Analgesia e sedazione in TI: come e perchè

Giovanni Mistraletti, MD
Dipartimento di Anestesiologia e Terapia Intensiva
Università degli Studi di Milano
AO San Paolo – Polo Universitario
Milano, Italy

Selected Topics in Anestesia e Terapia Intensiva
Udine, 23 febbraio 2012

Premessa

Tutto quello che dirò è GIA' a vostra disposizione **gratis** su internet !!!

Cliccare per credere:

www.sedaicu.it

Formazione degli operatori

Disponibilità sempre attiva di materiale utile al lavoro quotidiano

sedaICU

Mappa del sito | www.sedaen.it

Home | Chi siamo | Formazione | Letteratura | Corsi ECM | Agorà | cerca...

Home ▸ Formazione ▸ Strumenti ▸ Scale Validate

Scale Validate - strumenti "pronti all'uso"

In questa pagina puoi trovare dei files immediatamente utili per il tuo lavoro quotidiano.
Se vuoi, aggiungi questa pagina ai preferiti del tuo browser!

Per misurare il dolore:
- Verbal Numeric Rating (VNR)
- Behavioral Pain Scale (BPS)

Per misurare sedazione ed agitazione:
- Richmond Agitation Sedation Scale (RASS) - scheda di pronto utilizzo
- Tavola sinottica delle scale di sedazione/agitazione
- Protocollo ABC (Girard TD, Lancet 2008)

Per misurare il delirium:
- Livello di coscienza e funzionamento cognitivo
- Confusion Assessment Method for the ICU (CAM-ICU) - manuale di istruzioni
- CAM-ICU - spiegazione breve
- CAM-ICU - scheda di lavoro
- CAM-ICU - diagramma di flusso
- CAM-ICU - schede tascabili
- CAM-ICU - 10 consigli da tenere sempre a mente
- CAM-ICU - scheda per valutazioni crociate

Un reparto di Terapia Intensiva è un unico organismo... Non si può curare gli ammalati senza prendersi cura anche degli operatori.

Link veloci

Gestire il dolore

Flowchart dolore

Dichiarazione conflitto di interessi …

… nessuno !

Analgesia e sedazione in TI: come e perchè

Giovanni Mistraletti, MD
Dipartimento di Anestesiologia e Terapia Intensiva
Università degli Studi di Milano
AO San Paolo – Polo Universitario
Milano, Italy

Selected Topics in Anestesia e Terapia Intensiva
Udine, 23 febbraio 2012

Analgesia e sedazione in TI: come e perchè ?

Giovanni Mistraletti, MD
Dipartimento di Anestesiologia e Terapia Intensiva
Università degli Studi di Milano
AO San Paolo – Polo Universitario
Milano, Italy

Selected Topics in Anestesia e Terapia Intensiva
Udine, 23 febbraio 2012

“Divinum est sedare dolorem”

Ippocrate, 400 a.C.

Perché effettuare analgo-sedazione in Terapia Intensiva? E' davvero necessaria?

- Confort ottimale per paziente
- Riduzione della "risposta di stress"
- Riduzione complicanze cardiache e respiratorie
- Aiuto nelle procedure diagnostiche/terapeutiche
- Diminuzione di sintomi di agitazione e delirium

Effetti collaterali di analgesici e sedativi…

- Sepsi
- Ipotensione, bradicardia, disturbi cardiaci
- Insufficienza respiratoria
- Ileo
- Ristagno venoso, trombosi venosa profonda
- Svezzamento ritardato dalla ventilazione meccanica
- Permanenza prolungata in T.I.
- Aumento costi
- Impossibilità valutazione alterazioni SNC

Quali «strategie sedative» nella storia recente?

- **’80: I pazienti devono adattarsi ai macchinari**
  - *Sedazione profonda e immobilità!*

Quali «strategie sedative» nella storia recente?

- **'80: I pazienti devono adattarsi ai macchinari**
  - *Sedazione profonda e immobilità!*

- **'90: I macchinari devono adattarsi ai pazienti, ma i ricordi della T.I. sono spaventosi e angoscianti!**
  - *No mio-rilassanti, ancora sedazione profonda*

Quali «strategie sedative» nella storia recente?

- **'80: I pazienti devono adattarsi ai macchinari**
  - *Sedazione profonda e immobilità!*
- **'90: I macchinari devono adattarsi ai pazienti, ma i ricordi della T.I. sono spaventosi e angoscianti!**
  - *No mio-rilassanti, ancora sedazione profonda*
- **2000: Sedazione guidata da protocolli**
  - *Interruzione giornaliera*
  - *Sedazione basata sull'analgesia*

A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial

Thomas Strøm, Torben Martinussen, Palle Toft

Summary

Background Standard treatment of critically ill patients undergoing mechanical ventilation is continuous sedation. Daily interruption of sedation has a beneficial effect, and in the general intesive care unit of Odense University Hospital, Denmark, standard practice is a protocol of no sedation. We aimed to establish whether duration of mechanical ventilation could be reduced with a protocol of no sedation versus daily interruption of sedation.

Methods Of 428 patients assessed for eligibility, we enrolled 140 critically ill adult patients who were undergoing mechanical ventilation and were expected to need ventilation for more than 24 h. Patients were randomly assigned in a 1:1 ratio (unblinded) to receive: no sedation (n=70 patients); or sedation (20 mg/mL propofol for 48 h, 1 mg/mL midazolam thereafter) with daily interruption until awake (n=70, control group). Both groups were treated with bolus doses of morphine (2·5 or 5 mg). The primary outcome was the number of days without mechanical ventilation in a 28-day period, and we also recorded the length of stay in the intensive care unit (from admission to 28 days) and in hospital (from admission to 90 days). Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00466492.

Lancet 2010; 375: 475–80

Published Online January 29, 2010 DOI:10.1016/S0140-6736(09)62072-9

See Comment page 436

Department of Anesthesia and Intensive Care Medicine, Odense University Hospital (T Strøm MD, Prof P Toft DMSc), and Department of Biostatistics, Faculty of Health Sciences (Prof T Martinussen PhD), University of Southern Denmark, Denmark

Strom T, *Lancet*, 2010

- **2010: No sedation strategy ?!?!?**

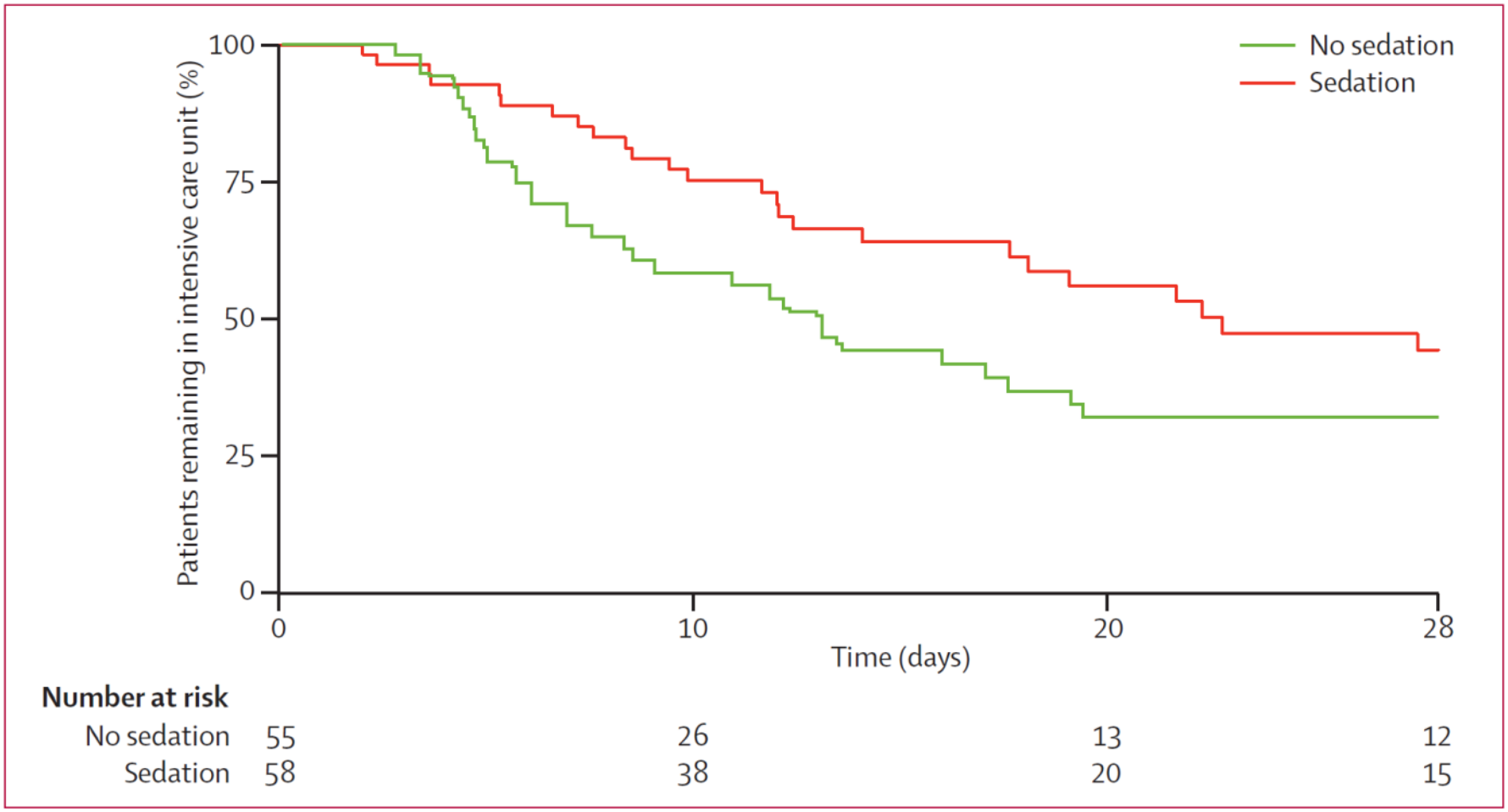


***Figure 2*: Kaplan-Meier plot of length of stay in the intensive care unit and number at risk from admission to 28 days**

Strom T, *Lancet,* 2010

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Tailored Awake Analgesia and Sedation in Critically Ill Patients

Giovanni Mistraletti, M.D.

- **2020: Pazienti il più svegli possibile,**
  con dolore controllato,
  con protocolli sul TARGET, non sul dosaggio dei farmaci!

Analgesia e sedazione in TI: come ? e perchè

Cosa dice la letteratura?

Giovanni Mistraletti, MD
Dipartimento di Anestesiologia e Terapia Intensiva
Università degli Studi di Milano
AO San Paolo – Polo Universitario
Milano, Italy

Selected Topics in Anestesia e Terapia Intensiva
Udine, 23 febbraio 2012

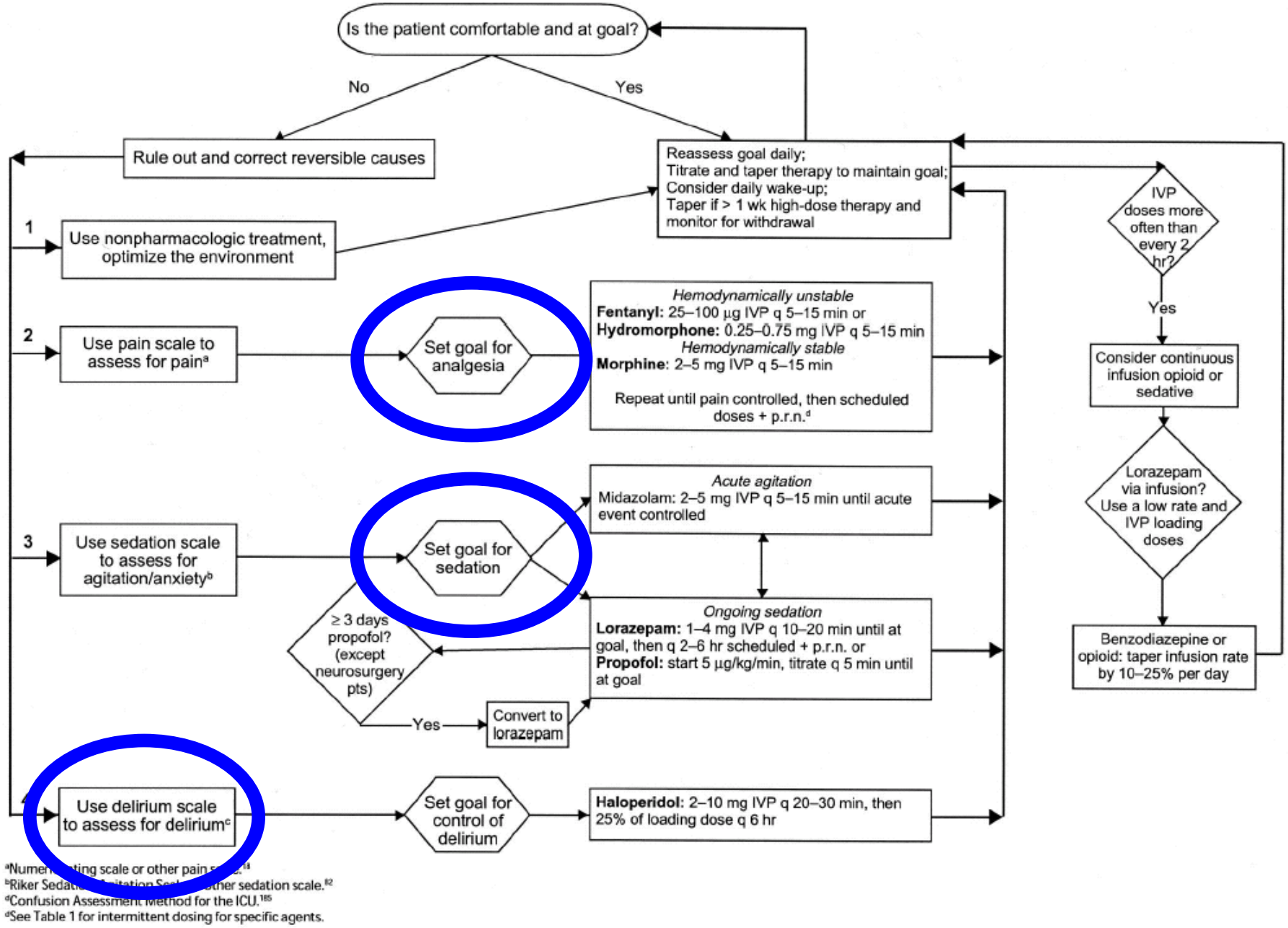
Guidelines CCM 2002
Task-force for ICU analgesia & sedation

Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult

Judith Jacobi, PharmD, FCCM, BCPS; Gilles L. Fraser, PharmD, FCCM; Douglas B. Coursin, MD; Richard R. Riker, MD; Dorrie Fontaine, RN, DNSc, FAAN; Eric T. Wittbrodt, PharmD; Donald B. Chalfin, MD, MS, FCCM; Michael F. Masica, MD, MPH; H. Scott Bjerke, MD; William M. Coplin, MD; David W. Crippen, MD, FCCM; Barry D. Fuchs, MD; Ruth M. Kelleher, RN; Paul E. Marik, MDBCh, FCCM; Stanley A. Nasraway, Jr, MD, FCCM; Michael J. Murray, MD, PhD, FCCM; William T. Peruzzi, MD, FCCM; Philip D. Lumb, MB, BS, FCCM. Developed through the Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), in collaboration with the American Society of Health-System Pharmacists (ASHP), and in alliance with the American College of Chest Physicians; and approved by the Board of Regents of ACCM and the Council of SCCM and the ASHP Board of Directors

Please remember for this evening reading:

Crit Care Med 2002, 30 (1) 119-141



Jacobi J, *Crit Care Med*, 2002

A new frontier in critical care: saving the injured brain.

E. Wesley Ely

Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial

Timothy D Girard, John P Kress, Barry D Fuchs, Jason W W Thomason, William D Schweickert, Brenda T Pun, Darren B Taichman, Jan G Dunn, Anne S Pohlman, Paul A Kinniry, James C Jackson, Angelo E Canonico, Richard W Light, Ayumi K Shintani, Jennifer L Thompson, Sharon M Gordon, Jesse B Hall, Robert S Dittus, Gordon R Bernard, E Wesley Ely

Lancet 2008; 371: 126–34

See Comment page 95

Department of Medicine (A E Canonico MD) **and Saint Thomas Research Institute** (J G Dunn RN), **Saint Thomas Hospital, Nashville, TN, USA; Department of Medicine, Division of Allergy, Pulmonary, and Critical Care Medicine** (T D Girard MD, J W W Thomason MD, B T Pun RN, J C Jackson PsyD, Prof R W Light MD, Prof G R Bernard MD, Prof E W Ely MD), **Center for Health Services Research** (T D Girard, J C Jackson, S M Gordon PsyD, Prof R S Dittus MD, E W Ely), **and Department of Biostatistics** (A K Shintani PhD, J L Thompson MPH), **Vanderbilt University School of Medicine, Nashville, TN, USA; VA Tennessee Valley Geriatric Research, Education and Clinical Center (GRECC), VA Service, Department of Veterans Affairs Medical Center, Tennessee Valley Healthcare System, TN, USA** (S M Gordon, R S Dittus,

Summary

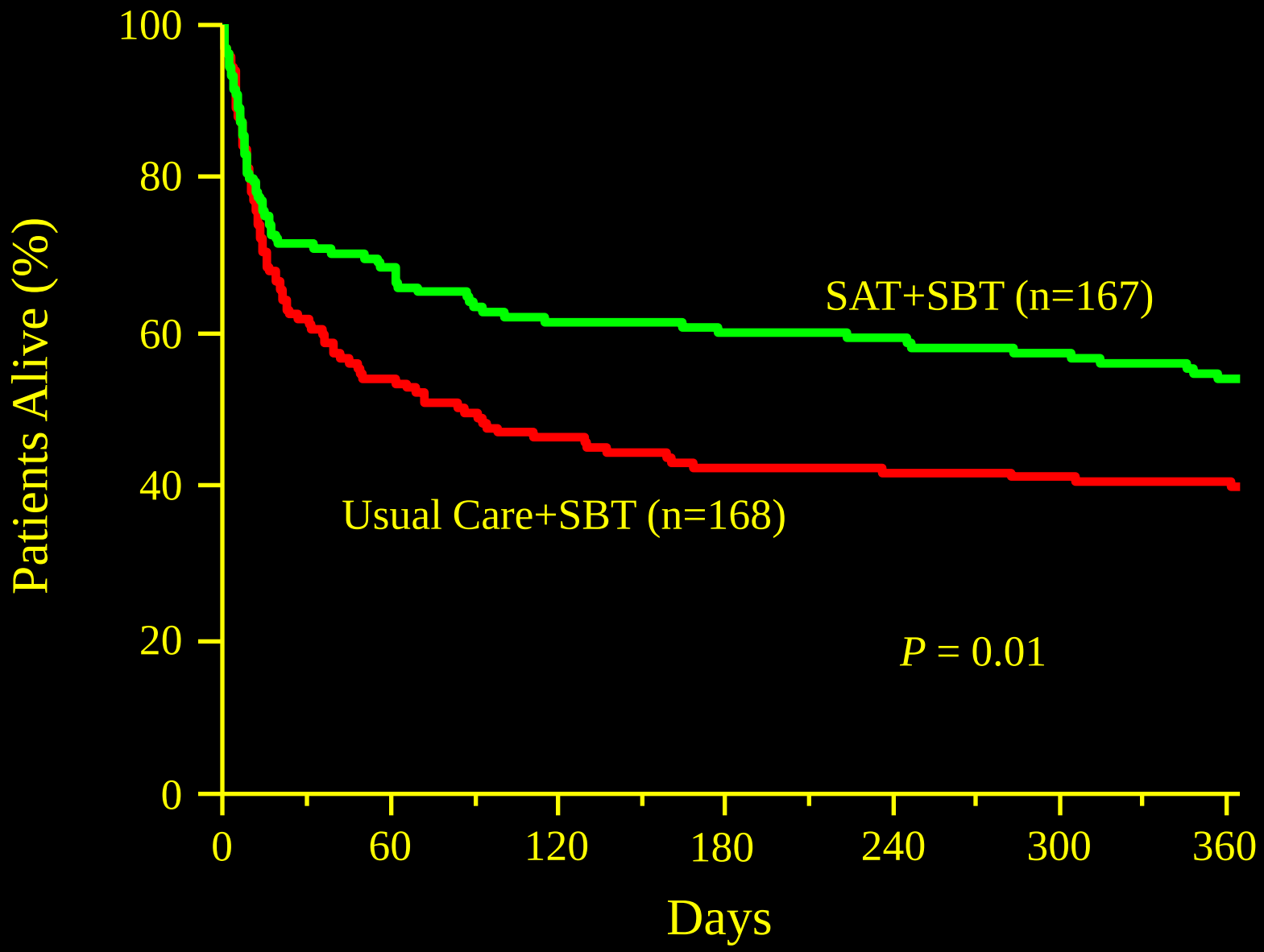
Background Approaches to removal of sedation and mechanical ventilation for critically ill patients vary widely. Our aim was to assess a protocol that paired spontaneous awakening trials (SATs)—ie, daily interruption of sedatives—with spontaneous breathing trials (SBTs).

Methods In four tertiary-care hospitals, we randomly assigned 336 mechanically ventilated patients in intensive care to management with a daily SAT followed by an SBT (intervention group; n=168) or with sedation per usual care plus a daily SBT (control group; n=168). The primary endpoint was time breathing without assistance. Data were analysed by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00097630.

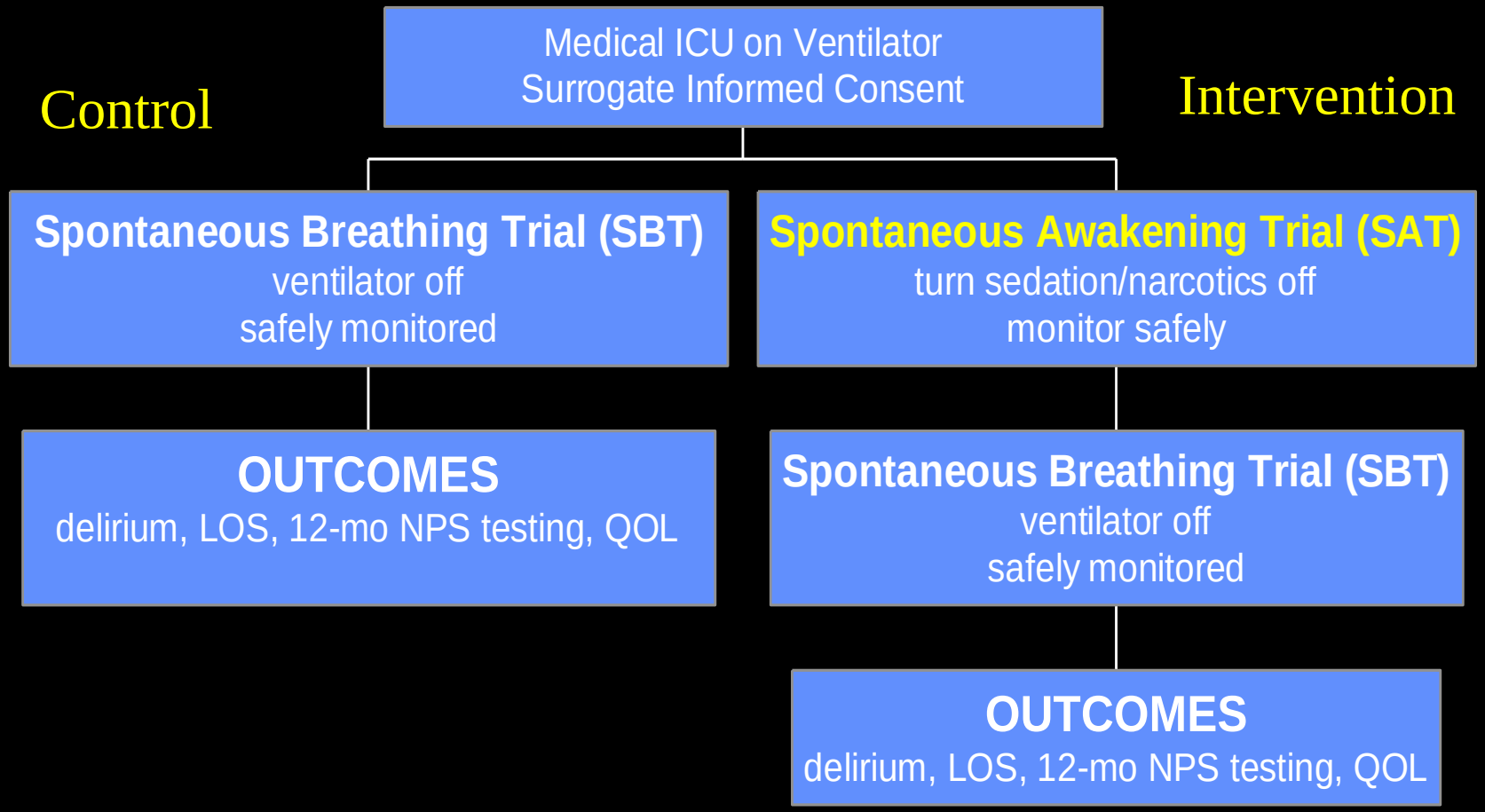
Findings One patient in the intervention group did not begin their assigned treatment protocol because of withdrawal of consent and thus was excluded from analyses and lost to follow-up. Seven patients in the control group discontinued their assigned protocol, and two of these patients were lost to follow-up. Patients in the intervention group spent more days breathing without assistance during the 28-day study period than did those in the control group (14·7 days *vs* 11·6 days; mean difference 3·1 days, 95% CI 0·7 to 5·6; p=0·02) and were discharged from intensive care (median time in intensive care 9·1 days *vs* 12·9 days; p=0·01) and the hospital earlier (median time in the hospital 14·9 days *vs* 19·2 days; p=0·04). More patients in the intervention group self-extubated than in the control group (16 patients *vs* six patients; 6·0% difference, 95% CI 0·6% to 11·8%; p=0·03), but the number of patients who required reintubation after self-extubation was similar (five patients *vs* three patients; 1·2% difference, 95% CI –5·2% to 2·5%; p=0·47), as were total reintubation rates (13·8% *vs* 12·5%; 1·3% difference, 95% CI –8·6% to 6·1%; p=0·73). At any instant during the year after enrolment, patients in the intervention group were less likely to die than were patients in the control group (HR 0·68, 95% CI 0·50 to 0·92; p=0·01). For every seven patients treated with the intervention, one life was saved (number needed to treat was 7·4, 95% CI 4·2 to 35·5).

Interpretation Our results suggest that a wake up and breathe protocol that pairs daily spontaneous awakening trials (ie, interruption of sedatives) with daily spontaneous breathing trials results in better outcomes for mechanically ventilated patients in intensive care than current standard approaches and should become routine practice.

