

Daily Sedation Vacation

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Introduction

- Sedation

a fundamental and essential part of ICU care to reduce distress and suffering and to enable the application of mechanical ventilation

- 90% of patients showed evidence of anxiety disorder

Bone RC, Hayden WR, Levine RL et al. Recognition, assessment and treatment of anxiety in the critical care patient. Dis Mon 1995;31:296-359 (169 References)

- Agitation occurred at least once in 71% of patients in a medical-surgical ICU

Fraser GL, Prato S, Berthiaume D et al. Evaluation of agitation in ICU patients: Incidence, severity, and treatment in the young vs elderly. Pharmacotherapy 2000;20:75-82

Before starting sedation for agitated critically ill patients,

- Look for reversible causes of agitation
- Provide adequate analgesia and make sure that the patient is pain-free

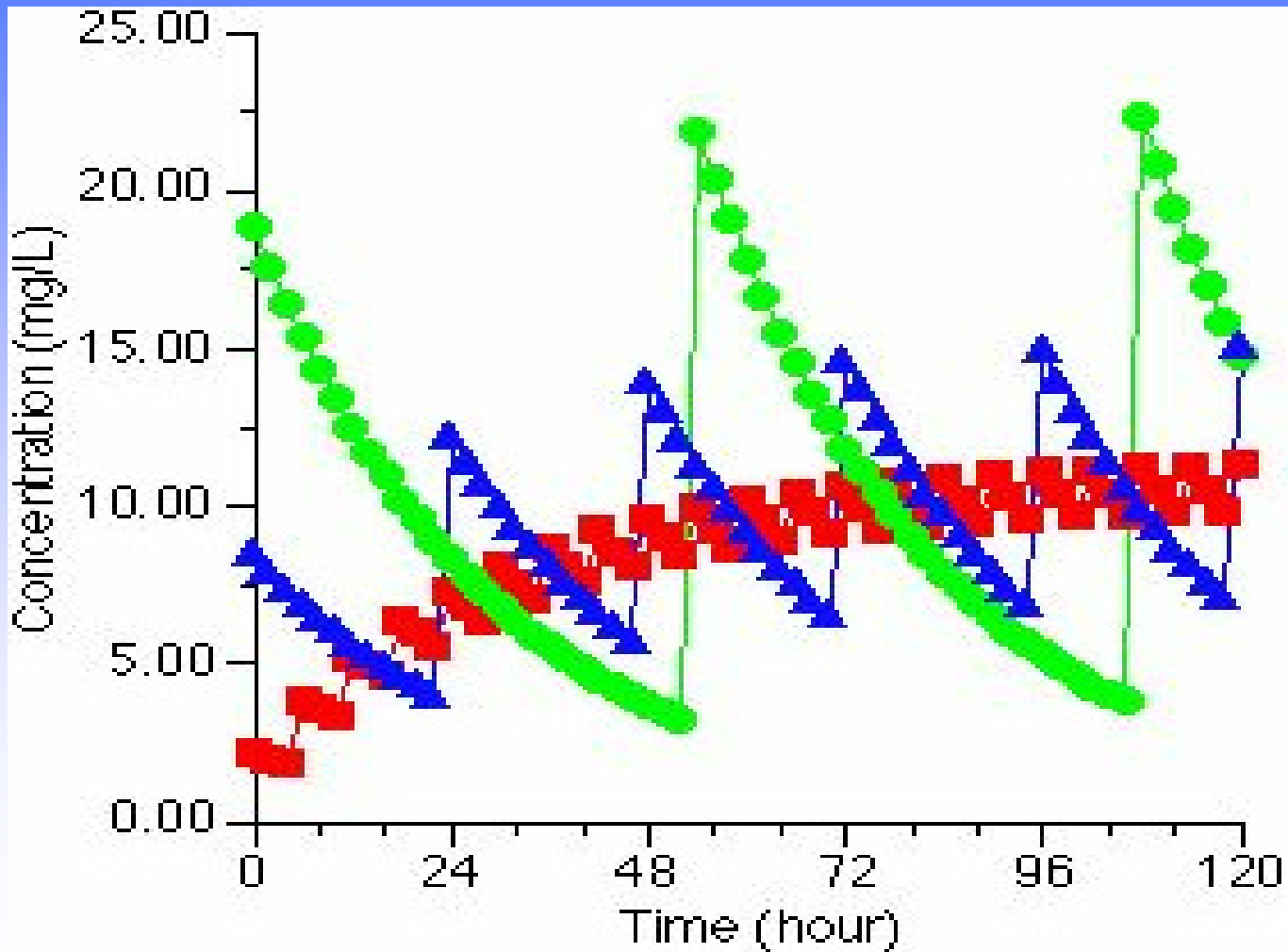
Drugs for sedation

- Benzodiazepines
- Opioid analgesics
- Neuroleptics
- Propofol
- Other drugs eg Ketamine
 - Dexmedetomidine
 - Thiopentone
 - Xenon

