Review Article
Open Access
CrossMark

Evaluation of Sedation for the Unconscious Patient: Are We Still Far Away?

Abstract

In our daily practice in intensive care unit, one of the "cornerstones" is to achieve adequate sedation for every patient. Intensive care unit (ICU) patients are often sedated, and a good hypnotic monitoring is important to assure an optimal level of sedation for every patient. Sedation monitoring can be achieved using subjective or objective methods. The most recent recommendations on management of sedation were published by Critical Care Medicine in January 2013. They recommend the use of subjective methods as the primary method to monitor sedation, with the use of objective methods only in paralyzed and comatose patients, in whom subjective methods cannot be used. Unfortunately in these last recommendations, the objective methods of sedation monitoring are listed without indicating any of them as the best method actually available to assure an adequate sedation. The aim of our study is to review the characteristics of each objective method of sedation monitoring, in order to understand which is the most appropriate in the current state. We found that several objective methods are adequate to monitor the level of sedation in paralyzed or comatose patients, although the data needs to be considered with caution, Bispectral Index (BIS) is suggested as the best method for monitoring sedation in most studies.

Keywords: Sedation; Intensive care unit; Electroencephalogram; Auditory evoked potentials

Volume 1 Issue 2 - 2014

Laurenza C, Mattei A, Antonelli S, Cappiello D, Carassiti M
Department of Anesthesia and Intensive Care, University-Hospital School of Medicine Campus Bio-Medico, Italy

Correspondence: Massimiliano Carassiti, Department of Anesthesia and Intensive Care, University-Hospital School of Medicine Campus Bio-Medico, via Alvaro del Portillo 21, 00128 Rome, Italy, Tel +39-062-2541-1181, Fax +39-062-2541-1952; Email m.carassiti@unicamous.it

Received: May 19, 2014 | **Published:** June 12, 2014

Abbreviations: ICU: Intensive Care Unit; EEG: Electroencephalogram; BIS: Bispectral Index; PSI: Patient State Index; NI: Narcotrend Index; SE: State Entropy; RE: Response Entropy; AEP: Auditory Evoked; Potentials; MLAEP: Middle Latency Auditory Evoked Potentials; LLAEP: Long Latency Auditory Evoked Potentials; AAI: Auditory Arx Index

Introduction

Whenever sedation is used, an appropriate monitoring is useful to achieve an adequate level of sedation based on the needs of the patient. The sedation monitoring assures the optimization of sedation's quality, avoiding the side effects of under sedation (increased stress, agitation, hypertension, tachycardia, poor adaptation to ventilation and accidental extubation) and over sedation (prolonged mechanical ventilation, deep venous thrombosis, unrecognized cerebral injuries).[1,2] Furthermore, a recent survey conducted in Canadian ICUs showed that only few ICUs have a sedation protocol.[3] and even where sedation protocols exist, the observational studies indicate a poor compliance to the protocols. Therefore, a scientific approach based on the protocols for monitoring and adjusting sedation level may lead to improved outcomes. The methods for sedation monitoring in ICU may be subjective (clinical scales) or objective (evoked potentials and parameters electroencephalogram derived). The most recent recommendations on management of sedation, published by Journal of Critical Care Medicine in January 2013, recommend using the subjective methods as the primary method to monitor the sedation in ICU; the objective methods should only be used for monitoring sedation when subjective methods cannot be used because the patient is comatose or paralyzed. In these last guidelines,[1] the available objective methods of sedation monitoring are listed, without recommending any of them as the best measurement system of sedation which is actually available. The aim of our study is to review the characteristics of each objective method of sedation monitoring, in order to understand what is the best one for monitoring sedation in the current state? We reviewed studies concerning objective methods of sedation monitoring mentioned by Barr J et al.[1] in the most recent recommendations on management of sedation, as well as two additional methods, the Electroencephalogram (EEG) and the Auditory Arx Index (AAI). We searched personal files and the OVID MEDLINE and PubMed databases from January 2000 until May 2014, using the terms "sedation monitoring", "electroencephalogram", "auditory evoked potentials", "bispectral index", "entropy", or "narcotrend" or "patient state index" each combined with the terms "critical care", "critical illness", "intensive care", "ICU", and "intensive care unit". One reviewer has evaluated the titles and the abstracts of all the identified articles then has selected the relevant literature. We considered only the papers published in English language. We looked for studies that examined the ease of use, validity and inter individual reliability of each method, in order to understand if sedation monitoring can rely on them. The validity of a new measurement method is usually determined by comparing measurements made with the new method with either measurements obtained by the gold standard ("criterion validity") methods or a standard reference measure that is considered valid according to a logically derived construct ("construct validity"). Since there is no available gold standard measure for monitoring sedation, it is only possible to estimate "the construct validity".

In order to simplify, we decided to consider the performance of the single objective methods without comparing the performance of two or more methods. In addition to collecting objective methods performance data, we collected the following data: administration of sedatives (device performance could be related to analgo-sedative drugs used), administration of neuromuscular blocking (there is agreement in literature that electro-myographic activity interferes with spontaneous or evoked electroencephalographic activity),[4,5] models of tested devices and the presence of patients with positive anamnesis for neurological diseases (differences among studies with

regards both to models of tested devices and to exclusion criteria for patients with positive anamnesis for neurological diseases can cause data heterogeneity which could interfere with interpretation of the results).[6,7]

Inclusion criteria of the articles in our review were:

a. Studies classified as clinical trials.

b. Studies whose population was composed of adult patients (age≥15 years) admitted in ICU.

c. Studies using clinical ratings or the effective predicted concentrations of sedative as reference standards for "construct validity" estimate.

Table 1 reports clinical scales, which are used, as reference standard of the objective methods, in the studies included in our review.

