Association between opioid dose escalation and time to death in a comfort measures only population

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Purpose. Opioids are crucial to the relief of pain and dyspnea experienced by patients dying in the hospital setting; however, there are concerns about the association of opioid dosage with hastened death via opioid-induced respiratory depression, and there is little published evidence regarding the association between opioid dose escalation and time to death in the inpatient comfort measures only (CMO) population.

Methods. The medical records of adult patients admitted to 2 hospitals who had an active CMO order at the time of death and received opioid dose escalations after CMO pronouncement were assessed in a retrospective cohort study. Patients were categorized into higher and lower opioid dose escalation groups according to an institutional palliative care symptom guide. A Cox proportional hazards model was constructed to test the associations between dose escalation group, patient sex, opioid naivety, palliative care consultation, and opioid dosage after CMO pronouncement (independent variables) and time to death (dependent variable).

Results. In the 71-patient cohort, 39 patients (54.9%) were male and 32 (45.1%) were female. The mean (SD) age of patients was 67.2 (16.6) years. Higher dose escalation ($n = 46$, 64.8%) was associated with a nonsignificant decrease in survival time compared to lower dose escalation ($n = 25$, 35.2%), with a mean difference in time to death of 19.8 hours (hazard ratio [HR], 1.67; 95% confidence interval [CI], 0.94-2.97). Receipt of a palliative care consult ($n = 56$, 78.9%) during the final hospital visit was associated with increased survival time (mean difference, 20.1 hours; HR, 0.32; 95% CI, 0.16-0.63).

Conclusion. Time to death in an inpatient CMO population was not significantly associated with the degree of opioid dose escalation.

Keywords: death, end-of-life care, opioid, pain, pain management, palliative care

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Pain and dyspnea are the most common symptoms experienced by patients with advanced illness. Over 20% of the general patient population and 80% of those with cancer or AIDS experience pain of at least a 5 on a 10-point scale during the last days of life.[1,2] Pain of this severity commonly causes detrimental effects on quality of life when not effectively treated.[3] Additionally, family members and caregivers may experience anxiety and apprehension.[4]

Opioid analgesics are recommended for moderate to severe pain and dyspnea.[5,6] When used for pain relief, opioids act as an agonist of the μ opioid receptors located in both the central and peripheral nervous systems.[7] This agonistic action produces analgesia. Studies have shown that opioids also have a positive effect on relief of dyspnea, though the mechanisms by which this occurs are still not well understood.[8,9]

Despite the clinical utility of opioids, there are several concerns regarding their use for the management of pain and dyspnea, including opioid-induced constipation, pruritus, and, most importantly, respiratory

depression. Opioid-induced respiratory depression (OIRD) is a rare and serious adverse effect. Previous literature suggests that pulmonary disease, obstructive sleep apnea, renal impairment, obesity, and significant dose escalations may increase this risk.[10-12]

Hospital inpatients near the end of life may be specifically susceptible to OIRD because they are often more medically complex (including specific risk factors for OIRD), and opioid escalations can be more aggressive in end-of-life patients than in other populations.[13] A study by Ventafridda and colleagues[14] found that for over 50% of patients with terminal cancer, physical symptoms in the 2 days before death became unendurable and only controllable by palliative sedation. However, several studies conducted in the outpatient hospice population have reported improved patient survival and decreased risk of OIRD when opioid doses are adequately titrated according to pain.[15-18] Conversely, a study by Portenoy and colleagues[19] found a weak association between high opioid dosage and survival in the hospice setting. Although they did not assess for changes in survival based on opioid dose escalation, they concluded that opioid dosage explained little of the variance in survival in their population and that concern for hastening death does not justify limiting opioid therapy in hospice patients.

