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REVIEW

Utilizing Bi-Spectral Index (BIS) for the monitoring of sedated adult ICU patients: a systematic review

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ABSTRACT

BACKGROUND: The ideal level of sedation in the ICU is an ongoing source of scrutiny. At higher levels of sedation, the current scoring systems are not ideal. BIS may be able to improve both. We evaluated literature on effectiveness of BIS monitoring in sedated mechanically ventilated (MV) ICU patients compared to clinical sedation scores (CSS).

EVIDENCE ACQUISITION: For this systematic review, full text articles were searched in OVID, MEDLINE, EMBASE, and Cochrane databases from 1986-2014. Additional studies were identified searching bibliographies/abstracts from national/international Critical Care Medicine conferences and references from searched articles retrieved. Search terms were: "Clinical sedation scale", "Bi-Spectral Index", "Mechanical ventilation", "Intensive Care Unit". Included were prospective, randomized and non-randomized studies comparing BIS monitoring with any CSS in MV adult (>18 year old) ICU patients. Studies were graded for quality of evidence based on bias as established by the GRADE guidelines. Additional sources of bias were examined.

EVIDENCE SYNTHESIS: There were five studies which met inclusion criteria. All five studies were either unclear or at high risk of bias for blinding of participants and blinding of outcome assessment. All papers had at least one source of additional high risk, or unclear/unstated bias.

CONCLUSIONS: BIS monitoring in the mechanically ventilated ICU patient may decrease sedative drug dose, recall, and time to wake-up. The studies suggesting this are severely limited methodologically. BIS, when compared to subjective CSSs, is not, at this time, clearly indicated. An appropriately powered randomized, controlled study is needed to determine if this monitoring modality is of use on the ICU.

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In mechanically ventilated patients, sedative/analgesic agents are often used to minimize discomfort of the endotracheal tube, ventilator, and the underlying pathologic process. Because of related complications and cost, significant care is required to ensure appropriate use of sedative/analgesics in these patients. However, determining the appropriate level of sedation based on clinical sedation scales (CSSs) may be difficult at higher levels of sedation.[1] The use of an objective monitor of sedation, continuous Bispectral (BIS) Index

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monitoring, well established in the operating rooms (OR),[2-5] has not been adequately studied in the intensive care unit (ICU).

While utilization of physiologic parameters — such as variation in blood pressure, heart rate, and respiratory rate — or a change in the sympathetic response resulting in tearing, sweating, and/or restlessness may be used to titrate sedative/analgesic medication, these are suboptimal in ensuring amnesia and analgesia in patients unable to express their discomfort. A more optimal manner to assess the depth of sedation in MV ICU patients is *via* one of a number of computed clinical sedation scores (CSSs).[6] Interobserver variability has been a concern with the use of these CSSs, with potential for decreased reliability and validity,[7] resulting in an over- or under-sedated patient.[8]

As of the date of this writing, we have found no systematic review or meta-analysis reporting on which sedation assessment modality or tool is best suited for critically ill, MV ICU patients. In 2013 the American College of Critical Care Medicine (ACCM) Pain, Agitation and Delirium (PAD) study performed a limited meta-analysis of the effect of sedative choice on ICU length of stay, but did not evaluate the influence of sedation tools — CSS *versus* EEG based tools — on ICU-related outcomes.[9]

Over-sedated patients may have delayed weaning,[10] an increased incidence of ventilator associated events from prolonged mechanical ventilation [10] and increased drug use and costs.[10, 11] Conversely, under-sedated patients may suffer anxiety and agitation, and a resultant increased incidence of adverse events such as awareness and recall, post-traumatic stress disorder**,** and delirium, as well as — potentially — an inappropriate use of neuromuscular blocking agents (NMBAs).[11, 12]

This systematic review of sedation assessment modalities — CSS's *versus* BIS monitoring — in MV ICU patients is performed to ascertain whether BIS monitoring, compared with commonly used CSSs, provides significant benefit in clinically measurable outcomes: amount of sedatives/analgesics, ventilator days, ICU and hospital LOS and mortality, and complications such as delirium and recall.

Evidence acquisition

Protocol and registration

We developed a systematic review protocol with pre-specified inclusion and exclusion criteria for study selection, outcome measurements and analysis. The project was registered with PROSPERO (www.crd.york.ac.uk), # CRD42015017267.

Eligibility criteria

Type of studies

All prospective randomized controlled trials evaluating and comparing the effect of BIS monitoring in sedated, MV ICU patients with any of the CSSs were pre-planned to be included. If there were an inadequate number of prospective randomized studies — less than 5 to 8 — we considered it acceptable to include non-randomized prospective studies. No language, publication status or publication date restrictions were imposed. Correlation studies of BIS and CSSs were excluded since this was not an objective of this review.

Type of participants

Adults (>18 years old) admitted to the ICU requiring sedation/analgesia for MV were included. Non-ventilated patients were excluded.

Type of intervention

The intervention (BIS monitored) group compared any version of BIS monitors to CSSs.

Type of comparator

The control group included any CSS, such as Ramsay Sedation Scale (RSS), Richmond Agitation Sedation Scale (RASS), Sedation Agitation Scale (SAS), and Glasgow Coma Scale (GCS). Some studies used physiologic parameters — blood pressure, heart rate, respiratory rate and anxiety — to titrate sedative/analgesics/anesthetic in the control group.[4, 10, 16]

Type of outcome measures

The primary outcome measure was ICU LOS.[10] Secondary outcome measures included duration of MV, sedative/analgesic dosage/cost, presence or absence of delirium, and infection.[11-13]

Information sources

The search strategy for studies in this systematic review was both automated and manual. We used electronic databases, reviewing reference from the lists of articles searched to identify trials to be included in the systematic review. For the automated search, the databases used included the digital libraries of PubMed, CCRCT (Cochrane Central Register of Controlled Trials *via* the Cochrane Library), CDSR (Cochrane Database of Systematic Reviews *via* the Cochrane Library), Ovid, Medline and EMBASE. No language limitations were applied. The titles and abstracts of identified references were reviewed, and reference lists of pertinent trials and systematic reviews were used to identify additional studies.

We also searched conference proceedings of the American Thoracic Society (1994-2013), Society of Critical care Medicine (1994-2013), European Society of Intensive Care Medicine (1994-2013) and American College of Chest Physicians (1994-2013). We searched for unpublished and ongoing trials in www.clinicaltrials.gov. We contacted the manufactures of commercially available BIS monitoring devices for published and unpublished data (Aspect, Colorado).

Search

With the guidance of an expert medical librarian, we searched for eligible studies using the following Medical Subject Heading groupings "bi-spectral index AND sedation scale AND intensive care unit AND mechanical ventilation" (Supplementary Tables I, II online content only). For EMBASE, we used the same MESH terms as in OVID MEDLINE. The same search criteria were used across database resources.

Study selection

Eligibility assessment and data abstraction were performed independently in an un-blinded standardized manner by two reviewers, and repeated by a second set of two reviewers. Abstracted data included eligibility criteria, baseline characteristics, interventions, outcomes, and methodological quality. Instances of disagreement between the reviewers were resolved by consensus among the investigators.

Inclusion criteria

Participants: adults (>18 years old) admitted to the ICU requiring sedation and MV.

