative care patients [9, 29, 39]. However, potential safety issues include the risk for bradycardia, arrhythmias, and both hyper- and hypotension [25]. Initial ECG monitoring for selected patients, dose reductions in case of hepatic dysfunction, and avoiding loading doses may reduce the risk for safety problems [25]. Besides, in patients with advanced cancer and refractory symptoms, some risks for adverse effects might be acceptable. In the current study, two patients had temporary hypotension, but there were no dexmedetomidine-related treatment withdrawals.

Several papers describe the prolonged use of dexmedetomidine in palliative care [29, 30, 39, 42]. One case report described

continuous intravenous dexmedetomidine infusion for 76 days, and another intrathecal administration that was still ongoing when the report was written [29, 39]. In pediatric palliative care, treatment lengths up to 111 days are described, and one adolescent palliative care patients used continuous dexmedetomidine in a home care setting for nearly 3 years [30, 42]. One of our patients received dexmedetomidine for little less than 4 months, and we report almost 1 year of accumulated treatment experiences. Altogether, the published literature so far supports the potential for long-term use of dexmedetomidine in palliative care.

Implications and Further Work

Based on previous and current findings, dexmedetomidine may have potential for more widespread use in palliative cancer care, both regarding indications and length of treatment. However, its use in palliative care is only supported by weak evidence. To ensure patient safety and to establish a better body of knowledge, larger studies with improved design are needed. Future studies may also address the potential for utilization of dexmedetomidine earlier during palliative care.

CONCLUSIONS

No firm conclusions can be drawn from the current study. Still, in a retrospective study of nine palliative cancer patients, the introduction of adjuvant dexmedetomidine by anesthesiologists in an APCU was safe and resulted in reduced opioid consumption for patients late in the disease trajectory.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article. The Rapid Service Fee was funded by the authors.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. Erik Torbjørn Løhre, Augstein Svedahl, and Morten Thronæs treated the patients. Erik Torbjørn Løhre, Augstein Svedahl, Gunnhild Jakobsen, Tora Skeidsvoll Solheim, Pål Klepstad, and Morten Thronæs contributed to the conception, design, analysis, and/or interpretation of data and drafted the manuscript. Gunnhild Jakobsen prepared tables and figure. All authors reviewed the manuscript.

Prior Presentation. Preliminary study results were presented at the 12th International Seminar of the European Palliative Care Research Centre, November 2022, Aarhus, Denmark.

Disclosures. Erik Torbjørn Løhre, Augstein Svedahl, Gunnhild Jakobsen, Tora Skeidsvoll Solheim, Pål Klepstad, and Morten Thronæs have nothing to disclose.

Compliance with Ethics Guidelines. The study was approved by the Regional Committee for Medical and Health Research Ethics and by the Research Committee of the Cancer Clinic, St. Olavs hospital, Trondheim University Hospital. The study was conducted in accordance with the Declaration of Helsinki.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Teunissen SC, Wesker W, Kruitwagen C, de Haes HC, Voest EE, de Graeff A. Symptom prevalence in patients with incurable cancer: a systematic review. J Pain Sympt Manag. 2007;34(1):94–104.

2. Seow H, Barbera L, Sutradhar R, Howell D, Dudgeon D, Atzema C, et al. Trajectory of performance status and symptom scores for patients with cancer during the last six months of life. J Clin Oncol. 2011;29(9):1151–8.

3. Fallon M, Giusti R, Aielli F, Hoskin P, Rolke R, Sharma M, et al. Management of cancer pain in adult patients: ESMO clinical practice guidelines. Ann Oncol. 2018;29(Supplement_4):iv166–91.

4. Prommer E. Midazolam: an essential palliative care drug. Palliat Care Soc Pract. 2020;14:2632352419895527.

5. Kotlinska-Lemieszek A, Paulsen O, Kaasa S, Klepstad P. Polypharmacy in patients with advanced cancer and pain: a European cross-sectional study of 2282 patients. J Pain Sympt Manag. 2014;48(6):1145–59.

