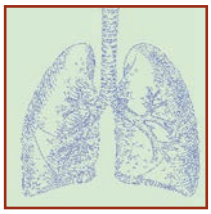

Bispectral Index for Titrating Sedation in ARDS Patients During Neuromuscular Blockade

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Background Despite a lack of data from intensive care patients, bispectral index monitors are often used to measure the depth of sedation for critically ill patients with acute respiratory distress syndrome (ARDS) who require continuous neuromuscular blocking agents.
Objective To evaluate differences in the effectiveness and safety of monitoring sedation by using bispectral index or traditional methods in patients with ARDS who are receiving continuous neuromuscular blocking agents.
Methods This noninterventional, single-center, retrospective cohort study included adult patients with ARDS who are receiving a neuromuscular blocking agent. Daily sedation and analgesia while a neuromuscular blocking agent was being administered were compared between patients with and patients without orders for titration based on bispectral index values. Clinical outcomes also were evaluated.
Results Overall, sedation and analgesia did not differ between patients with and patients without titration based on bispectral index. Compared with patients without such titration, patients with bispectral index–based titration experienced more dose adjustments for the sedation agent (median [interquartile range], 7 [4-11] vs 1 [0-5], respectively, $P<.001$) and the analgesic (1 [0-2] vs 0 [0-1], respectively; $P=.003$) during the first 24 hours of neuromuscular blockade, but this was not associated with any difference in clinical outcomes.
Conclusions Titration based on bispectral index did not result in a significant difference in sedation or analgesia exposure, or clinical outcomes, from that achieved with traditional sedation monitoring in patients with ARDS who were receiving a neuromuscular blocking agent, despite more dose adjustments during the first 24 hours of receiving the neuromuscular blocking agent. (*American Journal of Critical Care.* 2019;28:377-384)

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Patients with acute respiratory distress syndrome (ARDS) may require both deep sedation and continuous neuromuscular blocker agents (NMBAs) to facilitate synchrony with mechanical ventilation. Guidelines for managing sedation and analgesia in critically ill patients strongly recommend targeting deep sedation in those who require an NMBA.[1,2] Unfortunately, sedation depth cannot be accurately assessed by using traditional subjective methods, such as the Richmond Agitation-Sedation Scale (RASS), when patients are receiving an NMBA.

Historically, because traditional monitoring could not be accurately performed while a patient was receiving an NMBA, deep sedation (eg, RASS score -4 to -5) would be achieved before the NMBA was initiated, and then a constant level of sedation would be maintained during NMBA administration; a landmark trial supporting the use of NMBA in ARDS partly used this method.[3] Bispectral index (BIS) monitors have more recently been used in the intensive care unit (ICU) as a tool for monitoring sedation. BIS has been proposed as a low-labor alternative to serial RASS and as an objective measure when assessing sedation in a patient receiving a paralytic. Exploration of its use to ease clinician workload is ongoing.[4]

Bispectral index monitors have recently been used in the ICU as a tool for monitoring depth of sedation.

Despite the lack of data supporting their use among the ICU population, BIS monitors are frequently used to measure the depth of sedation in critically ill patients requiring a continuous NMBA, thus warranting investigation of the practice. At our institution, nursing titration instructions that depend directly on BIS readings have been used for managing sedation in patients with ARDS who require an NMBA. This affords us an opportunity to assess the impact of BIS monitoring on sedation by comparing these patients with patients in whom sedation is not titrated on the basis of BIS. The goal of our study was to assess the effect of titration based on BIS on sedation and analgesia exposure in critically ill patients with ARDS who require a continuous NMBA.

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Materials and Methods

Study Design

This retrospective cohort study was designed to assess differences in safety and effectiveness between sedation titration based on BIS values and an approach that does not use BIS values in critically ill patients with ARDS who are receiving an NMBA. We performed the study at Cleveland Clinic Main Campus, a large, tertiary care academic medical center located in Cleveland, Ohio; the center's institutional review board approved the study.