Improved one-year survival



The ABC trial



Analgesia e sedazione in TI:

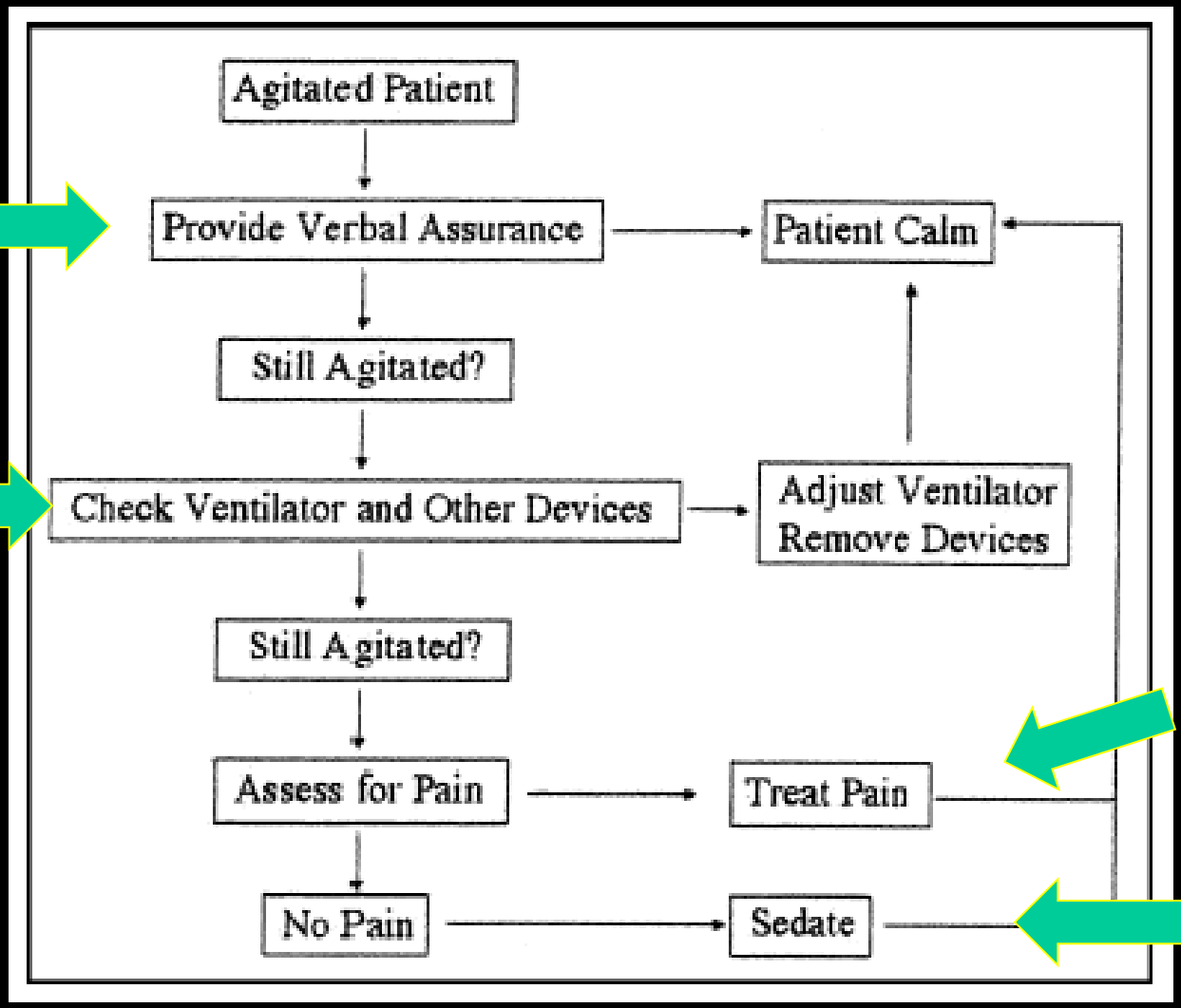
come ? e perchè

Con quale obiettivo ?

Giovanni Mistraletti, MD
Dipartimento di Anestesiologia e Terapia Intensiva
Università degli Studi di Milano
AO San Paolo – Polo Universitario
Milano, Italy

Selected Topics in Anestesia e Terapia Intensiva
Udine, 23 febbraio 2012

Key steps for ventilated patients



1°

2°

3°

4°

Hogart DK, *Curr Op Crit Care,* 2004

Sedazione e analgesia nelle Terapie Intensive tedesche: cosa accade nella pratica reale?

- Coma
- St. Dolore
- St. Verbale
- Soporoso
- Tranquillo
- Agitato

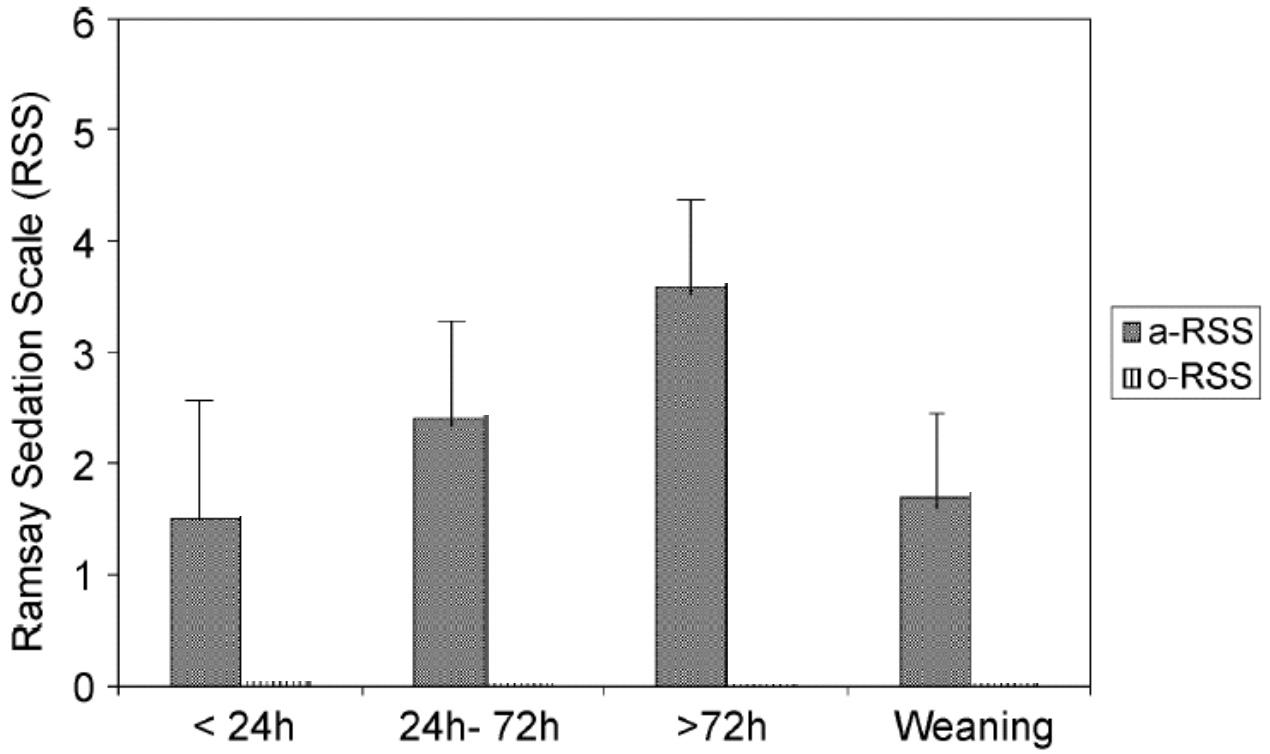


Fig. 1 Mean SD of the value on the Ramsay sedation scale that which aimed at (*a-RSS*) and that which was obtained (*o-RSS*). $^{*}p \leq 0.05$ (Mann-Whitney *U* test)

Martin J, *Intensive Care Med,* 2006

Sedazione e analgesia nelle Terapie Intensive tedesche: cosa accade nella pratica reale?

- Coma
- St. Dolore
- St. Verbale
- Soporoso
- Tranquillo
- Agitato

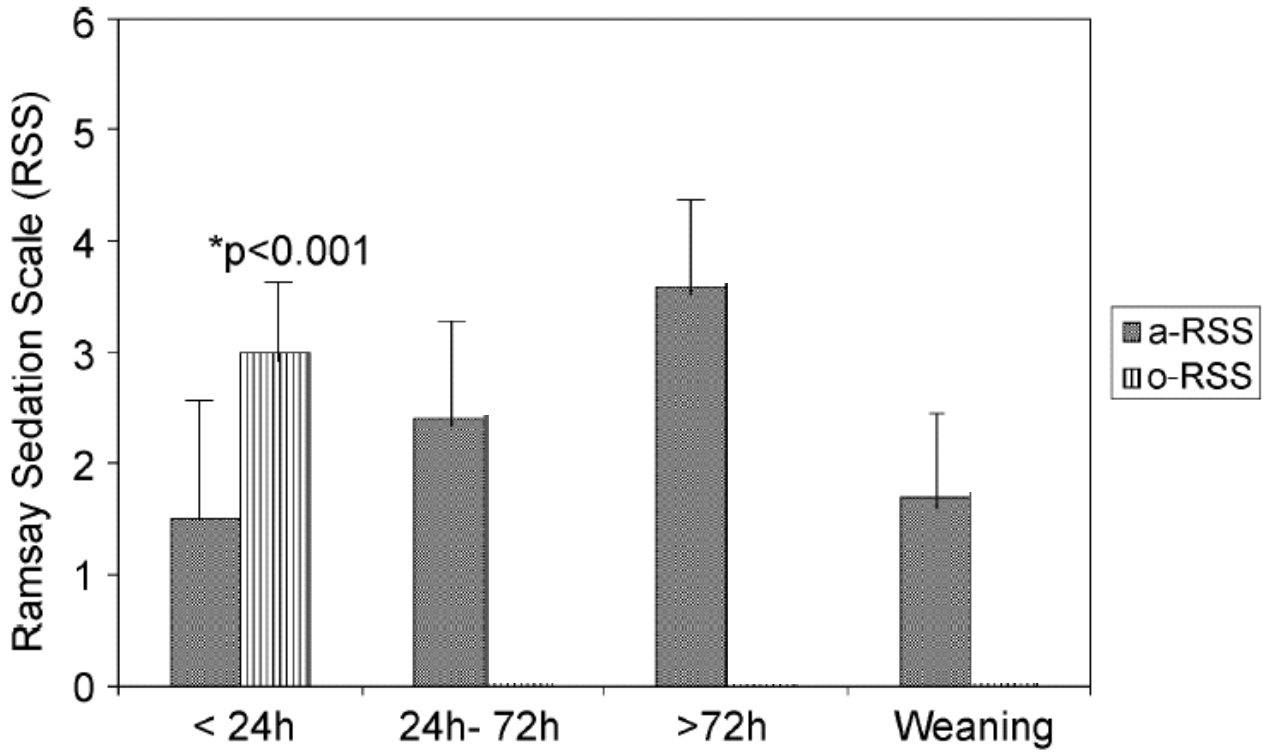


Fig. 1 Mean SD of the value on the Ramsay sedation scale that which aimed at (*a-RSS*) and that which was obtained (*o-RSS*). $^{*}p \leq 0.05$ (Mann-Whitney *U* test)

Martin J, *Intensive Care Med,* 2006

Sedazione e analgesia nelle Terapie Intensive tedesche: cosa accade nella pratica reale?

- Coma
- St. Dolore
- St. Verbale
- Soporoso
- Tranquillo
- Agitato

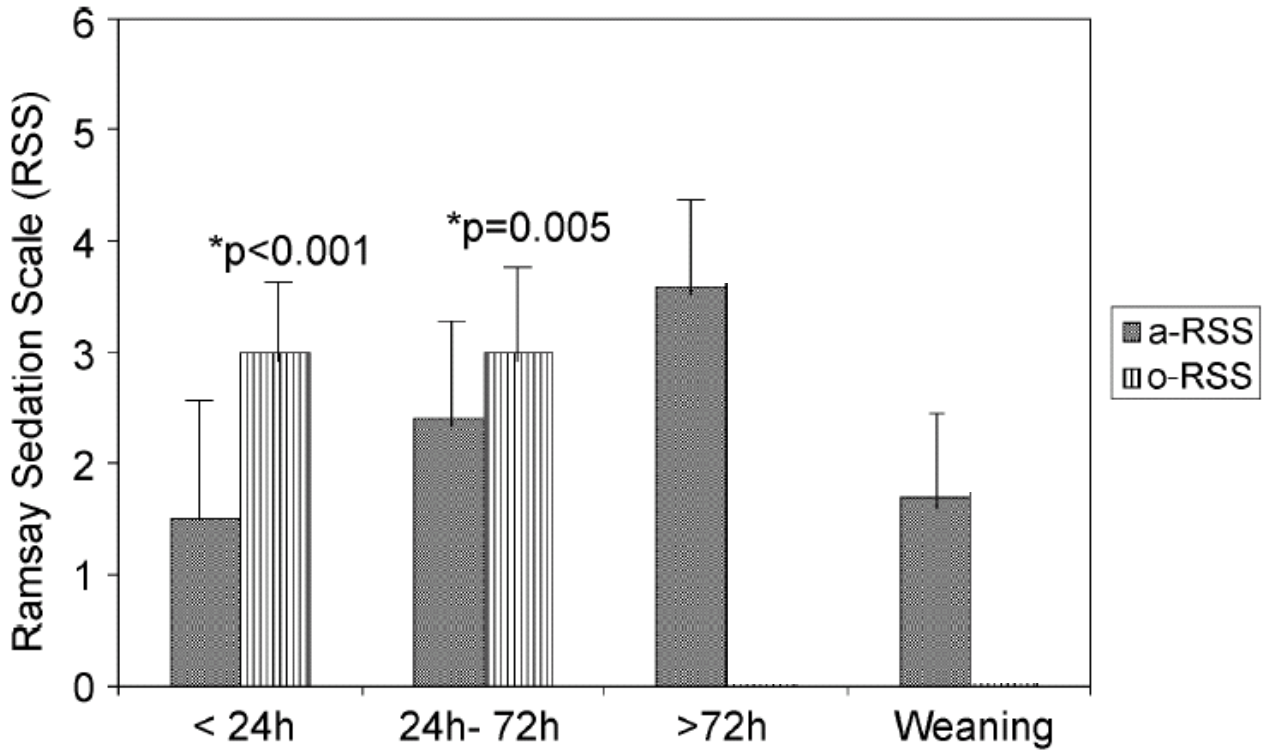


Fig. 1 Mean SD of the value on the Ramsay sedation scale that which aimed at (*a-RSS*) and that which was obtained (*o-RSS*). $^{*}p \leq 0.05$ (Mann-Whitney *U* test)

Martin J, *Intensive Care Med,* 2006

Sedazione e analgesia nelle Terapie Intensive tedesche: cosa accade nella pratica reale?

- Coma
- St. Dolore
- St. Verbale
- Soporoso
- Tranquillo
- Agitato

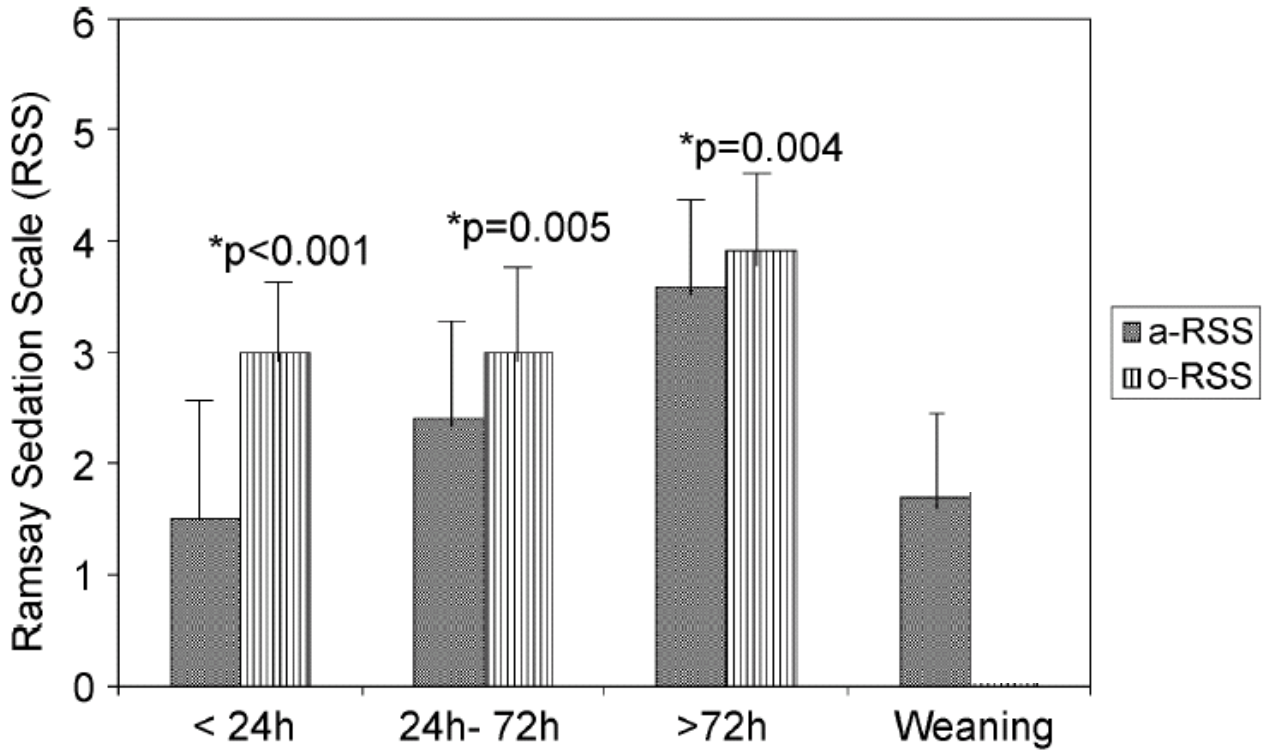


Fig. 1 Mean SD of the value on the Ramsay sedation scale that which aimed at (*a-RSS*) and that which was obtained (*o-RSS*). $^{*}p \leq 0.05$ (Mann-Whitney *U* test)

Martin J, *Intensive Care Med,* 2006

Sedazione e analgesia nelle Terapie Intensive tedesche: cosa accade nella pratica reale?

- Coma
- St. Dolore
- St. Verbale
- Soporoso
- Tranquillo
- Agitato

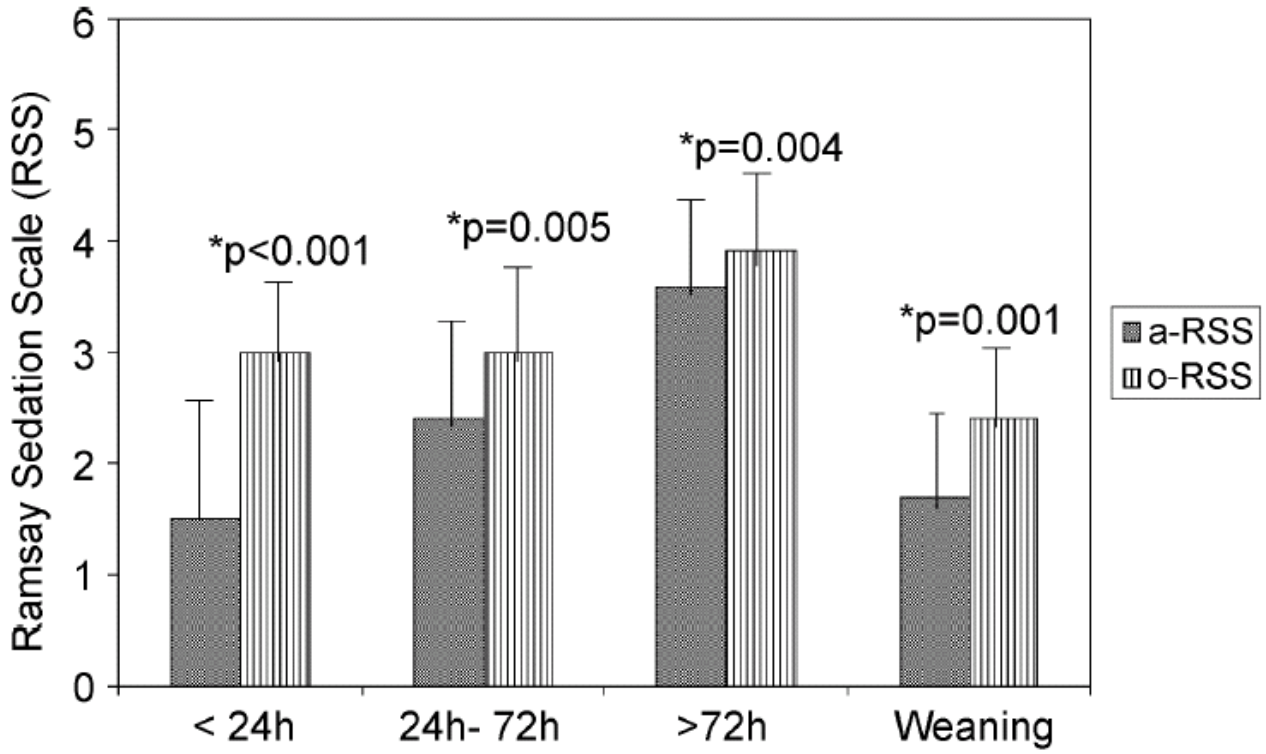


Fig. 1 Mean SD of the value on the Ramsay sedation scale that which aimed at (*a-RSS*) and that which was obtained (*o-RSS*). $^{*}p \leq 0.05$ (Mann-Whitney *U* test)

Martin J, *Intensive Care Med,* 2006

OPEN ACCESS

This is the original (English) version.
The translated (German) version starts at p. 16.

Review Article

Evidence and consensus-based German guidelines for the management of analgesia, sedation and delirium in intensive care – short version

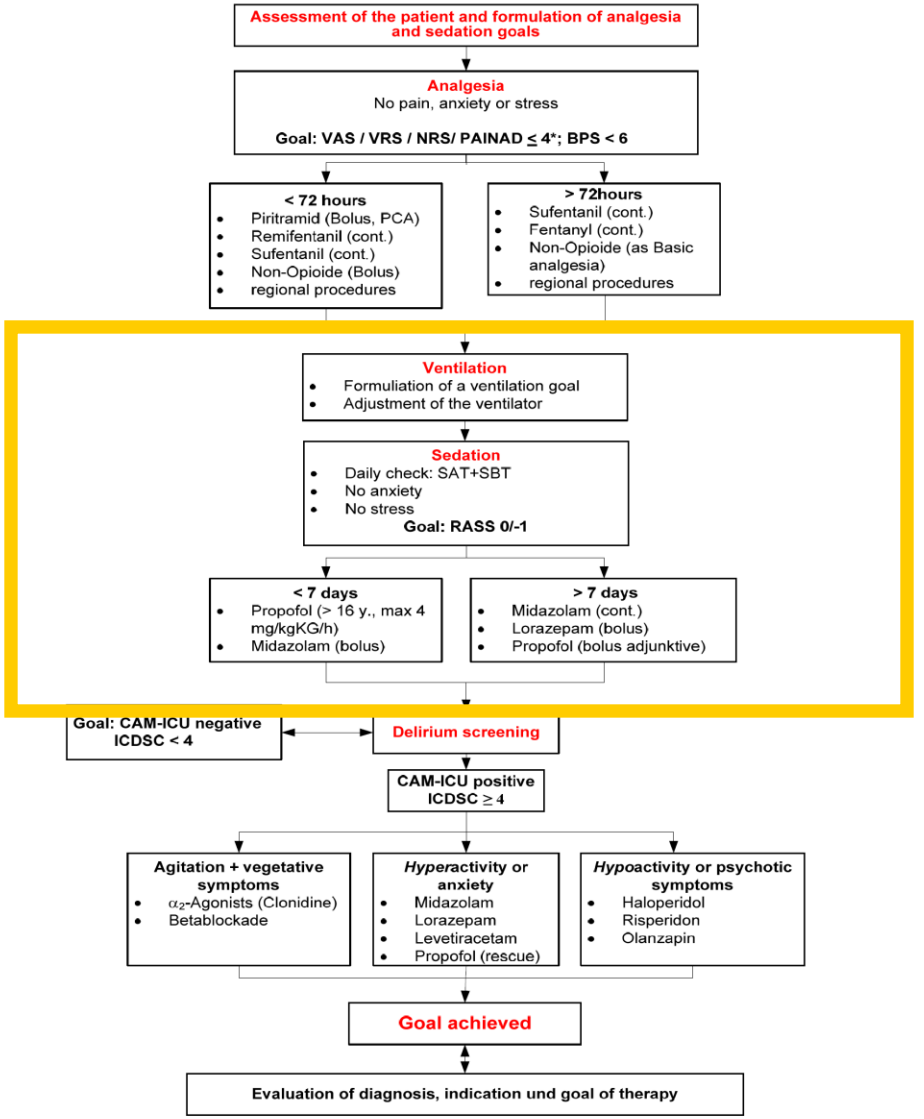
Jörg Martin[1]
Anja Heymann[2]
Katrin Bäsell[3]

Abstract

Targeted monitoring of analgesia, sedation and delirium, as well as their appropriate management in critically ill patients is a standard of care in intensive care medicine. With the undisputed advantages of goal-oriented therapy established, there was a need to develop our own

Martin J, *Ger Med Sci,* 2010

2. Overall-scheme for analgesia, sedation and delirium treatment in adults



* dependent on the individual pain acceptance of th patient,

RASS: Richmond Agitation Sedation Scale (-5 to +4)

VAS: Visual Analogue Scala, VRS: Verbale Rating Scala, NRS: Numeric Rating Scale (0-10)

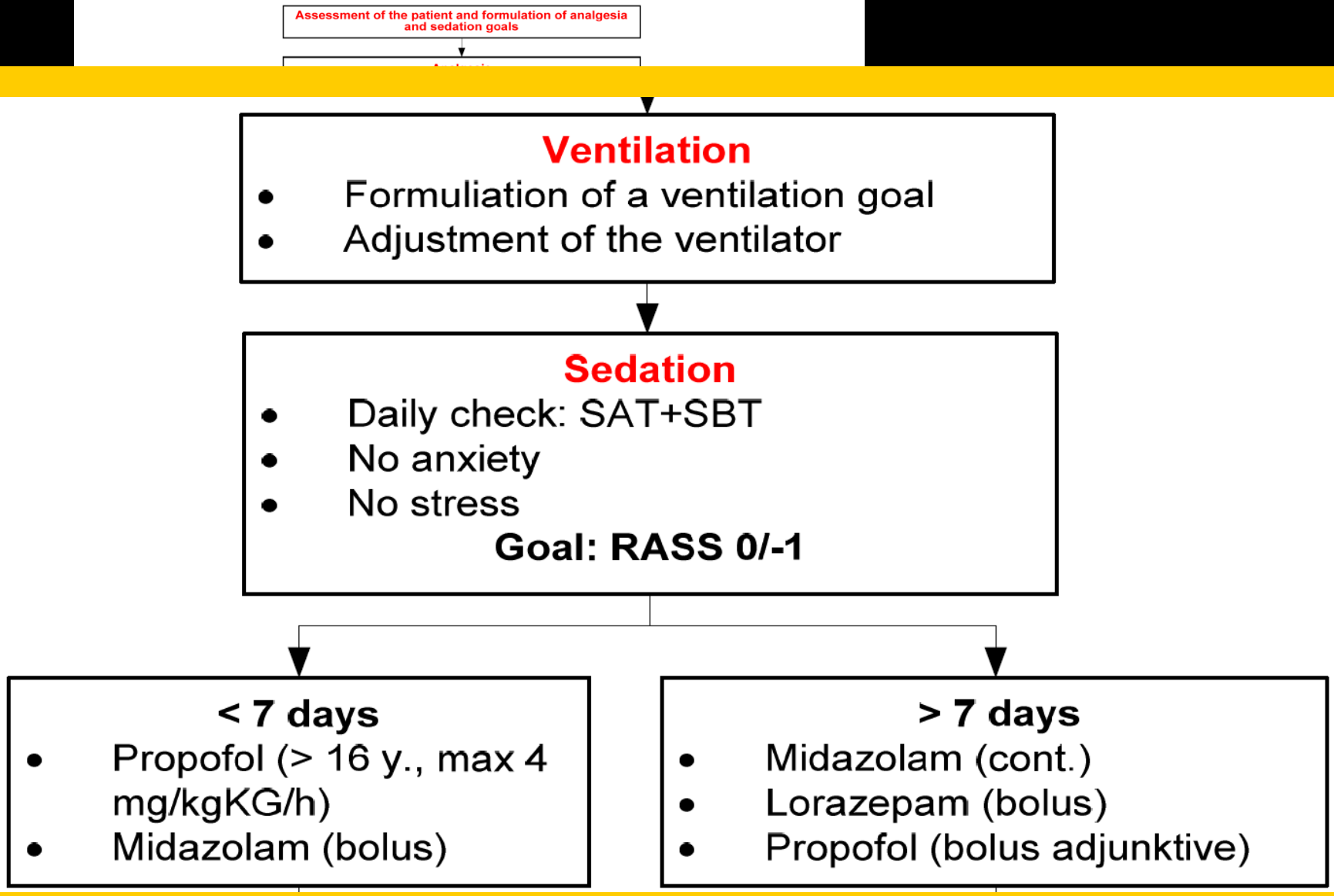
BPS: Behavioral Pain Scale (3-12), PAINAD: Pain Assessment in Advanced Dementia (0-10)

CAM-ICU: Confusion Assessment Method for the ICU (positive/negative)

ICDSC: Intensive Care Delirium Screening Checklist (0-8)

Martin J, *Ger Med Sci,* 2010

2. **Overall-scheme for analgesia, sedation and delirium treatment in adults**



RASS: Richmond Agitation Sedation Scale (-5 to +4)

VAS: Visual Analogue Scala, VRS: Verbale Rating Scala, NRS: Numeric Rating Scale (0-10)

BPS: Behavioral Pain Scale (3-12), PAINAD: Pain Assessment in Advanced Dementia (0-10)

CAM-ICU: Confusion Assessment Method for the ICU (positive/negative)

ICDSC: Intensive Care Delirium Screening Checklist (0-8)

Martin J, *Ger Med Sci,* 2010

QUADRO SINOTTICO
SCALE DI SEDAZIONE/AGITAZIONE IN TERAPIA INTENSIVA

	RICHMOND AGITATION SEDATION SCALE RASS	BLOOMSBURY SEDATION SCORE BLOOMSBURY	RAMSAY SEDATION SCORE RAMSAY	MOTOR ACTIVITY ASSESSMENT SCALE MAAS	RIKER SEDATION-AGITATION SCALE SAS	OBSERVER'S ASSESSMENT OF ALERTNESS AND SEDATION OAAS	
Aggressivo	+4		1	6	7		Aggressivo
Molto agitato	+3			5	6		Molto agitato
Agitato	+2	+3			5		Agitato
Irrequieto	+1	+2		4			Irrequieto
Sveglio e tranquillo	**0**	**+1**	**2**	**3**	**4**	**5**	**Sveglio e tranquillo**
Sonnolento	-1	0	3	2	3	4	Sonnolento
Sedazione leggera	-2	-1				3	Sedazione leggera
Sedazione moderata	-3		4	1	2	2	Sedazione moderata
Sedazione profonda	-4	-2	5		1	1	Sedazione profonda
Non risvegliabile	-5	-3	6	0		0	Non risvegliabile

Evocated potential - BISpectral Index - Entropy

Auditory Event-Related Potentials, Bispectral Index, and Entropy for the Discrimination of Different Levels of Sedation in Intensive Care Unit Patients

Matthias Haenggi, MD*
Heidi Ypparila-Wolters, PhD†
Sarah Buerki, cand. med.*
Rebekka Schlauri, cand. med.*
Ilkka Korhonen, PhD†
Jukka Takala, MD, PhD*
Stephan M. Jakob, MD, PhD*

BACKGROUND: Sedation protocols, including the use of sedation scales and regular sedation stops, help to reduce the length of mechanical ventilation and intensive care unit stay. Because clinical assessment of depth of sedation is labor-intensive, performed only intermittently, and interferes with sedation and sleep, processed electrophysiological signals from the brain have gained interest as surrogates. We hypothesized that auditory event-related potentials (ERPs), Bispectral Index® (BIS), and Entropy® can discriminate among clinically relevant sedation levels.