6. Haider A, Azhar A, Nguyen K, Dev R, Naqvi SMA, Naqvi SMA, et al. Concurrent use of opioids with benzodiazepines or nonbenzodiazepine sedatives among patients with cancer referred to an outpatient palliative care clinic. Cancer. 2019;125(24):4525–31.

7. Henson LA, Maddocks M, Evans C, Davidson M, Hicks S, Higginson IJ. Palliative care and the management of common distressing symptoms in advanced cancer: pain, breathlessness, nausea and vomiting, and fatigue. J Clin Oncol. 2020;38(9):905–14.

8. Roberts SB, Wozencraft CP, Coyne PJ, Smith TJ. Dexmedetomidine as an adjuvant analgesic for intractable cancer pain. J Palliat Med. 2011;14(3):371–3.

9. Mupamombe CT, Luczkiewicz D, Kerr C. Dexmedetomidine as an option for opioid refractory pain in the hospice setting. J Palliat Med. 2019;22(11):1478–81.

10. Hilliard N, Brown S, Mitchinson S. A case report of dexmedetomidine used to treat intractable pain and delirium in a tertiary palliative care unit. Palliat Med. 2015;29(3):278–81.

11. Uusalo P, Al-Ramahi D, Tilli I, Aantaa RA, Scheinin M, Saari TI. Subcutaneously administered dexmedetomidine is efficiently absorbed and is associated with attenuated cardiovascular effects in healthy volunteers. Eur J Clin Pharmacol. 2018;74(8):1047–54.

12. Gerlach AT, Murphy CV, Dasta JF. An updated focused review of dexmedetomidine in adults. Ann Pharmacother. 2009;43(12):2064–74.

13. Weerink MAS, Struys M, Hannivoort LN, Barends CRM, Absalom AR, Colin P. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. Clin Pharmacokinet. 2017;56(8):893–913.

14. Ashraf MW, Uusalo P, Scheinin M, Saari TI. Population modelling of dexmedetomidine pharmacokinetics and haemodynamic effects after intravenous and subcutaneous administration. Clin Pharmacokinet. 2020;59(11):1467–82.

15. Nelson LE, Lu J, Guo T, Saper CB, Franks NP, Maze M. The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. Anesthesiology. 2003;98(2):428–36.

16. Chen K, Lu Z, Xin YC, Cai Y, Chen Y, Pan SM. Alpha-2 agonists for long-term sedation during mechanical ventilation in critically ill patients. Cochrane Database Syst Rev (Online). 2015;1:CD010269.

17. Thomas B, Lo WA, Nangati Z, Barclay G. Dexmedetomidine for hyperactive delirium at the end of life: an open-label single arm pilot study with dose escalation in adult patients admitted to an inpatient palliative care unit. Palliat Med. 2021;35(4):729–37.

18. Bush SH, Lawlor PG, Ryan K, Centeno C, Lucchesi M, Kanji S, et al. Delirium in adult cancer patients: ESMO clinical practice guidelines. Ann Oncol. 2018;29(Suppl 4):iv143–65.

19. Hu J, Zhu M, Gao Z, Zhao S, Feng X, Chen J, et al. Dexmedetomidine for prevention of postoperative delirium in older adults undergoing

oesophagectomy with total intravenous anaesthesia: a double-blind, randomised clinical trial. Eur J Anaesthesiol. 2021;38(Suppl 1):S9–17.

20. Patel SB, Kress JP. Sedation and analgesia in the mechanically ventilated patient. Am J Respir Crit Care Med. 2012;185(5):486–97.

21. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA. 2009;301(5):489–99.

22. Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA. 2012;307(11):1151–60.

23. Prommer E. Review article: dexmedetomidine: does it have potential in palliative medicine? Am J Hosp Palliat Care. 2011;28(4):276–83.

