Premature Ending of a Medication Study in Dying Patients

delivering difficult news. Similar findings were reported by Dosanjh and colleagues.[7]

Residents in both campuses identified lack of training opportunities as one of the major barriers toward delivering difficult news. Only 42.1% of the residents in our study had received any form of formal training in delivering difficult news. A study conducted in Nigeria looking at breaking bad news among nurses and physicians showed that only 21% of the respondents had formal training to do so.[8] Similarly, health care providers in Tanzania reported minimal formal training in conducting complex discussions.[9] In addition, a study by Geeta et al. looking at perceptions of breaking bad news by final pediatric residents in India found that only 16% had received any formal training.[5]

The strength of our study includes the equal distribution of residents among the years and a relatively high overall response rate. The limitations of our study included the use of self-administered questionnaires introducing reporting bias as well as the low response rate from the residents in the Dar es Salaam campus.

Conclusion

Our study helps shed light on the barriers our resident face within our institution in sub-Saharan Africa when delivering difficult news to their patients. Although some barriers might be challenging to overcome, this study will help us design and implement effective strategies, unique to sub-Saharan Africa, to better train our resident in delivering difficult news to their patients.

Karishma Sharma, MBChB
Internal Medicine
Aga Khan University
Nairobi, Kenya

Jasmit Shah, PhD
Aga Khan University
Nairobi, Kenya

Sayed K. Ali, MD, FACP
Palliative Care
Aga Khan University
Nairobi, Kenya
E-mail: Sayed.karar@aku.edu

https://doi.org/10.1016/j.jpainsymman.2019.07.028

References

1. Fallowfield L, Jenkins V. Communicating sad, bad, and difficult news in medicine. Lancet 2004;363:312–319.

2. Sobczak K, Leoniuk K, Janaszczyk A. Delivering bad news: patient's perspective and opinions. Patient Prefer Adherence 2018;12:2397–2404.

3. Fisher K, Smith K, Gallagher T, Burns L, Morales C, Mazor K. We want to know: eliciting hospitalized patients' perspectives on breakdowns in care. J Hosp Med 2017;12:603–609.

4. Bernacki R, medicine SB-J internal. Communication about serious illness care goals: a review and synthesis of best practices. JAMA Intern Med 2014;174:1994–2003.

5. Geeta MG, Krishnakumar P. Breaking bad news-Perceptions of pediatric residents. Indian Pediatics 2017;54:685.

6. Lee HR, Yi SY. Delivering bad news to a patient: a survey of residents and fellows on attitude and awareness. Korean J Med Educ 2013;25:317–325.

7. Dosanjh S, Barnes J, Bhandari M. Barriers to breaking bad news among medical and surgical residents. Med Educ 2008;35:197–205.

8. Adebayo P, Abayomi O, Johnson P, Oloyede T, Oyelekan AA. Breaking bad news in clinical setting - health professionals' experience and perceived competence in southwestern Nigeria: a cross sectional study. Ann Afr Med 2013;12:205.

9. Lewis EG, Oates LL, Rogathi J, et al. "We never speak about death." Healthcare professionals' views on palliative care for inpatients in Tanzania: a qualitative study. Palliat Support Care 2018;16:566–579.

Premature Ending of a Medication Study in Dying Patients: Lessons Learned

To the Editor:

In this letter, we describe the premature discontinuation of a medication study in dying patients. Despite a feasibility assessment, recruitment rates were far below expectations. Suggestions for future studies are proposed.

Morphine is the most frequently used opioid for the treatment of pain at the end of life. However, the active metabolites of morphine start to accumulate when renal function decreases. The accumulation of M3G is associated with neurotoxic adverse effects like delirium, allodynia, and hyperalgesia.[1] By contrast, the central effects of circulating metabolites of oxycodone are negligible.[2] Theoretically, oxycodone for the treatment of pain in dying patients, with a diminished renal function, should therefore result in a reduced occurrence of the neurotoxic adverse effects like delirium in comparison to morphine. To investigate this hypothesis, a randomized, controlled, multicenter trial was designed to compare the prevalence of delirium between oxycodone and morphine, administered by continuous subcutaneous infusion (CSCI), for the treatment of pain in dying patients with a diminished renal function. The study population consisted of residents of hospices and somatic or psychogeriatric wards of nursing homes,

