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Description of Continuous Palliative Sedation Practices in a Large Health Region and Comparison with Clinical Practice Guidelines

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ABSTRACT

Background: Published reports of continuous palliative sedation therapy suggest heterogeneity in practice. There is a paucity of reports that compare practice to clinical guidelines.

Objectives: To assess adherence of continuous palliative sedation practices with criteria set forth in local clinical guidelines, and to describe other features including prevalence, medication dosing, duration, multidisciplinary team involvement and concurrent therapies.

Design: Retrospective chart review.

Settings/Subjects: We included cases in which a midazolam infusion was ordered at the end of life. Study sites included four adult hospitals in the Calgary health region, two hospices and a tertiary palliative care unit.

Measurements: Descriptive data, including proportion of deaths involving palliative sedation therapy, number of criteria documented, midazolam dose/duration, concurrent symptom management therapies and referrals to spiritual care, psychology or social work.

Results: Continuous palliative sedation therapy occurred in 602 out of 14360 deaths (4.2%). Full adherence to criteria occurred in 7% of cases. Most commonly missed criteria were: a “C2” goals of care designation order (comfort care focus in the imminently dying) (84%), and documentation of imminent death in the chart (55%). Concurrent medical therapies included

opioids in 98% of cases and intravenous hydration in 85% of cases. Few referrals were made to multidisciplinary care teams.

Conclusions: We found low adherence to palliative sedation guidelines. This may reflect the perception that some criteria are redundant or clinically unimportant. Future work could include a study of barriers to guideline uptake, and guideline modification to provide direction on concurrent therapies and multidisciplinary team involvement.

Key words: continuous palliative sedation therapy, terminal sedation, midazolam, practice guidelines, acute care, hospice

Introduction

Although palliative symptom management strategies are generally effective at managing physical suffering at the end of life, there remains a minority of cases involving intolerable symptoms that require continuous palliative sedation therapy (CPST). The Canadian Society of Palliative Care Physicians Task Force has published a framework for CPST which includes the use of pharmacologic agents with the primary aim of reducing consciousness and limiting use to cases of refractory and intolerable suffering in patients with advanced progressive illness—more explicitly patients in the last two weeks of life.[1]

The reported prevalence of CPST varies widely. A systematic review published in 2012 cited a mean frequency of 34.4%, with a range of 14.6-66.7%,[2] while a narrative review published in 2013 reported a range of 0-64%, with higher prevalence seen in hospices and tertiary cancer centres, and lower prevalence in clinical settings with specialist palliative care providers.[3] Further heterogeneity may stem from variations in medications used for CPST. An Italian multicentre prospective observational study reported the use of neuroleptics,[4] and the use of phenobarbital and lorazepam has also been cited.[5,6] In contrast, other sources, including large systematic reviews, cite midazolam as the most commonly recommended or used agent.[2,7-10] The use of proportional, intermittent, and deep continuous sedation have all been included in the

published literature on CPST.[2] This heterogeneity has made it challenging to compare practice across different settings.

In Calgary, CPST involves the use of a titrated continuous infusion of midazolam to achieve deep levels of sedation. Our practice is informed by a clinical practice guideline (CPG) that was locally disseminated 1999 and published in 2003.[11] The guideline includes the following elements: consultation with a palliative care physician; confirmation of intractable and intolerable suffering; and careful communication and documentation with patients and/or their family members (appendix A). This guideline conforms closely with the Canadian framework for CPST.[4]

Previous studies examined CPST practices without comparing data to guidelines,[2,8] or have included data from only a single care setting.[12] Our study adds value because we compare clinical practice to an established CPG, and we include a more broad and generalizable population from various acute care settings, as well as community-based hospice. We also include data from a tertiary palliative care unit, locally referred to as the "Intensive Palliative Care Unit" (IPCU), where palliative care physicians take on the role of attending physician. Patients are referred to the IPCU regardless of medical treatment goals or expected trajectory of disease, with the primary aim of providing symptom management for complex symptoms alongside inpatient medical management. In this study, we retrospectively examine CPST data over eight years. Our objective is to investigate alignment of local CPST practices with the criteria put forth by our local CPG. We also sought to provide descriptive features of local CPST practices, such as indications, concomitant use of medications for treatment of symptoms, other therapies (e.g., intravenous hydration), and level of involvement of multidisciplinary team

members (i.e. psychiatry, spiritual care and social work). In addition, we provide some exploratory analyses to compare CPST practices across three clinical contexts.

