

Analgo-sedation Practices and the Impact of Sedation Depth on Clinical Outcomes Among Patients Requiring Mechanical Ventilation in the ED

A Cohort Study

Robert J. Stephens, BS; Enyo Ablordeppey, MD, MPH; Anne M. Drewry, MD; Christopher Palmer, MD; Brian T. Wessman, MD; Nicholas M. Mohr, MD; Brian W. Roberts, MD; Stephen Y. Liang, MD, MPHS; Marin H. Kollef, MD; and Brian M. Fuller, MD

CHEST 2017; 152(5):963-971

e-Table 1. Medications used for endotracheal intubation in the emergency department

| Medication | All Subjects ^a n = 317 | Mortality Status | | |
|------------------------------|--------------------------------------|--------------------------|-----------------------|----------|
| | | Non-survivors (n= 46) | Survivors (n= 271) | <i>p</i> |
| Neuromuscular blocker, n (%) | 202 (63.7) | 27 (58.7) | 175 (64.6) | 0.443 |
| Succinylcholine | 79 (24.9) | 12 (26.1) | 67 (24.7) | 0.843 |
| Rocuronium | 36 (11.4) | 7 (15.2) | 29 (10.7) | 0.372 |
| None | | | | |
| Induction agent | | | | |
| Etomidate | 166 (52.4) | 19 (41.3) | 147 (54.2) | 0.104 |
| Ketamine | 114 (36.0) | 18 (39.1) | 96 (35.4) | 0.628 |
| Propofol | 9 (2.8) | 1 (2.2) | 8 (3.0) | 0.769 |
| Midazolam | 6 (1.9) | 1 (2.2) | 5 (1.8) | 0.880 |
| Ketamine/Propofol | 5 (1.6) | 1 (2.2) | 4 (1.5) | 0.725 |
| None | 17 (5.3) | 6 (13.0) | 11 (4.1) | 0.012 |

^a317 included patients were intubated in the emergency department.

45 patients were intubated pre-hospital (7 were given a neuromuscular blocker and 5 were given an induction agent).

52 patients were intubated at an outside hospital prior to transfer (6 were given a neuromuscular blocker and 2 were given an induction agent).

e-Table 2. Sedation variables in the intensive care unit during the first 48 hours of admission