Intervention: BIS monitoring.

Comparison: Sedation monitoring using a CSS.

Design: Randomized controlled trials; two prospective observational studies[16, 17] were also included.

Outcome: All outcomes. We pre-planned to accept any acceptable measure of effect, including, but not limited to, risk ratio, odds ratio or risk difference for binary outcomes, difference in means for continuous outcomes, hazard ratio for time-to-event outcomes.

Exclusion criteria

Studies done in the operation room (OR) or post anesthesia care unit (PACU), ICU patients not requiring MV, correlation studies of BIS with CSSs, any study involving Pediatric patients, any study involving non-ICU patients.

Data collection

Data collection process

A data extraction sheet (based on the Cochrane consumers and Communication Review Group's data extraction template) was developed. One review author extracted the following data (Study characteristics, study environment, study methods and study qual-

ity indicators) from the included studies and a second author checked the extracted data; this process was then repeated by a second group of two authors. Data were independently extracted from all studies fulfilling inclusion criteria.

Data elements

Data extracted from the studies included the study population demographics, age, gender, diagnosis, co-morbidities, length of stay and inclusion/exclusion criteria, study environment (describing the type of hospital and country), and the design and details of randomization procedure (Tables I, II, Supplementary Table III, online content only**)**. Data were also extracted regarding the study quality indicators and statistical analysis tool used as well as details of CSS used, sedatives and narcotics used, dosages and frequency of administration. We extracted details of BIS monitoring equipment, including the type of BIS monitor and software version. The individual study au-

TABLE I.—*Characteristics of the included studies - method.*

	Altaba Tena, *et al.*[17]	Kaplan, *et al.*[16]	Zhao, *et al.*[14]	Olson, *et al.*[13]	Weatherburn, *et al.*[10]
Aim of study	To determine if BIS use results in reduction of time spent on MV and reduced ICU length of stay, reduced early and late pneumonia development, reduced sedative dose, and complications?	To determine whether BIS-monitored titration of sedatives in ICU patients on continuous infusions of sedatives and paralytics was cost effective and reduced the incidence of the recall phenomenon.	To compare the value of BIS monitoring and SAS in guiding ICU sedation therapy for the patients undergoing short-term MV.	To assess whether monitoring sedation status using BIS as an adjunct to clinical evaluation was associated with a reduction in the total amount of sedative drug used in a 12 hour period.	To assess the effectiveness of the BIS monitor in supporting clinical sedation management decisions in mechanically ventilated ICU patients.
Study design	Prospective observational	Prospective observational	Prospective RCT	Prospective RCT	Prospective RCT
Method of recruitment	Not clear; appears to use BIS "when available" and based upon opinion of attending physician. All monitored *via* RASS.	Month 1 and 2 Control group, Month 3 and 4 Intervention arm	Not clear	Unclear. Informed consent from Patient's legal representative.	All eligible patients were recruited within 24 hours.
Study period	July 2009 to November 2010.	4 consecutive months	March 2008 to Feb 2009	Undefined	Undefined
Inclusion criteria	Medical-surgical patients admitted in the ICU in a level 2-3 teaching hospital, use of MV for at least 24 hours.	SICU patients	All adult patients aged between 18-60, admitted between Mar. 2008 and Feb. 2009 who received MV for more than 12 hours in ICU.	Adult MV patients admitted to the neurocritical care unit of a tertiary care hospital with a primary neurological or neurosurgical diagnosis and currently on propofol infusion?	All MV, likely to be ventilated for greater than 12 hours and receiving continuous infusion of Morphine and Midazolam.
Exclusion criteria	Under 18 years old or older than 80, postsurgical patients extubated in less than 3 hours, patients with a neurological condition (ischemic or hemorrhagic or trauma) because of risk of developing intracranial hypertension that can require deeper levels of sedation.	Severe brain injury with GCS <8	Patients with disturbance of consciousness, cardiovascular and cerebrovascular diseases, and liver/kidney diseases which can possibly impair the metabolism of the propofol and midazolam.	Frontal brain injury, required deep (barbiturate coma) sedation or were admitted for status epilepticus.	Intracranial injury, neurological disorder and facial burns.

TABLE II.—*Characteristic of included studies.*

	Altaba Tena, *et al.*[17]	Kaplan, *et al.*[16]	Zhao, *et al.*[14]	Olson, *et al.*[13]	Weatherburn, *et al.*[10]
Participant					
Description	Mechanically ventilated Patients admitted to a Medical-Surgical ICU in a Level 3-4 Teaching Hospital	SICU patients	Patients admitted by ICU at Beijing Tong Ren Hospital. March 2008 to February 2009.	Adult mechanically ventilated Patients admitted to the NeuroCritical Care Unit with primary neurological / neurosurgical diagnosis & receiving IV propofol.	Control: "Standard Care". BIS: Continuous monitoring until extubation or tracheostomy.
Number	N.=85 Control-54 BIS – 31	N.=57 Control-31 BIS-26	N.=105 SAS-63 BIS-42	N.=67 35-Ramsay Score 32-BIS	N.=50 25-Control 25-BIS
Age	>18 and <80 years (no mean given)	Unspecified	SAS: 39.2±10.4 BIS 39.5+7.8	Ramsay: 54.8±15.1 BIS: 57.8±19.8	Control: 50±22 BIS: 57±21
Gender	Male Control: 57.4% BIS: 77.4% (P=0.05)	Unspecified	Male 101 Female 4	Male Ramsay: 40% BIS: 50%	Male Control: 68% BIS: 64%
Severity of illness	Comorbidities given	Unspecified	APACHE II: SAS: 4.2±2.3 BIS: 3.6±2.6	APACHE IV: Ramsay: 67.4±20.3 BIA: 75.6±21.8 Admit GCS: Ramsay: 8.4+2.6 BIS: 7.6+2.7	APACHE II: median (IQR) Control: 14 (11, 20) BIS: 14 (11, 19)
Frequency of BIS monitoring	Upon admission and at 24 hours	Unspecified	Hourly	Unspecified	Every 1 hour
CONTROL					
CSS used	RASS	Vital signs changes after stimulation	SAS	Ramsay	Hourly subjective clinical assessment – HR, BP, Consciousness Level & Pupillary Size
Duration CSS monitoring	Unspecified	Unspecified	From the ICU admission to 0600 the next day.	12 hours	Unspecified
Sedative used	Midazolam/propofol	Lorazepam, Midazolam, and Propofol	Midazolam/ propofol	Propofol	Midazolam
Narcotic used	Morphine	Morphine	Fentanyl	Fentanyl prn	Morphine
NMB used	Cisatracurium	Yes, unspecified	Unspecified	Unspecified	Unspecified
Goals of sedation	BIS of 40-60	Control: Vital Signs after Stimulation. BIS: 70-80	SAS: 3-4 BIS: 50-70	Ramsay Score = 4 BIS between 60-70	Control: Normal HR, BP, LOC, & Pupillary Size BIS: >70
Duration of sedation	Weaning left up to physician judgment.	Unspecified	Median (IQR) SAS: 16 hours (13, 18) BIS: 14 (12.9, 17.1)	12 hours	Until extubation or tracheostomy
Outcome					
Principal outcome	Length of MV	Cost effectiveness of sedative and paralytic agents	Dosage of midazolam and propofol. Duration of MV and Sedation	Total dose of sedative drug used in 12 hours. Overall sedative use	Total amount of sedative, Amount of sedative administered over time
Secondary outcome	ICU stay, incidence of early and late pneumonia, dose of sedatives, costs, complications	Incidence of recall		Mean recovery time. Under sedation event	Length of MV and ICU LOS

thor's conclusions, study limitations, and other remarks were also noted.