Routes of administration of sedatives in ICU

- Intermittent bolus
- Bolus followed by infusion
- Continuous infusion

Steady state



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The Steady state concentration is proportional to dose, dosing interval, F/Cl

SS attained after $\sim 4-5 t_{1/2}$

Time to SS is independent of dosage

The fluctuations of concentration is proportional to dosing intervals and half-life

C_i = initial concentration before entering the eliminating organ

C_o = final concentration after coming out from the organ

F_u = fraction unbound

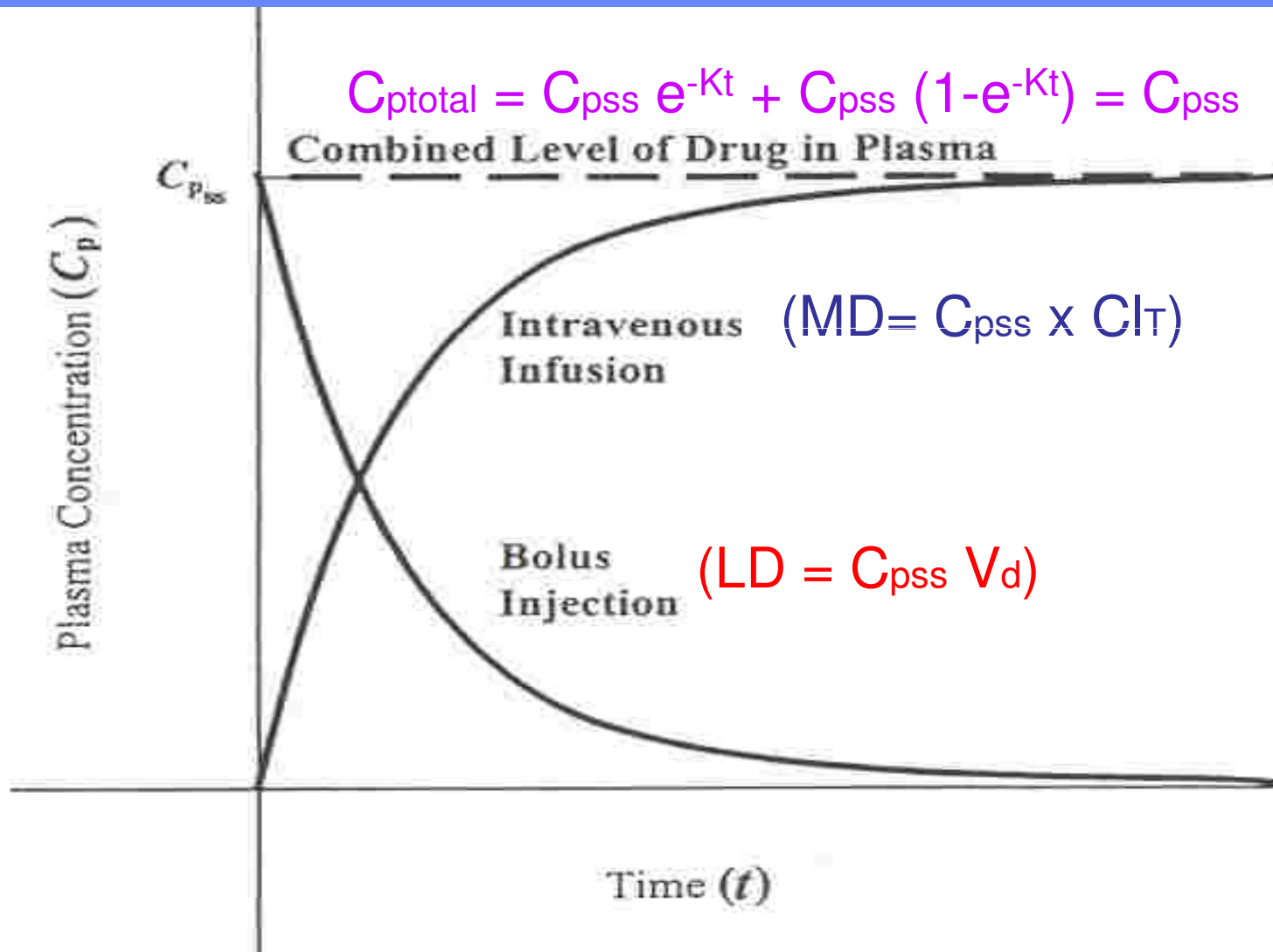
Cl_{int} = intrinsic clearance , enzyme activities of the organ