Adult patients (age ≥18 years) who had received a diagnosis of ARDS, required a continuous NMBA, and were admitted to 1 of 16 nonneurologic adult ICUs at a 1400-bed tertiary care medical center between January 2012 and September 2015 were included in the study. Diagnosis of ARDS was defined on the basis of consensus definitions: acute onset of hypoxemia (ratio of Pao_2 to the fraction of inspired oxygen [Fio_2] <300 mm Hg) during positive pressure ventilation and bilateral opacities on imaging studies that cannot be fully attributed to cardiac failure or fluid overload.[5] Continuous infusion of an NMBA for at least 24 hours without documented interruptions constituted receipt of an NMBA. At our institution, continuous infusion of an NMBA, with the dose determined on the basis of actual body weight, is titrated by train-of-4 monitoring to a usual goal of 2 of 4 twitches. We excluded patients with a documented indication for an NMBA (other than ARDS) and those who were transferred from an outside institution and for whom an NMBA was documented before transfer.

Patients screened without exclusion criteria were then divided into groups on the basis of the presence or absence of BIS titration instructions in the sedation administration instructions and BIS monitoring documented in the electronic medical record within 24 hours of initiating the continuous

NMBA. Patients with BIS-based titration parameters added to sedation orders after the initial 24-hour window were included in the non–BIS titration group. The Figure shows the patient screening and allocation process.

Data Collection and Study Outcomes

Data, including demographic information, severity of illness, ventilation parameters, sedation and analgesia doses, and delirium assessments, were collected from electronic medical records. We assessed the severity of illness at baseline using the Acute Physiology and Chronic Health Evaluation II score,[6] the Sequential Organ Failure Assessment score,[7] and baseline laboratory markers and vital signs. Data collected regarding sedation, analgesia, and delirium included all RASS scores, Confusion Assessment Method for the ICU scores, and BIS readings collected during the study period. Patients were considered to have a stable RASS score before initiating an NMBA if 2 documented scores immediately before NMBA administration were the same and sedation was not adjusted.

The primary objective was to compare daily sedation exposure (expressed as midazolam equivalents [milligrams] per day) and analgesia exposure (expressed as morphine equivalents [milligrams] per day) for patients receiving sedation with or without BIS-based titration for the duration of NMBA administration. We based the conversion of sedatives to midazolam equivalents per hour on previously published definitions: midazolam 5 mg = lorazepam 3 mg = propofol 200 mg.[8] Analgesics were converted to morphine equivalents: fentanyl 0.01 mg = hydromorphone 0.15 mg = morphine 1 mg.[9] We determined the mean daily sedation and analgesia for each patient for the duration of NMBA infusion on the basis of documented doses, durations, and administration of supplemental boluses.

A secondary objective of the study was to compare the number of changes to the sedation and analgesia doses and the number of bolus administrations within the first 24 hours of NMBA infusion. Another secondary objective related to sedation and analgesia was to compare changes in dose during the first 24 hours of NMBA infusion. Changes in the dose of the sedation agent and analgesic were converted to midazolam and morphine equivalents (milligrams) per hour, respectively.

Secondary clinical outcomes included the number of ventilator-free days in 28 days, the number of days outside the ICU in 28 days, 90-day mortality, and the number of coma- and delirium-free days in 14 days. We defined a ventilator-free day as the first day on which the patient was alive and successfully weaned from mechanical ventilation for longer than 48 hours.[10] We defined a delirium-free day as a day a patient was alive and had no positive score on the Confusion Assessment Method for the ICU; we defined a coma-free day as a day a patient was alive and had a RASS score of -3 or higher.[11] For all clinical assessments, we considered day 1 to be the day on which the NMBA was initiated.