Risk of bias in individual studies

The assessment of the risk of bias of individual studies included the following: random sequence generation, allocation concealment (a method in which researchers are unable to influence whether the patients end in treated or the control group), blinding of personnel and participants, blinding of outcome assessment, incomplete outcome data, selective reporting (ORBIT classification),[15] other sources of bias, and *a priori* protocol/analysis plan. Two authors assessed the risk collaboratively (DG and AJL).

Summary measures

Effect on ICU LOS was the primary measure of BIS utilization when compared to CSSs.

Planned method of analysis

While meta-analysis was our goal, extreme variability, inconsistency and heterogeneity across the studies made this impossible.

Evidence synthesis

Study selection

Of 385 potential studies, we identified 63 citations [7-14, 16-71] from search of electronic bibliographic databases. Five studies [10, 13, 14, 16, 17] met the inclusion criteria after excluding correlation articles, trials involving pediatric patients and duplicates; because there were only three randomized, controlled trials, we included two prospective observational studies [16, 17] in this systematic review (Figure 1). These five trials were included in qualitative synthesis and systematic review. While there was general agreement amongst all the reviewers, minor differences were resolved with the help of the

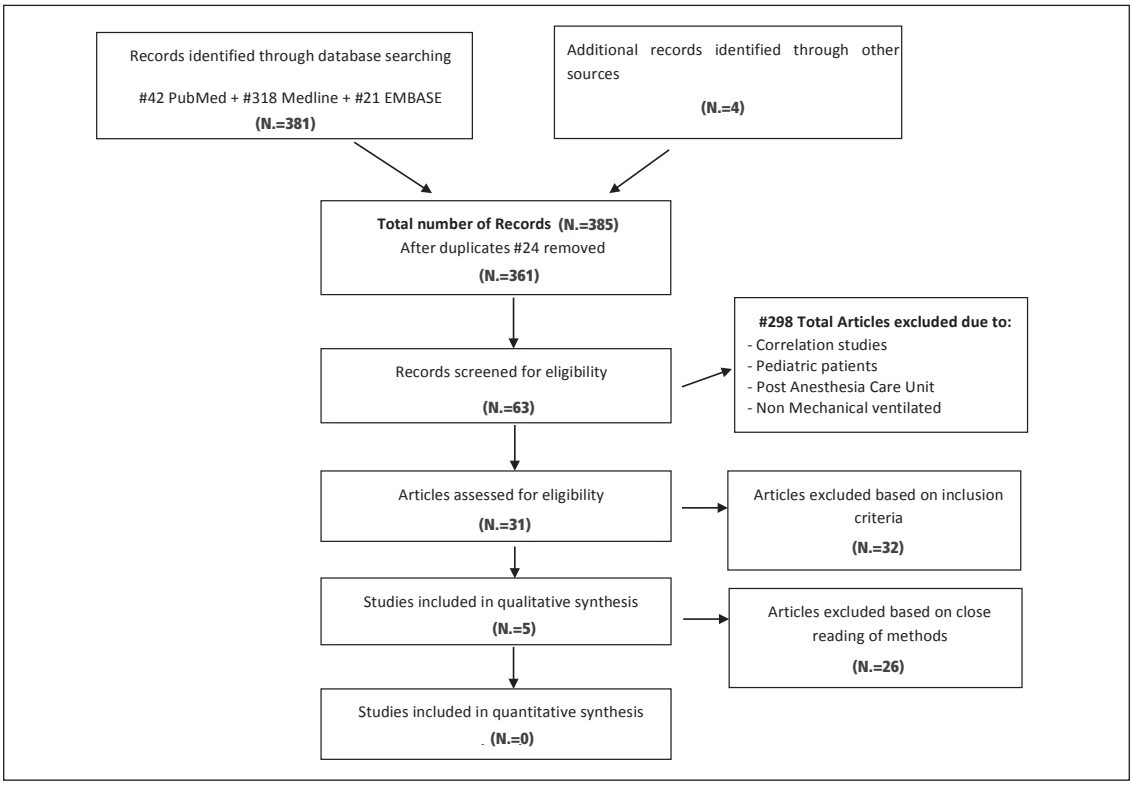

Figure 1.—PRISMA Flow Diagram for Study selection.

other investigators. Data was further analyzed in regards to clinical and physiologic attributes of the included studies, statistical tools used and conclusions provided by the authors.

Outcome

The main outcome was ICU LOS.[10] Other outcomes assessed were level of sedation, dosage of sedatives, duration of MV and adverse events such as delirium, infections, extubation failure, and mortality.[11, 12]

We accepted the author's goals of sedation, which were varied. We also considered other physiologic outcomes such as physiologic changes in blood pressure, HR, time to awakening and factors such as usage of daily sedation interruption and daily delirium assessment. Only one of the studies had a daily morning sedation interruption or daily delirium screening. Finally, we evaluated for adverse events, including ventilator associated events — which included early and late VAP — bacteremia, catheter associated-urinary tract infection (CA-UTI), technical complications and equipment use characteristics, including the comfort level and experience of the nurse in using the BIS monitor.

In general, there were hints that the use of BIS in the critically ill adult ICU patient was associated with use of lesser amounts of sedatives,[13] at lesser cost and with less recall;[14, 16] decreased MV days;[14] less delirium and a shorter time to wakeup.[13, 14] Although flawed, the study of Mahmood and colleagues [72] — not part of our analysis — showed a decrease in the use of sedation and analgesia, decrease in agitation and failure to extubate as well as the need for tracheostomy, and an approximate 4 day decreased length of stay. While these data cannot be taken as final, they are indications that this modality of monitoring requires rigorous study to determine its usefulness.

Risk of bias within studies

There was variability with regard to the intervention group, which had different versions of the BIS monitor. Control group variance was related to the CSS used. In general, outcome measures were not defined well; there were a limited number of studies for each outcome. While bias varied by study, all studies were either unclear or at high risk of bias with blinding of participants and personnel, and blinding of outcome assessment (Supplementary Table IV, online content online).

Statistical analysis

We could not reliably combine studies in a way that made scientific sense. Studies used different outcome measures, and were silent on, or used different, BIS monitors, which may have included a different algorithm to calculate sedation level. Moreover, the duration of the BIS monitoring was individualized by the study. Thus, we felt combining such overtly different studies could be potentially misleading.

Discussion

BIS CHARACTERISTICS

The BIS was introduced by Aspect Medical Systems in 1994 as a novel way to algorithmically measure the level of consciousness of a patient under general anesthesia by using a limited montage electroencephalogram. This is used in conjunction with other physiologic monitoring, such as electromyography, to estimate the depth of anesthesia and thereby minimize the possibility of intraoperative awareness. The US Food and Drug Administration (FDA) cleared BIS monitoring in 1996 for assessing the hypnotic effects of general anesthetics and sedatives. BIS is a practical, processed EEG parameter that measures the direct effects of sedatives on the brain. It is applied using a frontal montage and provides objective information about an individual patient's response to sedation/anesthesia.