| Drug | All Subjects n = 414 | Mortality Status | | p |
|--------------------------------------|-------------------------|--------------------------|-----------------------|--------|
| | | Non-survivors (n= 60) | Survivors (n= 354) | |
| Fentanyl | | | | |
| n (%) | 370 (89.4) | 48 (80.0) | 322 (91.0) | 0.011 |
| Cumulative dose (mcg) | 2532 (1406 - 4758) | 2540 (1407 - 4035) | 2532 (1404 - 4808) | 0.877 |
| Weight-based dose (mcg/kg) | 32.3 (17.4 - 60.0) | 33.0 (20.0 - 52.2) | 32.3 (17.2 - 60.1) | 0.898 |
| Propofol | | | | |
| n (%) | 259 (62.6) | 27 (45.0) | 232 (65.5) | 0.002 |
| Cumulative dose (mg) | 2374 (593 - 5809) | 2115 (264 - 5251) | 2413 (712 - 5813) | 0.450 |
| Weight-based dose (mg/kg) | 31 (7- 67) | 24 (4 - 68) | 31 (7 - 66) | 0.481 |
| Midazolam | | | | |
| n (%) | 212 (51.2) | 37 (61.7) | 175 (49.4) | 0.080 |
| Cumulative dose (mg) | 9.7 (4.0 - 48.2) | 6.0 (4.0 - 34.9) | 10.0 (4.0 - 51.6) | 0.436 |
| Weight-based dose (mg/kg) | 0.14 (0.05 - 0.59) | 0.08 (0.04 - 0.57) | 0.16 (0.05 - 0.59) | 0.450 |
| Dexmedetomidine | | | | |
| n (%) | 131 (31.6) | 4 (6.7) | 127 (35.9) | <0.001 |
| Cumulative dose (mcg) | 438 (148 - 1089) | 207 (69 - 665) | 444 (152 - 1104) | 0.239 |
| Weight-based dose (mcg/kg) | 5.7 (2.1 - 11.9) | 2.3 (0.7 - 5.5) | 5.9 (2.2 - 12.4) | 0.111 |
| Lorazepam | | | | |
| n (%) | 39 (9.4) | 6 (10.0) | 33 (9.3) | 0.868 |
| Cumulative dose (mg) | 2.0 (2.0 - 4.0) | 4.0 (3.1 - 10.0) | 2.0 (2.0 - 4.0) | 0.212 |
| Weight-based dose (mg/kg) | 0.03 (0.02 - 0.08) | 0.04 (0.03 - 0.14) | 0.03 (0.02 - 0.07) | 0.293 |
| Hydromorphone | | | | |
| n (%) | 33 (8.0) | 2 (3.3) | 31 (8.8) | 0.151 |
| Cumulative dose (mg) | 0.8 (0.5 - 1.4) | 1.5 (1.0 - NA) | 0.8 (0.4 - 1.3) | 0.341 |
| Weight-based dose (mg/kg) | 0.01 (0.01 - 0.02) | 0.02 (0.01 - NA) | 0.01 (0.004 - 0.02) | 0.500 |
| Oxycodone | | | | |
| n (%) | 24 (5.8) | 2 (3.3) | 22 (6.2) | 0.377 |
| Cumulative dose (mg) | 10.0 (6.3 - 28.8) | 12.5 (10.0 - NA) | 10.0 (5.0 - 35.0) | 1.0 |
| Weight-based dose (mg/kg) | 0.15 (0.09 - 0.39) | 0.15 (0.13 - NA) | 0.14 (0.08 - 0.4) | 0.877 |
| Morphine | | | | |
| n (%) | 10 (2.4) | 5 (8.3) | 5 (1.4) | 0.001 |
| Cumulative dose (mg) | 5.0 (2.0 - 16.9) | 10.0 (2.5 -18.8) | 4.0 (2.0 - 57.8) | 0.690 |
| Weight-based dose (mg/kg) | 0.06 (0.03 - 0.23) | 0.11 (0.04 - 0.24) | 0.06 (0.03 - 0.57) | 0.690 |
| Haloperidol | | | | |
| n (%) | 12 (2.9) | 0 (0) | 12 (3.4) | 0.148 |
| Cumulative dose (mg) | 15 (6 - 24) | NA | 15 (6 - 24) | NA |
| Weight-based dose (mg/kg) | 0.15 (0.09-0.24) | NA | 0.15 (0.09-0.24) | NA |
| Quetiapine | | | | |
| n (%) | 12 (2.9) | 1 (1.7) | 11 (3.1) | 0.538 |
| Cumulative dose (mg) | 75 (25 - 175) | 25 | 100 (25 - 200) | 0.333 |
| Weight-based dose (mg/kg) | 1.2 (0.36 - 2.4) | 0.297 | 1.6 (0.4 - 2.5) | 0.333 |
| ICU RASS first 24 Hours ^a | -3 (-4 to -2) | -4 (-5 to -3) | -3 (-3 to -2) | <0.001 |
| ICU RASS first 48 Hours ^b | -2 (-3 to -1) | -4 (-5 to -3) | -2 (-3 to -1) | <0.001 |

ICU=intensive care unit, RASS=Richmond Agitation-Sedation Scale.

^a Based on 6122 RASS measurements collected in the first 24 hours. Median of 15 (IQR 11-19) observations per patient in this time period.