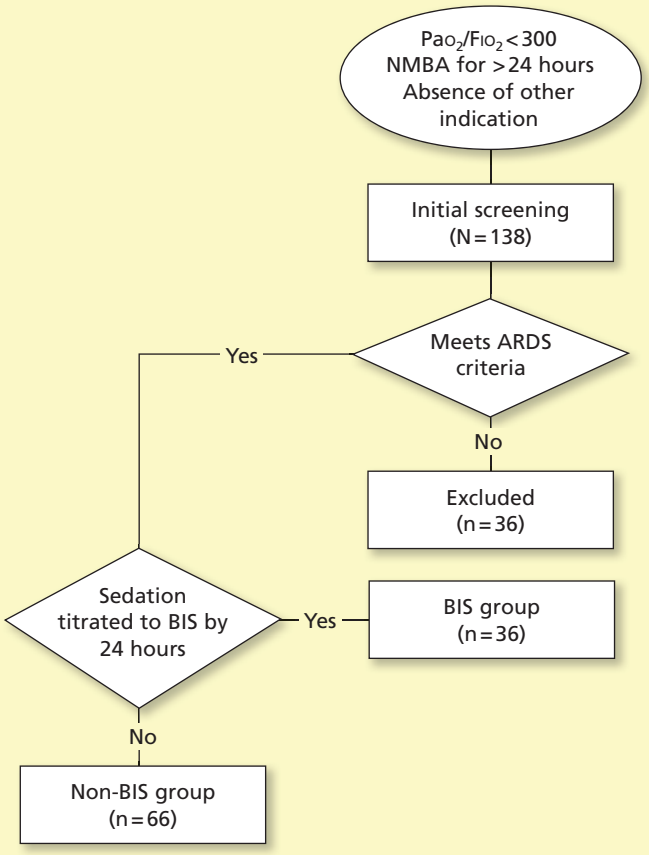

Figure Screening and allocation of patients for the study.

Abbreviations: ARDS, acute respiratory distress syndrome; BIS, bispectral index; NMBA, neuromuscular blocking agent; Pao_2/Fio_2, ratio of partial pressure of oxygen in arterial blood to fraction of inspired oxygen.

> The primary objective was to compare daily sedation and analgesia exposure for patients receiving sedation with or without BIS-based titration.

Statistical Analysis

We analyzed the primary outcome of daily sedation and analgesia exposure during NMBA infusion using the Mann-Whitney *U* test, and we analyzed nominal data using the χ^2 test or Fisher exact test, as appropriate. We assessed the normalcy of continuous data by visually examining a histogram and normal quantile plots. We analyzed continuous

Table 1
Use of bispectral index monitoring and neuromuscular blocking agents according to allocation at 24 hours after starting neuromuscular blockade[a]

Characteristic	BIS group (n = 36)	Non-BIS group (n = 66)
Titration parameters by 24 h	36 (100)	0 (0)
Titration to BIS at any time, median (IQR)	36 (100)	13 (20)
Time to BIS titration if ordered, h	2.5 (0.0-9.5)	44.7 (40.2-48.5)
Initial titration instructions for sedation		
Titrate to BIS ≥60	1 (3)	0 (0)
Titrate to BIS 40-60	32 (89)	0 (0)
Titrate to BIS ≤40	3 (8)	0 (0)
Titrate to RASS score ≥-3	0 (0)	27 (41)
Titrate to RASS score -4 or -5	0 (0)	30 (45)
Sedation/analgesia ordered as straight rate	0 (0)	9 (14)
Mean BIS, median (IQR)	40.7 (36.2-45.3)	44.7 (40.0-48.5)
NMBA used		
Atracurium	36 (100)	57 (86)
Cisatracurium	0 (0)	5 (8)
Vecuronium	0 (0)	4 (6)
Duration of NMBA infusion, median (IQR), h	55.8 (37.5-97.7)	62.5 (44.0-104.0)

Abbreviations: BIS, bispectral index; IQR, interquartile range; NMBA, neuromuscular blocking agent; RASS, Richmond Agitation-Sedation Scale.
[a] Unless otherwise indicated, data in the table are expressed as number (percentage) of patients.

nonnormally distributed data with the Mann-Whitney *U* test and continuous normally distributed data with the Student *t* test.

We performed multivariable analysis with standard linear regression to adjust for variables that might affect sedation exposure. Variables were entered into the model if they would, with biologic plausibility, affect required sedation doses or were associated with variability of BIS readings, and if they met the a priori statistical criterion of $P < .25$ in baseline univariate comparisons. All statistics were computed using STATA statistical software, version 14.1. A *P* value of .05 or less was considered statistically significant.

The BIS and non-BIS groups did not differ significantly in median daily sedation or analgesia exposure during NMBA administration.

Results

Baseline Characteristics of the Study Population

A total of 138 patients who were admitted to a nonneurologic ICU between January 2012 and September 2015 received an NMBA for more than 24 hours, had a Pao_2 to Fio_2 ratio less than 300, and had no documentation of a non-ARDS indication for NMBA. Of these patients, 36 failed to meet the ARDS criteria and were excluded. Of the remaining 102 patients, 36 patients (35.3%) had received administration instructions with titration parameters based on BIS within 24 hours after the NMBA was initiated; these patients comprised the BIS group. The remaining 66 patients (64.7%) formed the non-BIS group, among whom 13 (20%) had BIS-based titration instructions placed beyond the 24-hour cutoff for cohort allocation; the median time from NMBA initiation to placement of BIS titration parameters was 44.7 hours (Table 1).

