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

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 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”.

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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.

**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 [6].

**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.

**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].
| 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                                            | Deep sedation                                               |
|                              | 6     | No response to a light glabellar tap                                                  |                                                            |
| SAS Morandi et al. [8]       | 7     | Pulling at endotracheal tube, trying to remove catheters,                            | Agitated                                                    |
|                              | 6     | Does not calm, despite frequent verbal reminding of limits;                          |                                                            |
|                              | 5     | Anxious or mildly agitated, attempting to sit up, calms down to                       |                                                            |
|                              | 4     | Calm, awakens easily; follows commands                                               | Awake and calm                                              |
|                              | 3     | Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again,| Light sedation                                              |
|                              | 2     | Arouses to physical stimuli but does not communicate or follow commands,             | Moderate sedation                                           |
|                              | 1     | Minimal or no response to noxious stimuli, does not communicate or follow commands    |                                                            |
| RASS Morandi et al. [8]      | -4    | Overtly combative or violent; immediate danger to staff                                |                                                            |
|                              | -3    | Pulls on or removes tube(s) or catheter(s) or has aggressive behaviour towards staff. | Agitated                                                    |
|                              | -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,                       | Light sedation                                              |
|                              | -2    | Briefly (less than 10 s) awakens with eye contact to voice.                           |                                                            |
|                              | -3    | Any movement (but no eye contact) to voice.                                          |                                                            |
|                              | -4    | No response to voice, but any movement to physical stimulation                       | Deep sedation                                               |
| OAAS Hernandez-Gancedo et al. [14] | -5  | No response to voice or physical stimulation                                          |                                                            |
|                              | 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    | 3     | Agitated and restless                                                                |                                                            |
| Sackey et al. [15]           | 2     | Awake and uncomfortable                                                              |                                                            |
|                              | 1     | Awake but calm                                                                      | Awake and calm                                              |
|                              | 0     | Roused by voice, remains calm                                                         | Light sedation                                              |
|                              | -1    | Roused by movement or suction                                                        |                                                            |
|                              | -2    | Roused by painful stimuli                                                            | Moderate sedation                                           |
|                              | -3    | Unrousable                                                                          |                                                            |
| Awareness domain of the ATICE score Trouiller et al. [16] | 0     | Eyes closed, no mimic                                                               |                                                            |
|                              | 1     | Eyes closed, only facial mimic after strong, painful stimulation                     | Deep sedation                                               |
|                              | 2     | Eyes opening after strong, painful stimulation                                        |                                                            |
|                              | 3     | Eyes opening after light, painful stimulation                                        | Moderate sedation                                           |
|                              | 4     | Eyes opening after verbal order                                                      | Light sedation                                              |
|                              | 5     | Eyes openings spontaneously                                                          |                                                            |

RS: Ramsay sedation scale; SAS: Sedation Agitation Scale; RASS: Richmond 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.
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     |
| Hernández-Gancedo et al. [14]  | 50     | No  | P/R/M/F (Mo)     | No   | Un known               | Statistically significant (P<0.01) correlation between BIS and RS or OAAS scores: BIS-Ramsay: p=0.622; BIS-OAAS: p=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 significantly (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: p=0.012 in the isofluorane group; p=-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=0.46). 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 |
| Hernández-Gancedo et al. [19]  | 50     | No  | P/R/M/F. (Mo)    | No   | XP                     | Statistically significant (P<0.01) correlation (p=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 (r²=0.81), SAS (r²=0.725) and GCS (r²=0.665). 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 (r²=0.30), for SAS (r²=0.376) and for GCS (r²=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 |
| Study                          | Sample | N?  | Opioid/Sedative | N-B? | Software version of BIS | Results                                                                 | Blind? |
|-------------------------------|--------|-----|-----------------|------|------------------------|-------------------------------------------------------------------------|--------|
| 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 |
| 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: Т=-0.27 and -0.40 respectively | No |
| De Wit & Epstein [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 significant (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 significant (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 (statistically significantly P<0.01); in 8 patients (42%) the correlation was 0. | Un known |
| Lu et al. [33]                | 90     | No | P + F | No | XP | Statistically significant (P<0.01) correlation between BIS and RS score (Τ<0.60) | 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 |
Sample: Number of sample adult patients; N: Were neurological patients included? /: this symbol means "or". P: Propofol; R: Remifentanil; M: Midazolam; Mo: Morphine; (any drug): the administration of the drug written in brackets was optional; Dec: Dexmedetomidine; Op: Opioids; B: Benzodiazepines; S: Sulfentanil; L: Lorazepam; N-B?: Were Neuromuscular blockers administered to patients?; RS: Ramsay Sedation Score; GLM: General Linear Model; Pk: Probability that a sedation scale score correctly predicted if a patient was awake (Rs score 1-3) or deeply sedated (Rs score 4 and 5) was respectively 0.88 and 0.89. However the values of both SE and RE frequently overlapped between BIS values 4 and 5. B: Was medical-nurse staff who performed rating clinical scales, blinded to BIS numeric readings.