METHODS: We studied 10 patients after elective thoracic or abdominal surgery with general anesthesia. Electroencephalogram, BIS, state entropy (SE), response entropy (RE), and ERPs were recorded immediately after surgery in the intensive care unit at Richmond Agitation-Sedation Scale (RASS) scores of −5 (very deep sedation), −4 (deep sedation), −3 to −1 (moderate sedation), and 0 (awake) during decreasing target-controlled sedation with propofol and remifentanil. Reference measurements for baseline levels were performed before or several days after the operation.

RESULTS: At baseline, RASS −5, RASS −4, RASS −3 to −1, and RASS 0, BIS was 94 [4]

CONCLUSIONS: Neither ERPs nor BIS or Entropy can replace clinical sedation assessment with standard scoring systems. Discrimination among very deep, deep to moderate, and no sedation after general anesthesia can be provided by ERPs and processed electroencephalograms, with similar P_Ks. The high inter- and intraindividual variability of Entropy and BIS precludes defining a target range of values to predict the sedation level in critically ill patients using these parameters. The variability of ERPs is unknown.

(Anesth Analg 2009;109:807–16)

Actigraphy …

Journal of Critical Care (2009) **24**, 563–567

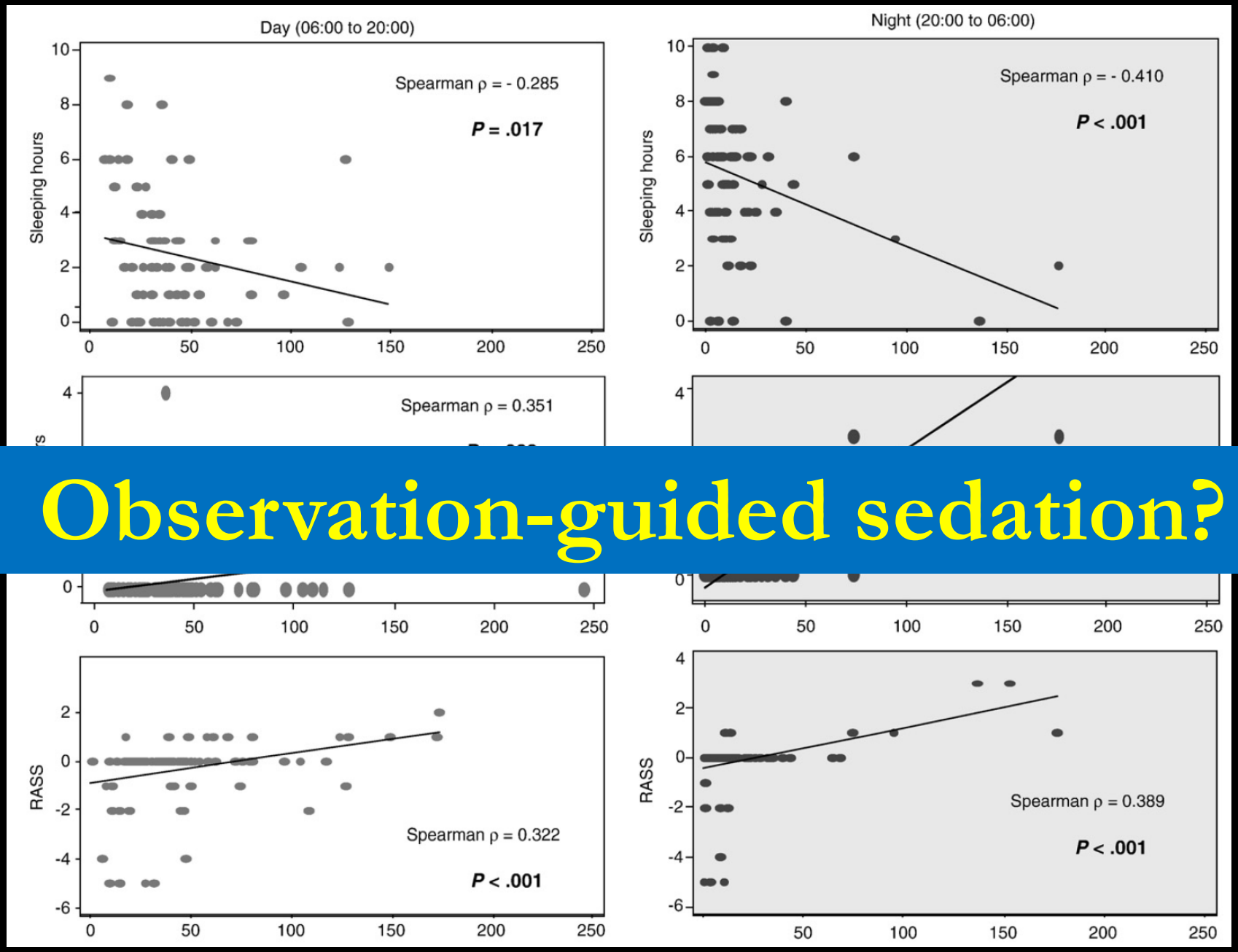
ELSEVIER

Journal of Critical Care

Actigraphic monitoring in critically ill patients: Preliminary results toward an "observation-guided sedation"

Giovanni Mistraletti MD[a,*], Martina Taverna MD[a], Giovanni Sabbatini MD[a], Elisabetta Carloni MD[a], Luca Bolgiaghi MD[a], Massimiliano Pirrone MD[a], Marco Cigada MD[b], Anne Lucia Leona Destrebecq[c], Franco Carli MD, MPhil[d], Gaetano Iapichino MD[a]

[a]*Istituto di Anestesiologia e Rianimazione, Università degli Studi di Milano, Azienda Ospedaliera San Paolo-Polo Universitario, 20142 Milano, Italy*
[b]*Servizio di Anestesia e Rianimazione, Azienda Ospedaliera Fatebenefratelli e Oftalmico, Milano, Italy*
[c]*Dipartimento di Medicina, Chirurgia e Odontoiatria, Università degli Studi di Milano, Azienda Ospedaliera San Paolo-Polo Universitario, Milano, Italy*
[d]*Department of Anesthesia, McGill University Health Centre, Montreal, Quebec, Canada*



Observation-guided sedation?

Mistraletti G, *J Crit Care Med*, 2009

Il livello di sedazione ideale
varia per ogni paziente
e per ogni momento della storia clinica…

Ma siamo disposti a desiderare
che i nostri pazienti critici
siano “il più svegli possibile”… ? ! ? !


TOMATOES
FAIT & WINEBRENNER
THOMPSON & HILLS
THE BRITISH CO-OPERATIVE SOCIETIES
This Mustard IS PREPARED FOR
BY THE
GROWERS from the finest LINCOLNSHIRE SEED
AND IS HIGHLY RECOMMENDED
MUSTARD
ANNE GEDDES

?

Analgesia e sedazione in TI:

come ? e perchè

Con quali farmaci ?

Giovanni Mistraletti, MD
Dipartimento di Anestesiologia e Terapia Intensiva
Università degli Studi di Milano
AO San Paolo – Polo Universitario
Milano, Italy

Selected Topics in Anestesia e Terapia Intensiva
Udine, 23 febbraio 2012

Quali farmaci usiamo ?

Society of Critical Care Medicine

(2002)

Analgesics → **morphine**, **fentanyl**, **hydromorphone**

Sedatives → **midazolam**, **propofol**, **lorazepam**

Anti-delirium → **haloperidol**

Available drugs

Analgesics:

- Opioids (morphin, fentanyl, sufentanil, alfentanil, hydromorfone, remifentanil, tramadol)
- NSAIDs, acetaminophen

Sedatives:

- BZDP (Diazepam, Lorazepam, Midazolam)
- Propofol
- $\mathbf{A}_{2}$-agonist (clonidine, dexmedetomidine)
- Atypical:
  - Butyrophenone (Haloperidol, Droperidol)
  - Etomidate
  - Ketamin
  - Barbiturates (Sodium thiopental, Phenobarbital)
  - Inhalational agents (Halogenated, Xenon)

For each sedative, please check:

- Farmacokinetics
- Neurological effects
- Cardio-respiratory effects
- Endocrine and metabolic effects

- Side effects

- Indications

Canadian survey of the use of sedatives, analgesics & NMBA in ICU…

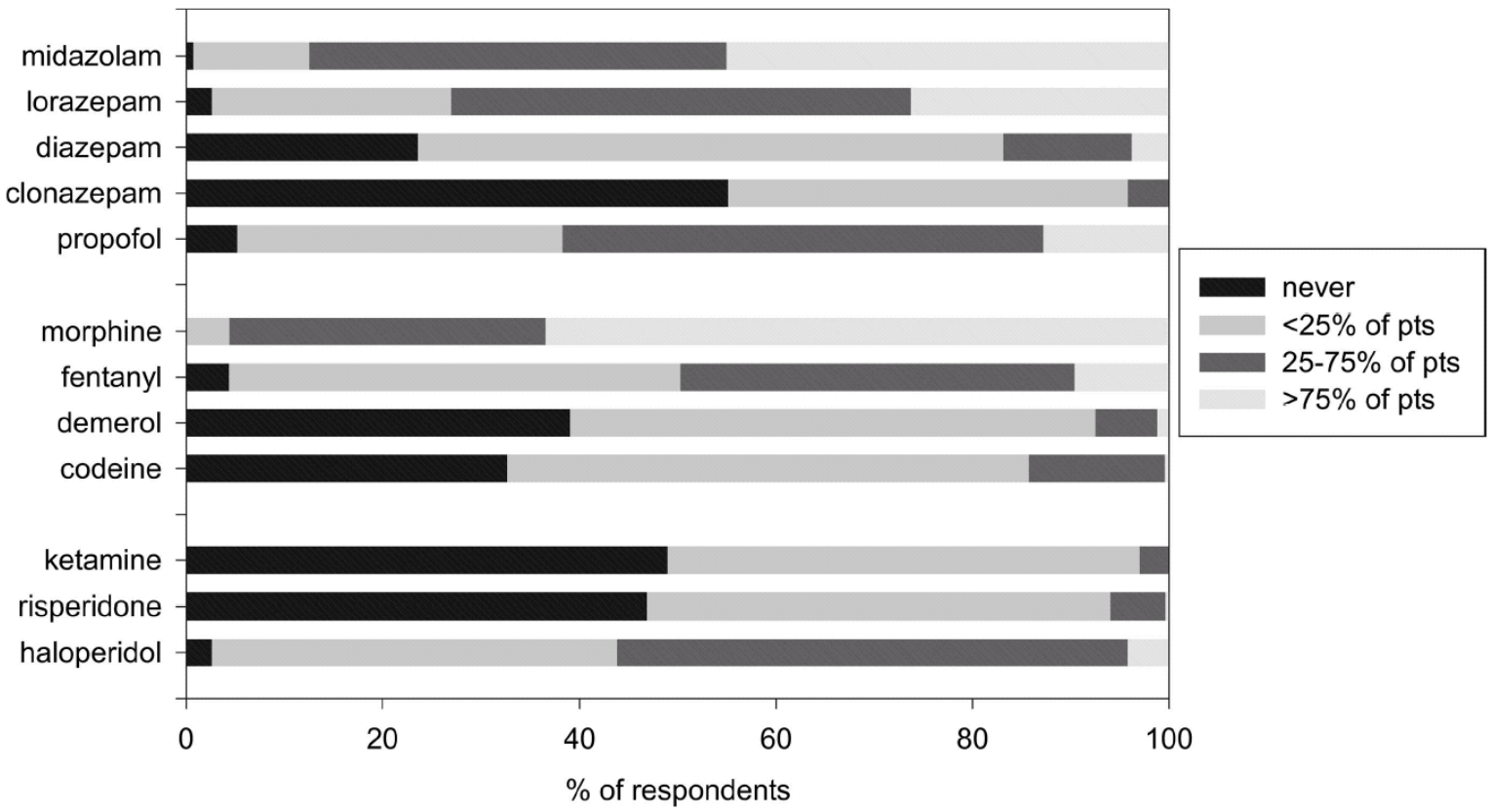


Figure 1. We asked respondents about the frequency of their use of each of these sedatives, analgesics, and antipsychotics.

Metha S, et al., *Crit Care Med*, 2006

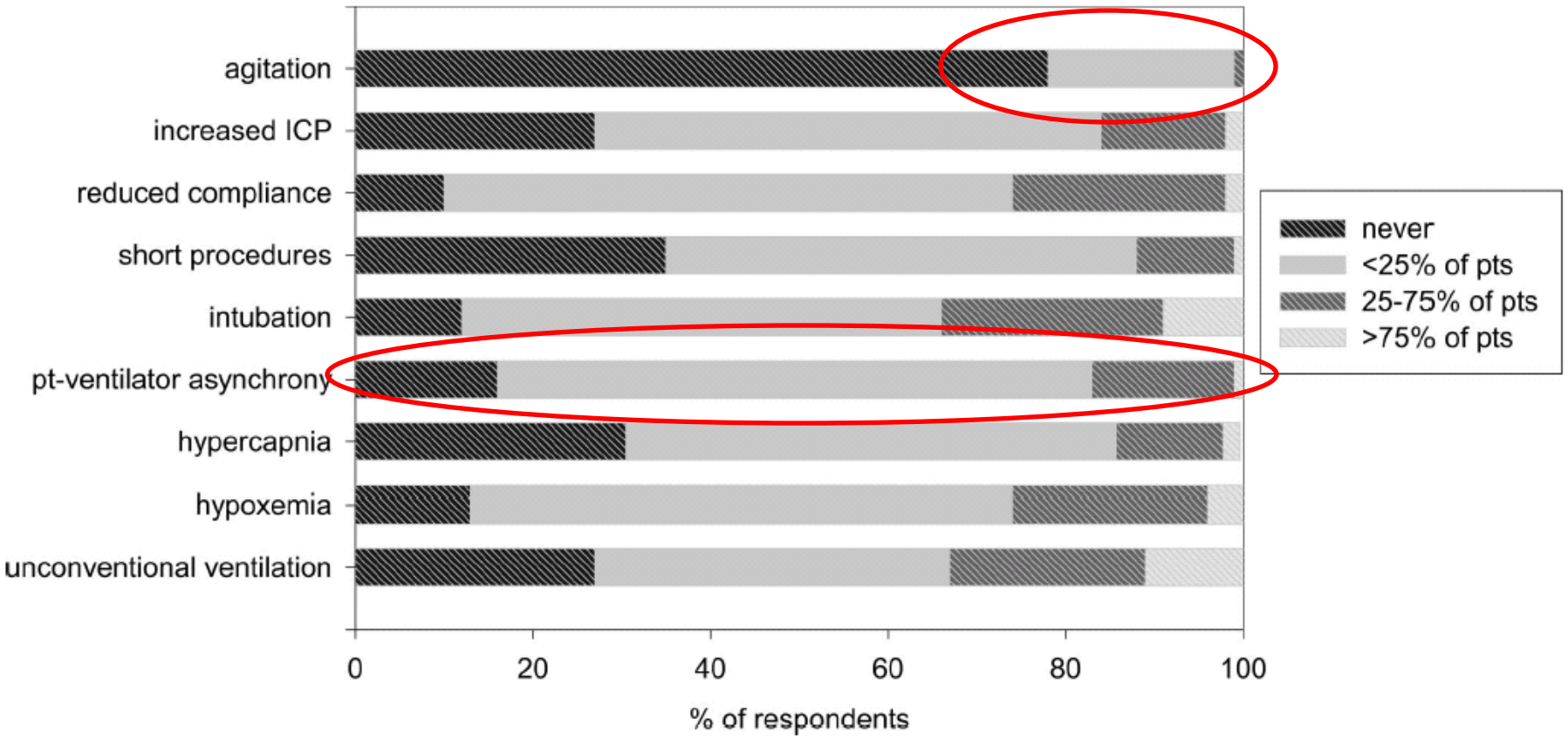


Figure 2. We asked respondents about the frequency of use of neuromuscular blockers for each of these indications. *ICP*, intracranial pressure; *pt*, patient.

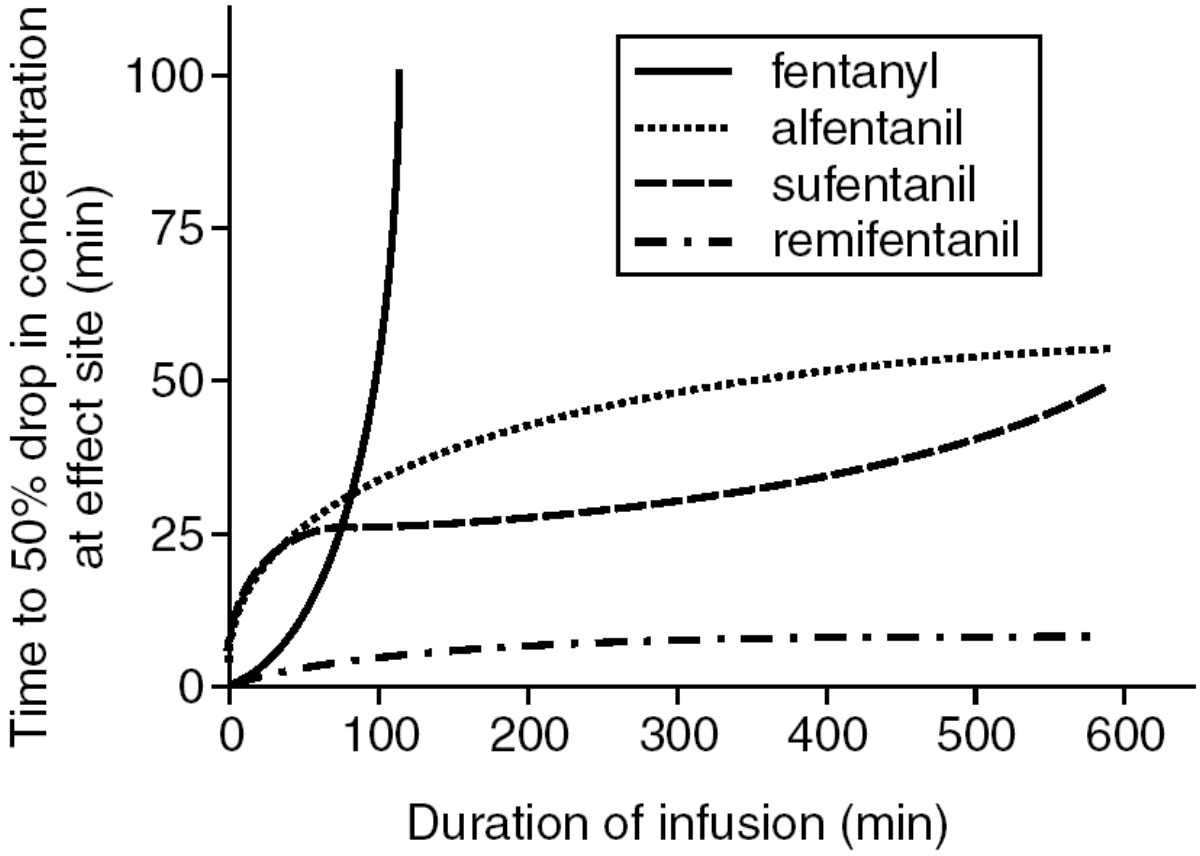
. . . ! ! !

Metha S, et al., *Crit Care Med*, 2006

Problems with current agents

Property	Lorazepam	Midazolam	Propofol	Opioids
Rapid onset		✓	✓	✓[a]
Short duration		✓	✓	✓[a]
Tolerance	✓	✓		✓
Prolonged weaning	?	✓		✓
Respiratory depression	✓	✓	✓	✓
Severe hypotension	✓	✓	✓	
Constipation				✓
Potential abuse	✓	✓	✓	✓
Inexpensive	✓			

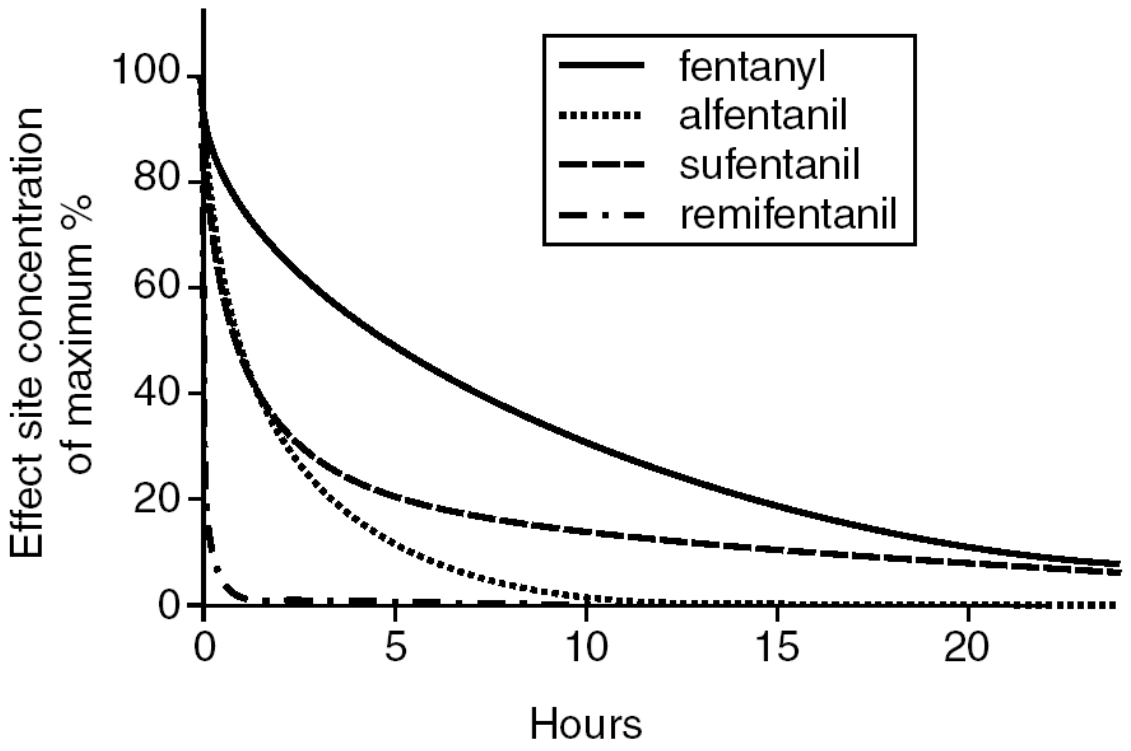
[a]Refers to new-generation opioids, particularly remifentanil.



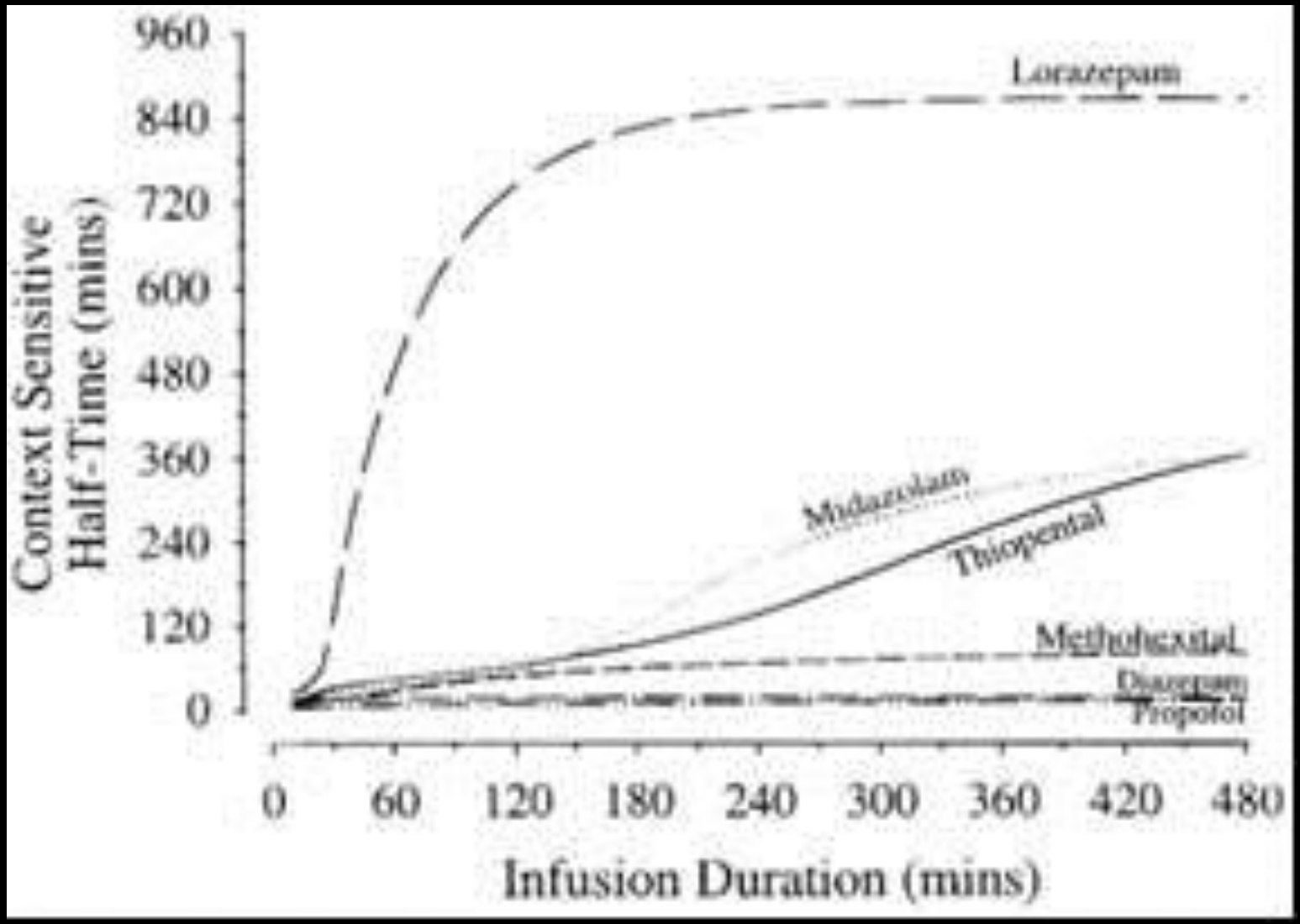
Context-sensitive half-times of remifentanil and the other 4-anilido-piperidine opioids. Remifentanil has a context-sensitive half-time of 3 to 4 minutes, regardless of the duration of infusion, whereas continuous infusion of the other opioids results in accumulation and considerable prolongation of effect, making these opioids intermediate-acting or long-acting agents, depending on the duration of infusion.

Egan TD, *Anesthesiology*, 1993

Figure 2



Decline of effect site concentrations of different opioids after 24 hours of infusion. The findings are expressed as percentage of the individual maximum effect site concentration. This figure was calculated using Stanpump simulation software (by Shafer S, University of Stanford, CA, USA) for a female individual (age 80 years, height 170 cm, body weight 80 kg) and the following infusion rates: remifentanil 0.15 µg/kg per minute, sufentanil 1 µg/kg per hour, alfentanil 1.5 mg/hour, and fentanyl 0.2 mg/hour.