Table 1 Clinical scales for monitoring sedation

Scale	Score	Meaning of the Score	Level of Sedation According our Criteria of Classification*
RS Morandi et al.[8]	1	Patient anxious, agitated or restless	Agitated
	2	Patient cooperative, orientated or tranquil	Awake and calm
	3	Patient responds to command only	Light sedation
	4	Brisk response to a light glabellar tap	Moderate sedation
	5	Sluggish response to a light glabellar tap	
	6	No response to a light glabellar tap	Deep sedation
	7	Pulling at endotracheal tube, trying to remove catheters, climbing over bed rail, striking at staff, thrashing side to side	
SAS Morandi et al.[8]	6	Does not calm, despite frequent verbal reminding of limits; requires physical restraints	Agitated
	5	Anxious or mildly agitated, attempting to sit up, calms down to verbal instructions	
	4	Calm, awakens easily; follows commands	Awake and calm
	3	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands	Light sedation
	2	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously	Moderate sedation
	1	Minimal or no response to noxious stimuli, does not communicate or follow commands	Deep sedation
RASS Morandi et al.[8]	+ 4	Overtly combative or violent; immediate danger to staff.	Agitated
	+ 3	Pulls on or removes tube(s) or catheter(s) or has aggressive behaviour toward staff.	
	+ 2	Frequent non-purposeful movement or patient–ventilator dyssynchrony	
	+ 1	Anxious or apprehensive but movements not aggressive or vigorous	
	0	Alert and calm	Awake and calm
	-1	Not fully alert, but has sustained (more than 10 s) awakening, with eye contact, to voice.	Light sedation
	-2	Briefly (less than 10 s) awakens with eye contact to voice.	
	-3	Any movement (but no eye contact) to voice.	Moderate sedation
	-4	No response to voice, but any movement to physical stimulation	Deep sedation
	-5	No response to voice or physical stimulation.	
OAAS Hernandez-Gancedo et al.[14]	5	Responds readily to name spoken in normal tone	Alert
	4	Lethargic response to name spoken in normal tone	Light sedation
	3	Responds only after name is called loudly and/or repeatedly	Moderate sedation
	2	Responds only after mild prodding or shaking	
	1	Does not respond to mild prodding or shaking	Deep sedation
Bloomsbury Sedation Scale Sackey et al.[15]	3	Agitated and restless	Agitated
	2	Awake and uncomfortable	
	1	Aware but calm	Awake and calm
	0	Roused by voice, remains calm	Light sedation
	-1	Roused by movement or suction	Moderate sedation
	-2	Roused by painful stimuli	
	-3	Unrousable	Deep sedation

Citation: Laurenza C, Mattei A, Antonelli S, et al. Evaluation of Sedation for the Unconscious Patient: Are We Still Far Away? *J Anesth Crit Care Open Access.* 2014;1(2):30–39. DOI: 10.15406/jaccoa.2014.01.00007

Table Continued...

Scale	Score	Meaning of the Score	Level of Sedation According our Criteria of Classification*
Awakeness domain of the ATICE score Trouiller et al.[16]	0	Eyes closed, no mimic	Deep sedation
	1	Eyes closed, only facial mimic after strong, painful stimulation	
	2	Eyes opening after strong, painful stimulation	Moderate sedation
	3	Eyes opening after light, painful stimulation	
	4	Eyes opening after verbal order	Light sedation
	5	Eyes opening spontaneously	Awake

RS, Ramsay sedation scale; SAS, Sedation Agitation Scale; RASS, Rchmond Agitation Sedation Scale; OAAS, Observer's Assessment of Alertness and Sedation; ATICE, Adaptation to Intensive Care Environment

*The following criteria of classification have been decided arbitrarily in order to simplify the understanding of studies results which are included in this review

Discussion

Objective methods for sedation monitoring.

Continuous electroencephalogram

The electroencephalogram (EEG) is the registration of the cortical electrical activity.

Practical use and speed of registration: It requires at least 2 pair of electrodes.[2] and its assessment requires special knowledge and takes a relatively long time.[8]

Performance in monitoring sedation: The studies on monitoring sedation with continuous EEG, which answered our inclusion criteria, were not found.

Bispectral Index (BIS), Patient State Index (PSI), Narcotrend Index (NI) and entropy

BIS, PSI and NI are indexes of EEG, i.e. they are dimensionless integers obtained from analysis of multiple descriptive EEG parameters, which are different depending on the type of index.[6,9-11] The entropy is a physical quantity that describes irregularity of a signal. The considered signal is, in case of sedation monitoring, the EEG and, in case of Response Entropy, the electromyography (EMG) and the EEG too. It is possible to compute the State Entropy (SE) or the Response Entropy (RE).[12] The State Entropy (SE) is based on the EEG dominant frequency ranges alone while the Response Entropy (RE) analyzing the complete range of frequencies, including both EEG and EMG components. The EEG signal component dominates the lower frequencies (up to about 30Hz) contained in the bio potentials existing in the electrodes and primarily reflects the cortical state of the patient. The electromyographic (EMG) component is created by muscle activity, and during anesthesia typically dominates at frequencies higher than 30Hz, showing an early response to the stimuli. The State Entropy (SE) includes the EEG-dominant part of the spectrum, and thus represents a stable indicator of the effect of hypnotics on the cortex. The Response Entropy (RE) includes both the EEG-dominant and EMG-dominant part of the spectrum, thus its value reacts fast to painful stimulus during surgery. Typically, during arousal (RE) rises first simultaneously with muscle activation and is some seconds later followed by (SE). The EEG indexes have been scaled to range between 0 (corresponding to an isoelectric EEG) and 100 (corresponding to an alertness state). An exception is SE, whose maximum value is 91 rather than 100. The devices that registering these indexes, are commercially available.

