

22. Grassi L, Berardi MA, Ruffilli F, et al. Role of psychosocial variables on chemotherapy-induced nausea and vomiting and Health-related quality of life among cancer patients: a European study. *Psychother Psychosom* 2015;84:339–347.
23. Lee K-M, Jung D, Hwang H, et al. Pre-treatment anxiety is associated with persistent chemotherapy-induced peripheral neuropathy in women treated with neoadjuvant chemotherapy for breast cancer. *J Psychosomatic Res* 2018;108:14–19.
24. Bani Mohammad E, Ahmad M. Virtual reality as a distraction technique for pain and anxiety among patients with breast cancer: a randomized control trial. *Palliat Support Care* 2019;17:29–34.
25. Kazuyuki N, Yoshiaki O, Isseki M, et al. A novel palliative care approach using virtual reality for improving various symptoms of terminal cancer patients: a preliminary prospective, multicenter study. *J Palliat Med* 2019;22:702–707.
26. Azevedo Sao Leao Ferreira K, Kimura M, Jacobsen Teixeira M. The WHO analgesic ladder for cancer pain control, twenty years of use. How much pain relief does one get from using it? *Support Care Cancer* 2006;14:1086–1093.

End of Life in the Neurological Intensive Care Unit: Is Extubating to Comfort Care Comfortable?



To the Editor:

Patients extubated to comfort care in the neurological intensive care unit (Neuro-ICU) comprise a unique population because their end-of-life signs of distress can be related to both neurological pathology and multisystem dysfunction. Previous studies have examined time to cardiac death after extubation to comfort care and its predictors,^{1,2} but there are few studies describing patients' distress developed after extubation and the time required to achieve observable distress control.³⁻⁷ The goal of this study is to determine if Neuro-ICU patients demonstrate persistent signs of distress after transitioning to comfort care and how long these take to treat.

Methods

This was a retrospective medical record review of all patients who died in the Neuro-ICU at one tertiary academic hospital from October, 2016, to October, 2017. The study was exempt from institutional review board oversight because it involved only patients who had died before the investigation. Inclusion criteria were neurological injury as cause of death and mechanical ventilation with extubation to comfort care. Exclusion criteria included age less than 18 years, pregnancy, penetrating brain injury, brain death, and receiving cardiopulmonary resuscitation within 24 hours of cardiac death. Also excluded were deaths with incomplete documentation

of life support withdrawal, medication administration, and responses to distress. Neuro-ICU patients whose physical location of death was in another unit were also excluded because of logistical difficulties.

The study's primary outcomes were to determine if neurologically devastated patients developed distress after extubation to comfort care and whether this persisted. Secondary outcomes included both time to distress control and time to cardiac death. Because the patients evaluated during this study were unconscious, signs of distress were collected from nursing notes, the documented reason for as needed (PRN) medication administration, and from the Pain Assessment Tool for Non-Cognizant Adults (Non-Cog), developed by University of California, Los Angeles, and used primarily in the intensive care units to evaluate for pain in nonverbal or unconscious adults.⁸

Because these patients were neurologically devastated and unable to report symptoms, the term "signs of distress" was used rather than "symptoms." Developing signs of distress immediately after extubation was defined as within 30 minutes after extubation. A persistent sign of distress was defined as requiring greater than 50% of the time between extubation and cardiac death to achieve control. We defined distress control as not receiving any PRN medications nor requiring any opioid dose adjustments to infusions or boluses for at least 1 hour. Time to distress control was reported in hours and derived from objective scales such as the Non-Cog, subjective nursing documentation, and the medication administration record.

Statistical Analysis

Continuous data such as time required to achieve distress control and time from extubation to cardiac death were reported as means, medians, and standard deviations (SD).

Results

Of the 79 deaths in the Neuro-ICU whose charts were reviewed, 41 were excluded (16 did not meet inclusion criteria, 22 met exclusion criteria, two had poor documentation, and one was restricted). The mean age of the 38 patients whose records were selected for review was 63.1 years (median 65.0, SD 16.9, range 20–96.9), with 22 patients (58%) identified as female. The three most common diagnoses before Neuro-ICU admission included hypertension (44.7%), malignancy (31.6%), and atrial fibrillation (21.1%). The most prevalent diagnoses for admission to the Neuro-ICU were nontraumatic subarachnoid or intracerebral hemorrhage (28.9%), traumatic subarachnoid or subdural hemorrhage (21.1%), cerebral infarction (21.1%), and