Q = blood flow at the organ

E = extraction ratio

user, 6/12/2006

Simultaneous iv bolus and iv infusion



- Bolus followed by continuous infusion of sedatives has become common practice
- Periods of over-sedation and under-sedation are minimized so that patient comfort is ensured

Problems of continuous infusion

- **Unpredictable pharmacokinetic and pharmacodynamic profiles of sedatives in the critically ill**
 1. Similar plasma concentrations can produce different effects
 2. Pathophysiologic changes occur within an individual patient
 3. Individual sedative needs constantly change
 4. Many of the sedative drugs exhibit multi-compartmental pharmacokinetics

- Prolongation of sedation after discontinuation of sedative drugs is frequent
- Patients may take longer time than expected to wake up

Causes of prolonged sedation after discontinuation of midazolam infusion

- High lipid solubility
- Increased volume of distribution
- Rate of metabolism affected by liver perfusion
- Active metabolites
- Drug interaction eg erythromycin decreases the clearance of midazolam

The use of continuous IV sedation is associated with prolongation of mechanical ventilation

*Kollef MH, Levy NT, Ahrens TS et al.
Chest 1998; 114(2):541-548*

- Prospective observational cohort study
- Medical ICU
- 242 consecutively ventilated patients
- 93 patients had continuous IV sedation while 149 patients received either bolus IV sedation (n=64) or no IV sedation (n=85)

Table 1—Baseline Patient Characteristics and Indication for Mechanical Ventilation Stratified According to Method of IV Sedation*

Variable	Continuous IV Sedation (n=93)	No Continuous IV Sedation (n=149)	p Value
Baseline characteristics			
Age	48.8±16.8	60.9±16.3	<0.001
Gender, No. (%)			
Male	42 (45.2)	79 (53.0)	0.234
Female	51 (54.8)	70 (47.0)	
Race, No. (%)			
White	57 (61.3)	71 (47.7)	0.071
Black	34 (36.6)	76 (51.0)	
Other	2 (2.1)	2 (1.3)	
COPD, No. (%)	40 (43.0)	47 (31.5)	0.071
Congestive heart failure, No. (%)	5 (5.4)	7 (4.7)	0.813
Underlying malignancy, No. (%)	18 (19.4)	29 (19.5)	0.983
APACHE II score	20.2±6.5	21.2±8.9	0.702
Predicted mortality	35.8±22.1	38.9±28.3	0.702
P/F ratio	175±107	232±152	0.006
Indication for Mechanical Ventilation			
Pneumonia, No. (%)	22 (23.7)	27 (18.1)	0.297
Drug overdose, No. (%)	5 (5.4)	15 (10.1)	0.197
ARDS / ALI	18 (19.4)	15 (10.1)	0.041
COPD/asthma, No. (%)	22 (23.7)	33 (22.2)	0.785
Pulmonary edema, No. (%)	11 (11.8)	16 (10.7)	0.793
Cardiac arrest, No. (%)	5 (5.4)	16 (10.7)	0.149
Pulmonary embolus, No. (%)	4 (4.3)	6 (4.0)	>0.999
Other, No. (%)	6 (6.4)	21 (14.1)	0.066

*Means are expressed±SD.

Table 3—Clinical Outcome Measures*

Outcome	Continuous IV Sedation (n=93)	No Continuous IV Sedation (n=149)	p Value
Length of MV, h	185±190	55.6±75.6	<0.001
LOS, ICU, d	13.5±33.7	4.8±4.1	<0.001
LOS hospital, d	21.0±25.1	12.8±14.1	<0.001
Acquired organ system derangements	3.1±2.2	2.5±1.4	0.018
Reintubation, No. (%)	14 (15.1)	7 (4.7)	0.005
Tracheostomy, No. (%)	15 (16.1)	13 (8.7)	0.080
Hospital mortality, No. (%)	28 (30.1)	50 (33.6)	0.576

*Mean±SD.

Table 4—Adjusted Outcomes According to Administration of Continuous IV Sedation*

Variable	Continuous IV Sedation (n=93)	No Continuous IV Sedation (n=149)	p Value
Length of MV, h	148 (121, 175)	78.7 (68.9, 88.6)	<0.001
Length of intensive care, d	9.6 (8.4, 10.9)	7.2 (6.6, 7.7)	0.007
LOS hospital, h	19.4 (16.7, 22.1)	13.8 (12.8, 14.9)	<0.001

*Values shown are means per patient and 95 percent CIs. Outcome variables have been adjusted for age, gender, severity of illness, mortality, indication for mechanical ventilation, use of chemical paralysis, presence of a tracheostomy, and the number of acquired organ system derangements.