Practical use and speed of registration: Their registration is simple and fast both because the number of electrodes is limited (four electrodes) and also because the estimate of the index is automatic and complete in less than one minute.[13]

Performance in monitoring sedation: No study on NI was found according to our search criteria. Results of studies assessing BIS, SE and RE, PSI, performance are summarized in Table 2,[4,14-35] Table 3[17-19,36] and Table 4[37,38] respectively. With regard to the BIS, several models of devices registering it have been created. These models differ in the software algorithm used to calculate these indexes[6] more frequently, in the ways of filtering the EMG artifacts.[7]

Auditory evoked potentials (AEP)

The AEP are the differences of potential that are produced in the neuroanatomical structures of the auditory pathway of a patient receiving an auditory stimulus. The AEP are represented like positive or negative waves that can be identified measuring their latency and their amplitude. The AEP are categorized on the basis of the latency of the response following the auditory stimulus: the short latency AEP, named "brainstem auditory evoked potentials", which are produced in the acoustic nerve and in the brainstem;[39] the middle latency auditory evoked potentials (MLAEP), which are produced in the thalamus and auditory temporal cortex;[40] the long latency auditory evoked potentials (LLAEP), which are produced in the auditory temporal cortex.[39] MLAEP occur within 20-70 ms from the auditory stimulus and are constituted by the waves Na, Pa, Nb, P1 and P2.[41,42] The prominent peak of the LLAEP is the N100 wave, which occurs after 80-150 ms from the auditory stimulus.

AEP registering devices are commercially available.

Practical use and speed of registration: The MLAEP and LLAEP registration is not easy. It is time consuming[43] and operator dependent.[39]

Performance in monitoring sedation: The results of studies assessing MLAEP and LLAEP performance are summarized in Table 5.[17,40,44]

Auditory Arx index (AAI)

The AAI is an index that is obtained extracting specific information from MLAEP.[45] The AAI is a dimensionless integer that ranges between 0 (corresponding to an isoelectric EEG) and 100 (corresponding to an alertness state). The AAI registering devices are commercially available.[46]

Practical use and speed of registration: AAI is obtained easily and quickly for the following reasons: only three electrodes are required for registering.[11,47] the value of AAI is computed automatically by devices and the AAI acquisition requires 2-6 seconds.[47]

Table 2 Results of the studies assessing the performance of BIS as an indicator for depth of sedation

Study	Sample	N?	Opioid/ Sedative	N-B?	Software version of BIS	Results	Blind?
Doi M et al.[4]	40	Un known	P+F	No	XP	BIS correlated statistically significantly (P<0.01) with the RS score 2,3,4,5,6 (mean value of ρ: -0.66); BIS predicted the RS score (Pk 0.790±0.022)	No
Hernandez-Gancedo et al.[14]	50	No	P/R/M/F (Mo)	No	Un known	Statistically significative (P<0.01) correlation between BIS and RS or OAAS scores: BIS-Ramsay: ρ=0.622; BIS-OAAS: ρ=0.593. This correlation was lost in the midazolam group where the level of sedation was significantly (P<0.05) deeper; when RS 6 and OAAS 1 measurements were excluded, the BIS and sedation scales scores correlated significatively (P<0.05) in the midazolam group.	Un known
Sackey et al.[15]	20	No	Isoflurane/M (Mo)	No	XP	Correlation between BIS and every Bloomsbury Sedation Score: ρ=0.012 in the isofluorane group; ρ= -0.057 in the midazolam group.	Yes
Trouiller et al.[16]	62	No	M/P+F/R	No	XP	Paired measurements of BIS and sedation (measured with the ATICE score) were obtained. A paired measurement with BIS >60 at deep sedation (ATICE Awakeness≤2) was defined as discordant. Patients were considered discordant if their individual ratio of number of discordant measurements to number of total measurements during deep Sedation was above the median discordance ratio of the overall cohort. Discordance between high BIS values (BIS>60) and deep clinical sedation (ATICE Awakeness≤2) was frequently observed: median individual discordance ratio was 32%	Un known
Haenggi et al.[17]	10	No	P+R	Unknown	XP	Probability that BIS correctly predicted (Pk) if a patient was awake (RASS 0), lightly/ mildly sedated (RASS -1 to -3) or deeply sedated (RASS-4 and-5) was 0.85. The values of BIS frequently overlapped between RASS score -4 and RASS scores -1/-2/-3	Un known
Haenggi et al.[18]	44	No	F,M and/or P	Unknown	XP	BIS correlated statistically significantly (P<0.01) with RS score (r=-0.426). Wide inter individual variability; BIS was not able to discriminate between light to moderate sedation RS scores 1-4 and moderate to deep sedation RS scores 5-6.	Un known

Citation: Laurenza C, Mattei A, Antonelli S, et al. Evaluation of Sedation for the Unconscious Patient: Are We Still Far Away? *J Anesth Crit Care Open Access.* 2014;1(2):30–39. DOI: 10.15406/jaccoa.2014.01.00007

Table Continued...