Table 1

Initial Sign of Distress Developed After Extubation of Patients to Comfort Care in the Neurological Intensive Care Unit (n = 28)

Sign of Distress	N
Respiratory symptom (e.g., labored breathing, increased work of breathing, dyspnea, coughing, or terminal congestion)	9
Pain (intermittent pain expression or perceived pain)	3
Anxiety, agitation, delirium	1
Vital sign abnormality (e.g., heart rate, blood pressure, or respiration rate \geq 10% above baseline)	1
Signs of distress (e.g., dilated pupils, perspiring, flushing, diaphoretic, abnormal movements)	0
Pain + vital sign abnormality + signs of distress	1
Respiratory symptom + pain	6
Respiratory symptom + signs of distress	1
Respiratory symptom + vital sign abnormality	4
Respiratory symptom + pain + vital sign abnormality	1
Respiratory symptom + pain + vital sign abnormality + signs of distress	1

neurological malignant neoplasm—primary or secondary (13.2%).

Of the 38 patients, 28 (73.7%) developed signs of distress, with 23 (60.5%) patients developing signs of distress immediately after extubation. Table 1 displays initial signs of distress observed or documented by the nurse. Twenty (52.6%) patients developed signs of distress that took $>50\%$ of their remaining time after extubation to attempt to achieve distress control. The median time in attempting to achieve distress control was 2.4 hours (mean: 4.1 hour, SD: 4.7 hours, range: 0.2–18.8 hours). The median time to cardiac death was 2.7 hours (mean: 4.7 hours, SD: 5.8 hours, range: 0.1–20.5 hours).

All patients who were extubated to comfort care were premedicated with an opioid. Twenty-seven patients received a morphine infusion initiated at a median time of 0.8 hours before extubation (mean: 3.3 hours, SD 6.3 hours, range: 0.2–24 hours). Twenty-two patients were premedicated with an anticholinergic. Twelve of those patients received transdermal scopolamine placed at a median time of 0.7 hours before extubation (mean 3.6 hours, SD 6.7 hours, range: 0.03 hours–23.4 hours). Four of the 38 patients (10.5%) received a benzodiazepine as premedication before extubation.

Of the 28 patients who developed signs of distress, the median intravenous morphine equivalent dosage received from time of extubation to time of death was 39.1 mg (mean: 58.5 mg, SD 56.4 mg, range: 2–229.9 mg). Nine of these patients also received lorazepam. The median dose of lorazepam received was 1 mg (mean: 3.22 mg, SD 5.7 mg, range: 0.5–18 mg).

Discussion

Little is known about the frequency of signs of distress after extubation to comfort care, how fast these

present themselves, and how quickly they are controlled. This study is unique in demonstrating that 74% of patients in the Neuro-ICU who were extubated to comfort care developed some sign of distress after extubation. Of the patients who developed signs of distress, 82% developed a sign of distress in the first 30 minutes after extubation, and 71% required more than 50% of their remaining time after extubation until cardiac death to achieve distress control. These retrospective data results suggest that not only do the majority of patients who are extubated to comfort care and remain in the Neuro-ICU develop signs of distress but that these may develop shortly after extubation and persist for much of the time until cardiac death.

The possibility of inadequate premedication is considered in the 23 patients who developed signs of distress immediately after extubation. Because circulating plasma levels of transdermal scopolamine are detected within 4 hours after placement and peak levels are usually obtained within 24 hours,⁹ ineffective premedication could contribute to comfort care patients' signs of respiratory distress or distress related to terminal congestion. Although all patients had a neurological pathology contributing cause of death, benzodiazepines were infrequently used before and after extubation. While national standard guidelines have not been set for extubation to comfort care, most articles, studies, and protocols recommend prophylactic intravenous bolus dose of both an opioid and a benzodiazepine.²⁻⁷

Because patients extubated to comfort care in the Neuro-ICU are often unconscious and are unable to communicate, health care providers and family members are unable to know with certainty whether the observed signs of distress are resulted from physical discomfort or altered physiology related to either the injury or the dying process. Our data have shown that respiratory distress was either the primary sign of distress or a component of distress that initially developed; however, signs of respiratory distress may be manifestations of disorders of ventilator control due to neurological pathology. In these situations, providers may need to provide education to family members and consider palliative sedation before and during extubation to prevent the perception of respiratory distress, such as labored breathing, tachypnea, and terminal congestion.