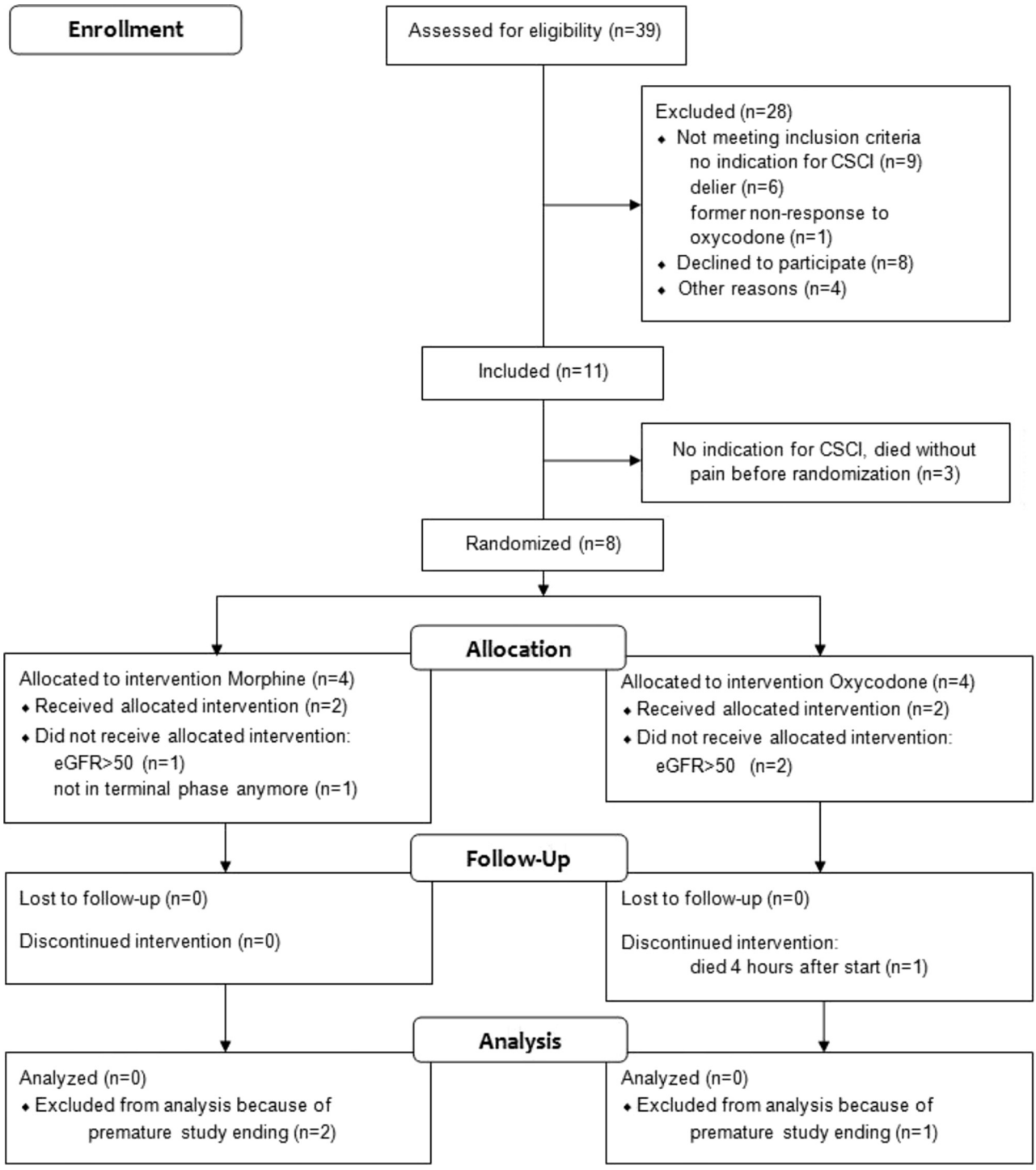

Fig. 1. Patient flowchart. CSCI = continuous subcutaneous infusion; eGFR = estimated glomerular filtration rate (ml/minute/1.73 m^2).

≥18 years, eligible for start of CSCI of an opioid for the treatment of pain in the dying phase. Patients with a diminished renal function, defined as an estimated glomerular filtration rate (eGFR Cockroft-Gault) of <50 mL/minute/1.73 m^2, were randomized between morphine and oxycodone. Based on a reported percentage of delirium in terminal patients of 86% and a difference of 15% as considered clinically relevant, 117 patients per group were needed (α 5%, 1 − β 80%).