- Patients receiving continuous IV sedation had nearly twice the duration of MV
- This association persisted despite adjustment for age, gender, severity of illness, mortality, indication for MV, use of neuromuscular blocking agents, presence of tracheostomy and the no of acquired organ system derangements
- The adjusted ICU and hospital LOS were statistically greater also

Limitations

- It was an observational study
- A single ICU examining only adult medical patients
- Benzodiazepines and narcotics were primarily employed
- The adequacy of sedation from the patients' perspective was not assessed

Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation

*Brook A, Ahrens T, Thomas S et al.
Crit Care Med 1999; 27(12):2609-2615*

- Randomized, controlled clinical trial
- Medical ICU
- 321 patients on ventilator randomly assigned to receive either protocol-directed sedation (n=162) or non-protocol-directed sedation (n=159)

1. Sedation needed-target to Ramsay score 3.
2. Exclude reversible causes of agitation.
3. Is pain likely?

Yes →

Fentanyl 25–50 µg every 5 mins until pain/agitation relieved.

↓

Requiring fentanyl bolus > every 2 hrs.

No ←

Morphine 1–5 mg up to every 2 hrs.

Is agitation causing acute deterioration (e.g., hypoxia, high peak airway pressures) necessitating immediate control?

No ↓

No ↓

Yes ↓

Diazepam or midazolam 2–5 mg every 5 mins until desired sedation level achieved.

↓

Requiring diazepam/midazolam bolus > every 2 hrs.

Yes →

Lorazepam infusion 0.5–1 mg/hr.

→

Targeted sedation achieved.

Yes ↗

Decrease fentanyl infusion by 25 µg/hr or lorazepam infusion by 0.25 mg/hr every 4 hrs until infusion discontinued.

↓

Reassess sedation regimen and Ramsay score every 4 hrs.

No ↘

Rebolus and increase fentanyl infusion by 25 µg/hr and/or rebolus and increase lorazepam infusion by 0.25 mg/hr.

↑

Lorazepam 1–4 mg up to every 2 hrs.

No ↓

Baseline patient characteristics and indication for mechanical ventilation stratified according to sedation strategy

Variable	Protocol-Directed Sedation (n = 162)	Non-Protocol-Directed Sedation (n = 159)	<i>p</i>
Age, yrs	57.8 ± 17.8	58.1 ± 19.1	.895
Gender, No. (%)			
Male	83 (51.2)	75 (47.2)	.466
Female	79 (48.8)	84 (52.8)	
Race, No. (%)			
White	95 (58.6)	90 (56.6)	.867
Black	66 (40.7)	68 (42.8)	
Other	1 (0.6)	1 (0.6)	
COPD, No. (%)	51 (31.7)	55 (34.6)	.554
CHF, No. (%)	20 (12.4)	21 (13.3)	.817
Underlying malignancy, No. (%)	29 (17.9)	20 (12.7)	.185
APACHE II score	23.1 ± 8.5	23.2 ± 9.1	.867
Predicted mortality (%)	45.8 ± 26.3	47.1 ± 27.3	.667
PaO ₂ /FIO ₂	208 ± 117	208 ± 125	.993
Indication for mechanical ventilation			
Pneumonia, No. (%)	34 (21.0)	47 (29.6)	.077
Drug overdose, No. (%)	7 (4.3)	6 (3.8)	.804
ARDS, No. (%)	4 (2.5)	2 (1.3)	.685
COPD or asthma, No. (%)	28 (17.3)	24 (15.1)	.594
Pulmonary edema, No. (%)	20 (12.4)	12 (7.6)	.151
Cardiopulmonary arrest, No. (%)	13 (8.0)	9 (5.7)	.402
Pulmonary embolism, No. (%)	1 (0.6)	2 (1.3)	.620
Sepsis, No. (%)	28 (17.3)	24 (15.1)	.594
Other ^a , No. (%)	27 (16.7)	33 (20.8)	.348

COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome.