Study	Sample	N?	Opioid/ Sedative	N-B?	Software version of BIS	Results	Blind?
Hernandez-Gancedo et al.[19]	50	No	P/R/M/F. (Mo)	No	XP	Statistically significant (P<0.01) correlation (ρ=-0.78) between BIS and RS (range RS 1-6). Which was independent of sedation level? Pk of RS score: 0.77±0.016. BIS values overlapped for RS 4,5,6.	Un known
Deogaonkar et al.[20]	30	Yes	sedative	Unknown	2.1.1 or XP	In 15 patients monitored with the BIS XP software, BIS values correlated statistically significantly (P<0.01) with the RASS (r^2: 0.81), SAS (r^2:0.725) and GCS (r^2:0.655). In 15 patients monitored with the BIS 2.1.1, BIS values correlated statistically. Significantly (P<0.05) with the RASS but the correlation was weaker: for RASS (r^2:0.30), for SAS (r^2: 0.376) for GCS (r^2: 0.274). These correlations were maintained in patients who received sedative medications. Wide inter individual variability of BIS values for each sedation scale value.	Un known
Turkmen et al.[21]	11	Un known	Dex	Yes	Unknown	Statistically significant (P<0.01) correlations between wakefulness/light sedation (RASS 0,-1 or -2) and BIS values (ρ: 0.9)	Un known
Mondello et al.[22]	20	No	P	Unknown	Unknown	Statistically significant (P<0.01) correlations between BIS and both RS scores (the variation range of RS was 2-6) and Propofol dosage.	Un known
Nasraway et al.[23]	19	Possible	sedative	No	No	BIS score correlated statistically significantly and positively with SAS score (the variation range of SAS was 1-3): r^2=0.36, P>0.05). There were no statistically significative differences between the mean BIS scores for each SAS level	Un known
Riess et al.[24]	44	No	P+M. (Op)	No	3.11	BIS correlated statistically significantly (P<0.01) with RS score (ρ:-0.64).	Un known
Von Dossow et al.[25]	44	No	P	No	3.04	At two different levels of sedation, moderate/deep sedation (RS 4,5,6) and light sedation/wakefulness (RS 2, 3), BIS and RS correlated (η coefficient: 0.90 for mean overall RS stages). There was statistically significant discrimination between RS 2-3 and RS 4-6 with BIS	Un known
Arbour et al.[26]	40	No	P/B. (Op)	Only 2 patients	XP	Statistically significant (P<0.01) positive correlation between BIS and SAS scores 1,2,3,4,5 (ρ: 0.502). Wide ranges of BIS scores were observed, especially in very sedated patients	Yes

Citation: Laurenza C, Mattei A, Antonelli S, et al. Evaluation of Sedation for the Unconscious Patient: Are We Still Far Away? *J Anesth Crit Care Open Access.* 2014;1(2):30–39. DOI: 10.15406/jaccoa.2014.01.00007

Table Continued...

Study	Sample	N?	Opioid/ Sedative	N-B?	Software version of BIS	Results	Blind?
Tonner et al.[27]	46	No	P+S	No	2.1 and XP	Statistically significant (P<0.01) correlation between BIS 2,1 /BIS XP with RS scores: τ = -0.27 and -0.40 respectively	No
De Wit & Epstein et al.[28]	18	No	P/L/Op	No	Unknown	SAS scores ranged from 1 to 5 and correlated statistically significantly (P<0.01) with BIS values (r^2 : 0.48 and 0.44 respectively) before and after clinical stimulation	Yes
Consales et al.[29]	40	No	P/M + Mo	No	Unknown	Correlation between RS and BIS: ρ=-0.75. At the deeper levels of sedation a wide range of BIS values corresponded to RS score 6	Un known
Ely et al.[30]	124	No	No formal protocol to guide analgesia/ sedation	Possible	3.4 and XP	Statistically significative (P<0.01) correlation between BIS X and BIS 3.4 with RASS: r^2=0.36 and 0.20 respectively. Considerable overlap of BIS-XP scores or BIS 3.4 scores across RASS levels.	Yes
Karamchandani et al.[31]	24	No	P+F	Unknown	3.21	Statistically significative (P<0.01) correlation between BIS and RASS scores (range of RASS scores between 0 and -3: (τ=0.56)	Yes
Frenzel et al.[32]	19	No	F+M. (ketamine, piritramide, or B)	No	XP	In 11 patients (58%) the correlation between BIS and each sedation scale score (the modified OAAS, the modified GCS, the modified RS, the Cook scale, and the SAS) was 0.55<τ<1.0 (statistical significatively P<0.01); in 8 patients (42%) the correlation was 0.	Un known
Lu et al.[33]	90	No	P + F	No	XP	Statistically significative (P<0.01) correlation between BIS and RS score (τ=-0.68)	Un known
Ogilvie et al.[34]	94	Un known	P (+ eventually M) + Mo/F	13 patients received N-B	VISTA model REF 185-0151	The linear correlation between BIS and RASS was statistically significant (P<0.01) but the strength of association between paired BIS and RASS was low (r^2=0.3831)	Un known
Kato et al.[35]	12	Patients with central nervous system disease were excluded	6 patients received P+R (R group); the other 6 patients received only P (Control group)	No	A2000-XP, version 4.0	In the R group, there was a statistically significant (P<0.05) correlation between RASS and BIS values (r^2=0.67) In the control group there was no statistically significant (P=0.50) correlation between RASS and BIS values (r^2=0.057)	No

Sample, Number of sample adult patients; N, Were neurological patients included?/, this symbol means "or". P, Propofol; F, fentanyl; R, Remifentanil; M, midazolam; Mo, Morphine; (any drug), the administration of the drug written in brackets was optional; Dex, Dexmedetomidine; Op, Opioids; B, Benzodiazepines; S, Sulfentanil; L, Lorazepam; N-B?, were Neuromuscular blockers administered to patients?; RS, Ramsay sedation score; OAAS, Observer's Assessment of Alertness and Sedation; ATICE, Adaptation to Intensive Care Environment; RASS, Richmond Agitation Sedation Scale; SAS, Riker Sedation-Agitation Scale; GCS, Glasgow Coma Scale; Pk of a sedation scale score, Probability of correctly predicting the rank order of a sedation scale score. R, Pearson's correlation coefficient; ρ, Spearman's correlation coefficient; r2, coefficient of determination; η, eta coefficient; τ, Kendall correlation coefficient; Blind, Was medical-nurse staff, who performed rating clinical scales, blinded to BIS numeric readings.