Methods

Design

This is a retrospective chart review of patients who received a midazolam infusion at the end of life for deep CPST. The participant selection criteria and study sites included aimed to identify cases that most likely received a midazolam infusion for CPST rather than other reasons, such as for procedural sedation or temporary sedation. Ethics approval was obtained from the University of Calgary Research Ethics Board (REB15-0904).

Setting/Population

We included patients from two community hospices and four adult acute care centres in the city of Calgary, which serves a population of approximately 1 million. The IPCU was treated as a separate study site. To calculate the proportion of deaths with CPST, we included all deaths in adults older than 18 years of age at all study sites but removed cases in which death was due to maternal mortality or trauma (appendix C).

The study included patients at each of the sites who: a) were older than 18 years old and died between February 1, 2007 and January 31, 2015; and b) had a midazolam infusion ordered while the patient had a resuscitation status (locally referred to as "goals of care designation") of "C1" or "C2," defined as maximal symptom control for conditions expected to lead to eventual death, or imminent death (within days), respectively.[13] The goals of care designations are used

within Alberta Health Services to describe resuscitative (R), medical (M) or comfort (C) care and provide direction on interventions and locations of care (appendix D). We also included patients who had a midazolam infusion order on their date of death, regardless of their resuscitation status. We excluded patients that were admitted to critical care during their midazolam infusion, as well as patients that were discharged alive as these were likely not CPST cases. We excluded cases without documented sedation goals.

Data Sources and Collection

All adult hospitals in Calgary and one of the hospices included in our study use an electronic medical record (EMR) which captures details of hospital admissions since January 2007. Physician and clinical nurse specialist documentation is still completed on a paper chart for each patient. The other hospice included in our study uses a paper chart to capture the details of a patient stay. Both electronic and manual chart review was completed due to: a) the unavailability of all required data on electronic records; and b) the absence of electronic medical records at one of the hospice sites.

Demographic details including age and gender were collected. Hospital stay variables included admission location, goals of care designation, type of attending service, length of stay and consultation requests (including palliative care, spiritual care, social work and psychiatry). On the IPCU, all admissions were considered to have the equivalent of a palliative care consultation as the attending physicians are formally trained in palliative care. Medication details included doses of midazolam at initiation and discontinuation, and duration of administration. We also abstracted other medications and therapies of interest after start of CPST, including intravenous fluids, other sedatives (propofol, methotrimeprazine and phenobarbital), anti-

emetics, anti-secretory agents, neuroleptics, antidepressants, laxatives, and opioid and non-opioid analgesics.

We selected a subset of cases, using a convenience sample, for manual chart review to gather data regarding patient suitability for CPST as this information was not available in the electronic medical record. At the community hospice site without an electronic medical record, all cases within the study time frame were included for manual chart review. We looked for documentation of the following items: presence of a terminal illness, expectation of imminent death within "days," goals of care designation of C2 versus other goals of care designation, the presence of an intractable symptom, documentation of informed consent by the patient or substitute decision maker, and referral to a palliative care specialist. These data comprise the criteria set forth by the CPG (Appendix A).

We also looked for the following data via manual chart review: presence of intolerable side effects to current or previous therapies, documentation that other therapies were assessed as being unlikely to provide benefit within a reasonable time frame, documentation that sedation at lighter levels failed to provide relief, presence of psychiatric symptoms, and target sedation goal. The target sedation goal was documented by use of one of two tools: the Richmond Agitation Sedation Scale (-5 for unarousable to +4 for combative), or the Riker Scale (1 for unarousable to 7 for dangerous agitation).[14,15] We combined these two scales as outlined in Appendix B, and then collapsed them into two categories: "deep sedation" and "moderate or light sedation".

Statistical Analysis

Analyses consisted of descriptive summaries of demographic variables and clinical variables using measures of central tendencies and frequency depending on variable type. All

variables were categorized under three discrete care contexts: (1) Hospice, (2) the Intensive Palliative Care Unit (IPCU), and (3) Hospital Inpatient Units.

We conducted exploratory analysis to compare the following between the three sites: a) midazolam infusion practices (e.g., differences in midazolam infusion duration and dosing); b) alignment with CPST guidelines; and c) depth of sedation. In addition, we compared alignment with CPST criteria, across all sites, and in cases that received a palliative care consultation versus those that did not. We made use of the Kruskal-Wallis test for nonparametric data and the chi-squared test for categorical data as appropriate.