Malacrida R, *Crit Care Med*, 1992

Sedation and analgesia in German ICU: how is it done in reality?

- Coma
- St. Dolore
- St. Verbale
- Soporoso
- Tranquillo
- Agitato

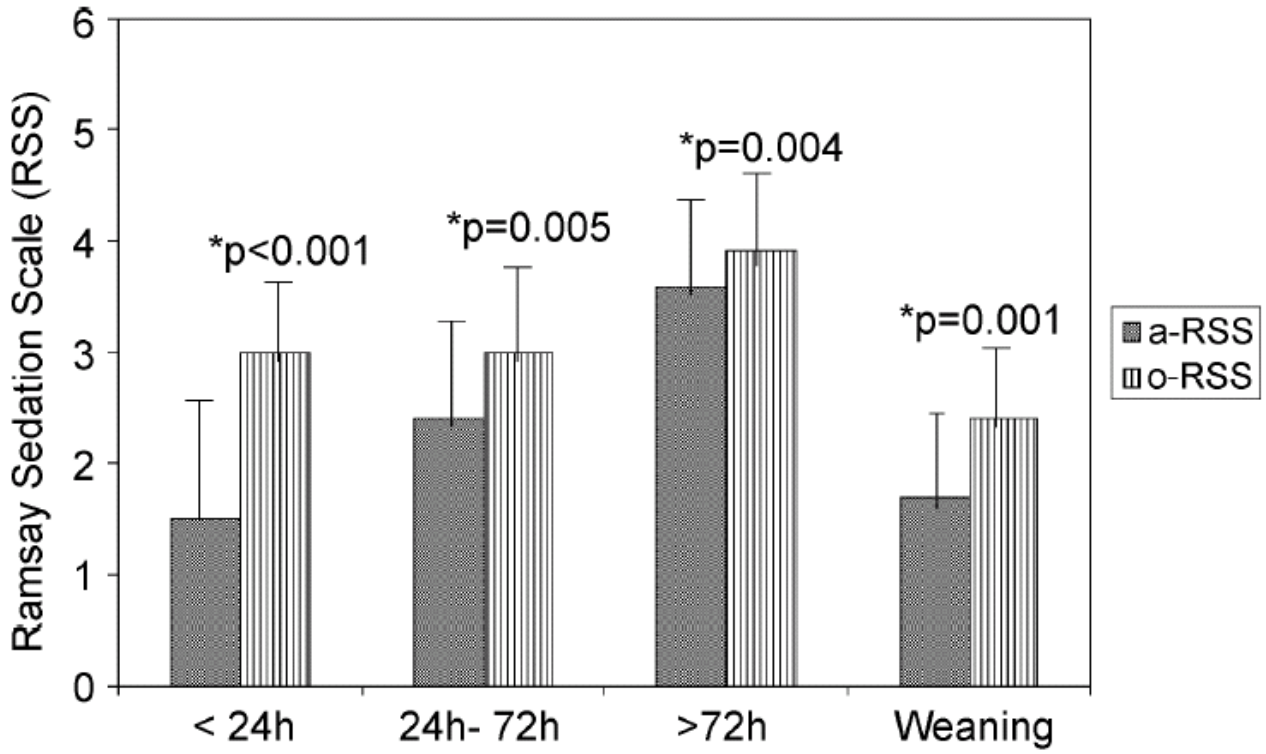


Fig. 1 Mean SD of the value on the Ramsay sedation scale that which aimed at (*a-RSS*) and that which was obtained (*o-RSS*). $^{*}p \leq 0.05$ (Mann-Whitney *U* test)

Martin J, *Intensive Care Med*, 2006

Goals of Analgo-Sedation

- Individualized approach to sedation
- Ability to tolerate physical enviroment
- Ability to tolerate ICU procedures
- Prevention/reduction of stress
- Patient safety

The ideal sedative…

Properties of the ideal sedative

Rapid onset and offset
Minimal respiratory depression
No effect on cardiovascular function
Inactive metabolites or lack of metabolites
Metabolism and elimination not dependent on hepatic function
Metabolism and elimination not dependent on renal function
No drug interactions
No pain on injection
No associated tolerance or withdrawal
Amnestic
Inexpensive

Angelini G, *Crit Care Clin,* 2001

- Realized in drug association ?

The American way

- Daily interruption of sedation

The European way

- Analgesia-based sedation

- Have the “enteral approach” some advantages ?

CHEST Postgraduate Education Corner

CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE

Patient-Focused Sedation and Analgesia in the ICU*

Curtis N. Sessler, MD, FCCP; and Kimberly Varney, PharmD

Patient-focused sedation and analgesia in the ICU encompasses a strategy of comprehensive structured management that matches initial evaluation, monitoring, medication selection, and the use of protocols with patient characteristics and needs. This is best accomplished through interdisciplinary management by physicians, nurses, and pharmacists. An early consideration is that of the potential predisposing and precipitating factors, as well as prior sedative or analgesic use, factors that may influence pharmacologic and supportive therapy. Frequent monitoring with validated tools improves communication among clinicians and plays an important role in detecting and treating pain and agitation while avoiding excessive or prolonged sedation. Patient-focused management encompasses selecting medications best suited to patient characteristics, including the presence of organ dysfunction that may influence drug metabolism or excessive risk for side effects. The use of protocols to optimize drug therapy has emerged as a key component of management, resulting in reductions in the duration of sedation, mechanical ventilation, and ICU length of stay demonstrated with strategies to titrate medications to specific targets, daily interruption of sedation, intermittent rather than continuous therapy, and analgesia-based therapy. While much attention is paid to the initiation and maintenance of therapy, greater emphasis must be placed on careful de-escalation of therapy in order to avoid analgesic or sedative withdrawal. Finally, more work is needed to explore the relationship of critical illness and sedation management with long-term psychological outcomes.

(CHEST 2008; 133:552–565)

CHEST Postgraduate Education Corner

CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE

Patient-Focused Sedation and Analgesia in the ICU*

Curtis N. Sessler, MD, FCCP; and Kimberly Varney, PharmD

Patient-focused sedation and analgesia in the ICU encompasses a strategy of comprehensive structured management that matches initial evaluation, monitoring, medication selection, and the use of protocols with patient characteristics and needs. This is best accomplished through interdisciplinary management by physicians, nurses, and pharmacists. An early consideration is that of the potential predisposing and precipitating factors, as well as prior sedative or analgesic use, factors that may influence pharmacologic and supportive therapy. Frequent monitoring with validated tools improves communication among clinicians and plays an important role in detecting and treating pain and agitation while avoiding excessive or prolonged sedation. Patient-focused management encompasses selecting medications best suited to patient characteristics, including the presence of organ dysfunction that may influence drug metabolism or excessive risk for side effects. The use of protocols to optimize drug therapy has emerged as a key component of management, resulting in reductions in the duration of sedation, mechanical ventilation, and ICU length of stay demonstrated with strategies to titrate medications to specific targets, daily interruption of sedation, intermittent rather than continuous therapy, and analgesia-based therapy. While much attention might be placed on the initiation and maintenance of therapy, greater emphasis must be placed on careful de-escalation of therapy in order to avoid analgesic or sedative withdrawal. Finally, more work is needed to explore the relationship of critical illness and sedation management with long-term psychological outcomes.

(CHEST 2008; 133:552–565)

CHEST Postgraduate Education Corner

CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE

Patient-Focused Sedation and Analgesia in the ICU*

Sessler CN, *Chest,* 2008

La somministrazione di farmaci per via enterale o transdermica può avere un impatto in alcuni pazienti, soprattutto quelli che necessitano di una sedazione a lungo termine e una gestione specifica per l'analgesia, determinando una eliminazione o riduzione nei dosaggi endovena. [82]

[82] Cigada M et al, *Intensive Care Med* 2005

Analgesia e sedazione in TI:

come ? e perchè

Per quale via ?

Giovanni Mistraletti, MD
Dipartimento di Anestesiologia e Terapia Intensiva
Università degli Studi di Milano
AO San Paolo – Polo Universitario
Milano, Italy

Selected Topics in Anestesia e Terapia Intensiva
Udine, 23 febbraio 2012

Già nel 1989…

Anest. Rianim., 30, 75-78, 1989

TRATTAMENTO SEDATIVO POLIFARMACOLOGICO PER VIA ENTERALE IN PAZIENTI CRITICI

G. Iapichino, M. Borelli, G. Breda, R. Ciceri, S. Ferraris, M. Passoni

Introduzione

La sedazione è un presidio terapeutico abitualmente utilizzato nei reparti di rianimazione per alleviare il disagio del paziente e per una migliore applicazione delle varie tecniche di assistenza utilizzate (respiratoria, monitoraggio emodinamico: Merriman, 1981; Farina et al. 1981; Bion et al. 1986)

macopea dispone di molti più preparati ma che è generalmente considerata via di scarso affidamento nei pazienti critici.

Scopo del lavoro è presentare la nostra esperienza clinica sull'argomento.

Metodi

Iapichino G, *Anest Rianim,* 1989

La sedazione enterale: perché ?

- Minori effetti collaterali
- Minori costi
- Garantire gli obiettivi di sedazione… cosciente!!!
- Diminuito periodo di weaning (?)
- "Cinetica" più lenta: peggio… o meglio?
  (delirium)
- **Pz più svegli: è possibile ? ! ?**

PRESUPPOSTI

L’intestino funziona precocemente !!

E’ necessaria una sedazione profonda ?

IDROSSIZINA

Indicazioni:	antiistaminico, preanestesia
Effetti collaterali:	anticolinergici
Tossicità (> 45mg/kg):	depressione SNC convulsioni allucinazioni ipotensione
Dosi ridotte in:	insufficienza epatica/renale
Costo ospedaliero:	100 mg = 0.42 €
Dosi utilizzate:	6-12 mg/kg*die

Uno sguardo ai costi

Principio Attivo	Formulazione			Costo per unità	Dose massima	Massimo costo giornaliero
Idrossizina	Compresse		25mg	0.21€	600mg	5.54€
	Preparazione magistrale	100ml	5g	3.6€	600mg	**0.43€**
Lorazepam	Flacone	10ml	20mg	1.01€	16mg	**0.81€**
Propofol	Flacone 2%	50ml	1000mg	6.45€	6800mg	43.86€
	Flacone 1%	20ml	200mg	0.83€	6800mg	**28.22€**
Midazolam	Compresse	1ml	10mg	0.24€	336mg	**8.06€**

Il protocollo attualmente in vigore nella Terapia Intensiva del San Paolo:

Prime 24-48 ore: endovena

Propofol (1-4 mg/kg*h) oppure **Midazolam** (0.02-0.3 mg/kg*h)

associare ad entrambi **Morfina** o **Fentanyl** ev

Da subito: embricare sedazione "per os" (via SNG)

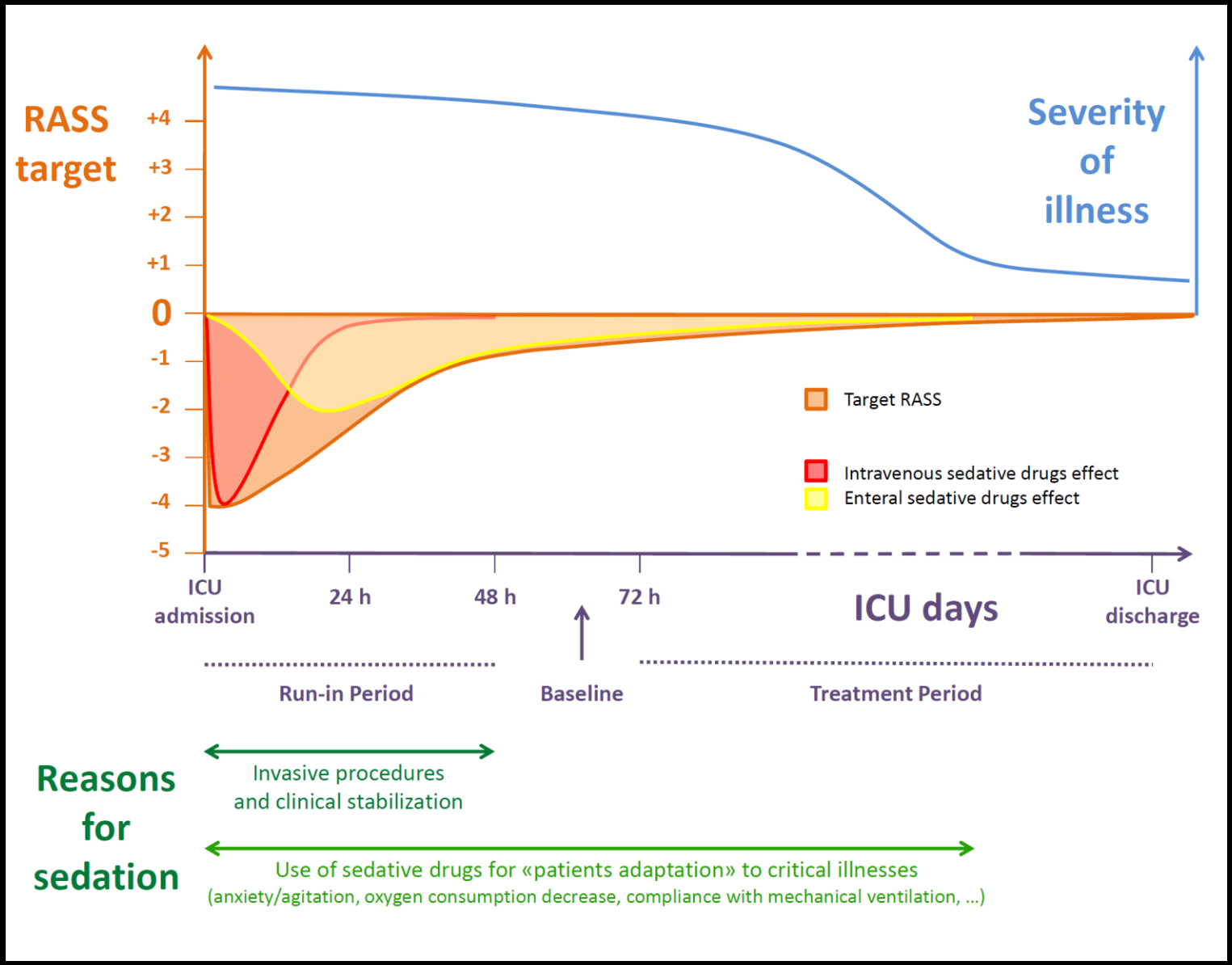
Idrossizina (6-12 mg/kg*die) ed eventualmente (se necessario)
Lorazepam (0.06-0.2 mg/kg*die)

associare ad entrambi **Morfina** o **Fentanyl** ev

In caso di Delirium: **Aloperidolo "**per os"

Oltre le 48 ore: stop sedazione endovena !

Our philosophy…



Mistraletti G, *in press*

Nel 2005 …

Intensive Care Med (2005) 31:482–486
DOI 10.1007/s00134-005-2559-7

BRIEF REPORT

Marco Cigada
Angelo Pezzi
Piero Di Mauro
Silvia Marzorati
Andrea Noto
Federico Valdambrini
Matteo Zaniboni
Morena Astori
Gaetano Iapichino

Sedation in the critically ill ventilated patient: possible role of enteral drugs

Cigada M, *Intensive Care Med,* 2005

Journal of Critical Care (2008) **23**, 349–353

ELSEVIER

Journal of Critical Care

Clinical Care

Conscious sedation in the critically ill ventilated patient

Marco Cigada MD[a,*], Davide Corbella MD[a], Giovanni Mistraletti MD[a], Chiara Reali Forster MD[a], Concezione Tommasino MD[a], Alberto Morabito PhD[b], Gaetano Iapichino MD[a]

[a] *Istituto di Anestesiologia e Rianimazione, Università degli Studi di Milano, Azienda Ospedaliera San Paolo di Milano, 20142 Milano, Italy*
[b] *Cattedra di Statistica Medica, Università degli Studi di Milano, Azienda Ospedaliera San Paolo di Milano, 20142 Milano, Italy*

Keywords:
Sedation;
Conscious sedation;
Enteral sedation;
Critically ill;
Mechanical ventilation

Abstract

Purpose: The aim of sedation is to provide comfort and minimize anxiety. However, adverse effects are noteworthy, and the optimal end point of sedation in intensive care unit patients is still debated. We analyzed if a level 2 on the Ramsay Scale (ie, awake, cooperative, oriented, tranquil patient) is suitable for an invasive therapeutic approach.

Materials and Methods: Forty-two patients requiring respiratory support and sedation for at least 4 days were enrolled in a prospective interventional cohort study aiming at maintaining patients awake and collaborative. The Ramsay score was recorded 3 times a day. Once a day, the nurse in charge evaluated adequacy of sedation according to the compliance with nursing care and therapeutic maneuvers in the previous 24 hours. Data were collected until patients were ventilated.

Results: Overall, 264 of 582 days were classified as conscious. Sedation was adequate in 93.9% of them. In conscious days, a higher Simplified Acute Physiology Score II score and male sex significantly correlated with inadequate sedation.

Conclusions: In a population of severe intensive care unit patients, conscious sedation was achieved in almost half of the days spent on ventilation. The positive implications (eg, on length of weaning and cost of sedation) of a conservative sedation strategy may be highly relevant.

Cigada M, *J Crit Care*, 2008

Table 3 Univariate analysis for observing a day of conscious sedation and for being adequately sedated in overall days or only in conscious sedation days

	Conscious sedation	Adequacy (in overall days)	Adequacy (in conscious days)
SAPS II	−0.01 (−0.04 to 0.02)	**−0.05 (−0.08 to −0.01)**	**−0.08 (−0.14 to −0.03)**
Age	0.02 (−0.01 to 0.05)	−0.01 (−0.05 to 0.03)	−0.01 (−0.09 to 0.07)
Male sex	−0.65 (−1.42 to 0.11)	**−1.53 (−2.49 to −0.58)**	**−2.90 (−5.22 to −0.58)**
Medical admission	−0.32 (−1.15 to 0.52)	0.31 (−0.87 to 1.49)	0.14 (−1.58 to 1.87)
Infection at admission	0.41 (−0.44 to 1.25)	−0.07 (−0.96 to 0.83)	0.21 (−1.53 to 1.95)
Trauma at admission	[a]	−0.02 (−1.00 to 0.97)	−0.73 (−2.94 to 1.49)
Open abdominal treatment	**−1.63 (−2.09 to −1.17)**	0.16 (−0.71 to 1.03)	0.13 (−2.11 to 2.37)
>8 d since ICU admission	–	**−0.99 (0.39 to 1.58)**	**1.36 (0.15 to 2.57)**
>2 d since ICU admission	**2.37 (1.51 to 3.24)**	–	−0.98 (−1.00 to 2.96)
Daily lowest Spo_2 >94%	**1.15 (0.53 to 1.76)**	0.84 (0.21 to 1.47)	−0.19 (−1.51 to 1.13)
Presence of shock	**−1.00 (−1.59 to −0.42)**	−0.53 (−1.15 to 0.09)	−0.67 (−1.86 to 0.53)
Presence of a tracheostomy	**0.98 (0.29 to 1.67)**	0.70 (−0.03 to 1.42)	1.46 (−0.26 to 3.17)

Values are correlation coefficients (95% confidence interval). Variables included in the multilevel analysis are in bold.

[a] Two trauma patients were always awake during ICU stay.

Cigada M, *J Crit Care*, 2008

"Conscious sedation"

non è possibile:

- giorni con shock
- tratt. addominale aperto

è "augurabile":

- dopo il 2° giorno in ICU
- se SpO_2 è sempre > 94%
- con la tracheostomia

Table 4 Multilevel analysis for observing a day of conscious sedation and for being adequately sedated in overall days or only in conscious sedation days

	Conscious sedation	Adequacy (in overall days)	Adequacy (in conscious days)
SAPS II	–	**−0.05 (−0.09 to −0.01)**	−0.06 (−0.11 to −0.02)
Male sex	–	−0.98 (−2.03 to 0.07)	**−21.24 (−23.38 to −19.10)**
Open abdominal treatment	**−2.10 (−3.48 to −0.73)**	–	–
>8 d since ICU admission	–	**−0.73 (0.06 to 1.40)**	0.68 (−0.52 to 1.88)
>2 d since ICU admission	**2.21 (1.26 to 3.16)**	–	–
Lowest Spo_2 >94%	**1.14 (0.49 to 1.79)**	0.79 (0.08 to 1.50)	–
Presence of shock	**−0.76 (−1.37 to −0.14)**	–	–
Presence of a tracheostomy	0.23 (−0.61 to 1.07)	–	–
Conscious sedation	–	**−0.87 (0.17 to 1.58)**	–
Constant	−2.05	[illegible]	25.36

Numbers are correlation coefficients (95% confidence interval). Significant values are in bold.

Cigada M, *J Crit Care,* 2008

"Conscious sedation" è correlata all'adeguatezza!

Intensive Care Med (2010) 36:1505–1513
DOI 10.1007/s00134-010-1874-9

ORIGINAL

Marek A. Mirski
John J. Lewin III
Shannon LeDroux
Carol Thompson
Peter Murakami
Elizabeth K. Zink
Michael Griswold

Cognitive improvement during continuous sedation in critically ill, awake and responsive patients: the Acute Neurological ICU Sedation Trial (ANIST)

2010: Continuous sedation in…

- critically ill
- awake
- responsive

} patients

Mirski MA, *Intensive Care Med,* 2010

QUINDI

Sedazione enterale:

- Adeguatezza non diversa (migliore?) rispetto a endovena
- Adeguata con Ramsay minore **(pz. più "svegli"… o fisiologicamente addormentati !!!)**
- Costi significativamente inferiori

Ma i farmaci per via enterale possono essere utilizzati fin dalle fasi precoci della patologia critica?

Studio sulla farmacocinetica della Melatonina somministrata via SNG

J. Pineal Res. 2010; 48:142–147
Doi:10.1111/j.1600-079X.2009.00737.x

Journal of Pineal Research

Clinical Aspects of Melatonin

Pharmacokinetics of orally administered melatonin in critically ill patients

Abstract: Critically ill patients exhibit reduced melatonin secretion, both in nocturnal peaks and basal daytime levels. Oral melatonin supplementation may be useful for known sedative and antioxidant properties. Its early enteral absorption and daily pharmacokinetics were determined in two cohorts of six high-risk patients in this prospective trial. During their third and fourth Intensive Care Unit (ICU) day, they underwent two different sets of repeated blood samples to detect serum melatonin levels through radio-immuno-assay. Cohort 1: samples taken at 20:00, 20:45, 21:30, 24:00, 03:00, 06:00, 14:00, 20:00 to describe the daily pharmacokinetics. Cohort 2: 20:00

Giovanni Mistraletti[1], Giovanni Sabbatini[1], Martina Taverna[1], Maria Adele Figini[1], Michele Umbrello[1], Paolo Magni[2], Massimiliano Ruscica[2], Elena Dozio[3], Roberto Esposti[4], Germana DeMartini[5], Franco Fraschini[5], Rita Rezzani[6], Russel J. Reiter[7] and Gaetano Iapichino[1]

Metabolic and endocrine effects of sedative agents

Giovanni Mistraletti, Francesco Donatelli and Franco Carli

Purpose of review

To bring to the attention of the clinician the metabolic effects of most common sedatives and analgesics used in critically ill patients.

Recent findings

Most patients admitted to the intensive care unit require

Introduction

Injury initiates a series of physiologic responses, the magnitude of which depends on the intensity of the stressor. The defense mechanisms are also related to the nature of the injury and are activated during the initial period. If the noxious stimulus persists, exhausting mechanisms

Mistraletti G, *Curr Op Crit Care,* 2005

Le potenzialità terapeutiche della melatonina in pazienti critici non sono MAI state indagate…

TABLE 1. BIOLOGIC FUNCTIONS AND PROCESSES THAT MAY BE AFFECTED BY MELATONIN AND SUGGESTED MECHANISMS OF ACTION IN HUMANS.

FUNCTION OR PROCESS	EFFECT	SUGGESTED MECHANISM	TYPE OF EVIDENCE
Sleep	Hypnotic effect and increased propensity for sleep	Hypothermic effect (at pharmacologic doses) Receptor-mediated action on limbic system	Placebo-controlled clinical trials
Circadian rhythm	Control of circadian rhythmicity and entrainment to light–dark cycle	Suppression of melatonin secretion by neural input from the eyes and suprachiasmatic nuclei Receptor-mediated effects on neural and peripheral tissues Thermoregulation	Studies in animals and in humans on the effects of light and the light–dark cycle on the pattern of melatonin secretion
Mood	Possible role in cyclic mood disorders (seasonal affective disorder, depression)	Unknown	Comparative clinical studies of the pattern of melatonin secretion and studies of phototherapy for mood disorders
Sexual maturation and reproduction	Inhibition of reproductive process	Inhibition of hypothalamic–pituitary–gonadal axis Effect on ovarian steroidogenesis	Studies in animals and comparative clinical studies of the pattern of melatonin secretion (during puberty and in women with ovarian cycles)
Cancer	Antineoplastic effects	Direct antiproliferative effects Enhanced immune response Scavenging of free radicals	Data from animal studies, in vitro studies of human neoplastic cells and cell lines, and a few small clinical studies
Immune response	Enhanced immune response	Increased interleukin production by T-helper lymphocytes	Studies in animals and a few uncontrolled studies in humans
Aging	Possible protective effects mediated by decreased cell damage	Scavenging of free radicals	Data from animal studies in animals

Riduce fase addormentamentamento

Aumenta il sonno REM

Migliora risposta immunitaria

(è «immunomodulante»)

Brzezinski A, *NEJM,* 1997

ESICM 2011

European Society of Intensive Care Medicine
24th annual congress
Berlin, 01-05 october 2011

UNIVERSITÀ DEGLI STUDI DI MILANO

Poster n° 0994

CLINICAL EFFECTS OF MELATONIN IN HIGH RISK CRITICALLY ILL

G. Mistraletti*, M. Tozzi*, S. Miori*, M. Taverna*,B. Cerri*, I. Galluccio*, M. Umbrello*, S. Salini°, Morabito§, F. Fraschini^, G. Iapichino*.

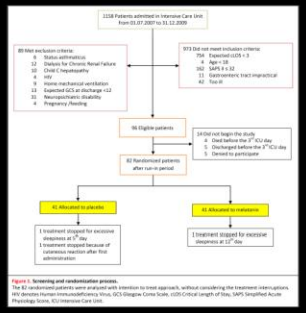
* Dipartimento di Anestesiologia, Terapia Intensiva e Scienze Dermatologiche, Università degli Studi di Milano.° Dipartimento di Scienze Economiche, Aziendali e Statistiche, Università degli Studi di Milano.
§ Cattedra di Biostatistica, Dipartimento di Medicina, Chirurgia e Odontoiatria, Università degli Studi di Milano.^ Dipartimento di Farmacologia, Chemioterapia e Tossicologia medica, Università degli Studi di Milano.

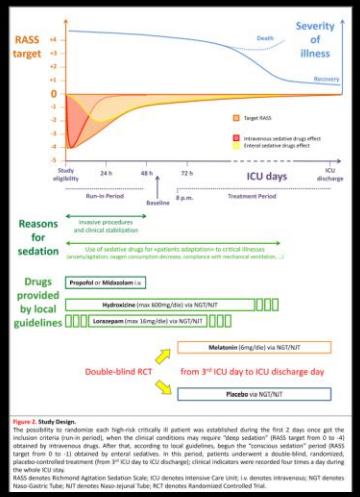
INTRODUCTION

Endogenous blood melatonin in critical patients is often dramatically low, in both basal levels and night peaks. Exogenous supplementation could determine hypnogogue, immunomodulating and antioxidant effects. Prolonged administration (possible undesirable effects: sleepiness, bronchospasm, accumulation) has not previously been described in critically ill.

OBJECTIVES

Evaluating safety and clinical effects of oral melatonin in high-risk critically ill [1] treated with conscious sedation [2].





METHODS

Double-blind RCT between placebo and melatonin (3 mg x 2), administered daily at 8 and 12 pm from the third ICU day until discharge. Inclusion/exclusion criteria: Figure 1. Study design and sedation protocol: Figure 2.