Citation: Laurenza C, Mattei A, Antonelli S, et al. Evaluation of Sedation for the Unconscious Patient: Are We Still Far Away? *J Anesth Crit Care Open Access.* 2014;1(2):30–39. DOI: 10.15406/jaccoa.2014.01.00007

Table 3 Results of the studies assessing the performance of Entropy (SE and RE) as indicator for depth of sedation

Study	Sample	N?	Opioids/ Sedatives	N-B	Results	Blind?
Haenggi et al.[17]	10	No	P+R	Un known	Probability that SE and RE correctly predicted (Pk) if a patient was awake (RASS 0), lightly/mildly sedated (RASS -1to-3) or deeply sedated (RASS -4 and -5) was respectively 0.88 and 0.89. However the values of both SE and RE frequently overlapped between RASS score -4 and RASS scores -1/-2/-3.	Un known
Haenggi et al.[18]	44	No	F, M and/ or P	Un known	SE and RE correlated statistically significantly (P<0.01) with the RS score (r =-0.372 for RE; r =-0.360 for SE); Wide inter individual variability; SE and RE were not able to discriminate between light to moderate sedation (RS scores 1 to 4) and deep sedation (RS scores 5 to 6).	Un known
Hernandez-Gancedo et al.[19]	50	No	P/R/M/F (Mo)	No	Statistically significative (P<0.01) correlation between SE-RS score (ρ: 0.71) and RE-RS score (ρ: 0.72). An overlap of Entropy values was found for every RS score between 4 and 6.	Un known
Walsh et al.[36]	30	No	P/M + Mo/ Alfentanil	No	The mean PK value of RE and SE for discriminating each RS score from all other scores was 0.713 and 0.710 respectively. The mean Pk value of RE and SE for discriminating awake/lightly sedated patients (RS score 1-3) from mildly/deeply sedated patients (RS score 4-6) was 0.750 and 0.748 respectively. Although median values did decrease as Ramsay scores progressed from 1 to 6, there was a wide range in values for each category, particularly for the RS 3-6 range. These ranged from values suggesting deep anesthesia (BIS<40) to values suggesting very light sedation or normal consciousness (>80) even for patients with RS score 5-6.	Yes

Sample, Number of sample adult patients; N, Were neurological patients included? /, this symbol means "or". P, Propofol; R, Remifentanil; F, Fentanyl; M, Midazolam; Mo, Morphine; (any drug), The administration of the drug written in brackets was optional; N-B?, Were Neuromuscular blockers administered to patients?; RS, Ramsay Sedation Score; RASS, Richmond Agitation Sedation Scale; Pk of a sedation scale score: Probability of correctly predicting the rank order of a sedation scale score; r, Pearson's correlation coefficient; ρ, Spearman's correlation coefficient; Blind, The medical-nurse staff, which performed rating clinical scales, blinded to SE or RE values.

Table 4 Results of the studies assessing the performance of Patient State Index (PSI) as indicator for depth of sedation

Study	Sample	N?	Opioids/ Sedatives	N-B?	Results	Blind?
Adesanya et al.[37]	50	No	P+Mo	No	Average weighted K coefficient was 0.16 between the RSS and PSI (poor correlation!)	Yes
Schneider et al.[38]	41	No	P+S	Un known	Univariate GLM analysis: significant differences between different RS scores. A post hoc test with Bonferroni correction found significant differences (p<0.05) in PSI between the different RS scores, except for differentiation of: RS score 5 from 4 and 6; RS score 2 from 3. PSI predicted the RS score (Pk 0.92±0.037)	Yes

Sample, Number of sample adult patients; N?, Were neurological patients included?/, this symbol means "or"; P, Propofol; Mo, morphine; S, Sulfentanil; N-B?, Were Neuromuscular blockers administered to patients?; RS, Ramsay Sedation Score; GLM, General Linear Model; Pk of a sedation scale score, Probability of correctly predicting the rank order of a sedation scale score; Blind, Was medical-nurse staff, who performed rating clinical scale, blinded to SEF 95% values.

Performance in monitoring sedation: Results of studies assessing performance of AAI are summarized in Table 6.[4,33]

The characteristics evaluated for each sedation monitoring device were easiness and the quickness of measuring depth of hypnosis, the validity and inter individual variability. A datum, acquired with certainty with our review, is that registration of EEG indexes (BIS, PSI, SE, and RE) and AEP indexes (AAI) is a simple and quick method of monitoring sedation; otherwise there is the continuous EEG or AEP registration. Studies on monitoring sedation with continuous EEG were not found according to our inclusion criteria; however there is agreement in literature that the continuous EEG can provide information about the level of sedation in the critically ill patients.[48-50] With regard to validity, there are few contrasting data on PSI. [37,38] All the studies performed to assess ability of SE, RE and AAI in monitoring sedation, have reported the data in favor of a certain validity of SE.[17-19,36] RE[17-19,36] and AAI[4,33] in sedation monitoring. However, these data result from heterogeneous studies who were conducted on small sample populations; besides, although the reported correlation between these objective methods (SE; RE, AAI) and the clinical scales was statistically significant in some studies, the strength of this correlation was not strong always.[18,33] The BIS validity has been tested by several clinical trials. Seven out of twenty-three studies .[4,17,18,20,21,25,29] reported a good or excellent validity of BIS in monitoring sedation; four of these studies.[4,17,19,25] are specific to test BIS validity in monitoring deep sedation levels. These encouraging data on BIS validity need to be considered with caution for four reasons. First there are also studies which report a modest or poor validity of BIS in monitoring sedation levels,[14–17,23,24,26–28,30–35] included the deep sedation levels.[14,18,23,26,27] Second clinical trials have been performed on small sample populations. Third, most of the studies do not specify if they are blind, reducing the reliability of their results. Finally the comparisons between studies are hindered by