All statistical analysis was conducted using SPSS version 22 (IBM SPSS Statistics for Windows, Armonk, NY).

Results

Participant Characteristics

A continuous midazolam infusion was ordered at the end of life in 602 out of a total of 14360 eligible deaths (4.2%).Mean age of participants was 65 years and 50% were men (table 1). The median hospital stay was 7.3 days (range 0-300.3).

Midazolam Dosing and use of Other Therapies

Of all continuous midazolam infusion orders, 466 (77%) were administered. 105 of the remaining 136 patients (77%) died within one day and no doses of midazolam were administered prior to death. In the other 31 cases, the reason for not initiating the order is unknown. The mean duration of midazolam infusion was 27.4 hours. Mean infusion rate was 1.4mg/hr at initiation, and 5.8mg/hr at the time of death. In addition to the continuous infusion, at least one

breakthrough dose of midazolam was administered in 287 (48%) of cases with a total mean breakthrough dose of 11.4 mg (table 2).

We found the mean duration of midazolam infusion to be significantly longer in the hospice setting (61.6 hours) compared to the IPCU (20.5 hours) and the hospital inpatients units (24.1 hours) ($p<0.01$). There was no statistically significant difference in the proportion of cases that had a midazolam infusion order that was not administered between sites ($p=0.05$). The mean initial midazolam infusion rate was significantly higher for the hospice cohort (2.5 mg/hr) compared to the IPCU (1.4 mg/hr) and hospital inpatient units (1.2 mg/hr) ($p<0.01$). The mean final midazolam infusion rate was similar at the hospice and IPCU sites (6.0mg/hr and 6.4mg/hr respectively) but these were both higher than the final infusion rate at the hospital inpatient units (5.5mg/hr) ($p<0.01$). Hospital inpatient units had a significantly smaller number of mean breakthrough doses in the first 24 hours while the hospice cohort had a significantly smaller number of breakthrough doses in the last 24 hours, but the total mean midazolam breakthrough dose was similar across sites (table 2).

Of all patients for whom CPST was ordered, 510 (85%) received concurrent intravenous fluids, 587 (98%) received opioids, 361 (60%) received antiemetics, 341 (57%) received neuroleptics other than methotrimeprazine, and 117 (19%) received methotrimeprazine. There were 76 (13%) referrals to psychiatry, 118 (20%) referrals to spiritual care services, and 16 (3%) referrals to social work (table 3).

Alignment with criteria set forth by CPST guidelines

138 cases underwent a manual chart review to obtain data regarding alignment with the criteria set forth by the CPST guidelines, as well as other characteristics of CPST cases (next section). There was a documented palliative care consultation in77% of cases (106/138).. All 6 criteria were documented in 7% of cases. Four or fewer criteria were documented in 58% of cases across all sites (80/138). The most frequently documented criteria were assessment of terminal illness and refractory symptoms in 88% and 85% of cases, respectively. The least frequently documented criterion was C2 goals of care designation (16%) (table 4).

We compared the alignment with CPST criteria across sites and found that the hospital inpatient unit had a statistically significantly lower mean number of documented criteria (3.5/6) compared to the IPCU (4.3) and hospice sites (4.4) ($p=0.026$) (table 4). Further analysis revealed that, *within the hospital inpatient cohort*, the group without a palliative care consultation had a significantly lower number of mean documented criteria (0.9) compared to the group with a palliative consult (4.2) ($p<0.01$; data not shown). We then compared the mean number of documented criteria in the group with a palliative consultation versus those without *across all sites* and found this to be a statistically significant difference (3.4/5 vs 2.1/5; $p<0.01$). Note that the denominator for the last analysis is 5, as we removed the criterion pertaining to palliative consultation because this was the variable of comparison (see supplementary table in appendix E).

Other Characteristics of CPST Cases

Table 5 displays other characteristics of CPST cases. In the manual chart review, we found that symptoms were inadequately controlled with therapies trialed prior to CPST in 78% of cases (n=107)—this was documented with the highest frequency in the hospice sample (n=31, 94%). In most cases (70%), sedation at lighter levels was trialed and did not provide adequate

relief of symptoms. The top three symptom indications for CPST were dyspnea, delirium and pain (table 5). There were a low number of cases with documented psychiatric issues, specifically anxiety (17|%) or depression (2%), in our chart review sample. Psychiatric symptoms were documented alongside of refractory physical symptoms and were not indications for CPST.