Recruitment started on June 1, 2018, and by February 1, 2019, 39 possible eligible patients were

identified. There were 27 patients classified as not eligible. Of one patient eligibility was not established. Of the noneligible patients, eight patients declined consent including 2 who died during the consent procedure. Consent was given by 11 patients, 3 of whom were not randomized because they had no indication for CSCI anymore and died without pain. Of the eight randomized patients, three patients were excluded afterward based on eGFR values >50 mL/minute/1.73 m^2, one patient was no longer considered in the terminal phase anymore, and one patient died four hours after the start of the study treatment (see Fig. 1). Only three of all identified patients completed study treatment, which was 52 patients below expected. Because this gap seemed insurmountable, the study was terminated prematurely.

Evaluation of the recruitment process revealed two factors mainly responsible for the poor results. First, six of the participants died before, during, or immediately after the period of obtaining informed consent, at least before any measurement could be completed. Before the start of this study, not much was known about the time span between start of CSCI with opioids and the moment of dying. Therefore, a survey among Dutch elderly care physicians was held and the time span was estimated at several days. However, during the study, the time span appeared to be rather less than 24 hours. This discrepancy might be explained by the extra critical evaluation of the indication for CSCI because of the study. Once the indication was set, study participation did not cause any delays.

Second, the renal function as established using eGFR in three of the 11 (27%) included patients appeared to be above the threshold of 50 mL/minute/1.73 m^2. Because the eGFR is based on serum creatinine levels and elderly and patients in the dying phase are known for lower protein intake and lower muscle mass, eGFR levels are often overestimated in these patients. A recent publication revealed a prevalence of about 50% of decreased eGFR levels in terminal patients, assessed three days (median, IQR 1−4) before death.[3] We hypothesize that the level of serum creatinine continues to decrease, resulting in a complete overestimation of renal function. Because renal insufficiency was a key element in the study, removal of this exclusion criterion was no option. Alternative tests like cystatin-C were considered; however, extra costs in this regard were not factored in, or logistically complicated because of transportation to an external laboratory, or not yet sufficiently standardized.

Considering that halfway the planned study period the number of patients who received study treatment was three, and that extension of the study to extra centers still would not lead to a substantially higher number of participants, the study was ended prematurely. No conclusion could be drawn concerning the association between delirium and prescription of morphine versus oxycodone in dying patients with diminished kidney function. However, this issue remains of utmost clinical importance in palliative care. We recommend to repeat the study in an earlier phase (prognosis 2−4 weeks) to answer the question whether the accumulation of morphine metabolites induces clinical relevant adverse effects. In addition, we recommend a study on renal function in terminal patients assessing multiple biomarkers such as cystatin-C.

Maurice Theunissen, PhD
Centre of Expertise in Palliative Care
Maastricht UMC+
Maastricht, The Netherlands
E-mail: maurice.theunissen@mumc.nl

Mark Martens, MD
Centre of Expertise in Palliative Care
Maastricht UMC+
Maastricht, The Netherlands
Department of Palliative Care
Zuyderland, Sittard-Geleen
The Netherlands

Daisy J.A. Janssen, PhD, MD
Department of Research & Education
CIRO, Centre of Expertise for Chronic Organ Failure
Horn, The Netherlands
Department of Health Services Research & Department of Family Medicine
CAPHRI—Care and Public Health Research Institute
Faculty of Health Medicine and Life Sciences
Maastricht University
Maastricht, The Netherlands

Jos M.G.A. Schols, PhD, MD
Department of Health Services Research & Department of Family Medicine
CAPHRI—Care and Public Health Research Institute
Faculty of Health Medicine and Life Sciences
Maastricht University
Maastricht, The Netherlands

Marieke H.J. van den Beuken-van Everdingen, PhD, MD
Centre of Expertise in Palliative Care
Maastricht UMC+
Maastricht, The Netherlands

https://doi.org/10.1016/j.jpainsymman.2019.07.027

Disclosures and Acknowledgments

This work was supported by funding from The Netherlands Organization for Health Research and Development (ZonMw), grant number 844001314, The Hague, The Netherlands and Envida, Maastricht, The Netherlands.