their heterogeneity regarding the clinical data of sample population, the type of sedative and analgesic drug administered to patients, use of neuromuscular blockers and software version of BIS. The main difference between the several BIS software is the ability to reject artifacts. The BIS XP is the last one created and it should be more valid for sedation monitoring than the previous ones, because of its greater ability to reject the artifacts.[7] The few studies comparing BIS XP software with other BIS software have reported a greater validity of BIS XP software in monitoring sedation.[20,27,30] With regard to inter individual reliability, it has been assessed for the AEP,[17] SE/RE[17,18,19,36] and BIS;[17–20,26,29,30] in all cases it was reported a wide inter individual variability. This is an important disadvantage because it makes difficult to set standard ranges of values assumed at each level of sedation. Therefore can be misleading to interpret isolated values of the above measures and it is advisable to consider their time trend. The evidence of a wide inter individual variability is understandable. In fact, the sedated patient's cerebral electrical activity is affected by several factors which depend on both patient and administered drug.[51] For example it is known that electromyographic (EMG) activity interferes significantly with the cerebral electrical activity. In no clinical trial, reporting wide inter individual variability, neuromuscular blockers were included explicitly in the study protocol; the only exception is Arbour R et al.[26]'s study where neuromuscular blockers were administered to two patients out of a total of forty patients. Therefore the presence of electromyographic (EMG) activity can be one of the reasons of the wide inter individual variability of the objective methods for sedation monitoring.

Table 5 Results of the studies assessing performance of AEP as indicators for depth of sedation

Study	Sample	N?	Opioids Sedatives	N-B	Examined data of AEP	Results	Blind?
Haenggi et al.[17]	10	No	P+R	Un known	LLAEP	N100 amplitudes did not differ significantly among sedation levels.	Un known
Ypparila et al.[40]	19	Un known	P (Op)	Un known	LLAEP	N100 amplitude differed statistically significatively (P<0.01) between moderate sedation (SAS score 2) versus light sedation (SAS score 3) vs. wakefulness (SAS score 4)	Un known
Musialowicz et al.[44]	22	No	P	Un known	MLAEP	During deep and moderate sedation (RS score respectively 6 and 4), Nb and Pa latencies increased statistically significantly (P<0.05) as compared to baseline RS score (i.e. the RS score obtained the day before surgery). During deep sedation (RS score 6) Na latency increased statistically significantly (P< 0.05) as compared to baseline RS score. During deep sedation (RS score 6) NaPa amplitude decreased statistically significantly (P<0.05) as compared to baseline RS score. During moderate sedation (RS score 4) NaPa amplitude decreased statistically significantly (P<0.05) as compared to baseline RS score.	Yes

Sample, Number of sample adult patients; N, Were neurological patients included? /, this symbol means "or". P, Propofol R, Remifentanil; Op, Opioids; (any drug), the administration of the drug written in brackets was optional; N-B, Were Neuromuscular Blockers administered to patients; SAS, Riker Sedation-Agitation Scale; RS, Ramsay Sedation Score; Blind, Was medical-nurse staff, who performed rating clinical scales, blinded to AEP values.

Table 6 Results of the studies assessing performance of AAI as an indicator for depth of sedation

Study	Sample	N?	Opioids/ Sedatives	N-B?	Results	Blind?
Doi et al.[4]	44	Un known	P+F	No	AAI correlated statistically significantly (P<0.01) with the RS score 2,3,4,5,6 (mean value of ρ:-0.794); AAI predicted the RS score (Pk 0.861±0.019).	No
Lu et al.[33]	90	No	P+F	No	Statistically significantly (P<0.01) correlation between AAI and RS score: Τ =-0.621.	Un known

Sample, Number of sample adult patients; N, Were neurological patients included? /, this symbol means "or". P, Propofol; F, Fentanyl; N-B, were Neuromuscular Blockers administered to patients? RS, Ramsay Sedation Score; Pk of a sedation scale score, Probability of correctly predicting the rank order of a sedation scale score; Τ, Kendall correlation coefficient; Blind, Was medical-nurse staff, who performed rating clinical scale, blinded to AAI values.

Conclusion

The conclusions that can be drawn from this review are the following: The subjective methods are superior to any of the objective ones and should be used if possible. As showed by Barr J et al.[1] the assessments of sedation degree cannot be based on objective methods because it is not possible to give definitive conclusions about their validity and their measurements are characterized by wide inter individual variability. Therefore the use of the objective methods for monitoring sedation should be considered only when the clinical scales show a poor ability or technical difficulties in monitoring deep hypnotic levels because the patient is unable to understand or to perform any command or the patient is sedated deeply (the clinical scales are not able to distinguish between deep sedation and cerebral electric silence).[6] Among the objective methods available, Bispectral index should be considered the first choice for the following reasons: its registration is easy and fast; up to now it is the most studied objective method for sedation monitoring; its validity has been acceptable in most of the studies. Furthermore the most recent software of Bispectral Index, as BIS XP is, shows a greater ability to reject the

Citation: Laurenza C, Mattei A, Antonelli S, et al. Evaluation of Sedation for the Unconscious Patient: Are We Still Far Away? *J Anesth Crit Care Open Access.* 2014;1(2):30–39. DOI: 10.15406/jaccoa.2014.01.00007

artifacts. As the range of BIS values for a given sedation scale value is large, documenting the trend changes in BIS values should be a more acceptable marker of level of consciousness than absolute BIS scores. In our opinion, its current value and perhaps that of other brain function monitors, including the Narcotrend©,[52] Patient State Index,[37] Entropy© Module[36] and SNAP II©[53]) may lie in the ability to provide more information of the degree of sedation among patients receiving neuromuscular receptor blocking agents. Despite the effectiveness of these methods at the current state, we need more evidence in this field to confirm the existing data in the literature.

Acknowledgements

The authors thank Carol Jeuell, reference librarian for his extensive work helping the authors to search and locate the literature and putting its experience on research software at the disposal of the author.