We compared the proportion of cases with deep versus moderate/light sedation at the three sites and found no statistically significant difference between groups (p=0.96), with almost two-thirds of cases involving deep sedation (table 5; p-value not shown).

Discussion

Across the variety of clinical settings included in our study, CPST occurred in 4.2% of total deaths as measured by continuous midazolam infusion. Most CPST cases included concomitant symptom management, especially opioid use in 98% of cases. We found that CPST documentation did not fully adhere to criteria set forth by our local CPG in 93% of cases, and that in more than half of cases, 4 or fewer of the 6 criteria were documented.

It is notable that, despite having a CPG in place for the last 16 years, and even though 77% of cases involved a palliative care consultation according to our manual chart review, documentation of criteria was low. In the manual chart review, more than half of the cases had ≤4/6 criteria documented. Similarly, a study from Ottawa showed 41% of CPST cases lacked documentation of informed consent, and 46% lacked mention of refractory symptoms.[12] In our study, paper documentation of a C2 goals of care designation was the most commonly missed criteria (84% of cases). In some cases, clinicians may not feel it is valuable to document this in

the chart, as the goals of care designation is reported in the EMR—when looking at EMR data, over half of cases had a C2 designation at the time of death (table 1). All (100%) of cases were associated with a C1 or C2 goals of care designation at the time of death, but 45% had a C1 rather than the C2 designation that is a pre-requisite as per our CPG. Clinicians may not feel it is necessary to change goals of care designation from C1 to C2 as the approach to care is the same in each, with the latter being different only in the formal recognition that death is imminent (hours to days). Furthermore, the C2 goals of care designation criteria and the criteria pertaining to documentation of imminent death may be redundant. After removing these two items, documentation of remaining clinical criteria occurred in most cases, ranging from 73-88% (table 4).

Further analysis showed that cases in the hospital inpatient units had a lower mean number of documented CPST criteria, and this appears to be driven by the cohort without a palliative care consultation. This suggests that palliative care consultation is beneficial when considering CPST, but our hypothesis-generating analysis should be tested in future work.

Our study sheds light on the way in which we practice CPST. Its use is low compared to other studies,[2,3] as it was ordered in only 4.2% of deaths. This could be due to our local practice to focus on deep sedation with midazolam, as opposed to the use of proportional sedation that is reported in many other studies,[2-4,7,8] or it may be due to long-established clinical guidelines that require consultation with a palliative care physician who may manage symptoms without the need for CPST in some cases. Most importantly, we looked at all deaths occurring at the study sites other than those due to trauma or maternal mortality. This is different than other studies, which have looked only at populations receiving palliative care services[2,4-6,8] and thus would be expected to have a higher prevalence of CPST. Nonetheless, in studies on CPST in patients

receiving palliative care services, there is a wide range of cited prevalence, from 1.33-51%, which likely stems from heterogeneity in definitional elements and medications used for CPST as well as practice setting.[19] A study published in 2006 that looked at the prevalence of deep continuous sedation in a random sample of deaths due to all causes in six countries found a prevalence of 2.5-8.5%.[20] This study is similar to ours in terms of the population, and our finding of 4.2% of deaths having CPST falls within this range.

The mean duration of CPST in our study was 27.4 hours. This is shorter than data coming from a nationwide Austrian study across 23 palliative care units, where median duration of CPST was 48 hours.[8] In a systematic review of 11 studies, the mean or median duration of CPST was found to be between 0.8 to 12 days.[2] Although it is challenging to compare our data with that from other studies given the heterogeneity in study design and types of CPST utilized (i.e. proportional vs deep), the duration of CPST from our study fell within local guidelines of "imminent death," which is assessed as being "within days" (appendix A).

As part of our exploratory analysis, the mean initial midazolam infusion rate was found to be significantly higher for the hospice cohort compared to the IPCU and hospital inpatient units, which may reflect typical practice within this setting, a greater proportion of cases requiring larger doses (e.g., due to agitated delirium) or cases in which intermittent dosing of midazolam was used prior to the infusion, allowing the physician to start at a higher infusion rate based on recent usage. There is no statistically significant difference in the proportion of cases that had a midazolam infusion order that was not administered between sites. The total mean midazolam breakthrough dose is similar across sites. This preliminary data should be interpreted with caution and explored further in future studies.