BIS was initially devised to monitor depth of anesthesia in the OR, as it was intended to replace or supplement Guedel's classification system for determining anesthetic depth. Use of the BIS monitor is thought to reduce

the incidence of intraoperative awareness during anesthesia.[4] Titrating anesthetic agents to a specific BIS index during general anesthesia in adults allows the anesthesiologist/anesthetist to adjust the amount of anesthetic agent to the needs of the patient, potentially resulting in a more rapid emergence from anesthesia**.** There are a wide range of BIS modules available currently on the market, including — in the USA — Phillips, GE, Datex-Ohmeda, Dräger Medical, Space labs, Nihon Kohden, Dixtal and Datascope.[5]

The key application of BIS monitoring is objective assessment of sedation in the patient's intraoperative and immediate peri-operative phase in the OR and recovery room. The not-so-established, and less frequent, usage of BIS is in the ICU, in postoperative patients who may have received neuromuscular blockade, close monitoring of sedation level in drug induced coma, and for sedation purpose during bedside procedures. It is in these areas that the utility of BIS could be explored.

Summary of evidence

This systematic review on comparison of diagnostic properties and efficacy of BIS monitoring and CSS is the first to summarize available validation studies. We found 5 studies [10, 13, 14, 16, 17] each of which evaluating different outcomes (Table III).

Among the included studies, Olson's was a prospective study randomizing patients to Ramsay scale or BIS monitoring in addition to Ramsay Scale.[13] The study began at 08.00 after consent was obtained. All patients were sedated with propofol. Patients had sedation stopped every 2 hours. Nurses were instructed to dose the propofol infusion to obtain a score of 4 in the control group, or a Ramsay score of 4 and a BIS value between 70 and 80 in the BIS monitoring group. The primary endpoint was the total dose of sedative medication used in 12 hours. There was an approximate 50% reduction in the amount of sedation used: BIS-augmentation 93.5±86.3 mL, Ramsay scale alone 157.8±119.2 mL (P=0.0146). The study's power analysis suggested 45 patients per group, but randomization was stopped in interim analysis because of the statistical significance achieved.

Zhao *et al.*[14] randomized patients to receive midazolam or propofol sedation. Sedation was suspended hourly and titrated to goals of BIS 50-70, SAS 3-4. The authors showed some differences in BIS-treated *versus* SAS treated patients. Percent total time under sedation, propofol and midazolam doses were all higher in the BIS group (P<0.05). However, the median time to wake-up was less in the BIS group (0 *versus* 15 minutes, P<0.05).

Weatherburn's study [10] was a prospective randomized trial in which patients sedated with morphine and midazolam were randomized to sedation titration based on a BIS score of greater than 70, or subjective clinical assessment which could be augmented based on clinician preference with a sedation scoring tool. The investigators found no differences in the total amount of sedation administered, nor in days of mechanical ventilation, or ICU length of stay. Among secondary outcomes, they did find that the amount of morphine used in BIS patients significantly increased over time (P<0.02 after Bonferoni correction).

There were two abstracts included in this review. Both were considered to be at high risk of bias as the provided information was considered inadequate. In the prospective observational study by Altaba Tena *et al.*[17] of 85 patients, there were not significant differences in duration of ventilation, total dose of sedatives, ventilator-associated pneumonia, or ICU or hospital length of stay. In Kaplan and Bailey's [16] prospective cohort trial, patients with GCS <9 were treated on alternating months either *via* apparent patient comfort guided by vital sign changes or using a BIS value between 70-80. There were significant differences in amount of sedation used and in the number of patients who recalled a frightening/painful experiences.

A study — which was not part of our original evaluation — of interest is that by Mahmood *et al.*[72] These investigators evaluated 110 traumatized patients, of whom 50% were from motor vehicular crashes, and 88% had

TABLE III.—*Results.*

Name of study/outcomes	Intervention	Control	P	Comments
3a. ALTABA TENA [17]	N.=31	N.=54		
Ventilator days Median (IQR)	4 (1, 10)	4 (2, 10.75)	0.33	NS
Early VAP N, (%)	3 (10%)	7 (13.5%)	0.46	NS
Late VAP	3 (9.7%)	11 (21.2%)	0.14	NS
Dosages propofol (mcg)	1996 (800, 4800)	4160 (1860, 6375)	0.15	NS
Dosages midazolam (mg)	155 (55, 279)	137 (54, 420)	0.87	NS
Dosages morphine (mg)	77 (33, 240)	96 (44, 214)	0.93	NS
Dosage cisatracurium (mg)	22.5 (10, 100)	42 (10, 100)	0.73	NS
Bacteremia	4 (13.3%)	12 (25%)	0.16	NS
UTI	1 (3.3%)	4 (7.7%)	0.39	NS
Tracheostomy	1 (3.2%)	6 (11.5%)	0.18	NS
AKI	15 (18%)	19 (22.8%)	0.1	NS
Failure to extubate	7 (11.1%)	14 (22.2%)	0.5	NS
LOS ICU days	7.5 (2, 17)	7.5 (4, 19)	0.51	NS
LOS Hospital days	20 (12, 36)	20 (9, 32)	0.57	NS
Mortality ICU	12 (14.1%)	16 (18.8%)	0.26	NS
3b. KAPLAN [16]	N.=26	N.=31		
Sedative cost per patient	$ 669±1362	$ 819±2045	>0.05	18% reduction in cost, NS
Lorazepam	18% reduction in usage		<0.05	Significant Difference
Midazolam	18% reduction in usage		<0.05	Significant Difference
Propofol	47% reduction in usage		<0.05	Significant Difference
Under sedated		**		15% who appeared sedated were less sedated by BIS
Over sedated	**			54% of BIS-monitored patients required less sedation than initially predicted by staff
Recall (frightening/painful events)	4%	18%	<0.05	Significant difference
3c. ZHAO (14)	N.=42	N.=63		
% total time under sedation	75.2%	52.8	<0.01	Significant difference
Time period 1 sedated	78.6%	22.2%	<0.01	Significant difference
Time period 2 sedated	88.1%	20.6%	<0.01	Significant difference
Time period 3 sedated	81.0%	31.7%	<0.01	Significant difference
Restlessness after Suction	81%	79.4%	> 0.05	NS
Increased endotracheal tube resistance	71.4%	74.6%	> 0.05	NS
Pain free during sedation	92.8%	93.6%	> 0.05	NS
Delirium after extubation	4.8%	1.6%	> 0.05	NS
Midazolam (mg/kg/hr)	0.1±0.02	0.09±0.02	<0.05	Significant difference
Propofol (mg/kg/hr)	0.95±0.23	0.86±0.2	<0.05	Significant difference
Duration of mechanical ventilation (median, interquartile range), hrs	16.5 (14.5, 19)	17.0 (15, 19)	> 0.05	NS
Sedation time (median, IQR), hrs	14 (12.9, 17.1)	16 (13, 18)	> 0.05	NS
Time to wake-up (median, IQR), min	0 (0, 20)	15 (0, 47)	<0.05	Significant difference