24. Schurr JW, Ambrosi L, Lastra JL, McLaughlin KC, Hacobian G, Szumita PM. Fever associated with dexmedetomidine in adult acute care patients: a systematic review of the literature. J Clin Pharmacol. 2021;61(7):848–56.

25. Gaertner J, Fusi-Schmidhauser T. Dexmedetomidine: a magic bullet on its way into palliative care-a narrative review and practice recommendations. Ann Palliat Med. 2022;11(4):1491–504.

26. Daly J, Willis K, Small R, Green J, Welch N, Kealy M, et al. A hierarchy of evidence for assessing qualitative health research. J Clin Epidemiol. 2007;60(1):43–9.

27. Soares LG, Naylor C, Martins MA, Peixoto G. Dexmedetomidine: a new option for intractable distress in the dying. J Pain Sympt Manag. 2002;24(1):6–8.

28. Seymore RJ, Manis MM, Coyne PJ. Dexmedetomidine use in a case of severe cancer pain. J Pain Palliat Care Pharmacother. 2019;33(1–2):34–41.

29. Huang G, Liu G, Zhou Z, Yang J, Su C. Successful treatment of refractory cancer pain and depression with continuous intrathecal administration of dexmedetomidine and morphine: a case report. Pain Ther. 2020;9(2):797–804.

30. Thienprayoon R, Meyer M, Flint H, Weidner N, Hirsch R. Use of continuous dexmedetomidine at home for nearly three years in a young woman with end-stage cyanotic congenital heart disease and cyclic vomiting. J Palliat Med. 2019;22(10):1289–92.

31. Mano A, Murata T, Date K, Kawata M, Sato M, Yamashita N, et al. Dexmedetomidine for dyspnoea. BMJ Support Palliat Care. 2020.

32. Piette V, Beernaert K, Cohen J, Pauwels NS, Scherrens AL, van der Werff Ten Bosch J, et al. Healthcare interventions improving and reducing quality of life in children at the end of life: a systematic review. Pediatr Res. 2021;89(5):1065–77.

33. Thronaes M, Lohre ET, Kvikstad A, Brenne E, Norvaag R, Aalberg KO, et al. Interventions and symptom relief in hospital palliative cancer care: results from a prospective longitudinal study. Support Care Cancer. 2021;29(11):6595–603.

34. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649–55.

35. Services UDoHaH. Common terminology criteria for adverse events (CTCAE), version 5.0. National Institute of Health, National Cancer Institute. 2017.

36. Association WM. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bull World Health Org World Health Org. 2001;79(4):373–4.

37. Talari K, Goyal M. Retrospective studies—utility and caveats. J R Coll Physicians Edinb. 2020;50(4):398–402.

38. Kaasa S, Loge JH, Aapro M, Albreht T, Anderson R, Bruera E, et al. Integration of oncology and palliative care: a Lancet Oncology Commission. Lancet Oncol. 2018;19(11):e588–653.

39. Hofherr ML, Abrahm JL, Rickerson E. Dexmedetomidine: a novel strategy for patients with intractable pain, opioid-induced hyperalgesia, or delirium at the end of life. J Palliat Med. 2020;23(11):1515–7.

40. Thomas B, Murrell L, Spendley P. Dexmedetomidine: admixture compatibility with palliative care drugs. BMJ Support Palliat Care. 2021. https://doi.org/10.1136/bmjspcare-2020-002583.

41. Wolfe A, Zhang J, Lapenskie J, Downar J, Kanji S. Stability of dexmedetomidine in polyvinyl chloride bags containing 0.9% sodium chloride intended for subcutaneous infusions. Int J Pharm Compd. 2021;25(4):330–5.

42. Burns J, Jackson K, Sheehy KA, Finkel JC, Quezado ZM. The use of dexmedetomidine in pediatric palliative care: a preliminary study. J Palliat Med. 2017;20(7):779–83.