Almost everyone in the acute care setting received intravenous hydration. A recent Austrian study of CPST practices in palliative care units found that patients receiving CPST were more likely to receive intravenous hydration than patients who were not sedated (48% vs 41%).[8] Our CPG makes no mention of concurrent intravenous hydration during CPST, and this is not unique to our health region: a recent systematic review of published guidelines found that nearly 1/3 of included guidelines did not provide guidance on intravenous hydration or nutrition.[10]

It is concerning that few referrals were made to spiritual care, psychiatry or social work. Spiritual care and social work are not core members of our palliative consult teams, which may partly explain the small number of referrals. Once again, our CPG provides little guidance on this, whereas other frameworks and published guidelines encourage involvement of a multidisciplinary team approach.[1,17] When considering cases for CPST, which are often associated with complex suffering of the patients and/or family, the management of such cases would presumably benefit from a multidisciplinary approach.

Study Strengths and Limitations

A strength of our study is that it involves a wider population than previously published work, including general acute care sites, the medically intensive IPCU, and community hospices. Our region was also one of the first to disseminate and publish clinical guidelines on CPST,[11] allowing us to compare several years of clinical practice with an established benchmark. Our use of a central EMR database across sites allowed us access to 8 years of data and, thereby, a large sample set.

One limitation of our study is the use of midazolam infusion as a proxy. It is possible that midazolam infusions were used for other purposes than CPST. There are limitations inherent to

retrospective data, but we attempted to minimize the inclusion of non-CPST cases by having a set of parameters that would most likely limit cases to those in which midazolam infusions were used for CPST rather than for other purposes (e.g., procedural sedation). These parameters include: a) including cases with a documented sedation goal, which is required for CPST but not temporary sedation; and b) excluding critical care cases as the purpose for using midazolam infusions in this setting are possible different.

Another limitation to this retrospective study is that we assume that documentation reflects practice. There may have been cases where physicians followed criteria in practice but failed to document adequately in the medical charts. However, lack of documentation is, in itself, problematic and it is still worthwhile to present such data. It is possible that other medications were used for CPST, but midazolam is broadly recognized as the most popular medication used for CPST,[18] and the most commonly recommended in published guidelines.[3,7,10]

Implications for Practice and Future Research

We found low adherence to criteria in the CPST guidelines even though these were locally established and long-standing, but with closer analysis this may raise more concerns with the guideline requirements than existing clinical practice. This work will trigger discussion about modifying our guideline to make it more practical for front-line clinicians. For example, the presence of both a "C2" goals of care designation and documentation that the patient is "imminently dying" may be redundant, and future work may include surveying palliative care physicians to assess whether one or both items should be removed.

CPST frameworks from both the Canadian Society of Palliative Care Physicians and the European Association for Palliative Care recommend that clinical practice guidelines provide guidance on concurrent hydration and nutrition,[1,17] and this study highlights the need to incorporate these in future iterations of the guideline. The importance of multidisciplinary team involvement in CPST should be emphasized in new guideline development, and this aligns with the Canadian framework for CPST.[1] The findings of this study are not only relevant to our local practice but can inform CPST practice and guideline development in other regions.

Future studies could include surveys of physicians' perspectives on existing CPST guidelines, with a focus on: a) preferences for guidance around concurrent care and multidisciplinary team involvement when considering CPST, and b) reasons for low adherence to specific criteria. Specifically, the conjecture that the most commonly missed criteria may be perceived to be unimportant or redundant can be explored in future studies. Change management strategies and regular quality audits may be needed to promote adherence.[16] Point-of-care tools such as decision aids in the EMR and mandatory documentation of CPST criteria, embedded into an EMR order set, may be useful ways to improve care.

Conclusion

In conclusion, CPST occurred in 4.2% of deaths in a wide variety of clinical contexts in a large health region over 8 years where there have been long-standing clinical practice guidelines informing its use. Adherence to certain criteria set forth by local CPST guidelines was low, which may reflect issues with the relevance of these criteria. Exploratory data suggests that there are differences between sites with regards to midazolam infusion practices, and that palliative consultation may help improve adherence to local guidelines, but these results need to be further explored in future studies.

Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

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