RESULTS

82 patients enrolled: age 72 [60–77] years, SAPS II 41 [34–54], Mechanical Ventilation 11 [6–22] days.
Diagnosis: 18 pancreatitis, 37 pneumonia or ALI/ARDS, 23 acute heart diseases, 4 trauma.
Admission type: 55 medical, 19 unscheduled surgery, 8 scheduled surgery.
Melatonin fastened weaning from sedative and analgesic drugs and from mechanical ventilation (Figure 3). It decreases the prevalence of infection with a higher effect in long term patients (Figure 4). Melatonin also guaranteed better hemodynamic stability (Table 1).
Neurologic monitoring demonstrated a melatonin significant effect in ameliorating all the observed characteristics (Table 2); particularly, melatonin helped in restoring a quite normal circadian rhythm. Differences in length of stay and ICU/hospital mortality were not significantly different.
Undesirable effects were not reported.

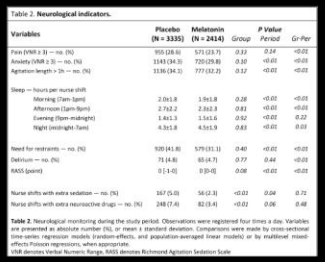


Table 2. **Neurological indicators.**

Variables	Placebo (N = 1335)	Melatonin (N = 2414)	Group	P Value Period	Gr·Per
Pain (VNR ≥ 3) — no. (%)	935 (28.6)	571 (23.7)	0.33	0.14	<0.01
Anxiety (VNR ≥ 3) — no. (%)	1143 (34.3)	720 (29.8)	0.10	<0.01	<0.01
Agitation length > 1h — no. (%)	1136 (34.1)	777 (32.2)	0.12	<0.01	<0.01
Sleep — hours per nurse shift					
Morning (7am-1pm)	2.0±1.8	1.9±1.8	0.28	<0.01	<0.01
Afternoon (1pm-9pm)	2.7±2.2	2.8±2.3	0.81	<0.01	<0.01
Evening (9pm-midnight)	1.4±1.3	1.5±1.6	0.92	<0.01	0.22
Night (midnight-7am)	4.3±1.8	4.5±1.9	0.83	<0.01	0.03
Need for restraints — no. (%)	920 (41.8)	579 (31.1)	0.40	<0.01	<0.01
Delirium — no. (%)	71 (4.8)	65 (4.7)	0.77	0.44	<0.01
RASS (point)	0 [-1-0]	0 [0-0]	0.08	<0.01	<0.01
Nurse shifts with extra sedation — no. (%)	167 (5.0)	56 (2.3)	<0.01	0.04	0.71
Nurse shifts with extra neuroactive drugs — no. (%)	248 (7.4)	82 (3.4)	<0.01	0.06	0.48

Table 2. Neurological monitoring during the study period. Observations were registered four times a day. Variables are presented as absolute number (%), or mean ± standard deviation. Comparisons were made by cross-sectional time-series regression models (random-effects, and population-averaged linear models) or by multilevel mixed-effects Poisson regressions, when appropriate.
VNR denotes Verbal Numeric Range. RASS denotes Richmond Agitation Sedation Scale

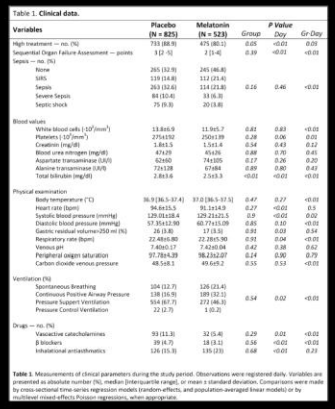


Table 1. **Clinical data.**

Variables	Placebo (N = 825)	Melatonin (N = 523)	P Value Group	Day	Gr·Day
High treatment — no. (%)	733 (88.8)	475 (80.1)	0.05	<0.01	0.03
Sequential Organ Failure Assessment — points	3 [2 -5]	2 [1-4]	0.19	<0.01	<0.01
Sepsis — no. (%)					
None	265 (32.9)	245 (46.8)			
SIRS	119 (14.8)	112 (21.4)			
Sepsis	263 (32.6)	114 (21.8)	0.16	0.46	<0.01
Severe Sepsis	84 (10.4)	33 (6.3)			
Septic shock	75 (9.3)	20 (3.8)			
Blood values					
White blood cells ($\cdot 10^3$/mm^3)	13.8±6.9	11.9±5.7	0.81	0.83	<0.01
Platelets ($\cdot 10^3$/mm^3)	275±192	250±139	0.28	0.06	0.01
Creatinin (mg/dl)	1.8±1.5	1.5±1.4	0.54	0.43	0.12
Blood urea nitrogen (mg/dl)	47±29	45±26	0.88	0.70	0.45
Aspartate transaminase (U/l)	62±60	74±105	0.17	0.26	0.20
Alanine transaminase (U/l)	72±138	67±84	0.89	0.80	0.43
Total bilirubin (mg/dl)	2.8±3.6	2.5±3.3	<0.01	<0.01	<0.01
Physical examination					
Body temperature (°C)	36.9 (36.5-37.4)	37.0 (36.5-37.5)	0.47	0.27	<0.01
Heart rate (bpm)	94.6±15.5	91.1±14.9	0.27	<0.01	0.3
Systolic blood pressure (mmHg)	129.01±18.4	129.21±21.5	0.9	<0.01	0.02
Diastolic blood pressure (mmHg)	57.35±12.90	60.77±15.09	0.85	0.10	<0.01
Gastric residual volumen/250 ml (%)	26 (3.8)	17 (3.5)	0.91	0.03	0.54
Respiratory rate (bpm)	22.48±6.80	22.28±5.90	0.91	0.04	<0.01
Venous pH	7.40±0.17	7.42±0.04	0.42	0.38	0.62
Peripheral oxigen saturation	97.78±4.39	98.23±2.07	0.14	0.90	0.79
Carbon dioxide venous pressure	48.5±8.1	49.6±9.2	0.55	0.53	<0.01
Ventilation (%)					
Spontaneous Breathing	104 (12.7)	126 (21.4)			
Continuous Positive Airway Pressure	138 (16.9)	189 (32.1)	0.54	0.02	<0.01
Pressure Support Ventilation	554 (67.7)	272 (46.3)			
Pressure Control Ventilation	22 (2.7)	1 (0.2)			
Drugs — no. (%)					
Vasoactive catecholamines	93 (11.3)	32 (5.4)	0.29	0.01	<0.01
β blockers	39 (4.7)	18 (3.1)	0.56	<0.01	<0.01
Inhalational antiasthmatics	126 (15.3)	135 (23)	0.68	<0.01	0.23

Table 1. Measurements of clinical parameters during the study period. Observations were registered daily. Variables are presented as absolute number (%), median [interquartile range], or mean ± standard deviation. Comparisons were made by cross-sectional time-series regression models (random-effects, and population-averaged linear models) or by multilevel mixed-effects Poisson regressions, when appropriate.

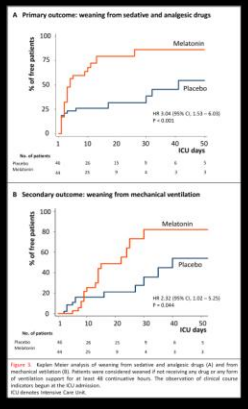


Figure 3. Kaplan Meier analysis of weaning from sedative and analgesic drugs (A) and from mechanical ventilation (B). Patients were considered weaned if not receiving any drug or any form of ventilation support for at least 48 continuative hours. The observation of clinical course indicators began at the ICU admission.
ICU denotes Intensive Care Unit.

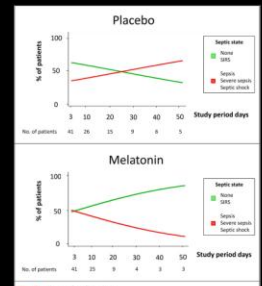


Figure 4. **Septic state of enrolled patients.**
The figures represent the percent of patients in that septic state considering the total number of patients still recovered in ICU in that day of their study period. The septic state was calculated according to the SCCM/ACCM criteria after the patients discharge, by patients charts revision operated by blind researchers. Comparisons were made with conditional fixed effects logistic regression, P<0.001.
SIRS denotes Systemic Inflammatory Reaction Syndrome, ICU denotes Intensive Care Unit

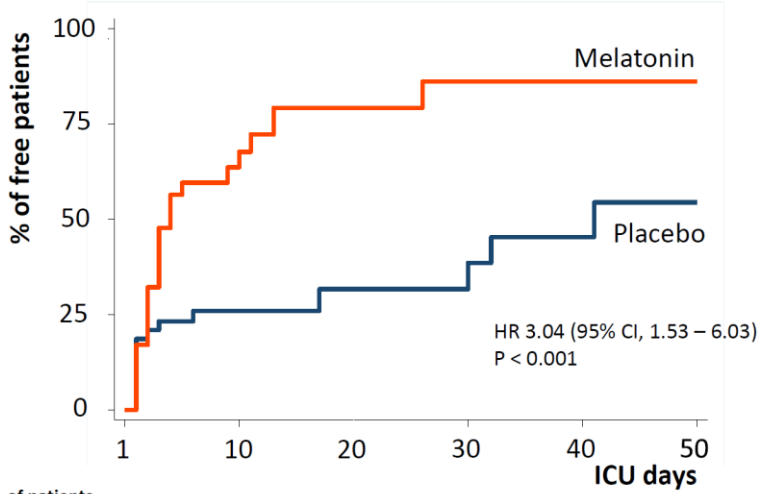
CONCLUSIONS

Melatonin administration was shown safe and useful regarding cardio-respiratory and neurological recovery. It determined fastened sepsis resolution in both lab measurements (WBC,PLT, bilirubin) and clinical observations (SOFA, septic state) probably due to its immunomodulating action and reactive oxygen species scavenging. The Melatonin group had faster ventilation weaning, probably due to lower sedation; nurse-observed decreased sleep hours in the morning/afternoon and increased in the night highlighted a quite restored circadian rhythm. Gastric residual volume was not different, as the need for bronchodilators; no excessive sleepiness was shown. No differences in ICU length of stay or ICU/hospital mortality were reported, being this study not powered for these outcomes. In two post-hoc analyses, Melatonin decreased MV days (p = 0.013 in patients treated > 7 days) and ICU mortality (p = 0.047 in patients treated > 40 days), suggesting the necessity of new and adequately powered studies for long-term ICU patients. (Clinicaltrial.gov n° NCT00470821)

REFERENCES

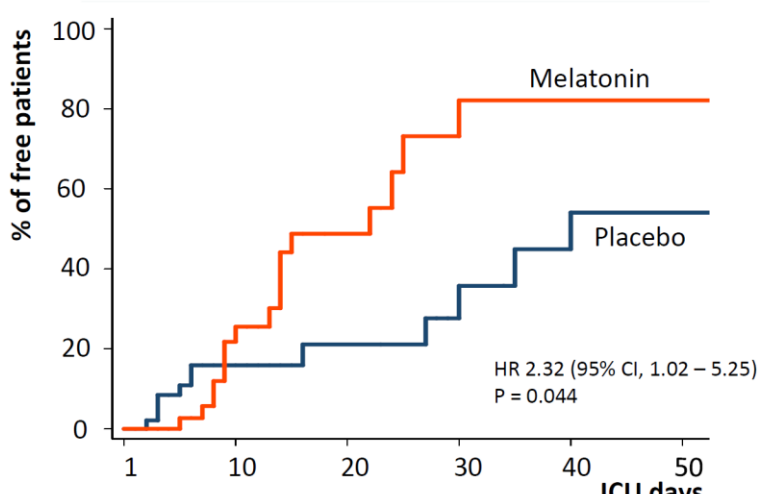
1. Iapichino G, et al. Crit Care Med. 2006;34:1039–1043.
2. Cigada M, et al. Journal of Critical Care. 2008;23:349–353.

A Primary outcome: weaning from sedative and analgesic drugs



No. of patients						
Placebo	46	26	15	9	6	5
Melatonin	44	25	9	4	3	3

B Secondary outcome: weaning from mechanical ventilation

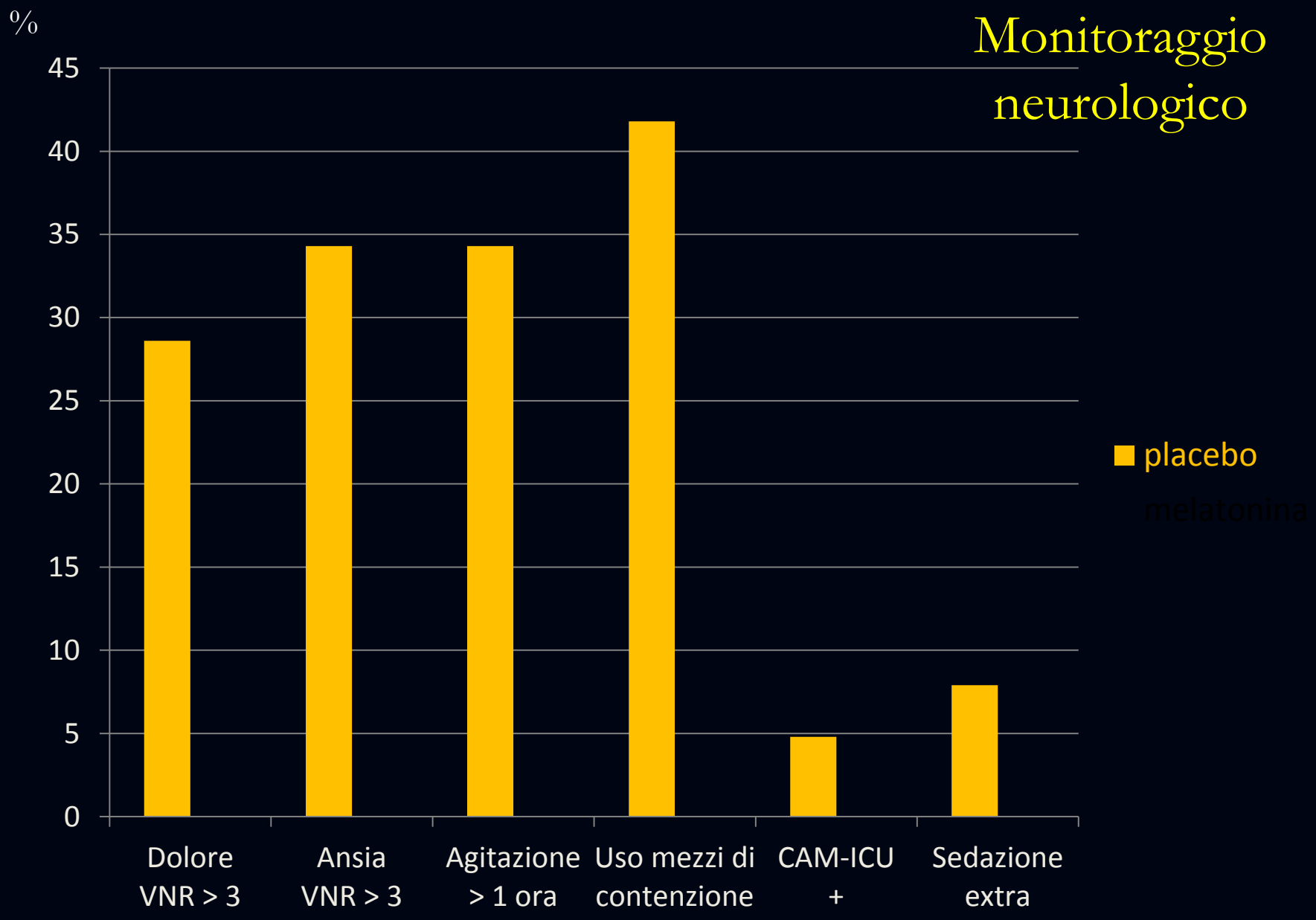


No. of patients						
Placebo	46	26	15	9	6	5
Melatonin	44	25	9	4	3	3

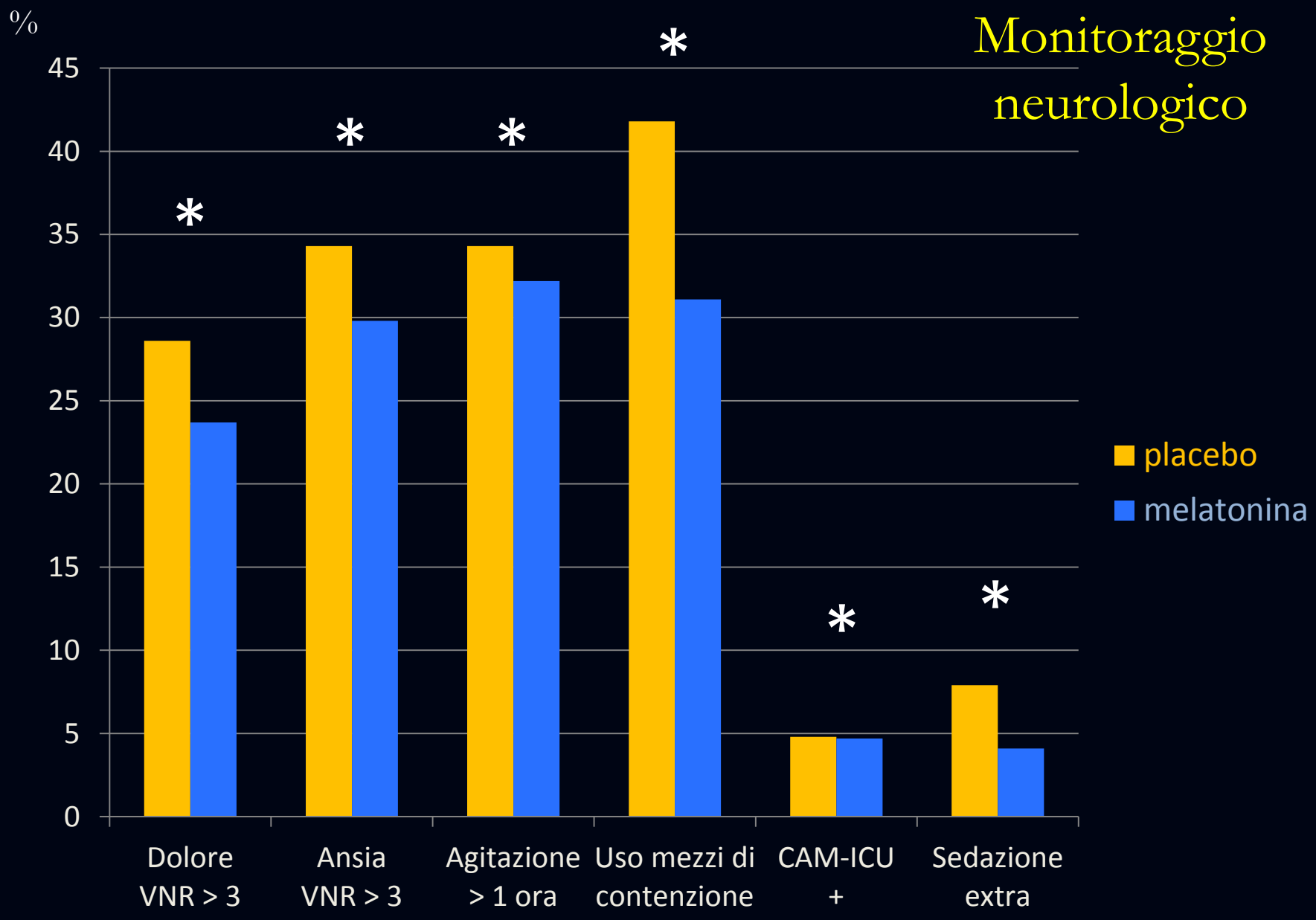
	Placebo (N=3335)	Melatonina (N=2414)	P value Group	P value Period	P value Gr*Per
RASS (point)					
+ 4	1 (0.1)	0 (0)			
+ 3	3 (0.2)	0 (0)			
+ 2	24 (1.0)	15 (0.8)			
+ 1	224 (8.8)	181 (9.5)			
0	1532 (60.1)	1287 (67.9)	*0.08*	*<0.01*	*<0.01*
- 1	299 (11.7)	226 (11.9)			
- 2	149 (5.9)	102 (5.4)			
- 3	196 (7.7)	45 (2.4)			
- 4	110 (4.3)	35 (1.9)			
- 5	9 (0.4)	4 (0.2)			
RASS at target – no. (%)	1660 (49.6)	1349 (55.1)	*0.87*	*0.36*	*0.12*
RASS under the target – no. (%)	810 (24.2)	643 (26.3)	*0.50*	*0.90*	*0.94*
RASS over the target – no. (%)	879 (26.2)	454 (18.6)	*0.62*	*0.32*	*0.05*

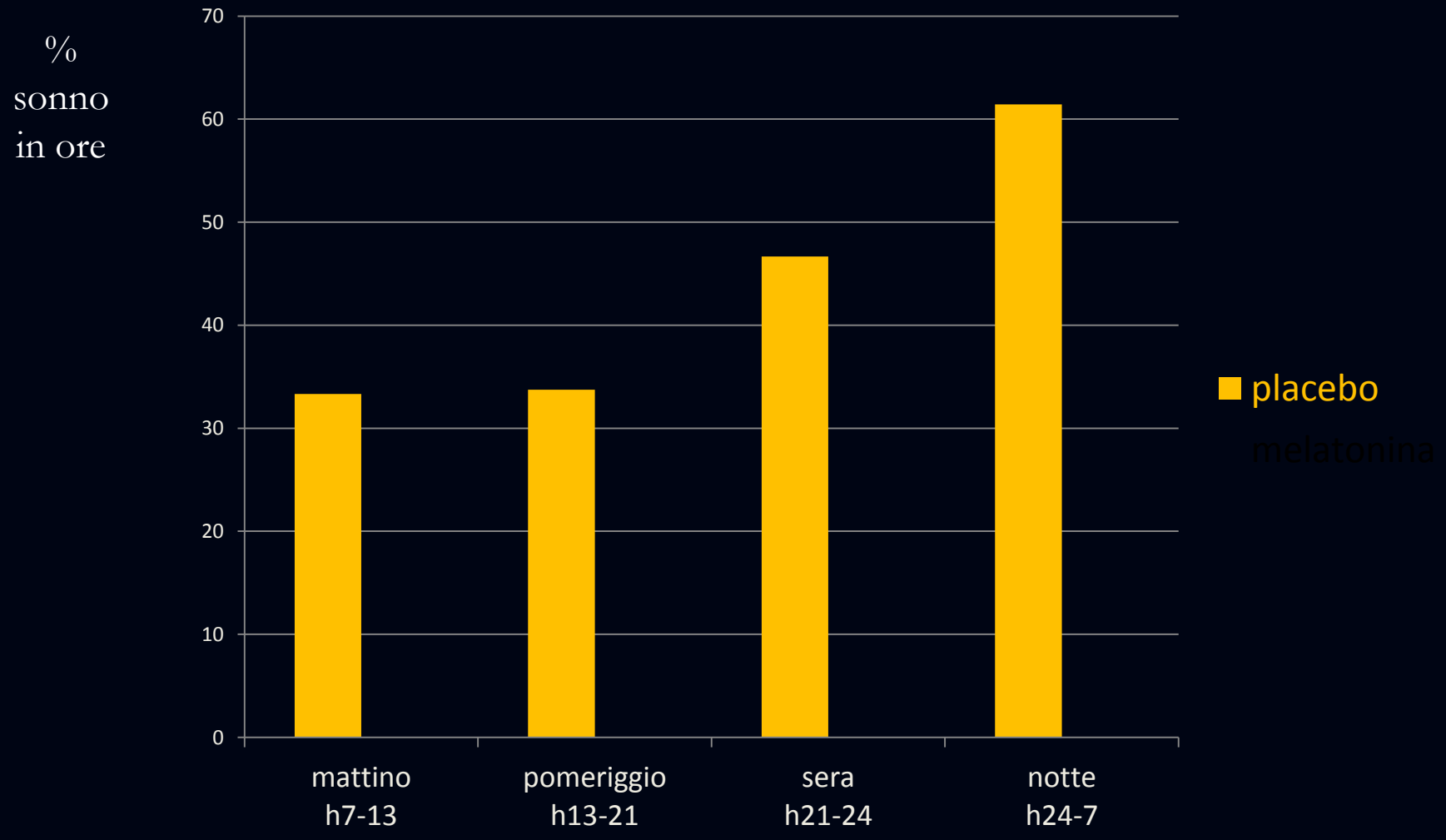
…ridotta la sedazione profonda. Migliorato l'adattamento!