Conflicts of Interset

None.

References

1. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med.* 2013;41(1):263–306.
2. Sessler CN, Grap MJ, Ramsay MAE. Evaluating and monitoring analgesia and sedation in the intensive care unit. *Crit Care.* 2008;12(Suppl 3):S2.
3. Mehta S, Burry L, Fischer S, et al. Canadian survey of the use of sedatives, analgesics, and neuromuscular blocking agents in critically ill patients. *Crit Care Med.* 2006;34(2):374–380.
4. Doi M, Morita K, Mantzaridis H, et al. Prediction of responses to various stimuli during sedation: a comparison of three EEG variables. *Intensive Care Med.* 2005;31(1):41–47.
5. Jeleazcov C, Schneider G, Daunderer M, et al. The discriminant power of simultaneous monitoring of spontaneous electroencephalogram and evoked potentials as a predictor of different clinical states of general anesthesia. *Anesth Analg.* 2006;103(4):894–901.
6. Dahaba AA. Different conditions that could result in the bispectral index indicating an incorrect hypnotic state. *Anesth Analg.* 2005;101(3): 765–773.
7. Le Blanc JM, Dasta JF, Kane–Gill SL. Role of the bispectral index in sedation monitoring in the ICU. *Ann Pharmacother.* 2006;40(3):490–500.
8. Morandi A, Watson PL, Trabucchi M, et al. Advances in sedation for critically ill patients. *Minerva Anestesiol.* 2009;75(6):385–391.
9. Schultz A, Siedenberg M, Ulrich G, et al. Comparison of narcotrend index, bispectral index, spectral and entropy parameters during induction of propofol–remifentanil anaesthesia. *J Clin Monit Comput.* 2008;22(2):103–111.
10. Theilen HJ, Adam S, Kuhlisch E, et al. Progressive electroencephalogram frequency deceleration despite constant depth of propofol–induced sedation. *Crit Care Med.* 2007;30(8):1787–1793.
11. Jensen EW, Litvan H, Revuelta M, et al. Cerebral state index during propofol anesthesia: a comparison with the bispectral index and the A–Line ARX Index. Anesthesiology. 2006;105(1):28–36.
12. Viertio–Oja H, Maja V, Sarkela M, et al. Description of the Entropy algorithm as applied in the Datex–Ohmeda S/5 Entropy Module. *Acta Anaesthesiol Scand.* 2004;48(2):154–161.
13. Ferenets R, Vanluchene A, Lipping T, et al. Behaviour of entropy/complexity measures of the electroencephalogram during propofol–induced sedation: dose–dependent effects of remifentanil. Anesthesiology. 2007;106(4):696–706.
14. Hernandez–Gancedo C, Pestana D, Pena N, Royo C, et al. Monitoring sedation in critically ill patients: bispectral index, Ramsay and observer scales. *Eur J Anaesthesiol.* 2006;23(8):649–653.
15. Sackey PV, Radell PJ, Granath F, et al. Bispectral index as a predictor of sedation depth during isoflurane or midazolam sedation in ICU patients. *Anaesth Intensive Care.* 2007;35(3):348–356.
16. Trouiller P, Fangio P, Paugam–Burtz C, et al. Frequency and clinical impact of preserved bispectral index activity during deep sedation in mechanically ventilated ICU patients. *Intensive Care Med.* 2009;35(12):2096–2104.
17. Haenggi M, Ypparila–Wolters H, Buerki S, et al. Auditory event–related potentials, bispectral index, and entropy for the discrimination of different levels of sedation in intensive care unit patients. Anesth Analg. 2009;109(3):807–816.
18. Haenggi M, Ypparila–Wolters H, Bieri C, et al. Entropy and bispectral index for assessment of sedation, analgesia and the effects of unpleasant stimuli in critically ill patients: an observational study. Crit Care. 2008;12(5):R119.
19. Hernandez–Gancedo C, Pestana D, Perez–Chrzanowska H, et al. Comparing Entropy and the Bispectral index with the Ramsay score in sedated ICU patients. *J Clin Monit Comput.* 2007;21(5):295–302.
20. Deogaonkar A, Gupta R, DeGeorgia M, et al. Bispectral Index monitoring correlates with sedation scales in brain–injured patients. *Crit Care Med.* 2004;32(12):2403–2406.
21. Turkmen A, Altan A, Turgut N, et al. The correlation between the Richmond agitation–sedation scale and bispectral index during dexmedetomidine sedation. *Eur J Anaesthesiol.* 2006;23(4): 300–304.
22. Mondello E, Siliotti R, Noto G, et al. Bispectral Index in ICU: correlation with Ramsay Score on assessment of sedation level. *J Clin Monit Comput.* 2003;17(5):271–277.
23. Nasraway SA SA Jr, Wu EC, et al. How reliable is the Bispectral Index in critically ill patients? A prospective, comparative, single–blinded observer study. *Crit Care Med.* 2002;30(7):1483–1487.
24. Riess ML, Graefe UA, Goeters C, et al. Sedation assessment in critically ill patients with bispectral index. *Eur J Anaesthesiol.* 2002;19:18–22.
25. Von Dossow V, Moshirzadeh M, Kastrup M, et al. Performance of the A–line Autoregressive Index (AAI) and of the Bispectral Index (BIS) at assessing depth of short–term sedation following cardiac surgery. *J Int Med Res.* 2009;37(3):611–620.
26. Arbour R, Waterhouse J, Seckel MA, et al. Correlation between the Sedation–Agitation Scale and the Bispectral Index in ventilated patients in the intensive care unit. *Heart Lung.* 2009;38(4):336–345.
27. Tonner PH, Wei C, Bein B, et al. Comparison of two bispectral index algorithms in monitoring sedation in postoperative intensive care patients. *Crit Care Med.* 2005;33(3):580–584.
28. De Wit M, Epstein SK. Administration of sedatives and level of sedation: comparative evaluation via the Sedation–Agitation Scale and the Bispectral Index. *Am J Crit Care.* 2003;12(4):343–348.
29. Consales G, Chelazzi C, Rinaldi S, et al. Bispectral Index compared to Ramsay score for sedation monitoring in intensive care units. *Minerva Anestesiol.* 2006;72(5):329–336.
30. Ely EW, Truman B, Manzi DJ, et al. Consciousness monitoring in ventilated patients: bispectral EEG monitors arousal not delirium. *Intensive Care Med.* 2004;30(8):1537–1543.
31. Karamchandani K, Rewari V, Trikha A, et al. Bispectral index correlates well with Richmond agitation sedation scale in mechanically ventilated critically ill patients. *J Anesth.* 2010;24(3):394–348.