It is important to explore the possible association between opioid dosage and survival in end-of-life patients, as this population is also at risk for undertreatment. The risk of OIRD may deter providers from initiating or escalating opioids when patients are most at need. Undertreatment of pain is common not only in patients with advanced malignant pain but also in patients suffering from end-stage diseases such as cardiac failure, chronic obstructive pulmonary disease, and end-stage renal disease.[20]

Hospital inpatients near the end of life are often designated to receive comfort measures only (CMO). The CMO designation denotes that the

KEY POINTS

- The association between opioid dosage and survival in patients nearing the end of life has been studied extensively in the hospice population, but there is no literature on this association in patients receiving comfort measures only (CMO).

- Higher opioid dose escalation may decrease time until death in the CMO population, while receipt of a palliative care consult may increase time until death.

- Additional research is needed to fully elucidate the effect of higher dose escalation in the CMO population.

patient and healthcare team have decided to focus on the quality instead of the quantity of life. The study described here aimed to examine the association between opioid dose escalation and time to death in the CMO setting.

Methods

A retrospective cohort study was conducted in 2 academic hospitals in western Pennsylvania. The study was approved by the institution's Committee for Oversight of Research and Clinical Training Involving Decedents. Informed consent requirements were waived, as only the medical records of deceased persons were reviewed. Patients were independently assessed for inclusion and exclusion by 2 reviewers, and discrepancies were discussed before proceeding to data collection.
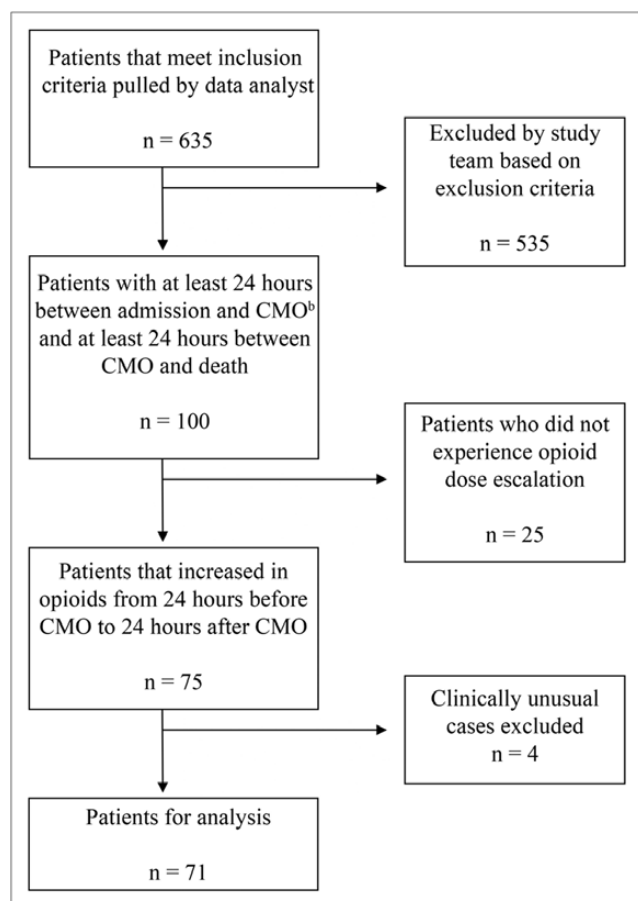
To be included in this study, patients had to have been over the age of 18 years at death, received a CMO order and were prescribed opioids, and ceased to breathe between January 1 and June 30, 2016. Patients were excluded from the study if less than 24

hours passed between admission and CMO status, if the patient was deceased less than 24 hours after CMO pronouncement, or if the patient's opioid dose was either decreased or was not changed within that 24-hour period (Figure 1). CMO was defined as patients who had a CMO order documented in the electronic health record.