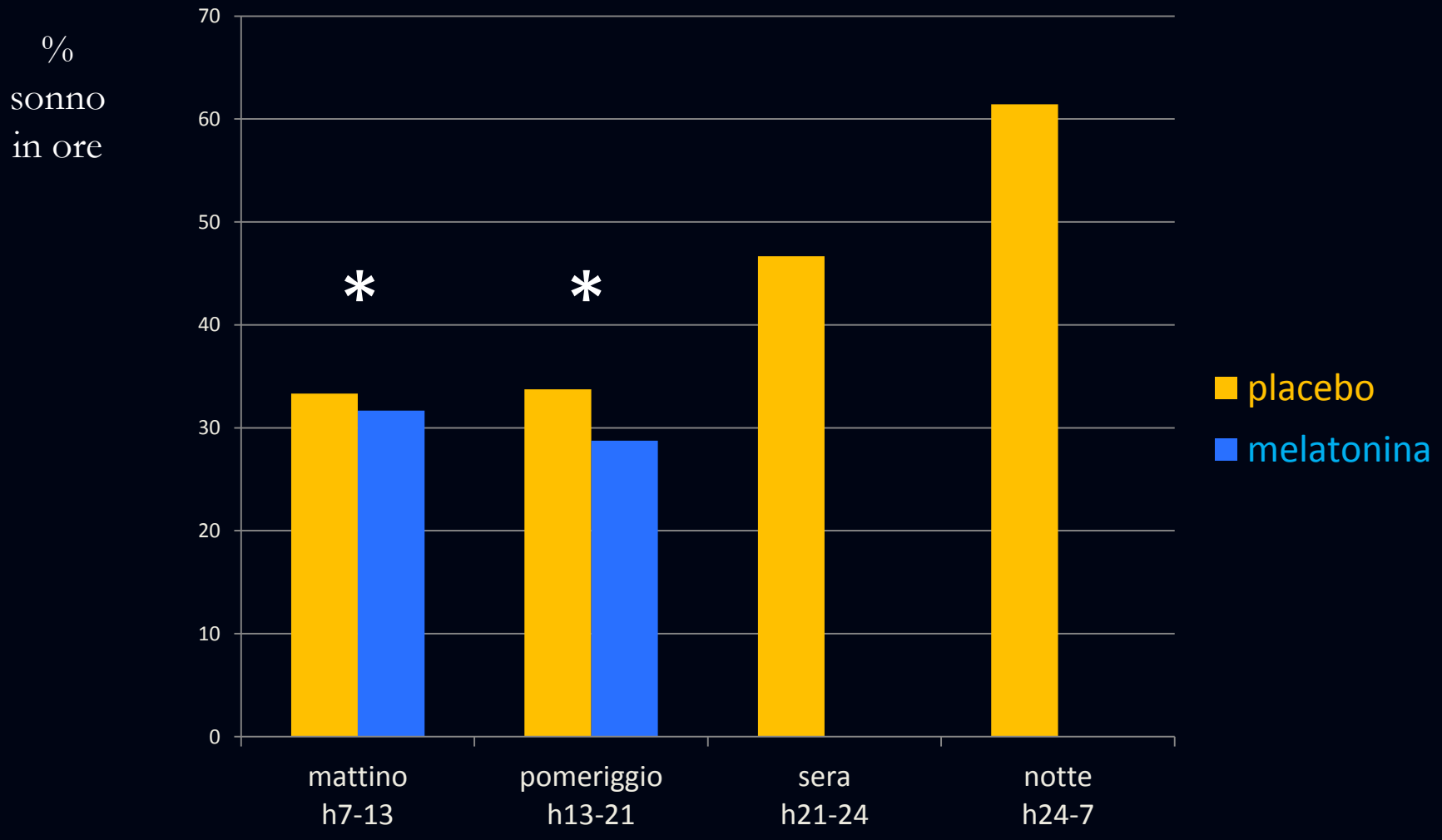
Monitoraggio neurologico

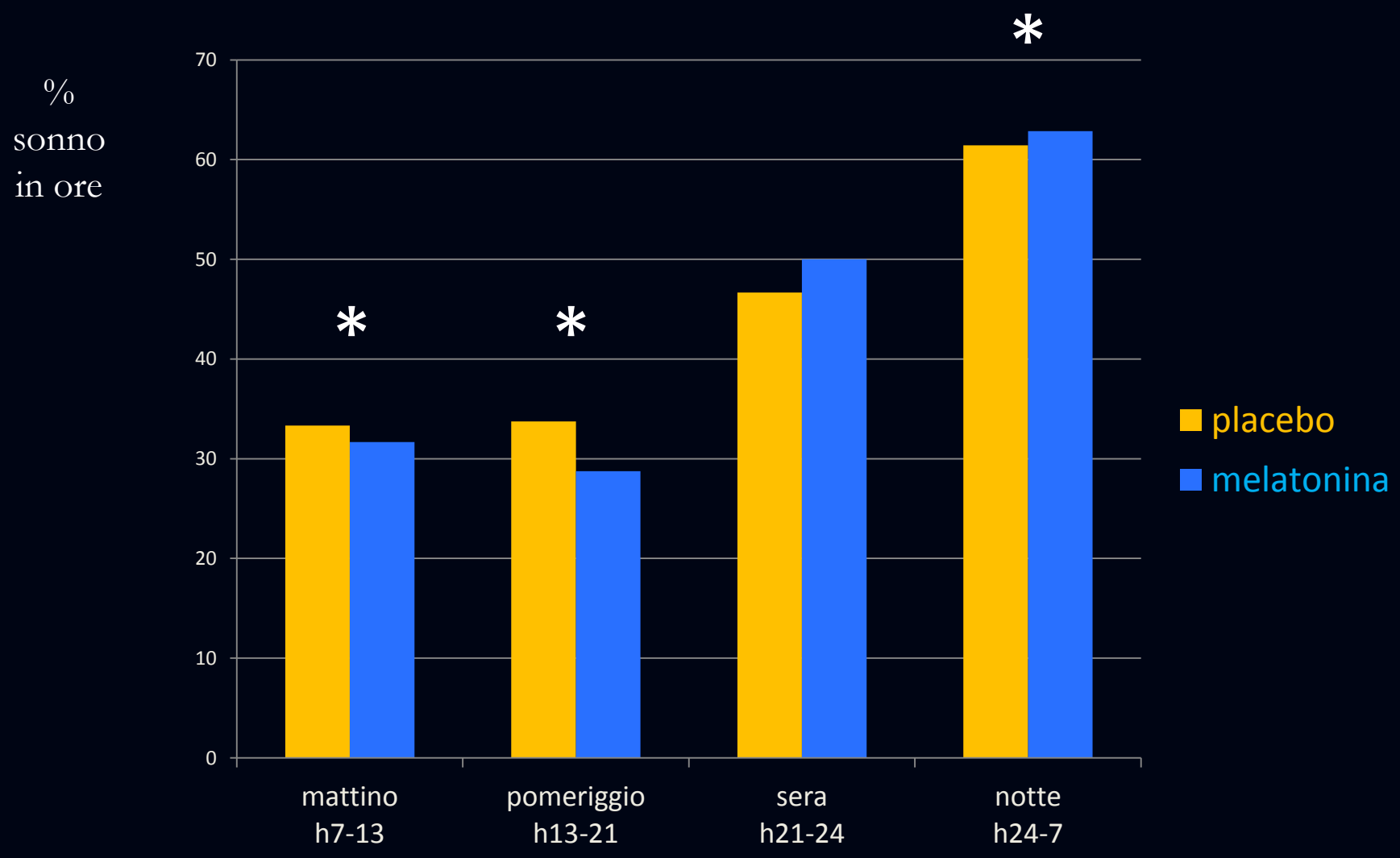


Monitoraggio neurologico



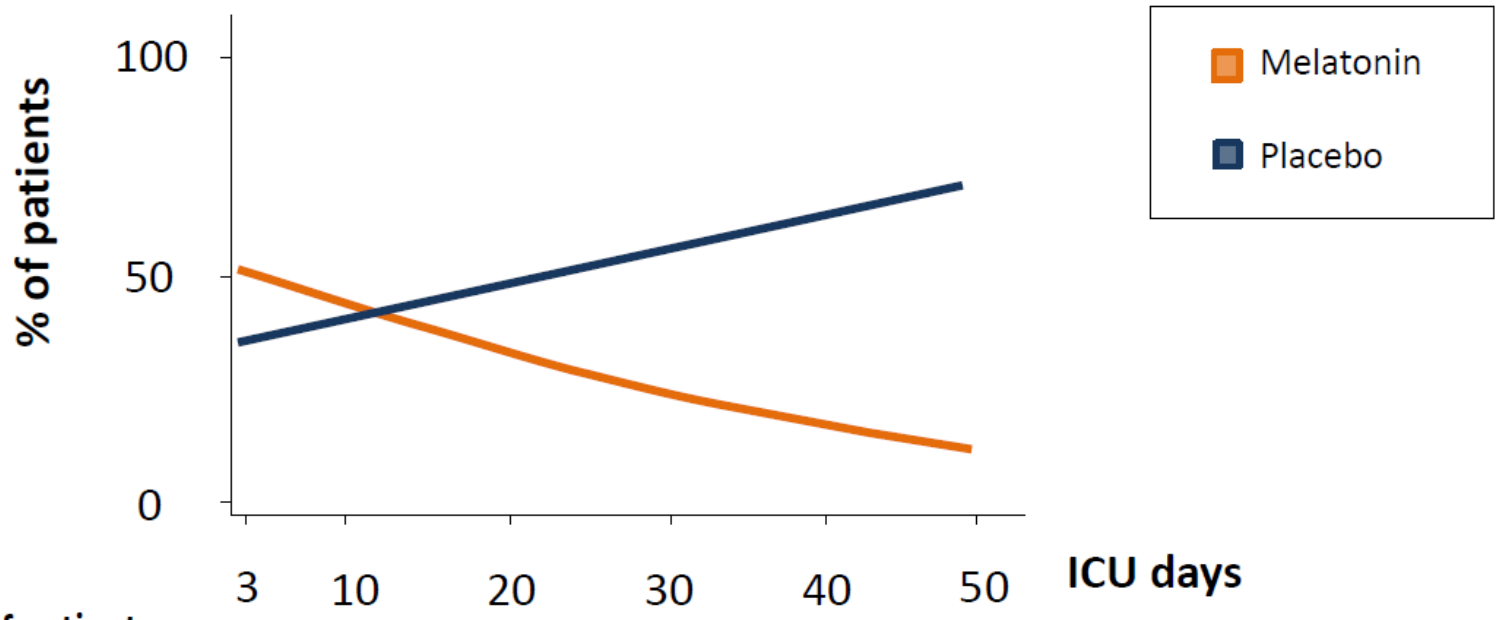

% sonno in ore
70
60
50
40
30
20
10
0
mattino h7-13
pomeriggio h13-21
sera h21-24
notte h24-7
placebo
melatonina


% sonno in ore
70
60
50
40
30
20
10
0
*
*
mattino h7-13
pomeriggio h13-21
sera h21-24
notte h24-7
placebo
melatonina

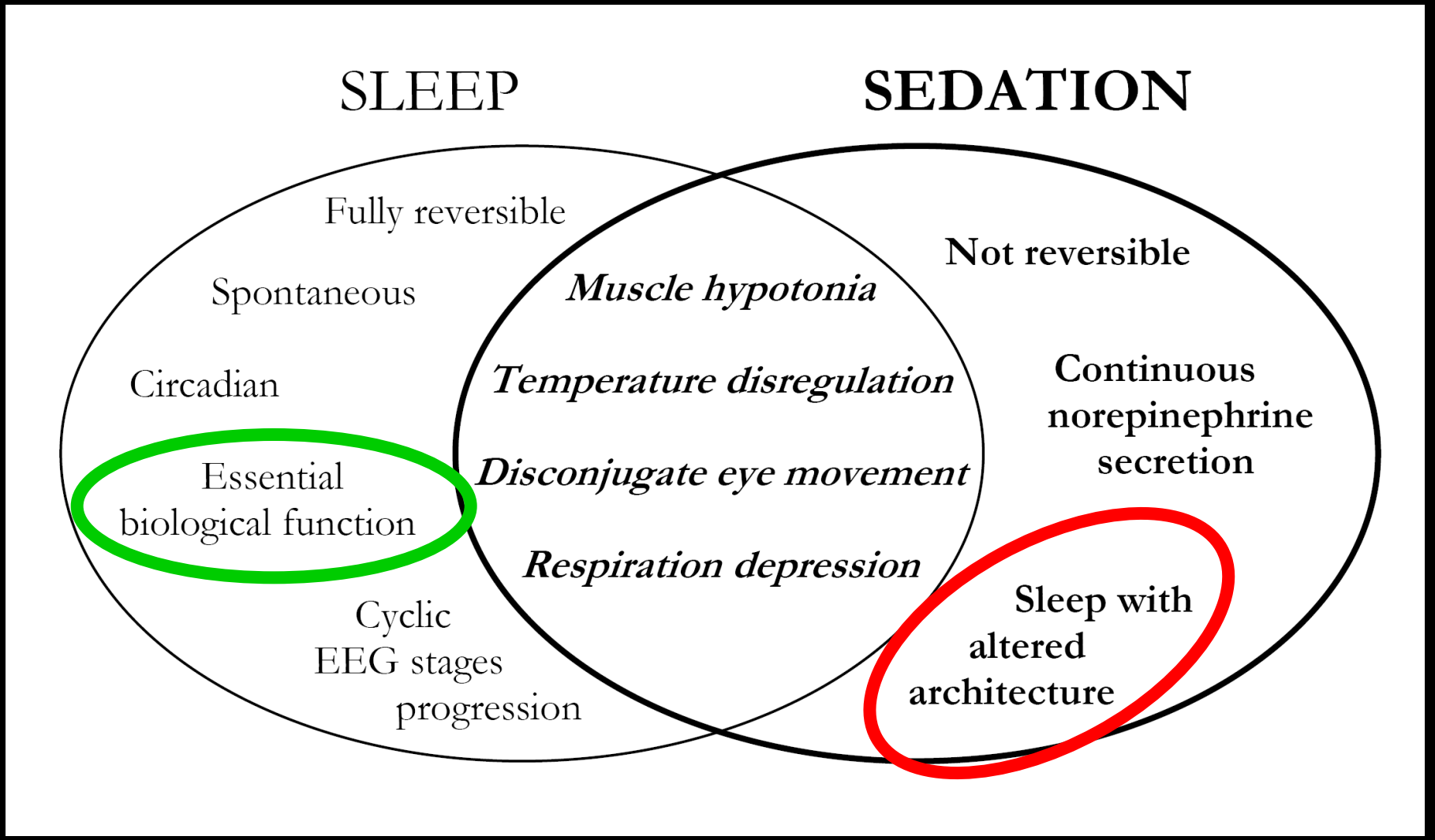

% sonno in ore
70
60
50
40
30
20
10
0
*
*
*
mattino h7-13
pomeriggio h13-21
sera h21-24
notte h24-7
placebo
melatonina

Variabili	**Placebo** (825 giorni)	**Melatonina** (593 giorni)	p
LOC HT - n (%)	733 (88.9)	475 (80.1)	0.033
SOFA - mediana [IQR]	3 [2-5]	2 [1-4]	<0.001
WBC - n/mm^3	13779±6886	11975±5762	0.006
STATO SETTICO			
no SIRS - n (%)	265 (32.9)	245 (46.8)	
SIRS - n (%)	119 (14.8)	112 (21.4)	
sepsi - n (%)	263 (32.6)	114 (21.8)	<0.001
sepsi severa - n (%)	84 (10.4)	33 (6.3)	
shock settico - n (%)	75 (9.3)	20 (3.8)	
Bilirubina tot - mg/dL	2.8±3.6	2.5±3.3	<0.001
AST - UI/L	62±60	74±105	0.207
ALT - UI/L	72±128	67±84	0.433
Azotemia - mg/dL	100±62	96±55	0.449
Creatininemia - mg/dL	1.8±1.5	1.5±1.4	0.123
Farmaci			
Vasoattivi *- n (%)*	93 (11.3)	32 (5.4)	0.005
Beta-bloccanti *- n (%)*	39 (4.7)	18 (3.1)	0.008
Antiasmatici *- n (%)*	126 (15.3)	135 (23)	0.227

Infection diagnosis prevalence



No. of patients						
Placebo	41	26	15	9	6	5
Melatonin	41	25	9	4	3	3



Mistraletti G, *Minerva Anestesiol* 2008

Fattori stressanti in T.I.

Novaes, *Intensive Carre Med*, 1997

Table 1 Ranking of stressors

Ranking	Description	Mean	Standard deviation
01	Have pain	3.36	1.01
02	Not being able to sleep	3.34	0.98
03	Having tubes in your nose or mouth	3.26	1.01
04	Not being in control of yourself	3.10	1.11
05	Being tied down by tubes	3.02	1.12
06	Not having treatments explained to you	3.02	1.22
07	Not being able to move your hands because of i. v. line	2.90	1.15
08	Not knowing when to expect things will be done to you	2.84	1.06
09	Being stuck with needles	2.80	1.18
10	Being thirsty	2.76	1.22
11	Having lights on constantly	2.72	1.25
12	Seeing family and friends for only a few minutes each day	2.66	1.22
13	Uncomfortable bed and/or pillow	2.64	1.26
14	Having no privacy	2.64	1.24
15	Nurses and doctors talking too loudly	2.54	1.15
16	Being bothered	2.52	1.15
17	Having to wear oxygen	2.50	1.20
18	Hearing other patients cry out	2.46	1.23
19	Being in a room that is too hot or too cold	2.46	1.05
20	Not knowing where you are	2.46	1.33
21	Not knowing what time it is	2.44	1.18
22	Unfamiliar and unusual noises	2.40	1.11
23	Having nurses be in too much of a hurry	2.40	1.14
24	Missing your husband or wife	2.34	1.19
25	Hearing the heart monitor alarm go off	2.26	1.16
26	Not knowing what day it is	2.20	1.21
27	Having the team use words you cannot understand	2.20	1.20
28	Being awakened by nurses	2.14	1.13
29	Having to look at the pattern of holes in the ceiling	2.14	1.25
30	Feeling the nurses are watching the machines closer than they are watching you	2.08	1.08
31	Having nurses constantly doing things around your bed	2.06	1.08
32	Hearing buzzers and alarms from machinery	2.02	0.91
33	Being cared for by unfamiliar doctors	1.96	1.18
34	Constantly being examined by doctors and nurses	1.96	1.11
35	Hearing the telephone ring	1.92	1.12
36	Being aware of unusual smells around you	1.92	1.07
37	Having strange machines around you	1.90	1.16
38	Having your blood pressure taken often each day	1.74	0.90
39	Not having the nurses introduce themselves	1.64	0.88
40	Seeing i. v. bags hanging over your head	1.58	0.91

L'utilizzo di farmaci ANALGESICI e SEDATIVI

gioca un ruolo chiave

nei disturbi del sonno

in Terapia Intensiva

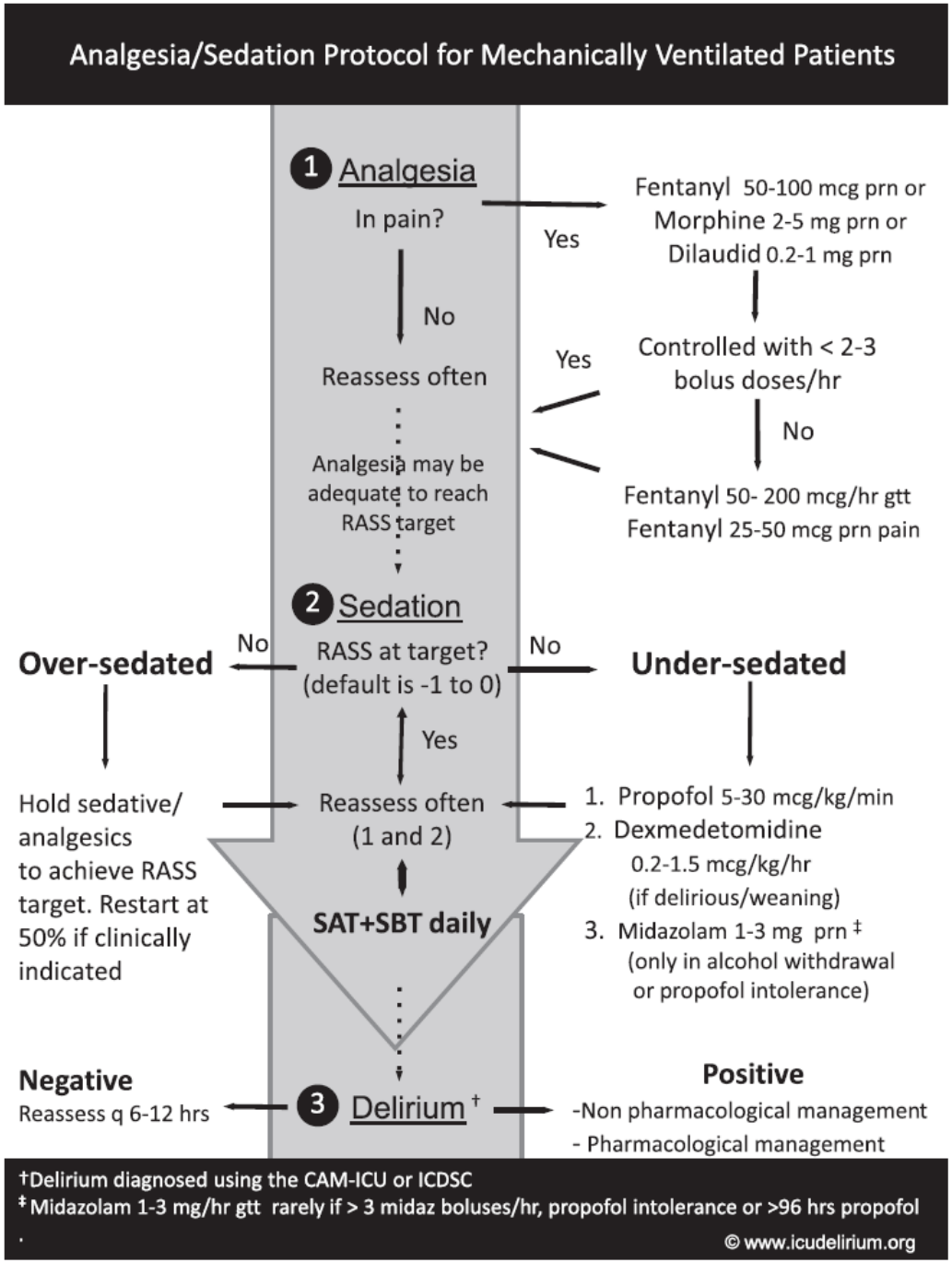
Analgesia e sedazione in TI: come e perchè

Concludendo:

indicazioni pratiche

Giovanni Mistraletti, MD
Dipartimento di Anestesiologia e Terapia Intensiva
Università degli Studi di Milano
AO San Paolo – Polo Universitario
Milano, Italy

Selected Topics in Anestesia e Terapia Intensiva
Udine, 23 febbraio 2012



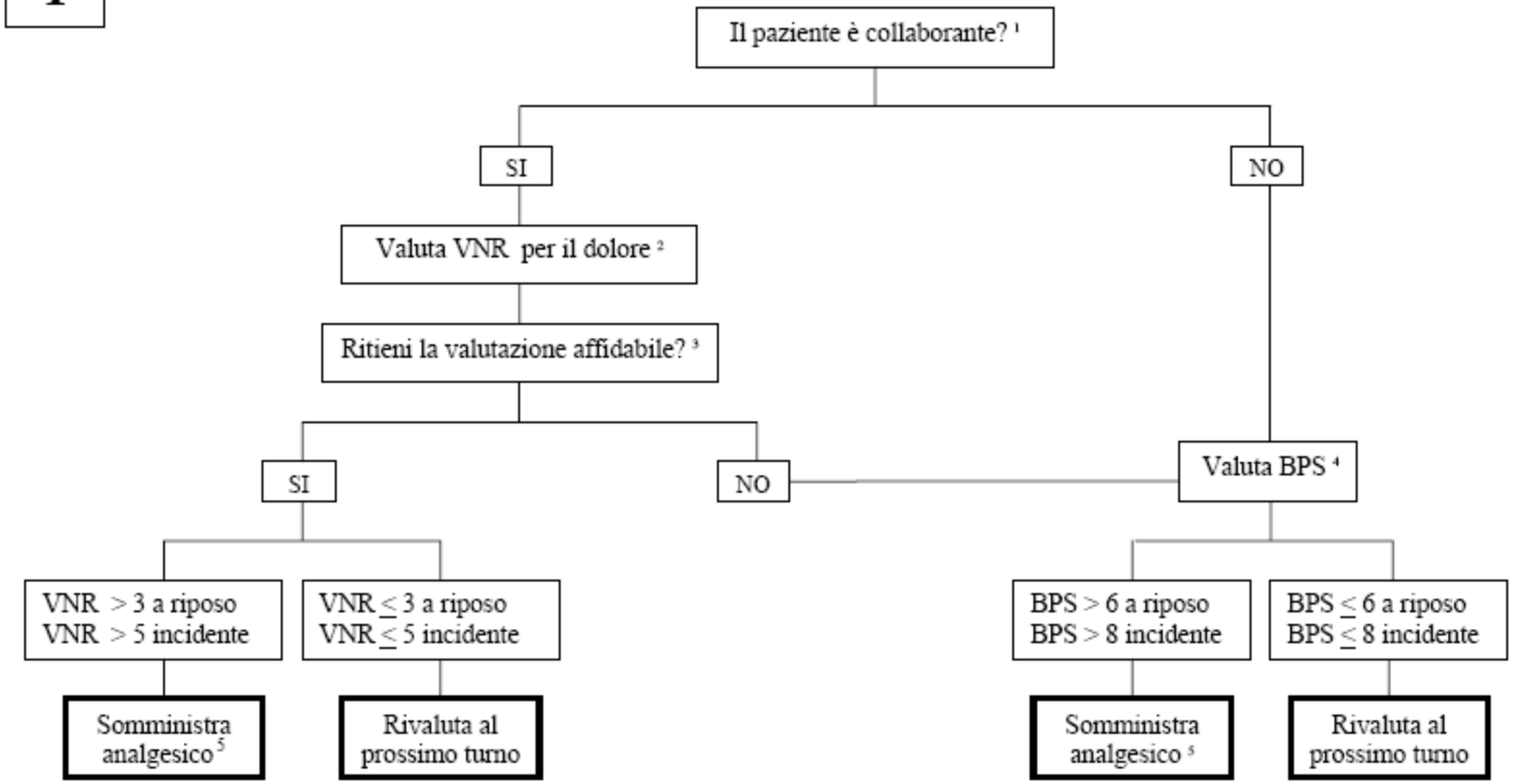
Vasilevskis, *CCM*, 2010

Analgesia – criteri generali

- I pazienti non devono avere dolore! (VNR<3)
- E' opportuno ridurre l'utilizzo di antidolorifici (soprattutto oppiacei) al minimo considerando gli effetti collaterali
- Sfruttando l' «effetto collaterale sedativo» degli oppiacei probabilmente si incorre in problemi evitabili…

1

GESTIONE DEL DOLORE IN TERAPIA INTENSIVA



[1] Considera non collaborante se: RASS < -2 / CAM-ICU ⊕ / presenza di patologie psichiatriche / deficit neurologici / incompatibilità linguistiche / sordità.

[2] *Verbal Numeric Rating (VNR)* 0 = dolore assente, 10 = massimo dolore immaginabile.
Chiedi:"Quanto è il suo dolore adesso, fra 0 e 10?".
Considera sia il dolore a riposo che il dolore incidente (es.: colpo di tosse, bronco aspirazione, …).

[3] Una rilevazione è affidabile se tiene conto dei parametri soggettivi con cui il paziente valuta il suo dolore: aspetti culturali, famigliari, religiosi, presenza di vantaggi secondari.

[4] *Behavioral Pain Scale (BPS)* 3 = dolore assente, 12 = massimo dolore
- *Espressione Facciale:* 1. Rilassata / 2.Fronte Aggrottata / 3. Occhi chiusi / 4. Digrignante
- *Arti Superiori:* 1. Immobili / 2. Piegati / 3. Contratti / 4. Retratti
- *Compliance alla Ventilazione:* 1. Adattato / 2. Tossisce / 3. Asincrono / 4. Non ventilabile

[5] **Morfina: endovena**
Bolo: 0.03 - 0.05 mg/kg ripetibile fino a 40 mg/die – Infusione continua: 5-30 γ/kg/h.

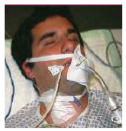
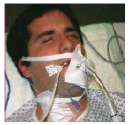
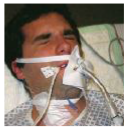
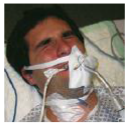
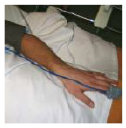
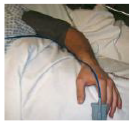
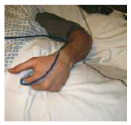
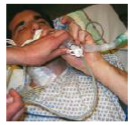
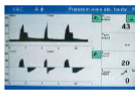
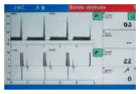
Fentanyl: endovena (da preferire se instabilità emodinamica/ allergia morfina/ insufficienza renale).
Bolo: 1-2γ/kg ripetibile fino a 500 γ/die – Infusione continua: 1-2γ/kg/h (max 150 γ/h).

Remifentanil: endovena (mai in bolo)
Bolo: mai – Infusione continua: 0.02-0.5γ/kg/min.

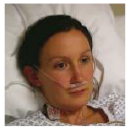
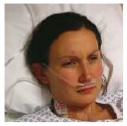
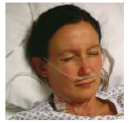
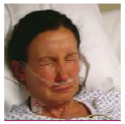
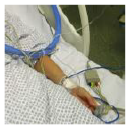
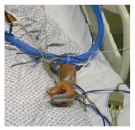
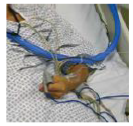
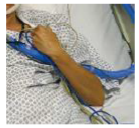
Considera Paracetamolo ev (max 15mg/kg ogni 6 h) / FANS / adiuvanti.

Misura comportamentale del dolore nei pazienti ricoverati in Terapia Intensiva
BEHAVIORAL PAIN SCALE (BPS)

BPS per pazienti intubati

	1	2	3	4
A	Espressione facciale			
				
	rilassato	fronte aggrottata	occhi chiusi	digrignante
B	Movimenti degli arti superiori			
				
	immobili	piegati	contratti	retratti
	Se indeciso: controlla il tono muscolare mobilizzando passivamente l'arto superiore			
C	Adattamento alla ventilazione meccanica			
				
	adattato	tossisce	asincrono	non ventilabile

BPS-NI per pazienti non intubati

	1	2	3	4
	Espressione facciale			
				
	rilassato	fronte aggrottata	occhi chiusi	digrignante
	Movimenti degli arti superiori			
				
	immobili	piegati	contratti	retratti
	Se indeciso: controlla il tono muscolare mobilizzando passivamente l'arto superiore			
	Vocalizzazione			
	non emette lamenti di dolore	si lamenta ≤3 volte/min e per ≤3 sec	si lamenta >3 volte/min o per >3 sec	emette urla o lamenti verbali o trattiene il respiro

A + B + C = **VALORE TOTALE BPS o BPS-NI** *da 3 (assente) a 12 (massimo), misura le manifestazioni comportamentali del dolore.*

Tratto da: Chanques G. et al., Intensive Care Medicine 2009, Vol. 35, 2060-2067
Tradotto in italiano da G. Mistraletti e S. Barello

Delirium

- E’ necessario monitorizzare la disfunzione neurologica acuta esattamente come quella degli altri organi vitali. Nessuna T.I. tralascerebbe di monitorizzare un’ipossia o un’ipotensione!