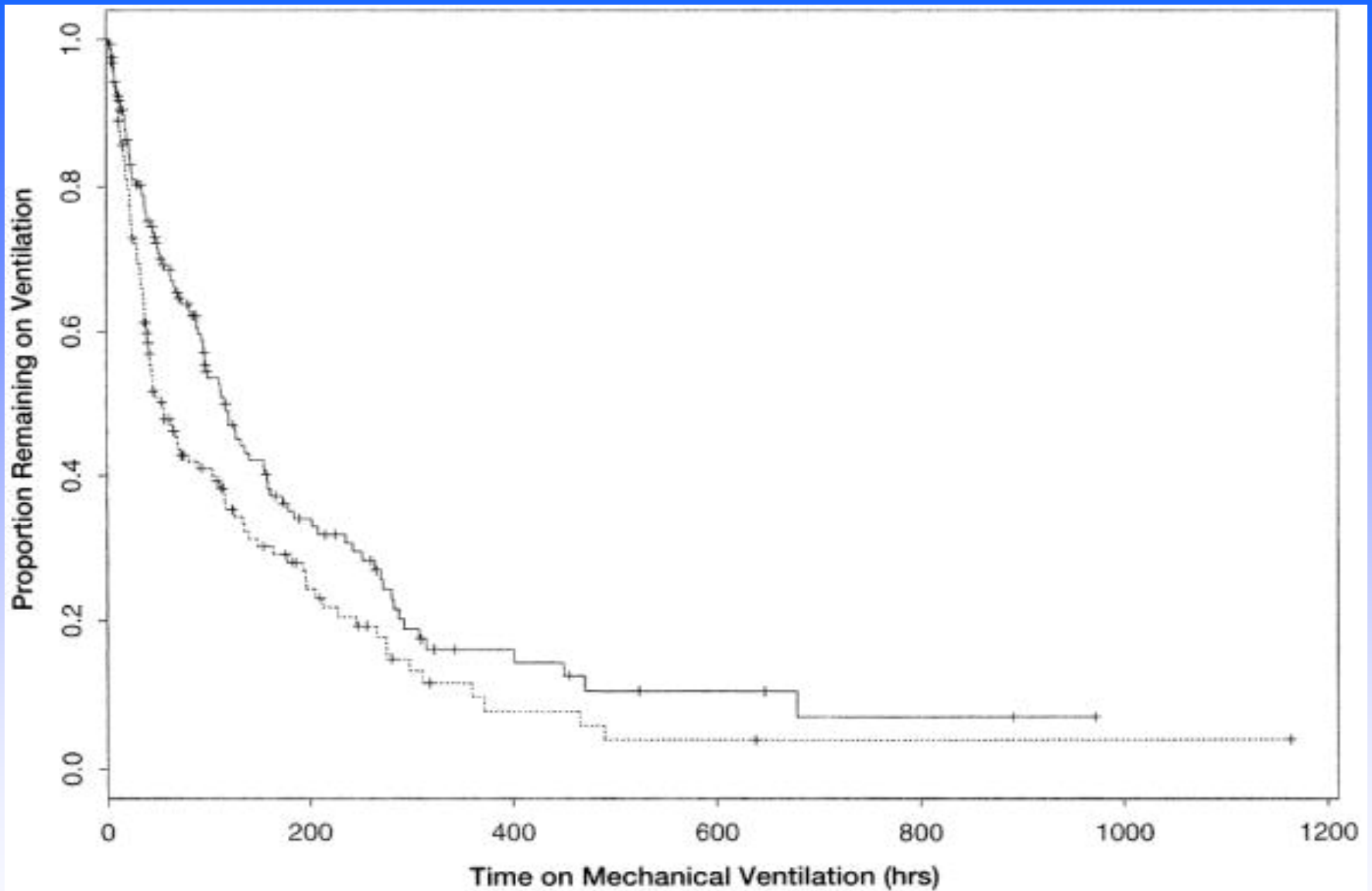
^aMultifactorial, neurologic, upper airway protection, postendoscopic procedure, or unclear cause for acute respiratory failure requiring mechanical ventilation.

No statistically significant differences for any patient variables or indications for mechanical ventilation were observed between the treatment groups when only the survivors were examined.

Clinical outcome measures

Outcome	Protocol-Directed Sedation (n = 162)	Non-Protocol-Directed Sedation (n = 159)	<i>p</i>
Length of MV, h	89.1 ± 133.6	124.0 ± 153.6	0.003
LOS, ICU, d	5.7 ± 5.9	7.5 ± 6.5	0.013
LOS, hospital, d	14.0 ± 17.3	19.9 ± 24.2	<0.001
Mortality, No. (%)	49 (30.3)	57 (35.9)	.342
Acquired organ system derangements	2.8 ± 1.4	2.9 ± 1.5	.737
Reintubation, No. (%)	14 (8.6)	21 (13.2)	.213
Tracheostomy	10 (6.2)	21 (13.2)	0.038

ICU, intensive care unit.