32. Frenzel D, Greim CA, Sommer C, et al. Is the bispectral index appropriate for monitoring the sedation level of mechanically ventilated surgical ICU patients? *Intensive Care Med.* 2002;28(2):178–183.

33. Lu CH, Ou–Yang HY, Man KM, et al. Relative reliability of the auditory evoked potential and Bispectral Index for monitoring sedation level in surgical intensive care patients. *Anaesth Intensive Care.* 2008;36(4):553–559.

34. Ogilvie MP, Pereira BM, Ryan ML, et al. Bispectral index to monitor propofol sedation in trauma patients. *J Trauma.* 2011;71(5):1415–1421.

35. Kato T, Koitabashi T, Ouchi T, et al. The utility of bispectral index monitoring for sedated patients treated with low–dose remifentanil. *J Clin Monit Comput.* 2011;26(6):459–463.

36. Walsh TS, Ramsay P, Lapinlampi TP, et al. An assessment of the validity of spectral entropy as a measure of sedation state in mechanically ventilated critically ill patients. *Intensive Care Med.* 2008;34(2):308–315.

37. Adesanya AO, Rosero E, Wyrick C, et al. Assessing the predictive value of the bispectral index vs patient state index on clinical assessment of sedation in postoperative cardiac surgery patients. *J Crit Care.* 2009;24(3):322–328.

38. Schneider G, Heglmeier S, Schneider J, et al. Patient State Index (PSI) measures depth of sedation in intensive care patients. *Intensive Care Med.* 2004;30(2):213–216.

39. Schneider G, Hollweck R, Ningler M, et al. Detection of consciousness by Electroencephalogram and Auditory Evoked Potentials. *Anesthesiology.* 2005;103(5):934–943.

40. Ypparila H, Nunes S, Korhonen I, et al. The effect of interruption to propofol sedation on auditory event–related potentials and electroencephalogram in intensive care patients. *Crit Care.* 2004;8(6):R483–R490.

41. Bell SL, Smith DC, Allen R, et al. Recording the middle latency response of the auditory evoked potential as a measure of depth of anaesthesia. A technical note. *Br J Anaesth.* 2004;92(3):442–445.

42. Palm S, Linstedt U, Petry A, et al. Dose–response relationship of propofol on mid–latency auditory evoked potentials (MLAEP) in cardiac surgery. *Acta Anaesthesiol Scand.* 2011;45(8):1006–1010.

43. Litvan H, Jensen EW, Galan J, et al. Comparison of conventional averaged and rapid averaged, autoregressive–based extracted auditory evoked potentials for monitoring the hypnotic level during propofol induction. *Anesthesiology.* 2005;97(2):351–358.

44. Musialowicz T, Hynynen M, Ypparila H, et al. Midlatency auditory–evoked potentials in the assessment of sedation in cardiac surgery patients. *J Cardiothorac Vasc Anesth.* 2005;18(5):559–562.

45. Iannuzzi E, Iannuzzi M, Mora B, et al. Relationship between A–line Autoregressive Index, Spectral Entropy and steady state predicted site–effect effective concentrations at 05–50–95 of propofol at different clinical endpoints. *Minerva Anestesiol.* 2005;75(12):692–697.

46. Litvan H, Jensen EW, Revuelta M, et al. Comparison of auditory evoked potentials and the A–line ARX Index for monitoring the hypnotic level during sevoflurane and propofol induction. *Acta Anaesthesiol Scand.* 2002;46(3):245–251.

47. Iselin–Chaves IA, El Moalem HE, Tong Joo Gan, et al. Changes in the Auditory Evoked Potentials and the Bispectral Index following propofol or propofol and alfentanil. *Anesthesiology.* 2000;92(5):1300–1310.

48. Friedman D, Claassen J, Hirsch LJ. Continuous electroencephalogram monitoring in the intensive care unit. *Anesth Analg.* 2009;109(2):506–523.

49. Guerit JM, Amantini A, Amodio P, et al. Consensus on the use of neurophysiological tests in the intensive care unit (ICU): electroencephalogram (EEG), evoked potentials (EP), and electroneuromyography (ENMG). *Neurophysiol Clin.* 2009;39(2):71–83.

50. Roustan JP, Valette S, Aubas P, et al. Can electroencephalographic analysis be used to determine sedation levels in critically ill patients? *Anesth Analg.* 2005;101(4):1141–1151.

51. Martorano P, Facco E, Falzetti G, et al. Spectral entropy assessment with auditory evoked potential in neuroanesthesia. *Clin Neurophysiol.* 2017;118(3):505–512.

52. Weber F, Steinberger M, Ritzka M, et al. Measuring depth of sedation in intensive care patients with the electroencephalographic Narcotrend Index. *Eur J Anaesthesiol.* 2008;25(2):123–128.

53. Springman SR, Andrei AC, Willmann K, et al. comparison of SNAP II and Bispectral Index monitoring in patients undergoing sedation. *Anaesthesia.* 2010;65(8):815–819.