(*To be continued*)

TABLE III.—*Results (continues).*

Name of study/outcomes	Intervention	Control	P	Comments
3d. Olson [13]	N.=32	N.=35		
Dose of propofol in 12 hr (mL)	93.5±86.3	157.9±119.2	0.0146	BIS augmented group needed half the sedative doses
Rate of infusion of propofol (mcg/kg/min)	14.6±12.2	27.9±20.5	0.0026	
Risk of propofol infusion exceeding manufacturer's recommended dosing guide (4 mg/kg/hr) %	0 subjects, 0%	8 subjects, 23%	0.0052	Non BIS group significantly more likely to receive Propofol at rates that exceeded manufacturer's recommended doses
Mean recovery time (min)	1.2±2.08	7.5±7.54	<0.0001	BIS augmented group had a rapid emergence from sedation
Number of under sedation events	0	0		BIS augmented group appeared safe
Fentanyl used mcg/12 hr	200	350	NS	
Weatherburn [10]	N.=25	N.=25		
Sedative dosage – midazolam (mean, 95% confidence intervals)	18.4 (10.9 – 30.9)	14.6 (8.8 – 24)	0.85	No significant differences in sedation/analgesia total doses. When doses of midazolam (P=0.03) and morphine (P=0.005) were trended over time in ICU, BIS- patients received more of both drugs
Analgesic – morphine	22.6 (14.9 – 34.5)	26.6 (17.5 – 40.4)	0.67	
Mechanical ventilation (mean [SD], days)	7.0±0.6	7.0±0.8	0.71	No significant difference
ICU LOS (Median, [IQR] days)	12 (6, 18)	8 (4, 14)	0.2	No significant difference

Note: Information taken from data / Tables in the original articles and / or after telephonic discussion with authors.

suffered head injury; average Glasgow Coma Scale score was 6.9±2.7. While the bias in this study is as remarkable as its results — there was no mention of randomization nor how it was done if it was done, there was no power analysis, and there was, finally, no mention of how the BIS was used nor the BIS value that was aimed for — use of BIS in this study resulted in a decrease in the use of sedation and analgesia, a decrease in agitation, failure to extubate, and tracheostomy, and an approximate 4 day decreased length of stay. While this study has its flaws, it is of great interest.

While BIS monitoring in the mechanically ventilated ICU patient may decrease sedative drug dose,[10, 14, 16, 72] recall,[16] and time to wake-up,[14] given the limitations of the studies and the decided lack of significant differences when using BIS alone or BIS-augmentation of standard clinical care, combined with the potential applicability of this mode of monitoring in the ICU, there is a compelling rationale to use BIS only in ICU patients in a properly powered randomized prospective trial. The clinical experience of one of the authors (AJL), using BIS in the ICU, leads us to think that this modality of monitoring will advantageous in decreasing ventilator days and drug dosages while preventing under-sedation.

Limitations of the study

The limitations of this systematic review are significant, as there were few studies meeting the inclusion criteria. Of the studies included, each had significant methodological limitations. Additionally, because of the heterogeneity between the studies regarding the CSS, BIS equipment, ICU setting and statistical analytical tools used, it is not possible to say with any confidence that BIS monitoring improves patient outcomes. More appropriately designed trials are required

to assess the efficacy of BIS monitoring in different ICU populations and settings.

Strengths

This systematic review was exhaustive, with strict inclusion and exclusion criteria used. Additionally, the senior investigators have extensive experience in neuromonitoring and utilization of perioperative BIS monitoring. Most importantly, this systematic review points out the need for a well-designed, randomized, controlled trial.

Conclusions

We performed a systematic review of randomized trials comparing CSSs with BIS in mechanically ventilated ICU patients. We found numerous issues related to study design, conduct, and quality that, to a great extent, dispute their validity and generalizability in evaluating how, or whether, BIS modality of sedation monitoring has a significant effect on clinical outcomes.

Implications for practice

BIS does not appear to be indicated based on the included studies; a properly powered randomized controlled study is needed. Indeed, the American College of Critical Care Medicine (ACCM), the Society of Critical Care Medicine (SCCM), the American College of Chest Physicians (ACCP), and the American Society of Health System Pharmacists (ASHP), in their clinical practice guideline for the sustained use of sedatives and analgesics in the critically ill patient point out that the routine use of BIS in the ICU is not recommended.[73]

Future research

The reliability of BIS has been questioned, in part, because its numerical calculation does not rely on an underlying physiological model of how the brain functions, nor on how awareness is generated. Additionally, the BIS value is insensitive to the commonly used anesthetic agent ketamine, which has a mechanism of pharmacological action different than the potent inhaled anesthetic agents. It is possible that different sedatives and analgesics will have a variable effect on the BIS-calculated sedation value, and may require differential validation. Future studies need to focus on the BIS monitoring of patients in different critical care settings, specifically, patients who are in the neuro-critical care unit or who have suffered cerebro-vascular accidents, traumatic brain injuries, and so forth.

Larger studies are required with better control of variables to adequately assess the influence of BIS monitoring on under-sedation, over-sedation, incidence of delirium, and outcomes resulting from prolonged duration of sedation and ICU LOS. In the context of these further studies, we recommend evaluation of infectious complications in BIS-monitored patients as well. It is intuitive — even if potentially incorrect — that if there is a decrease in the sedative dosage in the BIS group, there will be fewer ventilator days, a lesser incidence of ventilator associated events and, potentially, other infectious complications.

Key messages

— BIS monitoring in the mechanically ventilated ICU patient may decrease sedative drug dose, recall, and time to wake-up. The studies suggesting this are severely limited.

— BIS, when compared to subjective CSSs, is not, at this time, clearly indicated.

— An appropriately powered randomized, controlled study is needed to determine if this monitoring modality is of use in the ICU.

— Until this study is performed, we recommend that BIS be used cautiously in the ICU population.

References

1. Micek S, Barnes BJ, Grauer DW, Johnson DC. Long-term sedation with protocol-directed midazolam and l orazepam: a cost-effectiveness analysis. Crit Care Med 2004;32:A174.