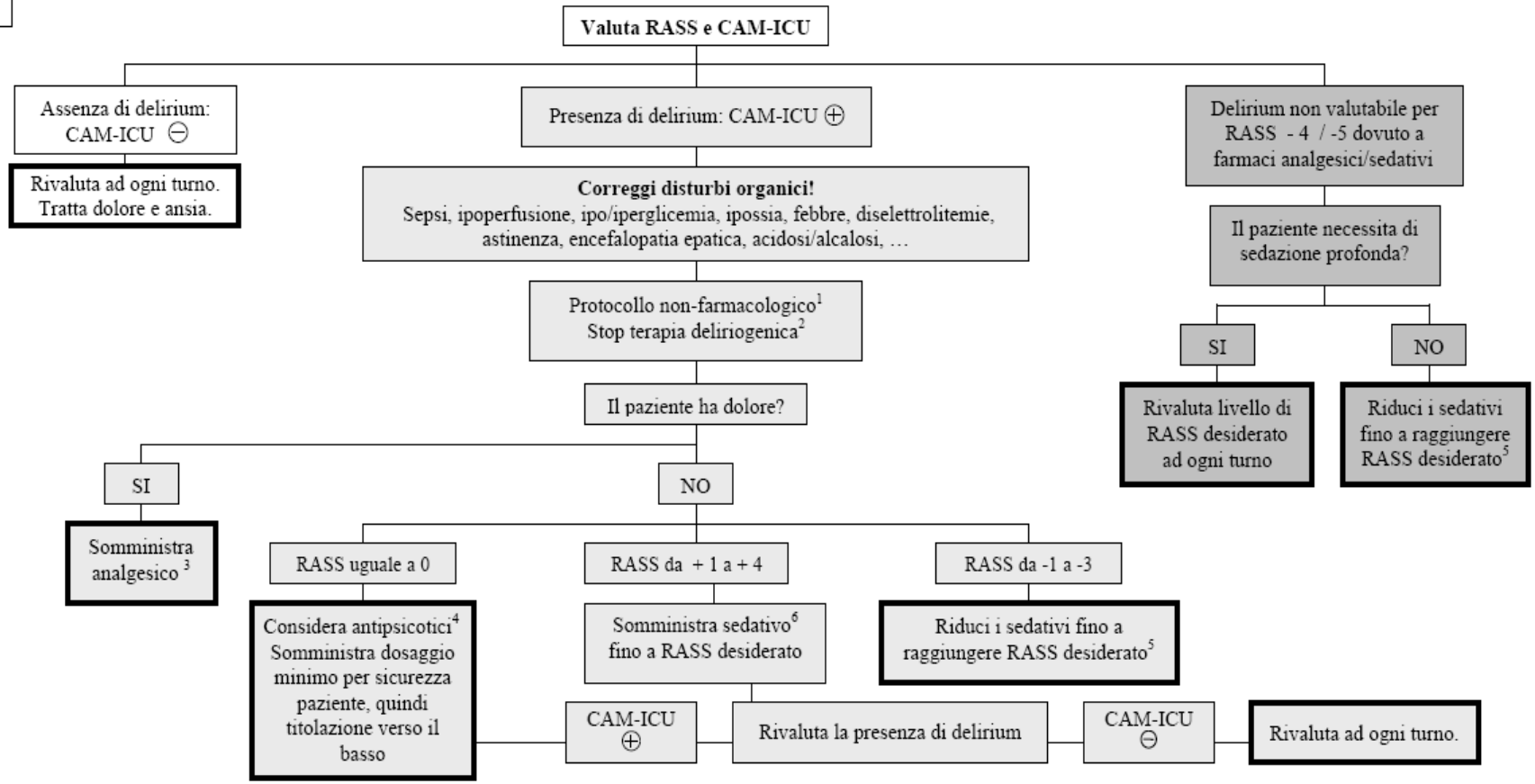
- E’ opportuno fare di tutto per PREVENIRE il delirium

- In caso di delirium è opportuno prima correggere le disfunzioni organiche, poi procedere a terapia non farmacologica

- In caso di permanenza del delirium, si passa a terapia antipsicotica secondo linee guida ospedaliere

3

GESTIONE DEL DELIRIUM IN TERAPIA INTENSIVA



[1] Protocollo non-farmacologico

Orientamento
- Utilizzo supporti visivi e uditivi personali.
- Incoraggia la comunicazione chiamando il paziente per nome.
- Disponibilità di oggetti personali del paziente.
- Coerenza di intervento dello staff medico/infermieristico.
- Impiego di TV/musica durante il giorno.

Ambiente
- Luci spente di notte, accese durante il dì; meglio se il pz. vede la luce del sole.
- Disincentiva il sonno diurno.
- Mobilizzazione del paziente e fisioterapia durante il giorno.
- Controlla l'eccesso di rumore (staff, strumentazione, visitatori) durante la notte.
- Evita procedure infermieristiche notturne.

[2] Considera interruzione/sostituzione di terapia deliriogenica: benzodiazepine, oppiacei, antidepressivi triciclici, propofol, anticolinergici, (metoclopramide, inibitori della pompa protonica, prometazina, difenidramina), altri neurolettici.

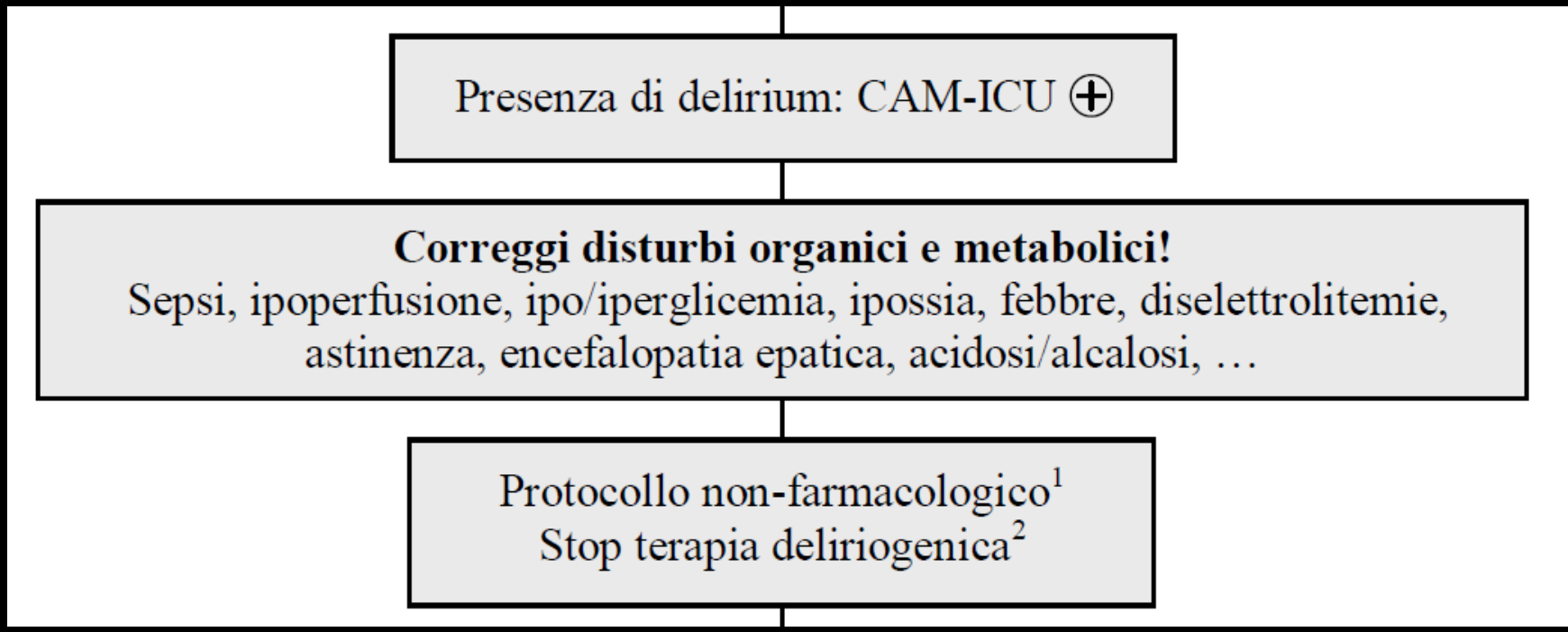
[3] Un adeguato controllo del dolore può ridurre il delirium. Preferisci somministrazione a boli. Stima con strumenti validati (VNR o BPS).

[4] Durante svezzamento dai sedativi, considera **aloperidolo** 0.5 -5 mg per os (0.5-1 mg se età > 65 anni) ogni 8 ore. Dose massima: 20 mg/die. Interrompere per iperpiressia, allungamento intervallo QT, rigidità muscolare.
Considera l'utilizzo di **antipsicotici atipici**: olanzapina, clotiapina, quetiapina, risperidone, ziprasidone, aripiprazolo.

[5] RASS sempre 'desiderato' = 0/-1 (paziente ben adattato nonostante patologia e invasività). Se necessario: RASS desiderato fra - 2 e - 4.

[6] *Sedazione endovena*: Propofol (max 6 mg/kg-h) o Midazolam (max 0.2 mg/kg-h) a boli ed eventuale infusione continua: somministra sempre il minimo dosaggio efficace.
Sedazione enterale: Idrossizina (max 600 mg /die) e Lorazepam (max 16 mg/ die): somministra sempre il minimo dosaggio efficace.
Melatonina 3 mg per 2 (ore 20 e 24) da ingresso fino a dimissione.

Nel caso di delirium…



…prima di tutto bisogna correggere le cause sottostanti…

…ed iniziare usando accorgimenti non farmacologici.

[1] Protocollo non-farmacologico

Orientamento

Utilizzo supporti visivi e uditivi personali.
Incoraggia la comunicazione chiamando il paziente per nome.
Disponibilità di oggetti personali del paziente.
Coerenza di intervento dello staff medico/infermieristico.
Impiego di TV/musica durante il giorno.

Ambiente

Luci spente di notte, accese durante il dì; meglio se il pz. vede la luce del sole.
Disincentiva il sonno diurno.
Mobilizzazione del paziente e fisioterapia durante il giorno.
Controlla l'eccesso di rumore (staff, strumentazione, visitatori) durante la notte.
Evitare procedure medico/infermieristiche notturne

Il problema più frequente è il paziente troppo sedato!

Enteral Conscious Sedation

vs

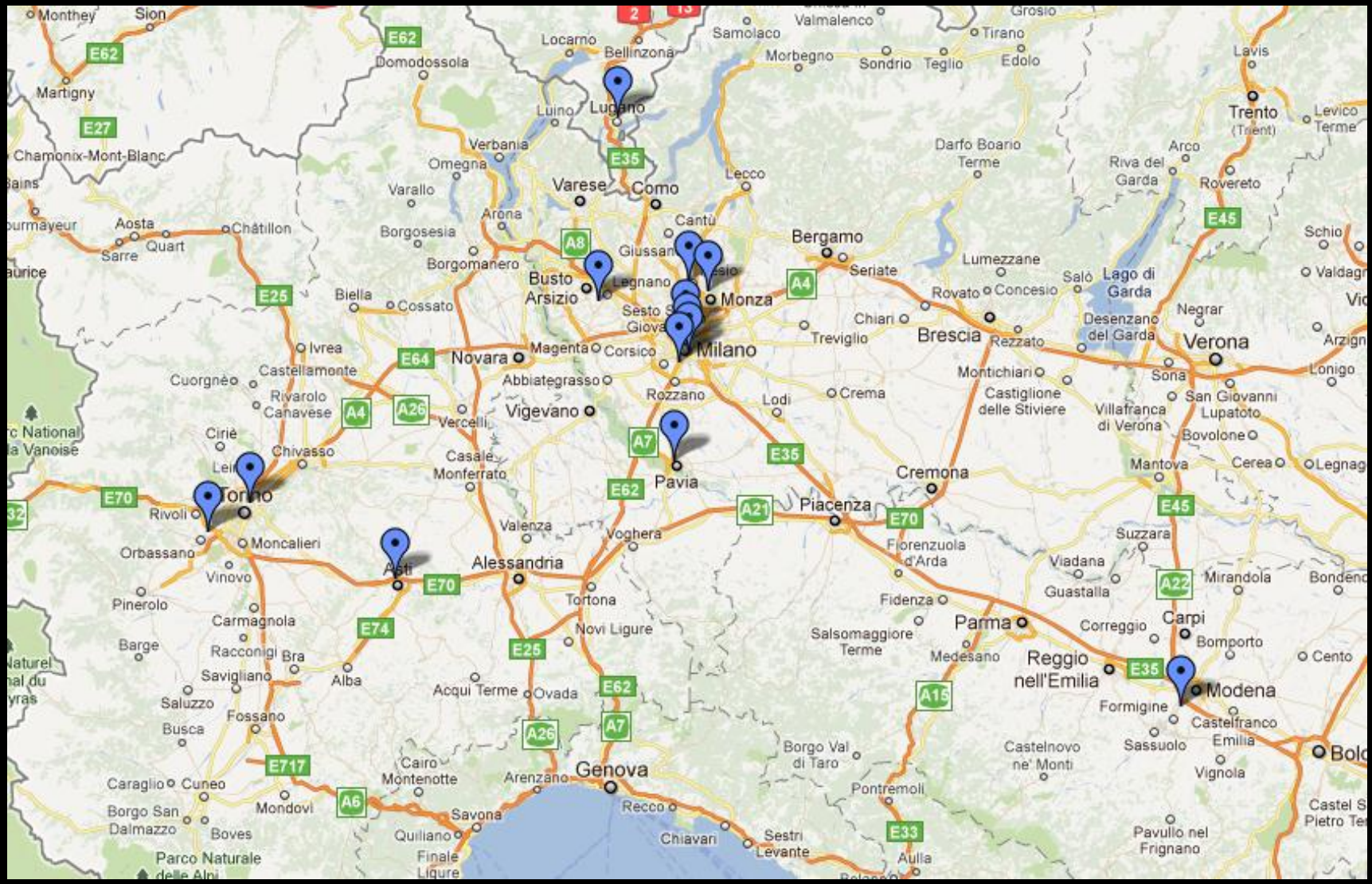
Standard Protocol Sedation

Melatonina + Idrossizina e Lorazepam SNG

Propofol o Midazolam ev

SCHEDA PROGETTO	
Titolo	STRATEGIE INNOVATIVE PER LA SEDAZIONE DEI PAZIENTI AD ALTO RISCHIO IN TERAPIA INTENSIVA
Area	AREA INTENSIVISTICA – TERAPIA INTENSIVA GENERALE

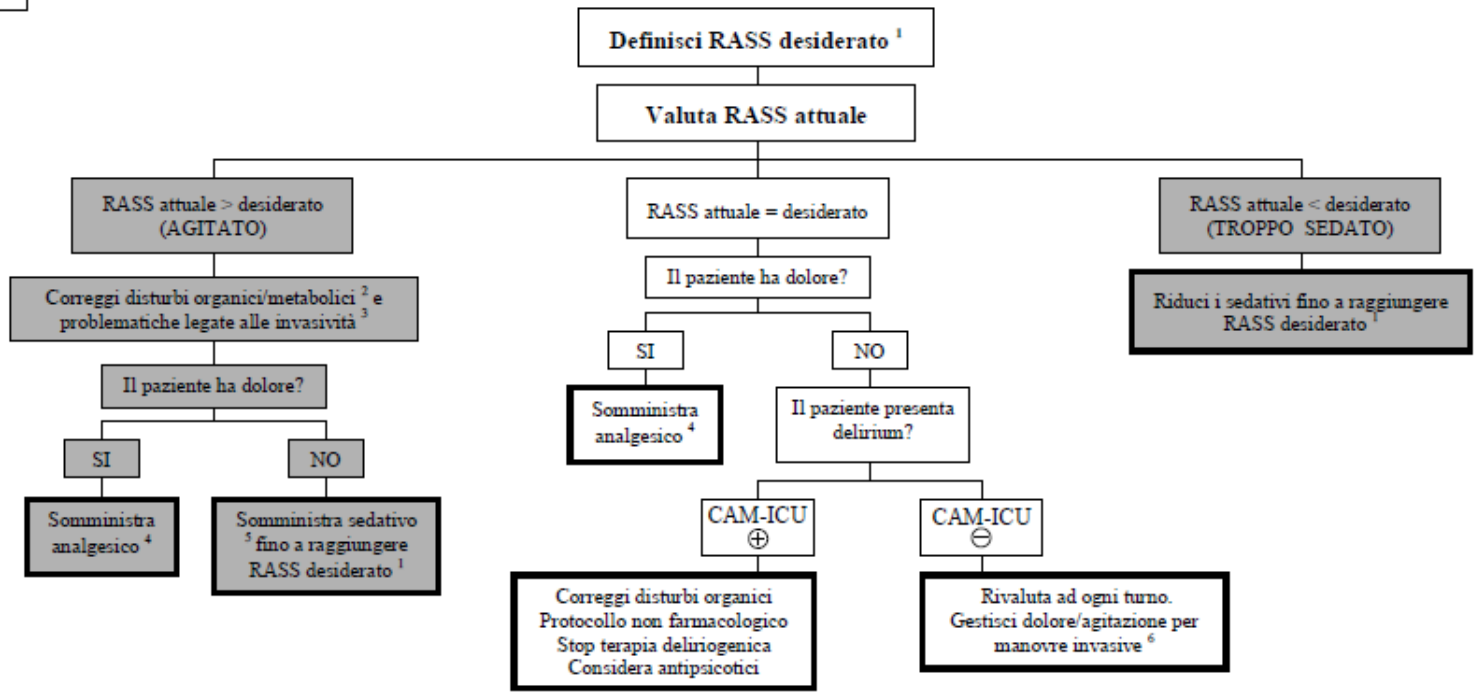
Centri partecipanti al WP1



Sedazione – criteri generali

2

GESTIONE AGITAZIONE/SEDAZIONE IN TERAPIA INTENSIVA



[1] **RASS sempre 'desiderato' = 0/-1** cioè paziente cosciente e ben adattato nonostante patologia e invasività.
Se le condizioni cliniche lo richiedono, RASS desiderato può essere fra -2 e -4.
Domanda costante: si può rendere più superficiale il livello di sedazione e quindi ridurre/stoppare l'utilizzo di sedativi?

[2] Sepsi, ipoperfusione, ipo/iperglicemia, ipossia, febbre, diselettrolitemie, astinenza, encefalopatia epatica, acidosi/alcalosi,...

[3] Modalità di ventilazione; aspirazione secrezioni bronchiali; adeguatezza posizionamento protesi respiratorie, incannulamenti vascolari, SNG, tubi di drenaggio, CV; decubito del paziente; mezzi di contenzione fisica,…

[4] Preferisci somministrazione a boli. Stima con strumenti validati (VNR o BPS).

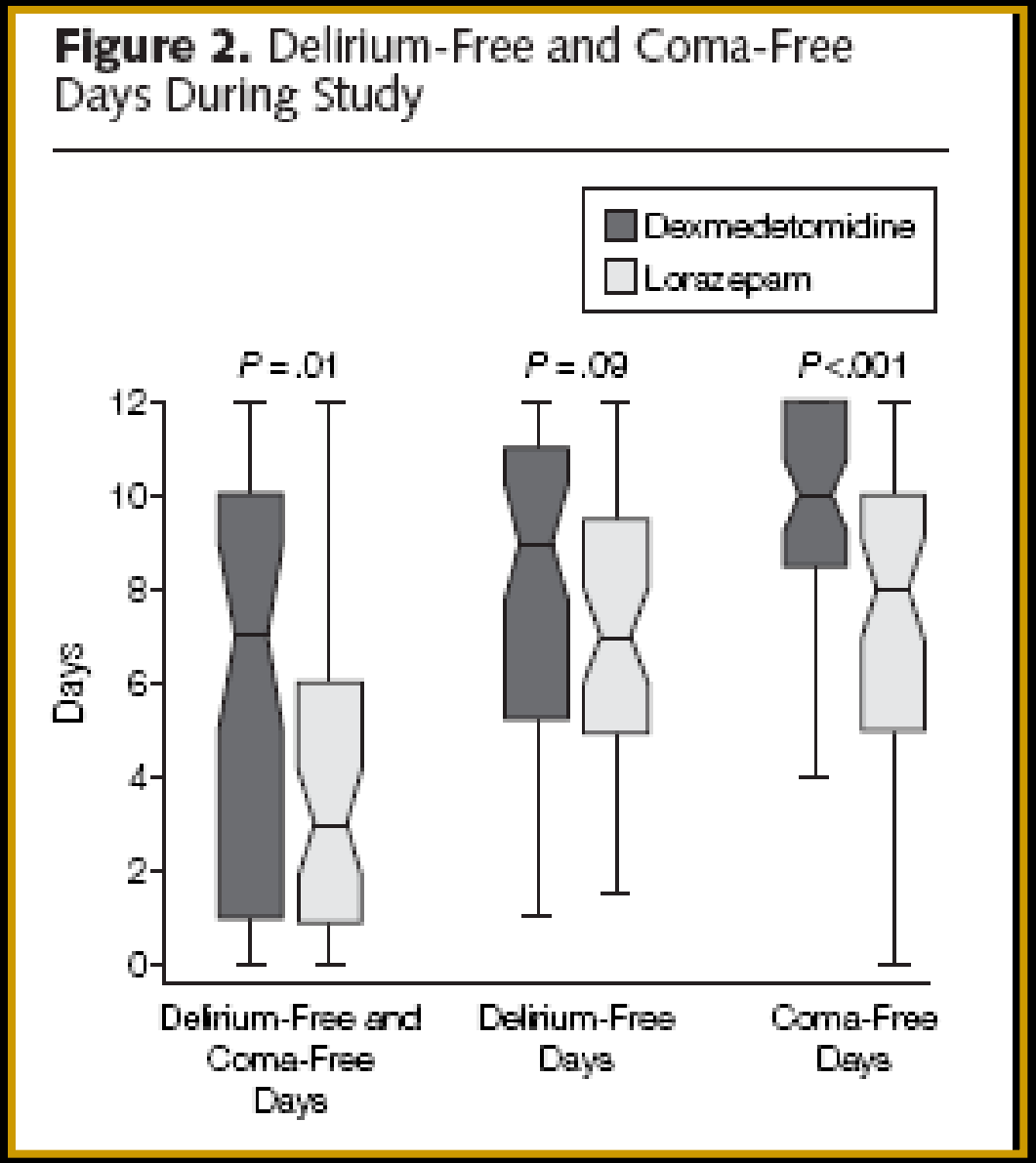
[5] *Sedazione endovena*: Propofol (max 6 mg/kg*h) o Midazolam (max 0.2 mg/kg*h) a boli ed eventuale infusione continua: somministra sempre il minimo dosaggio efficace.
Sedazione enterale: Idrossizina (max 600 mg/die) e Lorazepam (max 16 mg/die): somministra sempre il minimo dosaggio efficace.
Melatonina 3 mg per 2 (ore 20 e 24) da ingresso fino a dimissione.

[6] Valuta necessità di boli di analgesico e/o sedativo durante manovre invasive (posizionamento invasività, endoscopie, indagini diagnostiche, mobilizzazione paziente, …).

Dexmedetomidine vs Lorazepam

Effect of Sedation With Dexmedetomidine vs Lorazepam on Acute Brain Dysfunction in Mechanically Ventilated Patients

The MENDS Randomized Controlled Trial



Pandharipande P, *JAMA* 2007

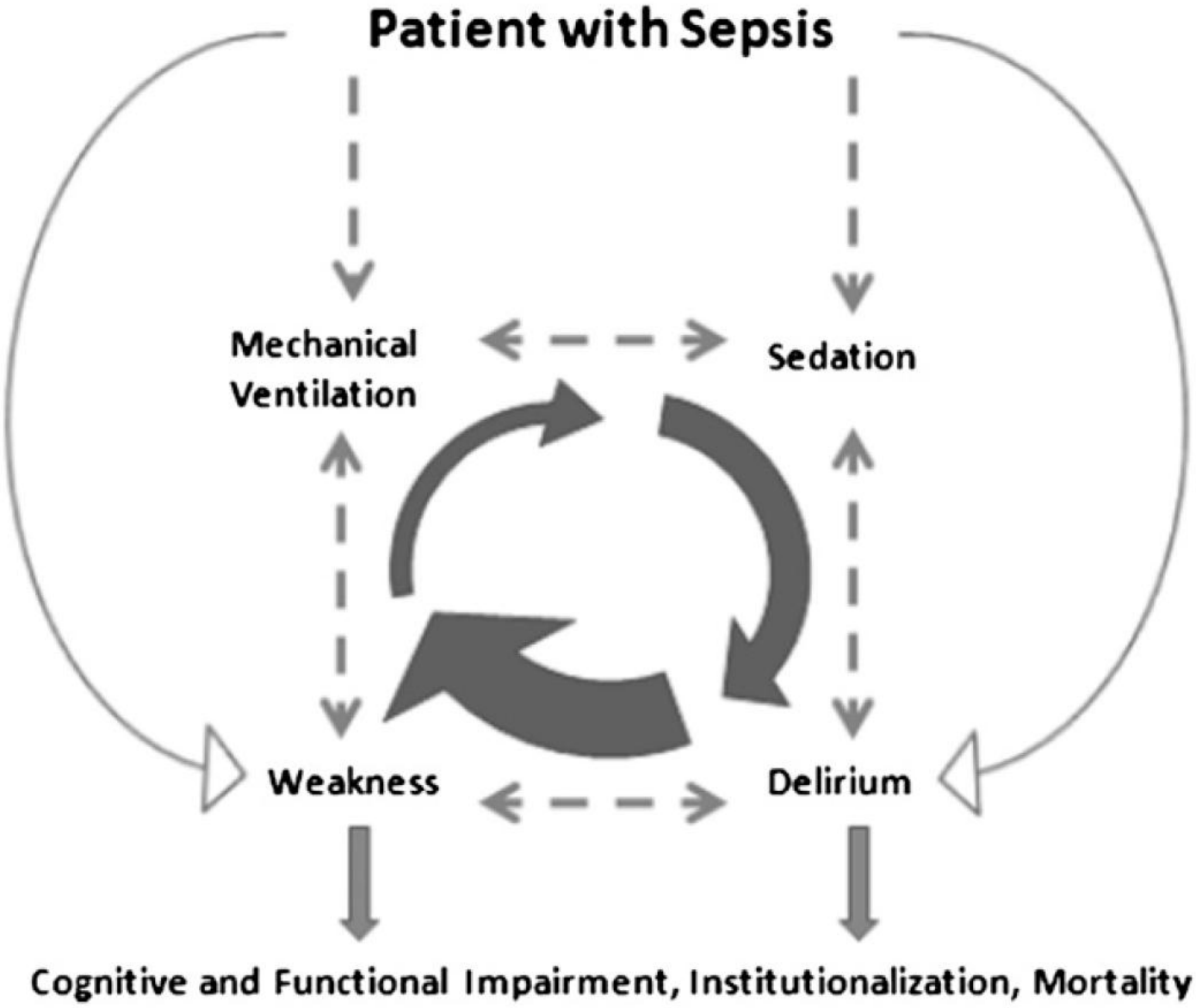


FIGURE 1. Relationship between ICU-acquired delirium and weakness in a patient with sepsis.

A wakening and

B reathing

C oordination

D elirium monitoring

E arly exercise

Vasilevskis, *Chest,* 2010

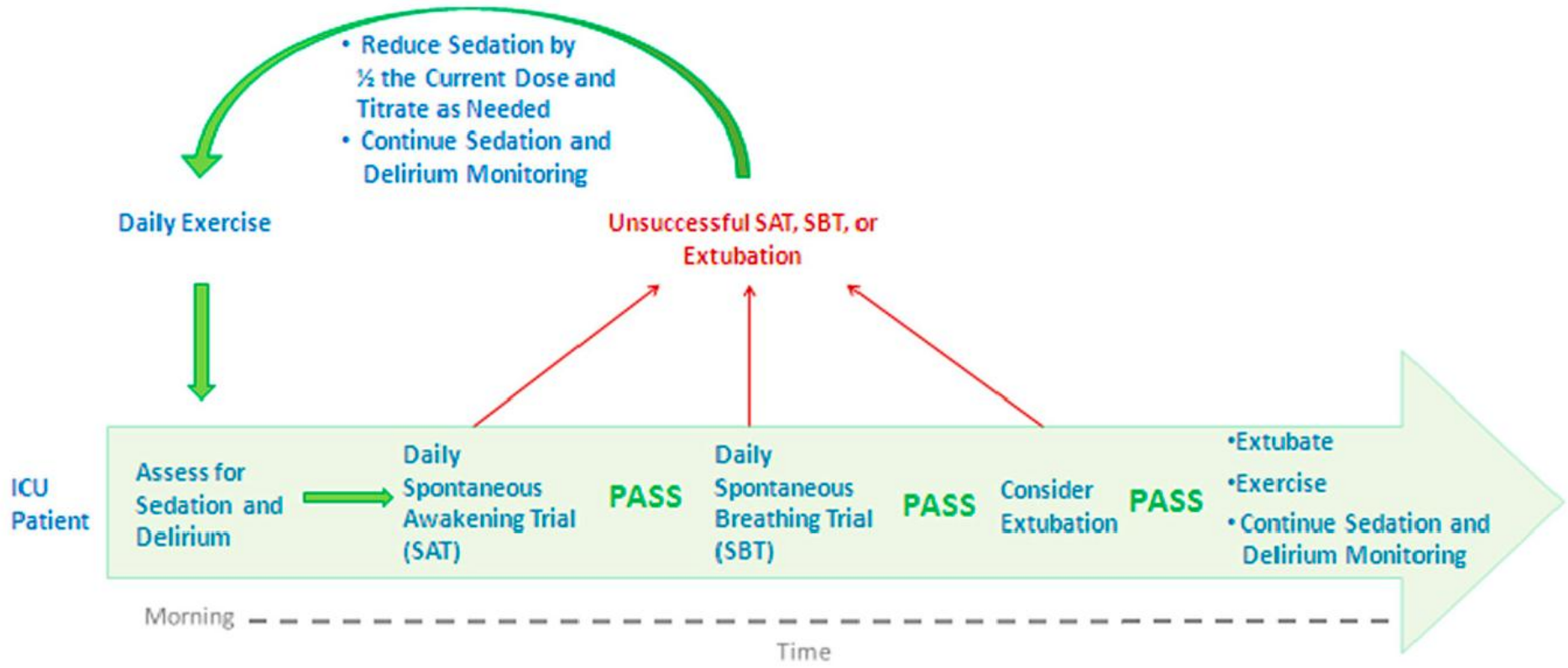


FIGURE 2. ABCDE is an ICU-acquired delirium and weakness mitigation strategy. This strategy is a protocolized bundle performed daily on mechanically ventilated and/or sedated patients in the ICU. This strategy is interdisciplinary by design and most effective when implemented by nursing, respiratory therapy, and physical therapy personnel working together as an ICU team. ABCDE = awakening and breathing coordination, delirium monitoring, and exercise/early mobility.