Kaplan-Meier curves of the probability of remaining on mechanical ventilation over time comparing patients managed with protocol-directed sedation (dotted line) with those receiving non-protocol-directed sedation (solid line)

Variable	Protocol-Directed Sedation (n = 162)	Non-Protocol-Directed Sedation (n = 159)	p
Continuous sedation infusion, No. (%)	66 (40.7)	66 (41.5)	.889
Continuous infusion agent, No. (%)			
Lorazepam	6 (9.1)	7 (10.6)	.770
Fentanyl	20 (30.3)	22 (33.3)	.709
Propofol	2 (3.0)	1 (1.5)	>.999
Morphine	5 (7.6)	8 (12.1)	.381
Lorazepam and fentanyl	33 (50.0)	28 (42.4)	.383
Duration of continuous infusion, d	3.5 ± 4.0	5.6 ± 6.4	0.003
Bolus sedation agent, No. (%)	118 (72.8)	127 (79.9)	.138
Bolus infusion agent, No. (%)			
Lorazepam	8 (6.8)	14 (11.0)	.246
Fentanyl	35 (29.4)	14 (11.0)	<0.001
Midazolam	6 (5.0)	6 (4.7)	.896
Morphine	5 (4.2)	3 (2.4)	.487
Haloperidol	2 (1.7)	0 (0.0)	.731
Lorazepam and fentanyl	63 (52.9)	90 (70.9)	0.005
Duration of bolus sedation, days	2.9 ± 3.9	3.4 ± 3.5	.248
Chemical paralysis, No. (%)	14 (8.6)	17 (10.7)	.534
Duration of paralysis, days	2.0 ± 1.2	2.9 ± 2.1	.213

Use of IV sedation and chemical paralysis

Limitations

- A single medical ICU
- The study was not blinded
- The impact of the sedation protocol on other outcomes eg occurrence of unplanned extubation and VAP were not assessed

Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation.

*Kress JP, Pohlman AS, O'Connor MF, Hall JB.
N Engl J Med 2000; 342:1471-1477*

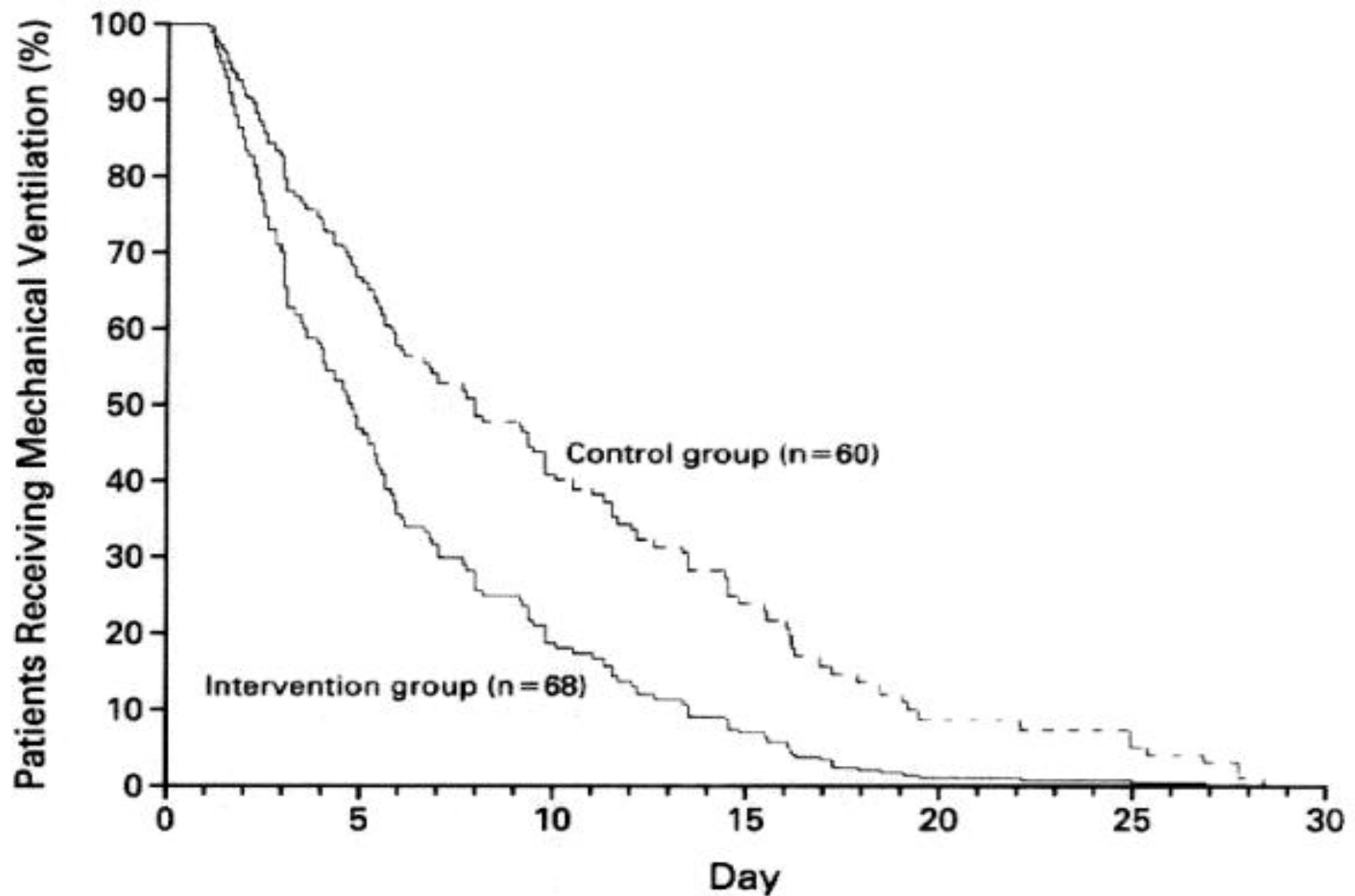
- A randomized controlled trial
- 128 adult patients randomized to:
 1. The intervention group, the sedative infusions were interrupted until the patients were awake, on a daily basis
 2. The control group, the infusions were interrupted only at the discretion of the clinicians in ICU