Limitations of this study include potential for sample bias related to the single site of analysis and the small sample size. Other limitations include the retrospective design and the risk of observer bias and documentation bias. The data also revealed that medications were generally provided for observations such as vital sign abnormalities or dilated pupils as signs of distress or symptomatology in patients with neurological pathology.

Despite these limitations, to the authors' knowledge, this is the first study to examine signs of distress that develop after extubation to comfort care in neurologically devastated patients. The findings from this descriptive study could help educate not only palliative care physicians but also any physician who will be caring for patients extubated to comfort care from the Neuro-ICU on what they could possibly expect in the development of signs of distress. This could hopefully change how providers approach patients who are planned for extubation to comfort care in terms of premedication or post-extubation liberalization of medications.

Conclusion

Almost 74% of patients extubated to comfort in the Neuro-ICU are likely to develop signs of distress requiring pharmacologic intervention; and of these patients who develop signs of distress, over 70% will develop persistent signs of distress that will be difficult to control.

Angela Yeh, DO
Christopher Pietras, MD
UCLA Department of Medicine
Division of Hospitalist Medicine
Palliative Care Program
Los Angeles, California, USA
E-mail: ayeh@mednet.ucla.edu

David Wallenstein, MD
UCLA Department of Family Medicine
Los Angeles, California, USA

Peifeng Hu, MD, PhD
UCLA Department of Medicine
Division of Geriatrics
Los Angeles, California, USA

<https://doi.org/10.1016/j.jpainsymman.2019.07.004>

Disclosures and Acknowledgments

The authors declare no conflicts of interest and did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Huynh TN, Walling AM, Le TX, et al. Factors associated with palliative withdrawal of mechanical ventilation and time to death after withdrawal. *J Palliat Med* 2013;16:1368–1374.
2. Varelas PN, Hacein-Bey L, Schultz L, et al. Withdrawal of life support in critically ill neurosurgical patients and in-hospital death after discharge from the neurosurgical intensive care unit. *J Neurosurg* 2009;111:396–404.
3. Kompanje EJO, van der Hoven B, Bakker J. Anticipation of distress after discontinuation of mechanical ventilation in

the ICU at the end of life. *Intensive Care Med* 2008;34:1593–1599.

4. Blinderman CD, Billings A. Comfort care for patients dying in the hospital. *N Engl J Med* 2015;373:2549–2561.

5. Von Gunten C, Weissman DE. Fast Fact and Concept #033 and #034: Ventilator Withdrawal Protocol 2001. End-of-Life Physician Education Resource Center. Available from <https://www.eperc.mcw.edu>. Accessed June 23, 2018.

6. Truog RD, Campbell ML, Curtis JR, et al. Recommendations for end-of-life care in the intensive care unit: a consensus statement by the American College of Critical Care Medicine. *Crit Care Med* 2008;36:953–963.

7. Rubenfeld GD, Crawford SW. Principles and practice of withdrawing life-sustaining treatment in the ICU. New York: Oxford University Press, 2001:127–147.

8. Siegel C. Pain Assessment Tool for Non-Cognizant Adults. Available from <https://www.uclahealth.org/palliative-care/Workfiles/Pain-Assessment-Tool-Non-Cognizant.pdf>. Accessed June 23, 2018.

9. Novartis Consumer Health, Inc. Transderm Scop (Scopolamine) transdermal system patch. Parsippany, NJ 2013. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/017874s0381bl.pdf. Accessed June 23, 2018.

Response to “Prophylactic Fentanyl Sublingual Spray for Episodic Exertional Dyspnea in Cancer Patients: A Pilot Double-Blind Randomized Controlled Trial”



Dear Editor:

We read with great interest the recent paper titled, “Prophylactic fentanyl sublingual spray for episodic exertional dyspnea in cancer patients: A pilot double-blind randomized controlled trial” by Hui et al.,¹ which reported the results of a pilot double-blind randomized controlled trial comparing the effect of two dose schedules of fentanyl sublingual spray for exertional dyspnea.

The authors reported that the use of a high-dose fentanyl sublingual spray was associated with a significant within-arm reduction in modified Borg scale dyspnea intensity between the first and second shuttle walk test. The results of their study are useful and may influence the management and assessment of dyspnea in our nursing practice. Under the assumption that morphine and oxycodone had better effects on dyspnea than did fentanyl, we—as nurses—considered whether a partial or complete switch to morphine or oxycodone was possible when patients using fentanyl experienced dyspnea. Such a clinical strategy has been reported recently, with similar findings.² Nevertheless, if a high-dose prophylactic fentanyl reduces exertional dyspnea, we