2. Gan TJ, Glass PS, Windsor A, Payne F, Rosow C, Sebel P, *et al.* Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. BIS Utility Study Group. Anesthesiology 1997;87:808-15.
3. Forestier F, Hirschi M, Rouget P, Rigal JC, Videcoq M, Girardet P, *et al.* Propofol and sufentanil titration with the bispectral index to provide anesthesia for coronary artery surgery. Anesthesiology 2003;99:334-46.
4. Myles P, Leslie K, McNeil J, Forbes A, Chan MT. Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial. Lancet 2004;363:1757-63.
5. Struys M, Versichelen L, Byttebier G, Mortier E, Moerman A, Rally G. Clinical usefulness of the bispectral index for titrating propofol target effect- site concentration. Anaesthesia 1998;53:4-12.
6. Soliman HM, Melot, C, Vincent JL. Sedative and analgesic practice in the intensive care unit: the results of a European survey. Br J Anaesth 2001;87:186-92.
7. De Jonghe B, Cook D, Appere-De-Vecchi C, Guyatt G, Meade M, Outin H. Using and understanding sedation scoring systems: a systematic review. Intensive Care Med 2000;26:275-85.
8. Jacobi J, Fraser GL, Coursin DB, Riker RR, Fontaine D, Wittbrodt ET, *et al.* Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 2002;30:199-241.
9. Barr J, Pandharipande PP. The pain, agitation, and delirium care bundle: synergistic benefits of implementing the 2013 Pain, Agitation, and Delirium Guidelines in an integrated and interdisciplinary fashion. Crit Care Med 2013;41:99-115.
10. Weatherburn C, Endacott R, Tynan P, Bailey M. The impact of bispectral index monitoring on sedation administration in mechanically ventilated patients. Anaesth Intensive Care 2007;35:204-8.
11. James ML, Olson DM, Graffagnino C. A pilot study of cerebral and haemodynamic physiological changes during sedation with dexmedetomidine or propofol in patients with acute brain injury. Anaesth Intensive Care 2012;40:949-57.
12. Kato T, Koitabashi T, Ouchi T, Serita R. The utility of bispectral index monitoring for sedated patients treated with low-dose remifentanil. J Clin Monit Comput 2012;26:459-63.
13. Olson DM, Thoyre SM, Peterson ED, Graffagnino C. A Randomized Evaluation of Bispectral Index-Augmented Sedation Assessment in Neurological Patients. Neurocrit Care 2009;11:20-7.
14. Zhao D, Xu Y, He W, Li T, He Y. [A comparison of bispectral index and sedation agitation scale in guiding sedation therapy: a randomized controlled study in patients undergoing short term mechanical ventilation]. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 2011;23:220-23. [Article in Chinese].
15. Kirkham JJ, Dwan KM, Altman DG, Gamble C, Dodd S, Smyth R, *et al.* The impact of outcome reporting bias in randomized controlled trials on a cohort of systematic reviews. BMJ 2010;340:c365.
16. Kaplan LJ, Bailey H. Bispectral index (BIS) monitoring of ICU patients on continuous infusion of sedatives and paralytics reduces sedative drug utilization and cost. Crit Care 2000;4:190.
17. Altaba Tena S, Mateu Campos L, Belenguer Muncharaz A, Ferrández S, Cebrian Graullera G, Alberto Rodrigo L, *et al.* Reduction in the duration of mechanical ventilation through bispectral index monitor. A preliminary study. Intensive Care Med 2012;38:0987.
18. Kim SY, Yang SY, Na SW, Jo VY, Koh SO. Low-dose remifentanil infusion during ventilator weaning and tracheal extubation in postoperative intensive care unit patients sedated with propofol-remifentanil: a randomised clinical trial. Anaesth Intensive Care 2012;40:656-62.
19. Yaman F, Ozcan N, Ozcan A, Kaymak C, Basar H. Assessment of correlation between bispectral index and four common sedation scales used in mechanically ventilated patients in ICU. Eur Rev Med Pharmacol Sci 2012;16:660-66.
20. LeBlanc JM, Oasta JF, Pruchnicki MC, Gerlach A, Cook C. Bispectral index values, sedation- agitation scores, and plasma Lorazepam concentrations in critically ill surgical patients. Am J Crit Care 2012;21:99-105.
21. Amigoni A, Mozzo E, Brugnaro L, Gentilomo C, Stritoni V, Michelin E, *et al.* Assessing sedation in a pediatric intensive care unit using Comfort Behavioural Scale and Bispectral Index: these tools are different. Minerva Anestesiol 2012;78:322-29.
22. Gelinas C, Tousignant-Laflamme Y, Tanguay A, Bourgau l t P. Exploring the validity of the bispectral index, the Critical-Care Pain Observation Tool and vital signs for the detection of pain in sedated and mechanically ventilated critically ill adults: A pilot study. Intensive Crit Care Nurs 2012;27:46-52.
23. Karamchandani K, Rewari V, Trikha A, Batra RK. Bispectral index correlates well with Richmond agitation sedation scale in mechanically ventilated critically ill patients. J Anesth 2012;24:394-98.
24. Lamas A, Lopez-Herce J. Monitoring sedation in the critically ill child. Anaesthesia 2010;65:516-24.
25. Haenggi M, Ypparil a-Wolters H, Buerki S, Schlauri R, Korhonen I, Takala J, *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;109:807-16.
26. Arbour R, Waterhouse J, Seckel MA, Bucher L. Correlation between the Sedation-Agitation Scale and the Bispectral Index in ventilated patients in the intensive care unit. Heart Lung 2009;38:336-45.
27. O l son DM, Thoyre SM, Peterson ED, Graffagnino C. A randomized evaluation of bispectral index-augmented sedation assessment in neurological patients. Neurocrit Care 2009;11:20-7.
28. Lamas A, Lopez-Herce J, Sancho L, Mencia S, Carrillo A, Jose Santiago S, *et al.* Responsiveness to stimuli of bispectral index, middle latency auditory evoked potentials and clinical scales in critically ill children. Anaesthesia 2008;63:1296-301.
29. Watson PL, Shintani AK, Tyson R, Pandharipande PP, Pun BT, Ely EW. Presence of electroencephalogram burst suppression in sedated, critically ill patients is associated with increased mortality. Crit Care Med 2008;36:3171-77.
30. Lu CH, Man KM, Ou-Yang HY, Chan SM, Ho ST, Wong CS, *et al.* Composite auditory evoked potential index *versus* bispectral index to estimate the level of sedation in paralyzed critically ill patients: A prospective observational study. Anesth Analg 2008;107:1290-94.
31. Haenggi M, Ypparila-Wolters H, Bieri C, Steiner C, Takala J, Korhonen I, *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:R119.
32. Lu CH, Ou-Yang HY, Man KM, Hsiao PC, Ho ST, Wong CS, *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;36:553-59.
33. Lamas A, Lopez-Herce J, Sancho L, Mencia S, Carrillo A, Santiago MJ, *et al.* Assessing sedation in critically ill children by bispectral index, auditory-evoked potentials and clinical scales. Intensive Care Med 2008;34:2092-99.