VARIABLE	INTERVENTION GROUP (N=68)	CONTROL GROUP (N=60)	P VALUE
Age (yr)			0.57
Median	57	61	
Interquartile range	42-71	40-74	
Sex (no.)			0.56
Male	34	26	
Female	34	34	
Weight (kg)			0.70
Median	69.9	66.0	
Interquartile range	58.9-90.2	60.4-78.8	
APACHE II score*			0.30
Median	20	22	
Interquartile range	15-25	16-25	
Permissive hypercapnia (no.)	12	15	0.42
Diagnosis (no.)			
Acute respiratory distress syndrome or pulmonary edema	20	15	0.72
Chronic obstructive pulmonary disease or ventilatory failure	22	17	0.76
Asthma	4	3	0.86
Sepsis	10	15	0.21
Delirium	8	5	0.73
Hemorrhagic shock	1	3	0.52
Cardiogenic shock	2	2	0.70
Drug overdose	1	0	0.95

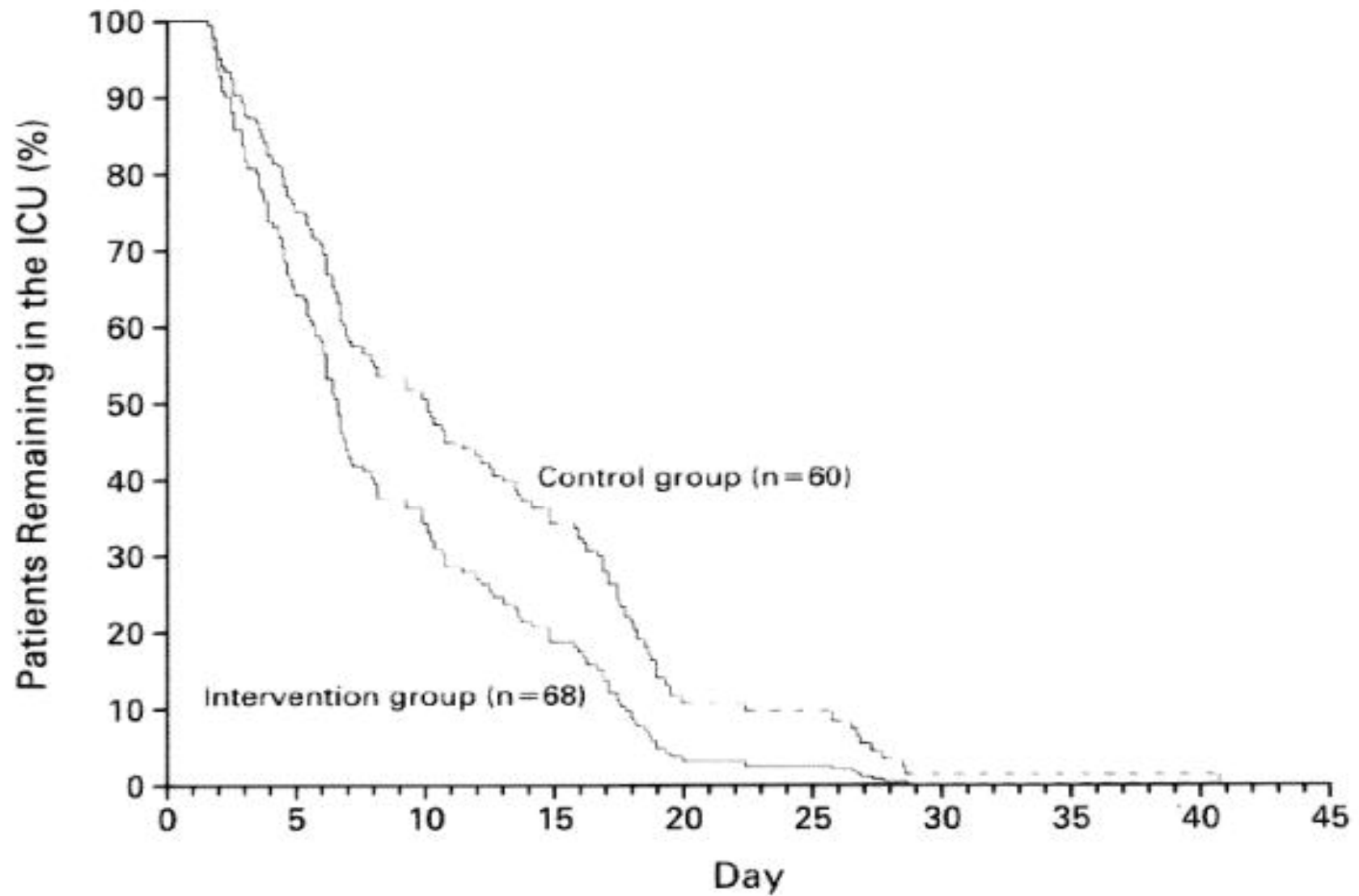
*APACHE II denotes Acute Physiology and Chronic Health Evaluation. The APACHE II is an assessment of the severity of illness, with possible scores ranging from 0 to 71 (increasing scores correlate with an increasing risk of in-hospital death).