^b Based on 12622 RASS measurements collected in the first 48 hours. Median of 30 (IQR 23-39) observations per patient in this time period.

e-Table 3. Secondary outcomes according to deep sedation in the emergency department. Deep sedation was defined as a Richmond Agitation-Sedation Scale of -3 to -5.

| Secondary Outcome (days) | Deep Sedation (n= 244) | No deep sedation (n= 137) | Between-Group Difference | 95% CI | <i>p</i> |
|--------------------------|------------------------|---------------------------|--------------------------|--------------|----------|
| Ventilator-free | 18.2 (10.3) | 21.8 (7.9) | -3.6 | -5.4 to -1.7 | < 0.001 |
| ICU-free | 16.1 (10.0) | 19.4 (7.8) | -3.3 | -5.1 to -1.5 | < 0.001 |
| Hospital-free | 11.9 (9.4) | 14.5 (8.4) | -2.6 | -4.5 to -0.8 | 0.005 |

ICU=intensive care unit, CI=confidence interval.

e-Table 4. Multivariable logistic regression models for subgroup analyses with survival to hospital discharge as the dependent variable.

| Variables | aOR | 95% CI | Standard Error | p |
|--|------|-------------|----------------|--------|
| Trauma patients (n=128) | | | | |
| Age | 1.05 | 1.01 - 1.08 | 0.02 | 0.011 |
| Vasopressor infusion | 9.43 | 2.31 - 38.6 | 0.72 | 0.002 |
| Race | 0.42 | 0.09 - 1.88 | 0.77 | 0.254 |
| ED SOFA | 1.03 | 0.74 - 1.43 | 0.17 | 0.867 |
| ED RASS level | 0.39 | 0.20 - 0.78 | 0.35 | 0.007 |
| Medical patients (n= 286) | | | | |
| Age | 1.02 | 0.99 - 1.04 | 0.01 | 0.191 |
| ED SOFA | 1.31 | 1.16 - 1.48 | 0.06 | <0.001 |
| Malignancy | 2.60 | 1.13 - 6.00 | 0.43 | 0.025 |
| Sepsis | 1.12 | 0.47 - 2.70 | 0.45 | 0.799 |
| ED RASS level | 0.79 | 0.63 - 0.99 | 0.12 | 0.045 |
| Patients given analgo-sedation in ED (n= 382) | | | | |
| Age | 1.02 | 0.99 - 1.04 | 0.01 | 0.140 |
| Vasopressor infusion | 2.48 | 1.08 - 5.72 | 0.43 | 0.033 |
| Malignancy | 2.23 | 0.94 - 5.27 | 0.44 | 0.069 |
| Immunosuppression | 1.50 | 0.55 - 4.11 | 0.51 | 0.426 |
| ED SOFA | 1.11 | 0.98 - 1.27 | 0.07 | 0.098 |
| Reason for mechanical ventilation | | | | |
| COPD | 2.25 | 0.55 - 9.29 | 0.72 | 0.261 |
| Sepsis | 0.76 | 0.30 - 1.88 | 0.47 | 0.547 |
| Trauma | 1.75 | 0.74 - 4.15 | 0.44 | 0.204 |
| ED RASS level | 0.77 | 0.62 - 0.95 | 0.11 | 0.014 |
| ICU dexmedetomidine use | 0.19 | 0.06 - 0.54 | 0.55 | 0.002 |
| Patients given dexmedetomidine in ICU excluded (n= 283) | | | | |
| Age | 1.02 | 1.00 - 1.04 | 0.01 | 0.043 |
| Vasopressor infusion | 3.09 | 1.30 - 7.35 | 0.44 | 0.010 |
| BMI | 0.97 | 0.93 - 1.01 | 0.02 | 0.159 |
| ED SOFA | 1.17 | 1.01 - 1.35 | 0.07 | 0.032 |
| Reason for mechanical ventilation | | | | |
| COPD | 1.48 | 0.27 - 8.23 | 0.88 | 0.657 |
| Sepsis | 0.91 | 0.35 - 2.37 | 0.49 | 0.850 |
| Trauma | 3.02 | 1.24 - 7.37 | 0.46 | 0.015 |
| ED RASS level | 0.77 | 0.63 - 0.95 | 0.11 | 0.016 |
| Patients intubated in the ED (n= 317) | | | | |
| Age | 1.01 | 0.98 - 1.03 | 0.01 | 0.567 |
| Vasopressor infusion | 2.28 | 0.95 - 5.48 | 0.45 | 0.067 |
| ED SOFA | 1.14 | 0.99 - 1.30 | 0.07 | 0.064 |
| Malignancy | 3.22 | 1.34 - 7.73 | 0.45 | 0.009 |
| Reason for mechanical ventilation | | | | |
| COPD | 2.39 | 0.59 - 9.79 | 0.72 | 0.224 |
| Sepsis | 0.76 | 0.30 - 1.91 | 0.47 | 0.554 |
| Trauma | 2.12 | 0.75 - 6.01 | 0.53 | 0.157 |
| ED RASS level | 0.78 | 0.63 - 0.97 | 0.11 | 0.028 |
| ICU dexmedetomidine use | 0.21 | 0.07 - 0.63 | 0.56 | 0.005 |