### 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                                                                 |
|------------------|--------|----|--------------------|------|-------------------------------------------------------------------------|
| Haenggi et al.   | 10     | No | P+R                | Un   | Probability that SE and RE correctly predicted if a patient was awake   |
| [17]             |        |    |                    | known| (RASS 0), lightly/mildly sedated (RASS -1 to -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 BIS values 4 and 5.             |
|                  |        |    |                    |      | B: Was medical-nurse staff who performed rating clinical                |
|                  |        |    |                    |      | scales, blinded to BIS numeric readings.                                |
|                  |        |    |                    |      |                                                                         |
| Haenggi et al.   | 44     | No | F, M and / or P    | Un   | Probability that SE and RE correctly predicted if a patient was awake   |
| [18]             |        |    |                    | known| (RASS 0), lightly/mildly sedated (RASS -1 to -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 BIS values 4 and 5.             |
|                  |        |    |                    |      | B: Was medical-nurse staff who performed rating clinical scales,        |
|                  |        |    |                    |      | blinded to BIS numeric readings.                                        |
|                  |        |    |                    |      |                                                                         |
| Hernandez-       | 50     | No | P/R/M/F (Mo)       | No   | Statistical significant (P < 0.01) correlation between SE and RE       |
| Gancedo et al.   |        |    |                    |      | scores (ρ: 0.71) and RE and RS scores (ρ: 0.72). An overlap of Entropy |
| [19]             |        |    |                    |      | values was found for every RS score between 4 and 5.                   |
|                  |        |    |                    |      |                                                                         |
| Walsh et al.     | 30     | No | P/M + Mo / Alfentanil | No | The mean Pk value of SE and RE for discriminating each RS score from all |
| [36]             |        |    |                    |      | 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; Mo: Morphine; (any drug): the administration of the drug written in brackets was optional; SE and RE correlated statistically significantly (P <0.01) with the RS score (r = -0.732 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).

### 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                                                                 |
|-----------------|--------|----|--------------------|------|-------------------------------------------------------------------------|
| Adesanya et al. | 50     | No | P+Mo               | No   | Average weighted K coefficient was 0.16 between the RSS and PSI         |
| [37]            |        |    |                    |      | (poor correlation!)                                                     |
| Schneider et al.| 41     | No | P+S                | Un   | Univariate GLM analysis: significant differences between different RS   |
| [38]            |        |    |                    | known| 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)                                 |
|                  |        |    |                    |      |                                                                         |

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: Probability of correctly predicting the rank order of a sedation scale score; Blind: Was medical-nurse staff, who performed rating clinical scales, blinded to SEP 95% values.
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].

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.

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

| Study                  | Sample | N? | 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 |
| Yppardla 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), Na 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? | 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 p-0.794); AAI predicted the RS score (Pk 0.861±0.019). | No     |
| Lu et al. [33]         | 90     | No | P+F       | Yes | Statistically significantly (P<0.01) correlation between AAI and RS score: $\tau$ = -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; $\tau$: Kendall correlation coefficient; Blind: Was medical-nurse staff, who performed rating clinical scale, blinded to AAI values.
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.

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 agreater ability to reject the 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 should be a more acceptable marker of level of consciousness than scale value is large, documenting the trend changes in BIS values. 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.

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