Patients included in the study were classified as having received either low or high opioid dose escalations. These groups were defined according to dose-escalation recommendations from the institution's *Palliative Care Symptom Guide*.[21] The guide recommends starting opioid-naïve patients at no more than 30 oral morphine equivalents (OME) daily and escalating non-naïve patients at a rate of no more than 100% over any 24-hour period. Therefore, low escalation was defined as an escalation of no more than 100% from 24 hours before a CMO order ("pre-CMO") to 24 hours after a CMO order ("post-CMO") or an opioid-naïve patient receiving no more than 30 OME in the 24 hours post-CMO, and high escalation was defined as a more than 100% dose escalation from 24 hours pre-CMO to 24 hours post-CMO or an opioid-naïve patient receiving over 30 OME in the 24 hours post-CMO. Cutoffs of 24 hours before and 24 hours after CMO pronouncement were used in order to accurately examine the total daily opioid dose escalation. As the needs of an individual CMO patient change rapidly, a 24-hour period was felt to be clinically representative of needs. It was felt that extrapolating doses from a period of less than 24 hours may have overrepresented true opioid consumption. This cutoff also enabled us to exclude patients who died due to more acute reasons, such as traumatic brain injury, and include only patients with advanced illness who were near the end of life.

The following data were collected by the study team: demographics (including patient age at time of CMO pronouncement, sex, race, date of birth), date and time of CMO pronouncement, date and time of death, opioid usage in the 24 hours prior

Figure 1. Overview of sample selection. CMO indicates order for comfort measures only.

and controlled for opioid naivety, post-CMO OME (which were significantly different between groups), age, sex, and receipt of a palliative care consult. A *P* value of <0.05 was considered statistically significant. Data were analyzed using Stata software (StataCorp LLC, College Station, TX).

Results

In this study, 635 patients were reviewed for eligibility. Of these, 535 patients (84%) were excluded because less than 24 hours had passed either between admission and CMO pronouncement or between CMO pronouncement and death. An additional 25 patients were excluded due to lack of escalation in opioid therapy from the 24 hours before to the 24 hours after CMO pronouncement. Finally, the authors unanimously agreed to exclude 4 opioid-naïve patients who received more than 100 OME in the 24 hours after CMO pronouncement (Figure 1) due to their representing unusual clinical cases.

Baseline characteristics of the final sample, which included 71 patients, are summarized in Table 1. Approximately 34% of patients in this population were opioid naïve. Among those who were not naïve, the mean (SD) percentage increase in OME was 765% (1,033%) from 24 hours before CMO to 24 hours after CMO pronouncement. The median Charlson Comorbidity Index score was 2 (interquartile range, 1-4). Among all patients, the mean (SD) time from CMO to death was 49.7 (27.2) hours.

Higher vs lower dose escalation and time to death. Twenty-five patients (*n* = 25, 35.2%) were classified as having received lower opioid dose escalation, while 46 (*n* = 46, 64.8%) were classified as having received higher opioid dose escalation. Figure 2 shows unadjusted survival curves for the high and low dose escalation groups. In adjusted models, high vs low dose escalation was associated with a higher hazard of death (hazard ratio [HR], 1.67; 95% confidence interval [CI], 0.94-2.97) (Figure 3). Following documentation of CMO

to CMO status, opioid usage in the 24 hours after CMO status, patient comorbidities (according to Charlson Comorbidity Index),[22] renal function, hepatic function, home medications, inpatient medications, previous opioid tolerance, emergency department visits in the past 6 months, and whether or not the patient was followed by the palliative care team in the hospital. Our institution's interprofessional palliative care team includes a physician, an advanced practice provider (either a physician assistant or nurse practitioner), a social worker, a chaplain, and a pharmacist. Most often the palliative care team is responsible for inpatient opioid dose titrations, especially when a patient's pain is due to cancer.

All opioid doses were converted to OME before analysis. Percent dose escalation, time from CMO to death in

hours, and time from observation to death in hours were calculated by the study team. Time from observation to death was defined as the time from 24 hours post-CMO to death. Inpatient benzodiazepine use was determined by whether or not the patient received a benzodiazepine during the 24 hours before or after CMO pronouncement.

