

*Timothy J. Brennan, Ph.D., M.D., Editor*

## Critical Care Medicine

*Jean Mantz, M.D., Ph.D., Editor*

### Early physical and occupational therapy in mechanically ventilated, critically ill patients: A randomised controlled trial. *Lancet* 2009; 373:1874–82

Sedative and analgesic medications used for mechanically ventilated (MV) patients in intensive care units (ICU) can promote adverse consequences, including prolonged MV and ICU length of stay, ventilator-acquired pneumonia, and ICU-related delirium. Various strategies to minimize these effects have been examined including sedation-based analgesia and daily interruption of sedation. Physical mobilization may also reduce the occurrence of MV-associated adverse consequences.

This randomized controlled study examined the effects of early physical mobilization on patients in the ICU and the number of patients returning to independent functional status (the ability to perform six activities of daily living and to walk independently) at hospital discharge. Duration of delirium and ventilator-free days were also measured.

Adult patients admitted in two ICUs with MV for less than 72 h were randomly assigned to early exercise and mobilization (intervention group,  $n = 49$ ) or standard care (control group,  $n = 54$ ). Both groups underwent daily interruption of sedation and repeated spontaneous breathing trials. Physical mobilization included incremental range of motion exercises, and progressive therapy continued on a daily basis throughout the patient's hospital stay. The assessment by physical therapy at the conclusion, six activities of daily living (e.g., eating, bathing, walking), was blinded to mobilization or standard care assignment.

Before admission, patients had functional independence (Barthel index score 85–100) and a moderate severity of illness (Acute Physiology and Chronic Health Enquiry II score 13–24). Patients in the intervention group underwent physical therapy after intubation, 5.9 days sooner than controls ( $P < 0.001$ ). More patients in the intervention group returned to independent functional status at hospital discharge (59% vs. 35%;  $P = 0.02$ ). Patients in the intervention group had higher Barthel index scores, a greater number of independent activities of daily living, farther unassisted walking distances at hospital discharge, a shorter duration of ICU-related delirium (2.0 days vs. 4.0 days;  $P = 0.02$ ), and more ventilator-free days (23.5 days vs. 21.1 day;  $P = 0.05$ ). Length of

stay in ICU and hospital were similar between groups. Desaturation ( $<80\%$ ) was the only serious adverse event.

### Interpretation

This well-designed study demonstrates that early physical mobilization with MV is feasible and safe for ICU patients with moderate severity of illness. Optimal management of sedation and analgesia, with early aggressive physical interventions, improved independent functional status, duration of MV, and reduced delirium. These findings support the use of a multimodal program of whole-body rehabilitation including efforts to minimize the use of sedative (hypnotic) drugs in ICU patients.

*Suggested by: Jean-Francois Payen, M.D., Ph.D.*

### Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: A multicenter randomized controlled trial. *Lancet* 2009; 374:293–300

Etomidate is the most often used sedative-hypnotic drug by physicians for rapid sequence intubation, specifically for hemodynamically unstable patients. However, etomidate may cause adrenal suppression after single-bolus administration leading to increased vasopressor requirements, length of hospital stay, and mortality as demonstrated by *post hoc* analyses.

In the study, a multicenter, randomized controlled trial, the effects on early and 28-day morbidity of a single-bolus dose of etomidate was compared with ketamine used for emergency tracheal intubation of critically ill patients. The primary end point was the maximum score of the sequential organ failure assessment (SOFA) during the first 3 days in the intensive care unit. Secondary end points included the change in SOFA ( $\Delta$ SOFA) and 28 day all-cause mortality.

Twelve emergency medical units or emergency departments and 65 intensive care units in France prospectively included 655 patients requiring sedation for emergency intubation. Patients were randomly assigned to receive either 0.3 mg/kg of etomidate ( $n = 328$ ) or 2 mg/kg of ketamine ( $n = 327$ ) for intubation. Group assignment was known only by the emergency medicine physician enrolling patients.

Data were analyzed for 234 patients in the etomidate group and 235 patients in the ketamine group. Both groups had statistically similar mean maximal SOFA scores (etomidate,  $10.3 \pm 3.7$ ; ketamine,  $9.6 \pm 3.9$ ;  $P = 0.056$ ) and  $\Delta$ -SOFA score. Both groups had a median intubation difficulty score of 1 ( $P = 0.70$ ), suggesting similar intubation conditions. Compared with the ketamine group, the etomidate group had a significantly higher percentage of patients

with adrenal insufficiency (86 *vs.* 48%; odds ratio, 6.7;  $P < 0.0001$ ). No serious adverse events occurred with either study drug. No difference in 28-day mortality rates between groups was noted.