Vasilevskis, *Chest,* 2010

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Tailored Awake Analgesia and Sedation in Critically Ill Patients

Giovanni Mistraletti, M.D.

- **2020: Pazienti il più svegli possibile,**
  con dolore controllato,
  con protocolli sul TARGET, non sul dosaggio o sul tipo di farmaci!

Il nostro obiettivo non può essere solo aggiungere giorni alla vita.

Dobbiamo aggiungere
vita a quei giorni !

R. Levi Montalcini

Formazione degli operatori: **www.sedaicu.it**

sedaICU

Mappa del sito | www.sedaen.it |

Home | Chi siamo | Formazione | Letteratura | Corsi ECM | Agorà | cerca...

"Non esiste un protocollo di sedazione perfetto, esiste il miglior trattamento per quel paziente in quel momento."

G. Iapichino

Home

BENVENUTI su sedaICU !

SedaICU.it è un sito utile a **infermieri e medici di Terapia Intensiva**, per lavorare meglio.
L'obiettivo è curare bene i pazienti critici, e così migliorare il loro outcome. Per ottenerlo, gli operatori devono avere occasioni di **formazione efficace**, che li renda più soddisfatti e più competenti.
Su www.sedaicu.it troverai indicazioni per usare i farmaci sedativi in **modo nuovo** e per operare il monitoraggio neurologico con strumenti validati.
Siamo davanti ad una grande sfida, un cambio epocale nell'approccio ai pazienti critici: non più "sedati profondamente", ma semplicemente **"adattati"** alla patologia critica ed alle cure invasive necessarie...

Stiamo assistendo in Terapia Intensiva ad una profonda sfida culturale: pazienti svegli, parenti presenti, staff consapevole dei limiti e delle possibilità. Non è facile "cambiare testa", ma è il primo passo per stare meglio. Tutti.

Link veloci

www.icudelirium.org

VANDERBILT UNIVERSITY MEDICAL CENTER

UNITED STATES DEPARTMENT OF VETERANS AFFAIRS

icudelirium.org

RESEARCH DESIGNED TO TURN MIRRORS INTO WINDOWS

HOME | DELIRIUM | SEDATION | OUTCOMES | REFERENCES | OUR GROUP

ICU DELIRIUM AND COGNITIVE IMPAIRMENT STUDY GROUP

delirium overview *and how to diagnose it*

Delirium is confusion that comes on very fast, sometimes in just a few hours. When someone becomes delirious, it means that they can not think clearly, have trouble paying attention and are not aware of what is going on around them. Sometimes they may even see or hear things that are not really there but seem very real to them.

Risk Factors Study | Terminology and Mnemonics | Assessment | Implementation of CAM-ICU | FAQ | Patients and Family

Search

sedation

Increased scrutiny has recently been placed on appropriate titration of sedative and analgesic medications in critically ill patients, especially those being treated with mechanical ventilation.

Sedation Resources | Wake Up and Breathe Study

A new frontier in critical care: saving the injured brain.

E. Wesley Ely, 2011

Con melatonina e idrossizina
per via enterale,
l' injured brain lo salvi anche meglio.

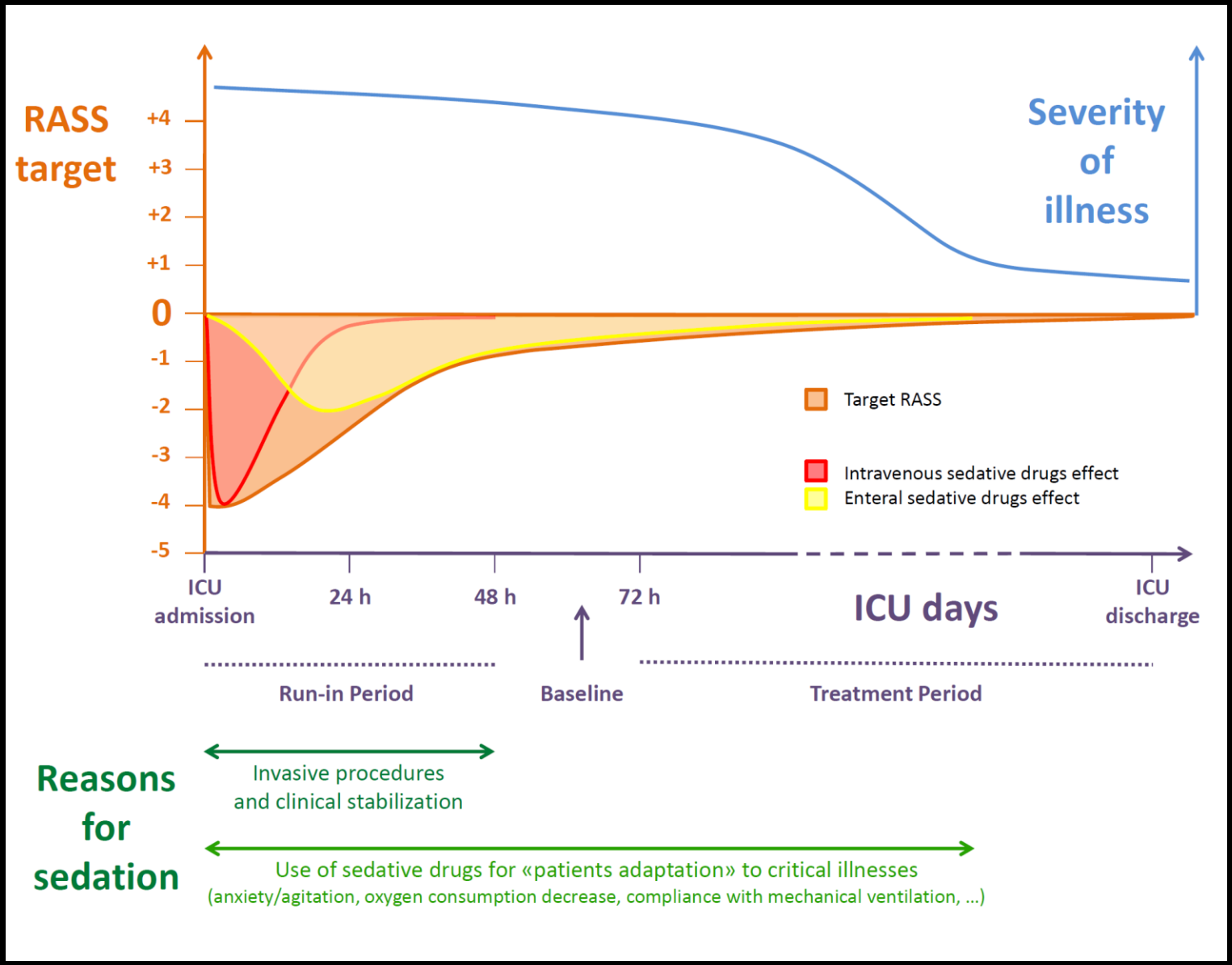
G. Mistraletti, 2012

Grazie dell'attenzione

giovanni.mistraletti@unimi.it

g.iapichino@unimi.it

Qual'è il RASS desiderato ?



Mistraletti G, *in press*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 16, 2010 VOL. 363 NO. 12

Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

Laurent Papazian, M.D., Ph.D., Jean-Marie Forel, M.D., Arnaud Gacouin, M.D., Christine Penot-Ragon, Pharm.D., Gilles Perrin, M.D., Anderson Loundou, Ph.D., Samir Jaber, M.D., Ph.D., Jean-Michel Arnal, M.D., Didier Perez, M.D., Jean-Marie Seghboyan, M.D., Jean-Michel Constantin, M.D., Ph.D., Pierre Courant, M.D., Jean-Yves Lefrant, M.D., Ph.D., Claude Guérin, M.D., Ph.D., Gwenaël Prat, M.D., Sophie Morange, M.D., and Antoine Roch, M.D., Ph.D., for the ACURASYS Study Investigators*

ABSTRACT

BACKGROUND

In patients undergoing mechanical ventilation for the acute respiratory distress syndrome (ARDS), neuromuscular blocking agents may improve oxygenation and decrease ventilator-induced lung injury but may also cause muscle weakness. We evaluated clinical outcomes after 2 days of therapy with neuromuscular blocking agents in patients with early, severe ARDS.

From Assistance Publique–Hôpitaux de Marseille Unité de Recherche sur les Maladies Infectieuses et Tropicales Émergentes (URMITE), Centre National de la Recherche Scientifique–Unité Mixte de Recherche (CNRS-UMR) 6236 (L.P., J.-M.F., A.R.) and Faculté de Médecine (A.L.), Université de la Méditerranée Aix–Marseille

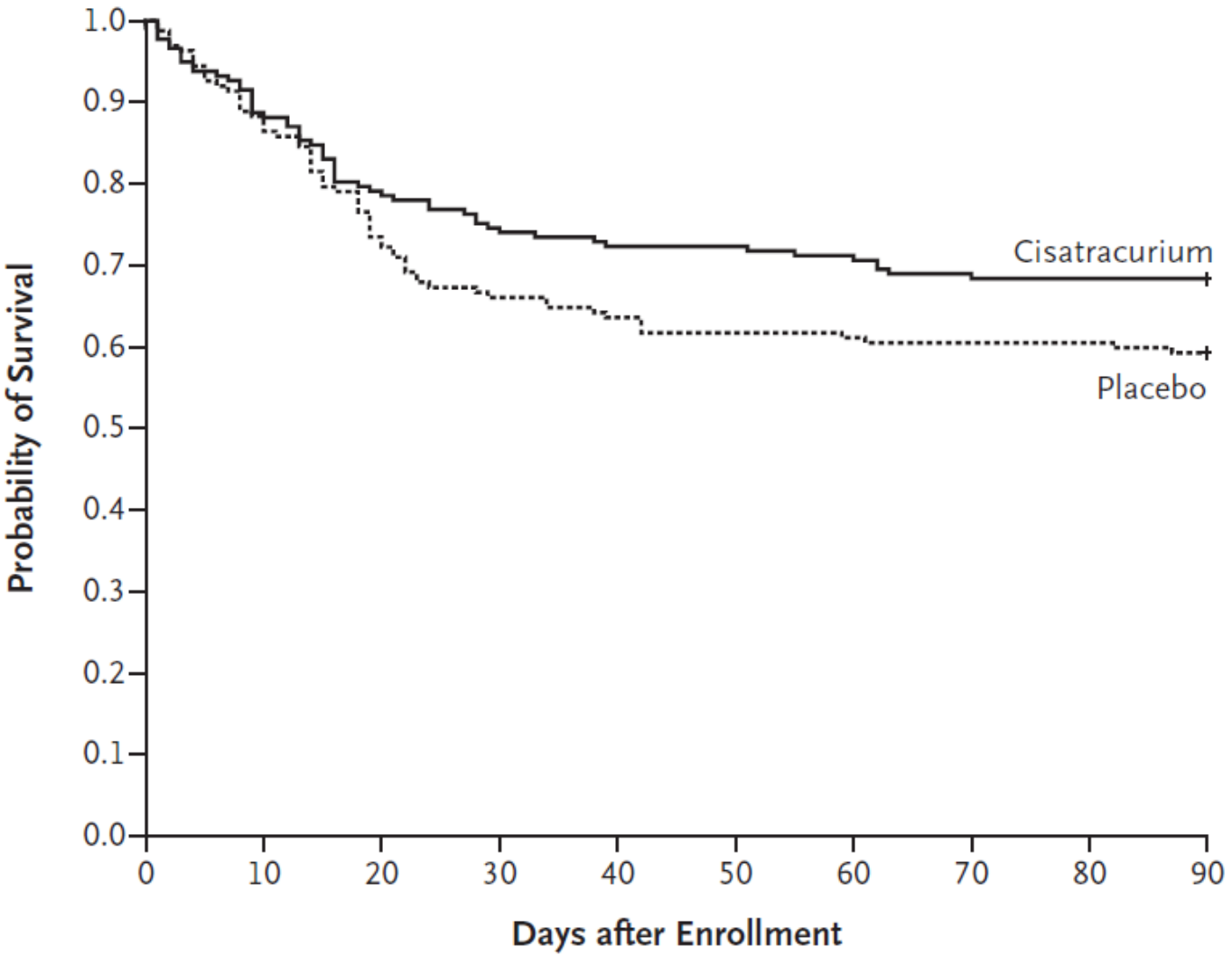


Figure 2. Probability of Survival through Day 90, According to Study Group.

Papazian, *NEJM*, 2010

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 16, 2010 VOL. 363 NO. 12

Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

Laurent Papazian, M.D., Ph.D., Jean-Marie Forel, M.D., Arnaud Gacouin, M.D., Christine Penot-Ragon, Pharm.D., Gilles Perrin, M.D., Anderson Loundou, Ph.D., Samir Jaber, M.D., Ph.D., Jean-Michel Arnal, M.D., Didier Perez, M.D., Jean-Marie Seghboyan, M.D., Jean-Michel Constantin, M.D., Ph.D., Pierre Courant, M.D., Jean-Yves Lefrant, M.D., Ph.D., Claude Guérin, M.D., Ph.D., Gwenaël Prat, M.D., Sophie Morange, M.D., and Antoine Roch, M.D., Ph.D., for the ACURASYS Study Investigators*

ABSTRACT

METHODS

In this multicenter, double-blind trial, 340 patients presenting to the intensive care unit (ICU) with an onset of severe ARDS within the previous 48 hours were randomly assigned to receive, for 48 hours, either cisatracurium besylate (178 patients) or placebo (162 patients). Severe ARDS was defined as a ratio of the partial pressure

6 to 8 ml per kilogram of predicted body weight. The primary outcome was the proportion of patients who died either before hospital discharge or within 90 days after study enrollment (i.e., the 90-day in-hospital mortality rate), adjusted for predefined covariates and baseline differences between groups with the use of a Cox model.

RESULTS

The hazard ratio for death at 90 days in the cisatracurium group, as compared with the placebo group, was 0.68 (95% confidence interval [CI], 0.48 to 0.98; P=0.04), after adjustment for both the baseline PaO_2:FIO_2 and plateau pressure and the Simplified Acute Physiology II score. The crude 90-day mortality was 31.6% (95% CI, 25.2 to 38.8) in the cisatracurium group and 40.7% (95% CI, 33.5 to 48.4) in the placebo group (P=0.08). Mortality at 28 days was 23.7% (95% CI, 18.1 to 30.5) with cisatracurium and 33.3% (95% CI, 26.5 to 40.9) with placebo (P=0.05). The rate of ICU-acquired paresis did not differ significantly between the two groups.

CONCLUSIONS

In patients with severe ARDS, early administration of a neuromuscular blocking agent improved the adjusted 90-day survival and increased the time off the ventilator without increasing muscle weakness. (Funded by Assistance Publique–Hôpitaux de Marseille and the Programme Hospitalier de Recherche Clinique Régional 2004-26 of the French Ministry of Health; ClinicalTrials.gov number, NCT00299650.)

(S.J.); Hôpital Font-Pré, Toulon (J.-M.A.); Hôpital Jean Minjoz, Besançon (D.P.); Hôpital Hôtel-Dieu, Clermont-Ferrand (J.-M.C.); Centre Hospitalier, Avignon (P.C.); Hôpital Caremeau, Nîmes (J.-Y.L.); Hôpital de la Croix-Rousse, Lyon (C.G.); and Hôpital de Cavale Blanche, Brest (G. Prat) — all in France. Address reprint requests to Dr. Papazian at Service de Réanimation Médicale, Hôpital Nord, Chemin des Bourrely, 13009 Marseille, France, or at laurent.papazian@ap-hm.fr.

*The ARDS et Curarisation Systematique (ACURASYS) study investigators are listed in the Appendix.

N Engl J Med 2010;363:1107-16.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

Neuromuscular

Laurent Papazian, M.D., Ph.D., Jean-M
Gilles Perrin, M.D., Anderson Loundou
Jean-Marie Seghboyan, M.D., Jean-Mich
Claude Guérin, M.D., Ph.D., Gwe

BACKGROUND

In patients undergoing mechanical vent
drome (ARDS), neuromuscular blockin
crease ventilator-induced lung injury but
ated clinical outcomes after 2 days of the
patients with early, severe ARDS.

METHODS

In this multicenter, double-blind trial,
unit (ICU) with an onset of severe AR
domly assigned to receive, for 48 hours
or placebo (162 patients). Severe ARDS
of arterial oxygen (PaO_2) to the fraction
with a positive end-expiratory pressure o
6 to 8 ml per kilogram of predicted bod
portion of patients who died either befo
study enrollment (i.e., the 90-day in-hos
covariates and baseline differences betw

RESULTS

The hazard ratio for death at 90 days in
the placebo group, was 0.68 (95% confid
adjustment for both the baseline PaO_2:F
Acute Physiology II score. The crude 90-d
in the cisatracurium group and 40.7%
(P=0.08). Mortality at 28 days was 23.7
and 33.3% (95% CI, 26.5 to 40.9) with
paresis did not differ significantly betw

CONCLUSIONS

In patients with severe ARDS, early ac
agent improved the adjusted 90-day surv
without increasing muscle weakness. (
Marseille and the Programme Hospitalie
the French Ministry of Health; ClinicalT

STUDY TREATMENT

Cisatracurium besylate (150-mg formulation, GlaxoSmithKline) and placebo were prepared in identical separate 30-ml vials for intravenous infusion. Peripheral-nerve stimulators were not permitted. The Ramsay sedation scale was used to adapt sedative requirements. The scale assigns the conscious state a score of 1 (anxious, agitated, or restless) to 6 (no response on glabellar tap). Once the assigned Ramsay sedation score was 6 and the ventilator settings were adjusted (Table 1), a 3-ml rapid intravenous infusion of 15 mg of cisatracurium besylate or placebo was administered,

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 16, 2010 VOL. 363 NO. 12

Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

Laurent Papazian, M.D., Ph.D., Jean-Marie Forel, M.D., Arnaud Gacouin, M.D., Christine Penot-Ragon, Pharm.D., Gilles Perrin, M.D., Anderson Loundou, Ph.D., Samir Jaber, M.D., Ph.D., Jean-Michel Arnal, M.D., Didier Perez, M.D., Jean-Marie Seghboyan, M.D., Jean-Michel Constantin, M.D., Ph.D., Pierre Courant, M.D., Jean-Yves Lefrant, M.D., Ph.D., Claude Guérin, M.D., Ph.D., Gwenaël Prat, M.D., Sophie Morange, M.D., and Antoine Roch, M.D., Ph.D., for the ACURASYS Study Investigators*

ABSTRACT

BACKGROUND

In patients undergoing mechanical ventilation for the acute respiratory distress syn-

From Assistance Publique–Hôpitaux de

BASELINE CHARACTERISTICS

We enrolled 340 patients, of whom 178 were randomly assigned to cisatracurium and 162 to placebo. We excluded 986 patients (Fig. 1). One patient in the cisatracurium group withdrew consent before treatment was started, and data for this patient were therefore not included in the analysis.

Era un congressista dello STAT che aveva appena assistito alla presentazione del Mistraletti !!!

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 16, 2010 VOL. 363 NO. 12

Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

Laurent Papazian, M.D., Ph.D., Jean-Marie Forel, M.D., Arnaud Gacouin, M.D., Christine Penot-Ragon, Pharm.D., Gilles Perrin, M.D., Anderson Loundou, Ph.D., Samir Jaber, M.D., Ph.D., Jean-Michel Arnal, M.D., Didier Perez, M.D.,

Table 2. Baseline Characteristics of the Patients, According to Study Group.*

Characteristic†	Cisatracurium (N=177)	Placebo N=162)	P Value
Age — yr	58±16	58±15	0.70
Tidal volume — ml/kg of predicted body weight	6.55±1.12	6.48±0.92	0.52
Minute ventilation — liters/min	10.0±2.5	10.1±2.2	0.83
PEEP applied — cm of water	9.2±3.2	9.2±3.5	0.87
Plateau pressure — cm of water	25.0±5.1	24.4±4.7	0.32
Respiratory-system compliance — ml/cm of water	31.5±11.6	31.9±10.7	0.71
FIO_2	0.79±0.19	0.77±0.20	0.33
PaO_2:FIO_2‡	106±36	115±41	0.03
pH	7.31±0.10	7.32±0.10	0.11
PaO_2 — mm Hg	80±24	85±28	0.09
$PaCO_2$ — mm Hg	47±11	47±11	0.62
Prone position or inhaled nitric oxide or almitrine mesylate — no. (%)	33 (18.6)	23 (14.2)	0.31
SAPS II§	50±16	47±14	0.15

CHEST Transparency in Health Care

Reducing Iatrogenic Risks

ICU-Acquired Delirium and Weakness—Crossing the Quality Chasm

Eduard E. Vasilevskis, MD; E. Wesley Ely, MPH, MD, FCCP; Theodore Speroff, PhD; Brenda T. Pun, RN, MSN, ACNP; Leanne Boehm, RN, MSN, ACNS-BC; and Robert S. Dittus, MPH, MD

ICUs are experiencing an epidemic of patients with acute brain dysfunction (delirium) and weakness, both associated with increased mortality and long-term disability. These conditions are commonly acquired in the ICU and are often initiated or exacerbated by sedation and ventilation decisions and management. Despite > 10 years of evidence revealing the hazards of delirium, the quality chasm between current and ideal processes of care continues to exist. Monitoring of delirium and sedation levels remains inconsistent. In addition, sedation, ventilation, and physical therapy practices proven successful at reducing the frequency and severity of adverse outcomes are not routinely practiced. In this article, we advocate for the adoption and implementation of a standard bundle of ICU measures with great potential to reduce the burden of ICU-acquired delirium and weakness. Individual components of this bundle are evidence based and can help standardize communication, improve interdisciplinary care, reduce mortality, and improve cognitive and functional outcomes. We refer to this as the "ABCDE bundle," for awakening and breathing coordination, delirium monitoring, and exercise/early mobility. This evidence-based bundle of practices will build a bridge across the current quality chasm from the "front end" to the "back end" of critical care and toward improved cognitive and functional outcomes for ICU survivors.

CHEST 2010; 138(5):1224–1233

Why should we adopt sedation scoring?

Objective assessment and
close, prospective control of the sedation level

- No over-sedation and under-sedation risks
- Optimal end-point for titration of sedation
- Prospective management of care
- Comparability of drugs effects

How to measure sedation level

- The "ideal" level varies with patients and time

- Great number of scales, but not validated in mesurement of sedative strategy changes

- Ramsay (BMJ 1974, with 6 levels – widely accepted)

1. Anxious and agitated
2. Cooperative, oriented and tranquil
3. Responds to command only
4. Brisk response to light glabellar tap or loud auditory stimulus
5. Sluggish response to light glabellar tap or loud auditory stimulus
6. No response to stimuli

Others “objective tools”

Plasmatic drug concentration

BIS (bispectral index)

Frontalis muscle electromiogram

Auditory evoked potentials

Lower-oesophageal contractility

Cerebral function monitoring

Narcotrend

Others "subjective tools"

GCS (Glasgow Coma Scale)

SAS (Sedation-Agitation Scale)

OAAS/S (Observers' Assessment of Alertness/Sedation Scale)

Bloomsbury Sedation Score

RASS (Richmond Agitation-Sedation Scale)

Comfort Scale

Motor Activity Assessment Scale

Linear Sedation Scale

Richmond Agitation-Sedation Scale (RASS)

Score	Term	Description
+4	Combative	Overtly combative, violant, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent nonpurposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive or vigorous
0	Alert and calm	
–1	Drowsy	Not fully alert, but has sustained awakening (eye opening/eye contact) to *voice (>10 seconds)*
–2	Light sedation	Briefly awakens with eye opening to *voice (>10 seconds)*
–3	Moderate sedation	Movement or eye opening to *voice* (but no eye contact)
–4	Deep sedation	No response to voice, but movement or eye opening to *physical stimulation*
–5	Unarousable	No response to voice or *physical stimulation*

With permission from Sessler CN, Richmond, Virginia, USA

Sessler CN, *Am J Respir Crit Care Med,* 2002

Ely EV, *JAMA,* 2003

What is the relationship with delirium?

- Sedatives and analgesics are independent risk factor for development of delirium in ICU.
- Moreover, in a dose-dependent way

Clearly demonstrated for :

- Lorazepam
- Midazolam
- Fentanyl

Pun B, *Chest* 2007

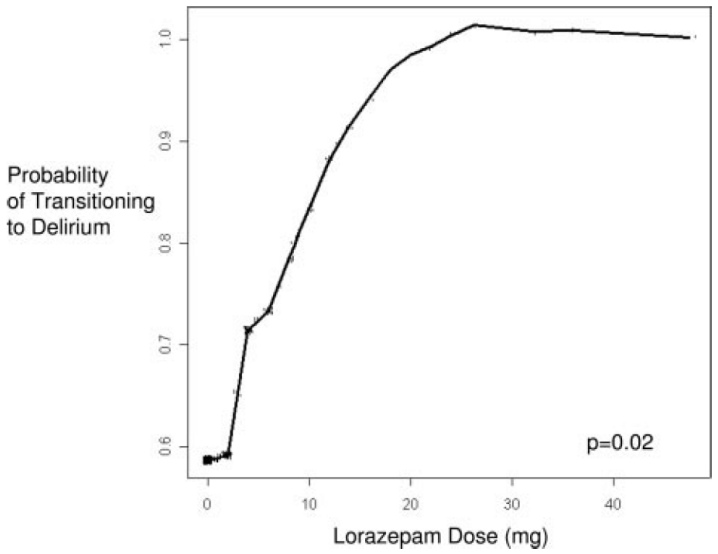


FIGURE 8. Lorazepam is an independent risk factor for transitioning to delirium in the ICU. The probability of transitioning to delirium increased with the dose of lorazepam administered in the previous 24 h. This incremental risk was large at low doses and plateaued at approximately 20 mg/d. Used with permission from Pandharipande et al.[60]

Valutazione dello stato di coscienza e monitoraggio del delirium

Fase 1 – Livello di Coscienza: RASS

Punteggio	Definizione	Descrizione	
+4	COMBATTIVO	Chiaramente combattivo, violento, imminente pericolo per sé o per lo staff	OSSERVAZIONE
+3	MOLTO AGITATO	Aggressivo, rischio evidente di rimozione invasività	
+2	AGITATO	Frequenti movimenti afinalistici, disadattamento alla ventilazione meccanica	
+1	IRREQUIETO	Ansioso ma senza movimenti aggressivi o vigorosi	
0	SVEGLIO E TRANQUILLO	Comprende i periodi di sonno fisiologico	
-1	SOPOROSO	Non completamente sveglio, apre gli occhi allo stimolo verbale, mantiene il contatto visivo > 10 secondi	STIMOLO VERBALE
-2	LIEVEMENTE SEDATO	Brevi risvegli allo stimolo verbale, contatto visivo < 10 secondi	
-3	MODERATAMENTE SEDATO	Movimenti o apertura degli occhi allo stimolo verbale (ma senza contatto visivo)	

Se RASS ≥ - 3 → somministra CAM-ICU (il paziente ha delirium oppure no?)

-4	SEDAZIONE PROFONDA	Nessuna risposta allo stimolo verbale, movimenti o apertura occhi alla stimolazione fisica	STIMOLO TATTILE
-5	NON RISVEGLIABILE	Nessuna risposta alla stimolazione tattile o dolorosa	

Se RASS ≤ -4 → RIVALUTA più tardi (paziente attualmente incosciente)

Sessler, et al. AJRCCM 2002; 166:1338-1344.[2]
Ely, et al. JAMA 2003; 289:2983-2991.[3]

Fase 2 – Funzionamento cognitivo: CAM-ICU

Punto 1: Alterazione acuta o fluttuazione dello stato mentale

e

Punto 2: Disattenzione

e

Punto 3: Alterato livello di coscienza **oppure** **Punto 4:** Pensiero disorganizzato

= presenza di DELIRIUM

Inouye, et al. Ann Intern Med 1990; 113:941-948.[1]
Ely, et al. CCM 2001; 29:1370-1379.[4]
Ely, et al. JAMA 2001; 286:2703-2710.[5]