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ORIGINAL ARTICLE

Effect of Protocolized Sedation on Clinical Outcomes in Mechanically Ventilated Intensive Care Unit Patients: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Mahad A. Minhas, MPH; Adrian G. Velasquez, MD, MPH; Anubhav Kaul, MD, MPH; Pedro D. Salinas, MD; and Leo A. Celi, MD, MS, MPH

Abstract

Objective: To assess the effects of protocolized sedation (algorithm or daily interruption) compared with usual care without protocolized sedation on clinical outcomes in mechanically ventilated adult intensive care unit (ICU) patients via a systematic review and meta-analysis of randomized controlled trials (RCTs).

Methods: We searched Ovid MEDLINE, EMBASE, Cochrane CENTRAL, Web of Science, and ClinicalTrials.gov from their inception to February 28, 2013. A random-effects model was used to synthesize risk ratios (RRs) and weighted mean differences (WMDs).

Results: Of 4782 records screened, 6 RCTs including 1243 patients met the inclusion criteria. Protocolized sedation was associated with significant reductions in overall mortality (RR, 0.85; 95% CI, 0.74 to 0.97; *P*=.02; number needed to treat, 20; *P*=.11), ICU length of stay (WMD, −1.73 days; 95% CI, −3.32 to −0.14 days; *P*=.03), hospital length of stay (WMD, −3.55 days; 95% CI, −5.98 to −1.12 days; *P*=.004), and tracheostomy (RR, 0.69; 95% CI, 0.50 to 0.96; *P*=.03; number needed to treat, 16.6; *P*=.04; 5 RCTs) compared with usual care. Protocolized sedation produced no significant differences in duration of mechanical ventilation (WMD, −1.04 days; 95% CI, −2.54 to 0.47 days; *P*=.18), reintubation (RR, 0.78; 95% CI, 0.52 to 1.15; *P*=.21; 3 RCTs), and self-extubation (RR, 1.49; 95% CI, 0.46 to 4.82; *P*=.51; 4 RCTs) compared with usual care. Included studies did not report delirium incidence.

Conclusion: In mechanically ventilated adults in closed, nonspecialty ICUs, protocolized sedation seems to decrease overall mortality (15%), ICU and hospital lengths of stay (1.73 and 3.55 days, respectively), and tracheostomy (31%) compared with usual care without protocolized sedation.

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More than 790,000 patients require mechanical ventilation each year in the United States.[1] Sedation is commonly used in the intensive care unit (ICU) to facilitate the use of mechanical ventilation and mitigate the symptoms of pain and agitation.[2] However, there is considerable variation in what constitutes optimal sedation; consequently, variation in sedation practice may lead to undersedation or, more likely, oversedation.[3] Inappropriate sedation, for example, oversedation, is associated with adverse clinical outcomes, including a longer duration of mechanical ventilation, prolonged ICU length of stay (LOS), episodes of delirium, and increased mortality.[4,5]

Protocolized sedation (algorithm or daily interruption) intends to reduce variation in clinical care by reducing subjectivity in clinical decision making, thus replacing ICU staff discretion with evidence-based protocols that standardize sedation management.[6] In 1999 and 2000, 2 landmark randomized controlled trials (RCTs) by Brook et al[7] and Kress et al,[8] respectively, suggested that protocolized (standardized) sedation significantly improved several clinical outcomes, including duration of mechanical ventilation, compared with usual care without protocolized (standardized) sedation. Between 2008 to 2011, 4 more RCTs[9-12] were published; chief among them was the study by Girard et al,[11] which reported more

From The Dartmouth Institute for Health Policy and Clinical Practice, Geisel School of Medicine at Dartmouth, Lebanon, NH (M.A.M., A.G.V., A.K.); Department of Critical Care, Newport Hospital, Newport, RI (A.G.V.); Department of Medicine, Lahey Hospital and Medical Center, Burlington, MA (A.K.); Department of Medicine—Section of Critical Care, Dartmouth-Hitchcock Medical Center,

Affiliations continued at the end of this article.

ventilator-free days; however, most studies had varying, and sometimes conflicting, results for common clinical outcomes reported across studies (eg, ICU LOS). To our knowledge, a quantitative summary of RCTs examining standardized vs nonstandardized discretionary sedation management does not exist.

We conducted a systematic review and meta-analysis of the current body of literature to summarize RCTs that evaluated protocolized sedation vs usual care without protocolized sedation in mechanically ventilated adult ICU patients and that reported 1 or more of the prespecified clinical outcomes.

METHODS

This systematic review and meta-analysis was guided by the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.[13]

Study Eligibility Criteria

We included RCTs that studied the effect of protocolized sedation vs usual care without protocolized sedation in mechanically ventilated adult (≥18 years old) ICU patients and reported 1 or more of the following clinical outcomes: mortality, duration of mechanical ventilation, ICU or hospital LOS, and incidence of tracheostomy, reintubation, self-extubation, and delirium. We defined protocolized sedation as either of the following 2 standardized sedation management strategies used to treat ICU patients: a sedation algorithm or a daily sedation interruption. We defined usual care as nonprotocolized, discretion-based sedation management (eg, clinician-directed sedation).

Search Methods

We searched the following databases from inception through February 28, 2013: Ovid MEDLINE, EMBASE, Cochrane CENTRAL, Web of Science, and ClinicalTrials.gov. We used Cochrane's Highly Sensitive Search Strategy for RCTs in MEDLINE.[14] No search had language or other limitations. One reviewer (M.A.M.) excluded duplicate articles and clearly ineligible studies based on title and abstract. Two reviewers (M.A.M. and A.G.V.) independently screened the remaining articles in full text to determine review eligibility based on the inclusion criteria. In all cases, a third reviewer (A.K.), or group consensus, resolved disagreements. Last, the reference section of included studies was searched. The Supplemental Appendix (available online at http://www.mayoclinicproceedings.org) provides full details of the Ovid MEDLINE search strategy.

Data Extraction

Two reviewers (M.A.M. and A.G.V.) independently conducted unblinded data extraction for each included study using standardized pro forma. Discrepancies were resolved via group discussion. Information extracted from each study included publication date, hospital location, sample size, ICU type and setup, sedatives used, sedation scale and weaning protocol use, follow-up, patient characteristics, inclusion and exclusion criteria, and clinical outcomes listed under study eligibility criteria.

Assessment of Bias Risk

We assessed methodological quality using Cochrane's domain-based risk of bias tool (Supplemental Figure; available online at http://www.mayoclinicproceedings.org).[15] Two reviewers (M.A.M. and A.K.) independently extracted data from each included study for the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias risk. A third reviewer (A.G.V.) resolved assessment disagreements.

Data Synthesis and Analysis

We used Cochrane Review Manager version 5.2 software to calculate summary risk ratios (RRs) and the number needed to treat (NNT) for dichotomous outcomes and weighted mean differences (WMDs) for continuous outcomes, along with their respective 95% CIs. A random effects model was used to account for variations in protocol design among the included studies.

Overall mortality was analyzed as follows: we pooled the longest followed mortality measure reported in each study, to avoid double counting. For example, Bucknall et al[12] reported both ICU and hospital mortality, but only hospital mortality was included in the overall mortality summary estimate.