VARIABLE	INTERVENTION GROUP (N=68)	CONTROL GROUP (N=60)	P VALUE
	median (interquartile range)		
Duration of MV, h	4.9 (2.5–8.6)	7.3 (3.4–16.1)	0.04
LOS ICU, d	6.4 (3.9–12.0)	9.9 (4.7–17.9)	0.02
Hospital	13.3 (7.3–20.0)	16.9 (8.5–26.6)	0.19
Midazolam	37	29	
Total dose of midazolam, mg	229.8 (59–491)	425.5 (208–824)	0.05
Average rate of midazolam infusion, mg/kg/h	0.032 (0.02–0.05)	0.054 (0.03–0.07)	0.06
Total dose of morphine (mg)	205 (68–393)	481 (239–748)	0.009
Average rate of morphine infusion (mg/kg/hr)	0.027 (0.02–0.04)	0.05 (0.04–0.07)	0.004
Propofol subgroup (no. of patients)	31	31	
Total dose of propofol (mg)	15,150 (3983–34,125)	17,588 (4769–35,619)	0.54
Average rate of propofol infusion (mg/kg/hr)	1.9 (0.9–2.6)	1.4 (0.9–2.4)	0.41
Total dose of morphine (mg)	352 (108–632)	382 (148–1053)	0.33
Average rate of morphine infusion (mg/kg/hr)	0.035 (0.02–0.07)	0.043 (0.02–0.07)	0.65

*Average rates of infusion were calculated as milligrams of drug per kilogram of body weight divided by the number of hours from the start of the infusion to its termination.



Kaplan-Meier Analysis of the Duration of Mechanical Ventilation, according to Study Group



Kaplan-Meier Analysis of the LOS in the ICU, according to the Study Group

In addition,

- 9% patients in the intervention group underwent diagnostic testing to assess changes in mental status compared with 27% patients in the control group ($p=0.02$)
- Complications eg removal of ETT occurred in 4% patients in the intervention group compared with 7% patients in the control group ($p=0.88$)

Limitations

- Patient discomfort as well as the cardiovascular effects of daily awakenings were not assessed

The long-term psychological effects of daily sedative interruption on critically ill patients

Kress JP, Gehlbach B, Lacy M et al.

Am J Respir Crit Care Med 2003;168:1457

- A follow-up study, comparing patients enrolled in the trial with contemporaneous survivors of critical illness treated without daily sedative interruption

- Patients who received daily sedative interruption did not experience adverse psychological outcomes and were less likely to have symptoms of post-traumatic stress disorder

Daily interruption of sedative infusions and complications of critical illness in mechanically ventilated patients

*Schweickert WD, Gehlbach BK, Pohlman AS et al.
Crit Care med 2004; 32:1272-1276*

- Blinded retrospective chart review of the database from the previous trial of 128 patients

Complication	Intervention, No.	Control, No.
VAP	2	5
Upper gastrointestinal hemorrhage	5	4
Bacteremia	4	7
Barotrauma	0	3
VTE	2	5
Cholestasis	0	1
Sinusitis	0	1
Total (No.)	13	26

VAP, ventilator-associated pneumonia; VTE, venous thromboembolic event.

- Patients with daily interruption of sedative infusions appear to have a lower complications related to prolonged mechanical ventilation eg VAP, bacteremia, barotrauma, venous thromboembolism, cholestasis and sinusitis

Conclusion

- **Lightening sedation decreases the amount of time spent on MV and therefore the risk of VAP**