At baseline (before study entry), both groups were similar with regard to age, severity of illness, severity of hypoxemia, and depth of sedation. We found a nonsignificant difference in weight between groups: patients in the BIS arm weighed 20 kg more than those in the non-BIS arm (106.4 vs 86.5 kg; $P = .06$). In addition, we found a significant difference in the use of BIS titration by ICU location: the medical ICU used BIS-based titration significantly more often than did surgical and cardiovascular ICUs ($P = .002$). With regard to baseline ventilation parameters, we found a significant difference in tidal volume: patients in the BIS group had higher volumes than patients in the non-BIS group (median 7.4 mL/kg ideal body weight [IQR 6.1-8.6] vs 6.3 mL/kg ideal body weight [4.7-7.8]; $P = .04$). Finally, more patients in the BIS group (48%) than in the non-BIS group (31%) had a stable RASS score before the NMBA was initiated, but this difference was not statistically significant ($P = .08$; Table 2).

Sedation and Analgesia Exposure

For the primary objective, we found no significant difference in median daily sedation or analgesia exposure during NMBA administration between the BIS and non-BIS groups (Table 2). In addition, no difference was found between the BIS and non-BIS groups with regard to change in the total median dose of either the sedative or the analgesic in 24 hours. The median number of doses of both the sedative (7 [IQR 4-11] vs 1 [IQR 0-5]; $P < .001$) and the analgesic (1 [IQR 0-2] vs 0 [IQR 0-1]; $P = .003$) were, however, adjusted more frequently for patients in the BIS group than for those in the non-BIS group. Although we found no difference in the median total dose change, patients with titration to BIS had a significantly larger absolute change in sedative dose during the first 24 hours than did the patients in the non-BIS group (2.40 vs 0.61 mg midazolam equivalent/h; $P = .006$; Table 3).

No difference was found in any clinical outcomes between the BIS and non-BIS groups, including median numbers of delirium-free and coma-free days in 14 days, median numbers of ventilator-free and ICU-free days in 28 days, and 90-day mortality,

Table 2
Baseline patient demographics and clinical status according to allocation at 24 hours after starting neuromuscular blockade[a]

Characterisitic	BIS group (n = 36)	Non-BIS group (n = 66)	*P*
Age, median (IQR), y	50 (39.5-58.0)	49.5 (40.0-59.0)	.60
Male sex	20 (56)	34 (52)	.43
Race			.18
White	24 (67)	50 (76)	
Black	10 (28)	10 (15)	
Other	0 (0)	4 (6)	
Unknown	2 (6)	2 (3)	
Weight, median (IQR), kg	106.4 (80.2-121.1)	86.5 (75.9-105.9)	.06
Intensive care unit			
Medical	34 (94)	45 (68)	
Surgical	1 (3)	6 (9)	
Cardiothoracic/cardiovascular	1 (3)	15 (23)	.002
Outside hospital transfer	23 (64)	44 (67)	.78
Documented history of alcoholism	5 (14)	7 (11)	.62
Pao_2/FIo_2 at baseline, median (IQR)	98.5 (69.5-141.0)	96.8 (75.0-126.7)	.90
SOFA score, median (IQR)	12 (10.0-15.5)	14 (12.0-15.0)	.12
APACHE II score, mean (SD)	30.5 (6.4) (n = 36)	29.2 (6.9) (n = 65)	.05
Tidal volume, median (IQR), mL/kg	7.4 (6.1-8.6)	6.3 (4.7-7.8)	.04
pH	7.22 (7.15-7.32)	7.21 (7.13-7.30)	.54
Pco_2, median (IQR), mm Hg	54 (48.5-71.0)	64 (49.0-77.0)	.24
RASS score before starting NMBA			
-4 or -5	10 (28)	24 (36)	.38
Stable	11 (31)	32 (48)	.08
Sedative used			
Propofol	24 (67)	36 (55)	.24
Benzodiazepine	31 (86)	48 (73)	.12
Both	19 (53)	18 (27)	.01
Total sedative exposure during NMBA, median (IQR), midazolam equivalents (mg)	62.3 (36.6-116.7)	69.3 (35.4-129.3)	.64
Total sedative exposure per day, median (IQR), midazolam equivalents (mg)	25.4 (18.3-39.1)	29.2 (15.9-40.0)	.83
Total analgesic exposure during NMBA, median (IQR), morphine equivalents (mg)	551.4 (340.2-1065.8)	762.2 (359.6-1803.3)	.18
Total analgesic exposure per day, median (IQR), morphine equivalents (mg)	225.4 (165.9-340.9)	304.0 (164.2-492.1)	.11