ED=emergency department, SOFA=sequential organ failure assessment, RASS=Richmond Agitation-Sedation Scale, COPD=chronic obstructive pulmonary disease, ICU=intensive care unit, BMI=body mass index, aOR=adjusted odds ratio, CI=confidence interval.

e-Table 5. Exploratory logistic regression models examining if any association existed between midazolam or propofol and survival to hospital discharge.

| Variables | aOR | 95% CI | P-value |
|---|------|-------------|---------|
| Model 1 (including below variables 1-8) | | | |
| ICU Propofol | 0.69 | 0.36 - 1.35 | 0.284 |
| ED RASS level | 0.75 | 0.61 - 0.92 | 0.005 |
| Model 2 (including below variables 1-8) | | | |
| ICU Midazolam | 1.27 | 0.68 - 2.41 | 0.456 |
| ED RASS level | 0.75 | 0.61 - 0.92 | 0.005 |
| Model 3 (including below variables 1-8) | | | |
| ICU Dexmedetomidine | 0.17 | 0.06 - 0.49 | 0.002 |
| ICU Propofol | 0.70 | 0.35 - 1.42 | 0.328 |
| ICU Midazolam | 1.43 | 0.75 - 2.74 | 0.280 |
| ED RASS level | 0.77 | 0.63 - 0.94 | 0.010 |
| Model 4 (including below variables 1-8) | | | |
| ED Propofol | 0.80 | 0.40 - 1.61 | 0.537 |
| ED RASS level | 0.75 | 0.61 - 0.92 | 0.005 |
| Model 5 (including below variables 1-8) | | | |
| ED Midazolam | 0.65 | 0.34 - 1.24 | 0.186 |
| ED RASS level | 0.75 | 0.61 - 0.92 | 0.005 |
| Model 6 (including below variables 1-8) | | | |
| ICU Dexmedetomidine | 0.17 | 0.06 - 0.49 | 0.001 |
| ED Midazolam | 0.67 | 0.35 - 1.30 | 0.236 |
| ED RASS level | 0.77 | 0.63 - 0.94 | 0.010 |
| Model 7 (including below variables 1-8) | | | |
| ICU Dexmedetomidine | 0.17 | 0.06 - 0.49 | 0.001 |
| ED Propofol | 0.81 | 0.40 - 1.64 | 0.563 |
| ED RASS level | 0.77 | 0.63 - 0.94 | 0.010 |

The original multivariable model reported in the manuscript (Table 3) included the following 8 variables: age, vasopressor infusion, malignancy, ED SOFA score, reason for mechanical ventilation (COPD, sepsis, trauma), and ED RASS level; along with ICU dexmedetomidine use (total of 9 variables). In these models, variables 1-8 from the original model were included in each analysis. We then combined several approaches in sequential fashion- substituting propofol or midazolam for dexmedetomidine, forcing all into the model, etc.

ED=emergency department, SOFA=sequential organ failure assessment, RASS=Richmond Agitation-Sedation Scale, COPD=chronic obstructive pulmonary disease, ICU=intensive care unit, aOR=adjusted odds ratio, CI=confidence interval.