Statistical analysis. Baseline characteristics were summarized using percentages or means with standard deviations. A power analysis was not conducted due to lack of published literature in this area. A Kaplan-Meier survival curve was constructed to test the association between dose escalation and time to death. To further adjust for potential confounders, we constructed a Cox proportional hazards model. The Cox model regressed time to death against dose escalation group

Table 1. Baseline Demographic Data and Opioid Usage by Study Group

Characteristic or Variable	Lower Opioid Dose Escalation (*n* = 25)	Higher Opioid Dose Escalation (*n* = 46)	*P* Value
Age, mean (SD), y	69.2 (18)	66.2 (16)	0.36
Sex, No. (%)			0.39
Male	12 (48)	27 (59)	
Female	13 (52)	19 (41)	
Race, No. (%)			0.20
Caucasian	19 (76)	39 (85)	
African American	5 (20)	3 (6)	
Other or not specified	1 (4)	4 (9)	
Charlson Comorbidity Index, median (IQR)	3 (1-4)	2 (1-4)	0.54
Time from CMO order to death, mean (SD), h	62.5 (35)	42.7 (18.7)	0.03
OME in 24 hours before CMO order, mean (SD)	125.2 (357.2)	24.4 (38.2)	0.55
OME in 24 hours after CMO order, mean (SD)	194.5 (515.8)	197.5 (291.2)	<0.001
Opioid dose escalation, mean (SD) %	40.5 (30.6)	1,012.8 (1,219.6)	<0.001
Opioid naïve, No. (%)[a]	13 (52)	11 (24)	0.02
Previous opioid tolerance at admission, No. (%)[b]	6 (24)	14 (30)	0.57
Active inpatient benzodiazepine order, No. (%)	23 (92)	40 (87)	0.52
Received palliative care consult, No. (%)	22 (88)	34 (74)	0.17
ED visit in past 6 months, No. (%)	17 (68)	26 (56)	0.35

Abbreviations: CMO, comfort measures only; ED, emergency department; OME, oral morphine equivalents.
[a]Opioid naïveté was defined as receipt of 0 OME in 24 hours before CMO order and at least 1 OME in 24 hours after CMO order.
[b]Opioid tolerance was defined as receipt of at least 60 mg of oral morphine, 30 mg of oral oxycodone, 8 mg of oral hydromorphone, or an equianalgesic dose of another opioid daily for 7 days or longer. If the patient had a prescription for as-needed opioid use, the maximum dose the patient could possibly take was used in the analysis.

status, those in the higher dose escalation group survived an average of 42.7 hours (SD, 18.7 hours), and those in the lower dose escalation group survived an average of 62.5 hours (SD, 35.2 hours). Between the groups, there was a mean difference in time until death of 19.8 hours. Inpatient benzodiazepine use and baseline median Charlson Comorbidity Index scores did not differ significantly between groups.

Palliative care consultation and time to death. Of the patients included in this study, 56 patients (78.9%) received a consultation by the palliative care team while in the hospital and survived an average of 53.9 (SD, 28.6) hours. Fifteen patients (21.1%) did not receive a consult and had an average survival of 33.8 (11.6) hours. In adjusted models, receipt of a consult from the palliative care team was associated

with a lower hazard of death (HR, 0.32; 95% CI, 0.16-0.63) (Figure 3). The mean difference in time to death between groups was 20.1 hours.

When stratified according to escalation group, 61% (*n* = 34) of the patients who received a palliative care consult and 80% (*n* = 12) of the patients who did not receive a palliative care consult were in the higher dose escalation group. Patients who received a palliative care consult survived longer than those who did not receive a consult, regardless of escalation group (mean [SD], 66.9 [35.3] hours and 45.6 [19.8] hours in the low and high dose escalation groups, respectively). In contrast, patients in the low and high dose escalation groups who did not receive a consult survived for an average of 30.6 (9.3) hours and 34.6 (12.3) hours, respectively.