34. de Wit M, Best AM, Epstein SK, Greenblatt DJ. Lorazepam concentrations, pharmacokinetics and pharmacodynamics in a cohort of mechanically ventilated ICU patients. Int J Clin Pharmocol Ther 2006;44:466-73.
35. Consales G, Chelazzi C, Rinaldi S, De Gaudio AR. Bispectral Index compared to Ramsay score for sedation monitoring in intensive care units. Minerva Anestesiol 2006;72:329-36.
36. Turkmen A, Altan A, Turgut N, Vatansever S, Gokkaya S. The correlation between the Richmond agitation-sedation scale and bispectral index during dexmedetomidine sedation. Eur J Anaesthesiol 2006;23:300-4.
37. Twite MD, Zuk J, Gralla J, Friesen RH. Correlation of the Bispectral Index Monitor with the COMFORT scale in the pediatric intensive care unit. Pediatr Crit Care Med 2005;6:648-53.
38. Riker RR, Fraser GL. Monitoring sedation, agitation, analgesia, neuromuscular blockade, and delirium in adult I CU patients. Semin Respir Crit Care 2001;22:189-98.
39. Tonner PH, Wei C, Bein B, Weiler N, Paris A, Scholz J. Comparison of two bispectral index algorithms in monitoring sedation in postoperative intensive care patients. Crit Care Med 2005;33:580-84.
40. Olofsson K, Alling C, Lundberg D, Malmros C. Abolished circadian rhythm of melatonin secretion in sedated and artificially ventilated intensive care patients. Acta Anaesthesiol Scand 2004;48:679-84.
41. Tobias JD, Berkenbosch JW. Sedation during mechanical ventilation in infants and children: dexmedetomidine *versus* midazolam. South Med J 2004;97:451-5.
42. de Wit M, Epstein SK. Administration of sedatives and level of sedation: comparative evaluation via the Sedation-Ag i tation Scale and the Bispectral Index. Am J Crit Care 2003;12:343-8.
43. Crain N, Slonim A, Pollack MM. Assessing sedation in the pediatric intensive care unit by using BIS and the COMFORT scale. Pediatr Crit Care Med 2002;3:11-4.
44. Mondello E, Siliotti R, Noto G, Cuzzocrea E, Sciollo G, Trimarchi G, *et al.*Bispectral Index in ICU: correlation with Ramsay Score on assessment of sedation level. J Clin Monit Comput 2002;17:271-7.
45. Cavaliere F, Antonelli M, Arcangeli A, Conti G, Costa R, Pennisi MA, *et al.* A low-dose remifentanil infusion is well tolerated for sedation in mechanically ventilated, critically-ill patients. Can J Anaesth 2002;49:1088-94.
46. Frenzel D, Greim CA, Sommer C, Bauerle K, Roewer N. Is the bispectral index appropriate for monitoring the sedation level of mechanically ventilated surgical I CU patients? Intensive Care Med 2002;28:178-83.
47. Berkenbosch JW, Fichter CR, Tobias JD. The correlation of the bispectral index monitor with clinical sedation scores during mechanical ventilation in the pediatric intensive care unit. Anesth Analg 2002;94:506-11.
48. Riker RR, Fraser GL, Simmons LE, Wilkins ML. Validating the Sedation-Agitation Scale with the Bispectral Index and Visual Analog Scale in adult ICU patients after cardiac surgery. Intensive Care Med 2001;27:853-8.
49. Simmons LE, Riker RR, Prato BS, Fraser GL. Assessing sedation during intensive care unit mechanical ventilation with the Bispectral Index and the Sedation-Agitation Scale. Crit Care Med 1999;27:1499-504.
50. da Silva C, Alves MM, El Halal MG, dos Pinheiro SS, Carvalho PR. A comparison of gradual sedation levels using the Comfort-B scale and bispectral index in children on mechanical ventilation in the pediatric intensive care unit. Rev Bras Ter lntensiva 2013;25:306-11.
51. Vaschetto R, Cammarota G, Colombo D, Longhini F, Grossi F, Giovanniello A, *et al.* Effects of propofol on patient-ventilator synchrony and interaction during pressure support ventilation and neurally adjusted ventilatory assist. Crit Care Med 2014;42:74-82.
52. Mencia S, Botran M, Lopez-Herce J, del Castillo J; Grupo de Estudio de Sedoanalgesia de la SECIP. Sedative, analgesic and muscle relaxant management in Spanish paediatric intensive care units. Ann Pediatr (Barc) 2011;74:396-404.
53. Senoglu N, Oksuz H, Dogan Z, Yildiz H, Demirkiran H, Ekerbicer H. Sedation during noninvasive mechanical ventilation with dexmedetomidine or midazolam: A randomized, double-blind, prospective study Curr Ther Res Clin Exp 2010;71:141-53.
54. Li XJ, Kang Y, Zhang C. A study of bispectral index monitoring in assessing the depth of sedation of patients under mechanical ventilation Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 2009;21:361-3.
55. Gu Q, Liu N, Ge M, Gao W. Application of the bispectral index monitor in mechanical ventilation in patients under sedation in the intensive care unit. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 2007;19:101-3.
56. Jaber S, Bahloul H, Guetin S, Chanques G, Sebbane M, Eledjam JJ. Effects of music therapy in intensive care unit without sedation in weaning patients *versus* non-ventilated patients. Ann Fr Anesth Reanim 2007;26:30-8.
57. Ma PL, Zhao JZ, Su JW, Li Q, Wang Y. Comparison of reliability of bispectral index and sedation-agitation scale in assessing the depth of sedation in patients treated with mechanical ventilation. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 2006;18:323-6.
58. Vet NJ, Ista E, de Wildt SN, van Oijk M, Tibboel D, de Hoog M. Optimal sedation in pediatric intensive care patients: a systematic review. Intensive Care Med 2013;39:1524-34.
59. Roberts DJ, Haroon B, Hall RI. Sedation for critically ill or injured adults in the intensive care unit: a shifting paradigm. Drugs 2012;72:1881-916.
60. Cidoncha EL, Mencia S, Riano B, Urbano J, Lopez – Herce J, Carrillo A. The assessment of sedation in the critically ill child on mechanical ventilation during tracheal suction. Ann Pediatr (Barc) 2009;70:218-22.
61. Hernandez-Gancedo CI, Pestana D, Pena N, Royo C, Perez-Chrzanowska H, Criado A. Monitoring sedation in critically ill patients: bispectral index, Ramsay and observer scales. Eur J Anaesthesiol 2006;23:649-53.
62. De Jong MM, Burns SM, Campbell ML, Chulay M, Grap MJ, Pierece CN, *et al.* Development of the American Association of Critical-Care Nurses' sedation assessment scale for critically ill patients Am J Crit Care 2005;14:531-44.
63. Long D, Horn D, Keogh S. A survey of sedation assessment and management in Australian and New Zealand paediatric intensive care patients requiring prolonged mechanical ventilation. Aust Crit Care 2005;18:152-7.
64. De Gaudio AR, Rinaldi S. Sedation in PACU: Indications, monitoring, complications. Curr Drug Targets 2005;6:729-40.
65. Roustan JP, Valette S, Aubas P, Rondouin G, Capdevila X. Can electroencephalographic analysis be used to determine sedation levels in critically ill patients? Anesth Analg 2005;101:1141-51.
66. Deogaonkar A, Gupta R, DeGeorgia M, Sabharwal V, Gopakumaran B, Schubert A, *et al.* Bispectral Index monitoring correlates with sedation scales in brain-injured patients. Crit Care Med 2004;32:2403-6.
67. Liu LL, Gropper MA. Postoperative analgesia and sedation in the adult intensive care unit: a guide to drug selection. Drug 2003;63:755-67.
68. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, *et al.* The Richmond Agitation-Sedation Scale – Validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002;166:1338-44.
69. Dewlin JW, Fraser GL, Kanji S, Riker SS. Sedation assessment in critically ill adults. Ann Pharmocother 2001;35:1624-32.