### Interpretation

A single-bolus dose of etomidate was not associated with significant increases in morbidity or mortality compared with ketamine in patients admitted to intensive care unit, although use in patients with sepsis was inconclusive. Pending future studies, ketamine should be considered a valuable alternative for intubation in critically ill patients, particularly in septic patients. Etomidate should be used cautiously in critically ill patients with septic shock.

*Suggested by: Samir Jaber, M.D., Ph.D.*

### Intensive *versus* conventional glucose control in critically ill patients. N Engl J Med 2009; 360:1283–97

A large body of recent work supports the association of increased blood glucose levels in hospitalized patients with adverse clinical outcome. However, whether tight glycemic control improves mortality in intensive care unit (ICU) patients remains controversial. Several lines of evidence suggest that this strategy has favorable impact in specific patient subpopulations, including cardiac surgical patients, medical, or pediatric ICU patients. The aim of this prospective, randomized, nonblinded study was to examine the effect of tight *versus* conventional glycemic control on outcome in patients admitted to the ICU.

The primary end point was the mortality rate of any cause within 90 days after randomization. Target blood glucose level was 81–108 mg/dl ( $<180$  mg/dl) in the intensive (conventional, respectively) glucose control group. Secondary outcome measures were survival time during the first 90 days, cause-specific death, duration of mechanical ventilation, renal-replacement therapy, and duration of stay in the ICU and hospital.

The two groups of patients (intensive control,  $n = 3,054$ ; conventional control,  $n = 3,050$ ) had similar baseline characteristics. The two treatment groups exhibited detectable glycemic separation (29 mg/dl). In contrast to recent previous trials, the 90-day mortality rate was increased in the intensive *versus* conventional glycemic control group (27.5 *vs.* 24.9%,  $P = 0.02$ ). Overall, the distribution of proximal causes of deaths were similar in the two groups ( $P = 0.12$ ). However, the rate of deaths from cardiovascular causes was higher in the intensive treatment group in comparison with the conventional treatment group (41.6 *vs.* 35.8%,  $P = 0.02$ ). Noteworthy, the number of episodes of severe hypoglycemia (blood glucose level  $<40$  mg/dl) was higher in the intensive glucose control group than in the conventional glucose control group (6.8 *vs.* 0.5%,  $P < 0.001$ ). The median duration of ICU or hospital stay and days of mechanical

ventilation or renal-replacement therapy was similar between the two groups. No difference in mortality was observed between medical and surgical ICU patients.

### Interpretation

These data are in sharp contrast with recent studies, suggesting the beneficial impact of tight glycemic control in ICU patients. Study differences include multicenter *versus* single-center trials, differences between populations receiving parenteral *versus* enteral nutrition, disparities in steroid treatment, the blood glucose levels in the conventional control groups, and difficulties in achieving the targeted blood glucose in the tight control group. This study suggests that tight glycemic control does not offer additional benefit in ICU, mechanically ventilated, patients.

*Suggested by: Jean Mantz, M.D., Ph.D.*

### Perioperative Medicine

*J. Lance Lichtor, M.D., and Joseph F. Antognini, M.D., Editors*

Incidence and sedation-related complications with propofol use during advanced endoscopic procedures. Clin Gastroenterol Hepatol July 14, 2009 (Epub ahead of print). doi: 10.1016/j.cgh.2009.07.008

Propofol is a popular sedative for endoscopic procedures because of its rapid onset of action and short duration of effect. The safe use of gastroenterologist-administered propofol is supported for advanced endoscopic procedures (*e.g.*, endoscopic retrograde cholangiopancreatography and endoscopic ultrasound). However, there are limited data on the administration of propofol by nurses and their ability to perform possible airway interventions required if patient rescue is necessary.

This single-institution prospective study evaluated the frequency of sedation-related complications associated with propofol use by three certified registered nurse anesthetists, under the direction of one anesthesiologist, in patients undergoing advanced endoscopic procedures including endoscopic retrograde cholangiopancreatography, endoscopic ultrasound, single-balloon or spiral overtube-assisted small-bowel enteroscopy, and enteral stenting. Sedation-related complications that were assessed included airway modifications (*e.g.*, chin lifts, modified face mask ventilation, and nasal airway), hypoxemia ( $\text{SaO}_2 < 90\%$ ), hypotension requiring vasopressors, and early procedure termination.

Of 799 patients enrolled, endoscopic ultrasound and endoscopic retrograde cholangiopancreatography were the most common procedures performed (52.9 *vs.* 42.1%), and 61% of patients had an American Society of Anesthesiologists class of 3 or higher. The majority of patients showed no response to intubation (87.2%). Hypoxemia, hypotension, and premature termination occurred in 12.8%, 0.5%, and 0.6% of patients, respectively. No patients required bag-