Age and time to death. Overall, the average age for our population was 67.2 (SD, 16.6) years. The average age for patients in the low dose escalation group was 69.2 (18.0) years, while the average age for patients in the high dose escalation group was 66.2 (15.9) years. Patients under the age of 65 (*n* = 31, 43.7%) survived an average of 44.1 (19.8) hours post-CMO, and patients over the age of 65 (*n* = 40, 56.3%) survived an average of 54.0 (31.3) hours post-CMO. Age was not significantly associated with time to death in the adjusted model (HR per 10-year increase in age, 0.93; 95% CI, 0.79-1.09).

Sex and time to death. In our population, 39 patients (54.9%) were male and 32 (45.1%) were female. Males survived an average of 42.7 (20.1) hours post-CMO, while females survived an average of 58.2 (32.2) hours post-CMO. Of the males, 27 (69.2%) received higher opioid dose escalations, while 12 (30.8%) received lower dose escalations. In the female cohort, 19 (59.4%) received higher dose escalations, while 13 (40.6%) received lower dose escalations. Females in the lower dose escalation group survived the longest, with an average survival of 70.8 (38.9) hours post-CMO, while males in the high dose escalation group survived the shortest

Figure 2. Kaplan-Meier survival curves for time to death by dose escalation group. "Time from observation" refers to the 24 hours after pronouncement of comfort measures only.
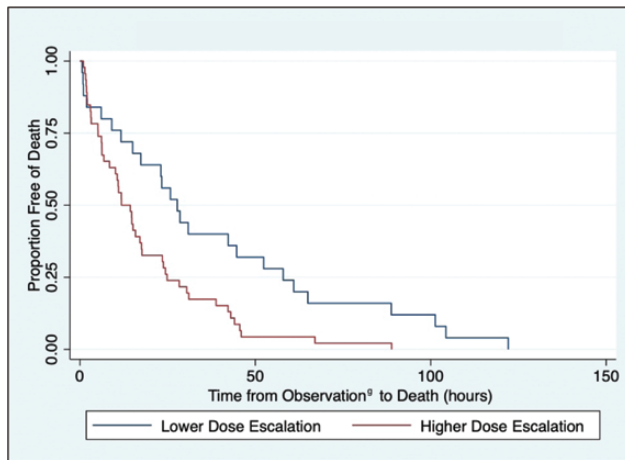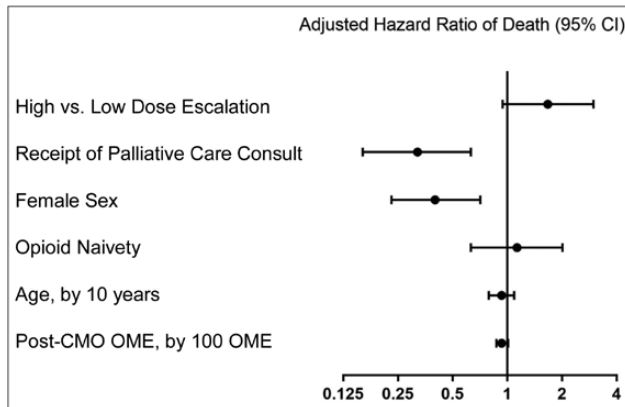

Figure 3. Results of Cox proportional hazards modeling. CI indicates confidence interval; CMO, comfort measures only pronouncement; OME, oral morphine equivalents.

Discussion

The study described here was, to our knowledge, the first to examine the impact of opioid dose escalations on time to death in an inpatient CMO population. In our population, higher opioid dose escalations were not significantly associated with survival time, while receipt of a palliative care consult was protective and increased time to death by 66%.

These findings are important, as previous research reports on this topic in the literature mostly focused on the hospice population. Those studies found that there was no increase in the risk of OIRD with high opioid doses when doses were adequately titrated according to pain level. In our population, more rapid dose escalations also did not appear to increase OIRD risk or significantly hasten death. These results are clinically meaningful because they demonstrate that opioids can be a safer treatment option for pain management at the end of life.