Ethical approval: MEC approval was given by METC azM/UM Maastricht, The Netherlands, Dec 6, 2017, number NL62110.068.17/METC172020.

This study was registered at EudraCT, number 2017-002192-25.

Data are available at request (corresponding author).

There are no conflicts of interest to report.

References

1. Ashby M, Fleming B, Wood M, Somogyi A. Plasma morphine and glucuronide (M3G and M6G) concentrations in hospice inpatients. J Pain Symptom Manage 1997;14:157–167.

2. Lalovic B, Kharasch E, Hoffer C, et al. Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: role of circulating active metabolites. Clin Pharmacol Ther 2006;79:461–479.

3. Masman AD, Tibboel D, Baar FP, et al. Prevalence and implications of abnormal laboratory results in patients in the terminal phase of life. J Palliat Med 2016;19:822–829.

A Randomized, Double-Blind, Multisite, Pilot, Placebo-Controlled Trial of Regular, Low-Dose Morphine on Outcomes of Pulmonary Rehabilitation in COPD

To the Editor

To date, opioids have not been shown to improve respiratory measures such as the six-minute walk test in the short term.[1] In the longer term, regular, low-dose opioids have been shown to reduce the intensity of chronic breathlessness.[2]

Fear of breathlessness is one factor that can deter people from participating in pulmonary rehabilitation, especially in people with more severe chronic obstructive pulmonary disease (COPD).[3] The hypothesis was that if day-to-day exertion could be increased before breathlessness supervened during the whole course of pulmonary rehabilitation by the use of regular, low-dose, sustained-release morphine, then patients' outcomes may improve to a greater degree.[4,5] This pilot study sought to understand the feasibility of recruitment to such an adequately powered Phase III study.

This early phase study was a multisite, double-blind, fixed-dose, randomized placebo-controlled trial of regular, low-dose sustained-release morphine. This was an early phase study with a priori stop/go parameters including the following: the feasibility of recruitment to the protocol, acceptability to clinicians and participants, and the signal of any difference between arms on which to base the sample size calculation for a definitive study and improve the measurable success of pulmonary rehabilitation in people with COPD and moderate-to-severe breathlessness at baseline.

It was conducted in three large university teaching hospital pulmonary rehabilitation outpatient programs in two states of Australia.

The following clinical eligibility criteria were included: adults (age ≥18 years) eligible for pulmonary rehabilitation and enrolled in the eight-week course; with moderate (40%–60% predicted FEV_1) or severe COPD (<40% predicted FEV_1)[6]; breathlessness score of 3 or 4 on the modified Medical Research Council (mMRC) breathlessness scale[7]; and on stable medications for breathlessness over the prior week except routine "as needed" medications.

The intervention was 20 mg mane of regular, sustained-release morphine (matched with blinded docusate with sennosides A and B) and the control was placebo morphine (matched with placebo laxative) for the eight weeks of outpatient pulmonary rehabilitation. All participants had access to open-label docusate with sennosides as needed.

The proposed outcome for the Phase III was change in 6 MW distance at eight weeks from baseline.[8] Elements for feasibility included recruitment and retention rates, safety, acceptability, and evaluation of the outcome measures (efficacy of the intervention, measurability, and variance). The first stop/go outcome was recruitment. It was hoped to recruit 20 people in the 12 months of the study in one site.

The study was registered before commencement and approved by all relevant Human Research Ethics Committees. All participants provided written informed consent. The study was registered on the Australian New Zealand Clinical Trials Registry (ANZCTR): 12615000121561.

A total of 1143 people were referred to pulmonary rehabilitation in the three sites during which the study was open. In total, only nine people were randomized in 18 months, of whom six completed the study.

The major reason for screen failure was the criterion for people to have an mMRC of 3 or 4. People referred to pulmonary rehabilitation in this study had mMRC scores of 1 or 2 almost entirely—people in these pulmonary rehabilitation services were universally ineligible because they did not meet the mMRC criteria. Safety, acceptability, and measures for the outcome of a definitive study could not be undertaken given the failure to recruit.

This study was conducted in large, research-active pulmonary rehabilitation services. The rate of recruitment was not adequate to justify further investment in this early phase study and negated any further planning for a phase III study. People with Level 3 or 4 mMRC breathlessness were (systematically) not referred to pulmonary rehabilitation.

GOLD 2019 guidelines recommend that pulmonary rehabilitation is one of the most cost-effective