70. Campbell ML, Bizek KS, Thill M. Patient responses during rapid terminal weaning from mechanical ventilation – A prospective study. Crit Care Med 1999;27:73-7.
71. Adesanya AO, Rosero E, Wyrick C, Wall MH, Joshi GP. Assessing the predictive value of the bispectral index *versus* patient state index on clinical assessment of sedation in postoperative cardiac surgery patients. J Crit Care 2009;24:322-8.
72. Mahmood S, Parchani A, El-Menyar A, Zarour A, Al-Thani H, Latifi R. Utility of Bispectral index in the management opf multiple trauma patients. Surg Neurol Int 2014;5:141-52.
73. Barr J, Fraser GL, Puntillo K, Ely EW, Gelinas C, Dasta JF, *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;41:263-306.

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Author's contributions.—Juan C. Montoya, Leena K. Gupta, H. Lester Kirchner, and A. Joseph Layon conceived of and designed the study. Juan C. Montoya and Leena K. Gupta initially reviewed the literature and provided initial evaluation of included papers; A. Joseph Layon, Beliz Bilgili, and David S. Gloss re-evaluated the literature search and the included and excluded papers; H. Lester Kirchner and Andrea L. Berger were statistical consultants for the study.

All the authors assisted in the writing, reviewing, and editing of the paper; all authors approved the final manuscript. All the authors attest to the integrity of the manuscript.

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For supplementary materials, please see the online version of this article.

SUPPLEMENTARY MATERIALS


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<html><head></head><body><pre style="word-wrap: break-word; white-space: pre-wrap;">Recent
queries in pubmed
Search,Query,Items found,Time
#17,"Search (#3 AND #12 AND #13 AND #14)",42,10:00:40
#16,"Search (#10 OR #12)",2463,09:58:47
#15,"Search (#10 OR # 12)",2379457,09:58:34
#14,"Search (#7 OR #8 OR #9)",75567,09:58:05
#13,"Search (#4 OR #5 OR #6)",120622,09:57:36
#12,"Search (#1 OR #2)",2463,09:57:10
#11,"Search (1 or 2)",12126088,09:56:49
#10,"Search (BIS monitor* OR bispectral*)",2463,09:56:05
#9,"Search mechanical ventilation*",27530,09:54:39
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#6,"Search intensive care units [Mesh]",57054,09:53:39
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#3,"Search sedation scale",3695,09:52:14
#2,"Search bispectral",2410,09:52:01
#1,"Search BIS monitor*",429,09:51:42
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Supplementary Figure 1.—PubMed search strategy.

	# ▲	Searches	Results	Search Type	Actions
	1	BIS monitor*.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, bt, sh, ct, de, md, sd, sa, ac, jn, pb, pg, yr, vo, ip, pu, ib, is, et, ey, cd, cl, dp, so] ▸	4089	Advanced	Display More ≫
	2	bispectral*.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, bt, sh, ct, de, md, sd, sa, ac, jn, pb, pg, yr, vo, ip, pu, ib, is, et, ey, cd, cl, dp, so] ▸	13165	Advanced	Display More ≫
	3	sedation scale*.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, bt, sh, ct, de, md, sd, sa, ac, jn, pb, pg, yr, vo, ip, pu, ib, is, et, ey, cd, cl, dp, so] ▸	4989	Advanced	Display More ≫
	4	intensive care*.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, bt, sh, ct, de, md, sd, sa, ac, jn, pb, pg, yr, vo, ip, pu, ib, is, et, ey, cd, cl, dp, so] ▸	521783	Advanced	Display More ≫
	5	mechanical ventilation*.mp. [mp=ti, ot, ab, nm, hw, kw, kf, px, rx, ui, an, tx, bt, sh, ct, de, md, sd, sa, ac, jn, pb, pg, yr, vo, ip, pu, ib, is, et, ey, cd, cl, dp, so] ▸	153611	Advanced	Display More ≫
	6	exp respiration, artificial/ ▸	109392	Advanced	Display More ≫
	7	1 or 2 ▸	13664	Advanced	Display More ≫
	8	7 and 3 and 4 ▸	541	Advanced	Display More ≫
	9	5 or 6 ▸	236388	Advanced	Display More ≫
	10	8 and 9 ▸	318	Advanced	Display More ≫

Supplementary Figure 2.—Medline (OVID) search strategy.

SUPPLEMENTARY TABLE I.—*Characteristic of included studies.*

	Altaba Tena, *et al.*[17]	Kaplan, *et al.*[16]	Zhao, *et al.*[14]	Olson, *et al.*[13]	Weatherburn, *et al.*[10]
PARTICIPANT					
Geographic location	ICU of the General Hospital of Castellon, Castellon, Spain	PA Hospitals, Philadelphia, PA	Tong Ren Hospital Beijing, PRC	Duke University Medical center, Durham, NC	Alfred Hospital, Melbourne, Victoria, Australia
Setting	Level 3-4 teaching hospital	SICU patients	ICU	Tertiary care NeuroCritical Care Unit	Intensive Care Unit: Trauma – 40% Medical – 30% Surgical – 16% TCV Surgery – 14%
Ethnicity	Unspecified	Unspecified	Chinese	Caucasian: Ramsay: 57%, BIS: 56% African American: Ramsay: 31%, BIS: 37% Native American: Ramsay: 8%, BIS: 3%	Unspecified
INTERVENTION					
Kind of BIS sensor	Infinity Delta from Dragger Medical Systems Inc.	Unspecified	Unspecified	BIS Quarto sensors	Quarto ZIP Prep four electrode
Kind of BIS monitor	BIS A 2000	Unspecified	Unspecified	BIS VISTA	Unspecified
BIS algorithm/ company	Aspect, Trabajo de Sedaction de la SEMICYUC	Unspecified	Unspecified	Aspect Medical Systems	BIS intervention tool developed
Duration of BIS monitoring	Unspecified	Unspecified	From the ICU admission to 0600 the next day.	12 hour	Until extubated or tracheostomy
Intervention providers	ICU Nurse with physician input	Unspecified	Unspecified	Nurses	Nurses (apparently hourly) and Physicians (on twice daily rounds)

SUPPLEMENTARY TABLE II.—*Assessment of risk of bias.*

	Altaba Tena [17]	Kaplan [16]	Zhao [14]	Olson [13]	Weatherburn [10]
Random sequence generation	High risk – no Randomization	Low risk –randomization by month	Unclear	Low risk – random number table	High risk – sequence generation not stated
Allocation concealment	High risk – no randomization	Low risk – randomization by month	Unclear	High risk – no allocation concealment	Low risk – sealed/ opaque envelopes used
Blinding of participants and personnel	High risk – no blinding	High risk – no blinding	Unclear	High risk – no blinding	High risk – no blinding
Blinding of outcome assessment	High risk – no blinding	High risk – no blinding	Unclear	High risk – no blinding	High risk – no blinding
Incomplete outcome data	Not stated	Unclear	Unclear	Not stated	Low risk – less than 10% did not complete
Selective reporting & ORBIT Classification	High risk/ORBIT=A	Unclear/ORBIT=A	Unclear/ORBIT=B	No risk/ORBIT=B	High risk/ORBIT=A
Other sources of bias	Use of BIS left up to physician choice and limited by availability. No comment on Conflict of Interest	No comment on conflict of interest	Unclear	ANOVA not done on co-variates	Low risk
A priori protocol/ analysis plan	High risk – not stated/high risk – no power analysis	High risk – not stated/high risk – no power analysis	Unclear/unclear	Yes/yes	Assumed – not stated/assumed – not stated