Quality of life was not assessed in our study. In our population, there was a mean 19.8-hour survival difference in patients receiving higher vs lower opioid dose escalations. It is important to consider not only changes in quantity of life but the potential increase in quality of life that may be associated with more effective management of pain and dyspnea. Although this was not measured in our population, an increased quality of life may be valued over an increased quantity of life.[23]

We also found that patients who were seen by the palliative care team in the hospital survived an average of 20.1 hours longer than those who did not receive a consult during their final hospital visit. Patients receiving a consult survived longer even when receiving higher opioid dose escalations. Our results suggest that involving the palliative care team with the care of each individual CMO patient can prolong quantity of life regardless of opioid dose escalations. This may be due to the palliative care team's specialization

(an average of 37.9 [11.8] hours) post-CMO. In the adjusted model, female sex was associated with increased time to death (HR, 0.41; 95% CI, 0.23-0.71).

Escalation group and opioid doses. The mean (SD) opioid dose in the 24 hours before CMO pronouncement was 125.4 (357.2) OME for the low dose escalation group, compared to 194.5 (515.8) OME in the 24 hours post-CMO, representing a 40.5% (SD, 30.6%) increase in OME between time points. For the high dose escalation group, the average pre-CMO opioid dose was 24.4 (38.2) OME, while the

average post-CMO opioid dose was 196.4 (381.7) OME; this represented an average percentage increase of 1,012.8% (SD, 1,219.6%) from the pre- to the post-CMO period. Pre-CMO doses did not significantly differ between the high and low dose escalation groups ($\chi^2 = 0.35$, $P = 0.55$, $df = 1$), while post-CMO doses did differ significantly between groups ($\chi^2 = 15.2$, $P < 0.01$, $df = 1$). High post-CMO OME was not associated with a significant difference in time to death in the adjusted model (HR per 100-OME increase, 0.93; 95% CI, 0.87-1.01).

in opioid dose titration and/or ability to focus on overall patient goals.

Limitations of the study included small population size, which was largely due to strict exclusion criteria that resulted in patients being excluded if the intervals from admission to pronouncement of CMO status and from CMO status to death were not at least 24 hours. We were also not able to assess whether opioid dose escalations were appropriate for each patient or whether the results were provider specific. Additionally, some of the confounding variables may have been correlated with outcomes, which made isolation of the true effects of each factor difficult. It is also probable that our findings were subject to residual confounding: Patients with a worse prognosis were probably more likely to receive higher opioid dose escalations in order to manage their conditions adequately as they worsened; likewise, patients may have received lower dose escalations if their conditions were less severe or more stable, both of which factors are associated with increased survival time. Finally, quality of life was not assessed in the study due to inconsistent documentation of this variable in the medical record, and data on surrogate markers for comfort were not collected or assessed.

Although we were unable to draw definitive results regarding the impact of opioids on time until death in CMO patients, our aim in conducting the study was to lay the foundation for future research in this population. Future studies should examine this association in a larger patient population, where patients are matched across escalation groups based on comorbidities, age, and other clinical confounders. Additionally, assessing quality of life and appropriateness of dose escalations would allow for balancing the risks and benefits of high dose escalations. An investigation into the differences in the level of dose escalation based on opioid dosage form is also warranted, and such research may offer insight into why patients would experience lower or higher opioid dose titrations.

Improved understanding of the association between opioid escalation and time to death will allow healthcare practitioners to maximize both the safety and efficacy of opioid regimens in CMO patients. Weighing the risks and benefits of initiating and escalating opioid therapy is particularly relevant in this population, because CMO patients are at increased risk for undertreatment of pain and opioid toxicities, including OIRD. Factors such as patient-specific comorbidities, analgesic requirements, concomitant medications, and desired quality of life should be accounted for to adequately balance these decisions.

Conclusion

Higher opioid dose escalation was associated with shorter survival (19.8 hours shorter on average) in a sample of CMO patients in an acute care setting. Given the potential for residual confounding in this study, additional research is needed to explore the impact of higher opioid dose escalation on survival in the inpatient CMO population.

Disclosures

The authors have declared no potential conflicts of interest.

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