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BIS, bispectral index; IQR, interquartile range; NMBA, neuromuscular blocking agent; Pao_2/FIo_2, ratio of partial pressure of oxygen to fraction of inspired oxygen; RASS, Richmond Agitation-Sedation Scale; SOFA, Sequential Organ Failure Assessment.

[a] Unless otherwise indicated, data in the table are expressed as number (percentage) of patients.

Table 3
Changes to sedation and analgesia during the first 24 hours of neuromuscular blockade in patients with acute respiratory distress syndrome with or without BIS titration parameters at 24 hours

Changes during first 24 h	Median (interquartile range) BIS group (n = 36)	Non-BIS group (n = 66)	*P*
Sedation changes (doses in midazolam equivalents [mg]/h)			
Total dose change	-0.15 (-3.72 to 1.67)	0.00 (0.00-0.75)	.27
Absolute value of total dose change	2.40 (0.78-5.00)	0.61 (0.00-3.00)	.006
No. of adjustments per patient in 24 h	7 (4-11)	1 (0-5)	<.001
Analgesia changes (doses in morphine equivalents [mg]/h)			
Total dose change	3.75 (0.00-10.00)	0.00 (0.00-5.00)	.89
Absolute value of total dose change	0.00 (0.00-6.25)	0.00 (0.00-5.00)	.11
No. of adjustments per patient in 24 h	1 (0-2)	0 (0-1)	.003

Abbreviation: BIS, bispectral index.

Table 4
Clinical and safety objectives in patients with acute respiratory distress syndrome under neuromuscular blockade with or without BIS titration parameters at 24 hours[a]

Clinical end point	BIS group (n = 36)	Non-BIS group (n = 66)	*P*
No. of ventilator-free days in 28 days, median (IQR)	0 (0-15)	0 (0-1)	.61
No. of ICU-free days in 28 days, median (IQR)	0 (0-11)	0 (0-5)	.48
No. of delirium-free/coma-free days in 14 days, median (IQR)	0 (0-1)	0 (0-6)	.43
90-day mortality	22 (61)	40 (61)	.96
Incidence of self-extubation	1 (3)	0 (0)	.50
No sedation at 24 hours	0 (0)	1 (2)	>.99
No analgesia at 24 hours	1 (3)	4 (6)	.65

Abbreviations: BIS, bispectral index; ICU, intensive care unit; IQR, interquartile range.
[a] Unless otherwise indicated, data in the table are expressed as number (percentage) of patients.

which was approximately 60% in both groups ($P = .96$; Table 4).

With regard to secondary safety outcomes, 1 patient with titration to BIS self-extubated after the NMBA was withdrawn, although this occurred more than 5 days after the NMBA had been discontinued. The non-BIS group contained more patients without active sedation or analgesia orders (n = 4) than did the BIS group (n = 1; $P = .65$).

Multivariable Analyses of Primary Sedation and Analgesia End Points

Because we found significant differences in baseline characteristics and factors that could affect sedation and analgesia exposure, we performed multivariable analysis via linear regression for the primary outcome of daily sedation exposure. After we adjusted for baseline age, weight, surgical or medical unit, Sequential Organ Failure Assessment score, a RASS score of -4 or -5 before the NMBA was initiated, a stable RASS score, and administration of propofol and benzodiazepine during NMBA infusion, we found that BIS monitoring did not significantly influence sedative or analgesia exposure (Supplemental Tables 1 and 2, available online only at www.ajcconline.org).

Discussion

BIS monitoring was originally developed for use in surgical patients undergoing anesthesia, but its utility has not been well studied in the ICU. Indeed, although current practice guidelines for pain, agitation, and delirium recommend objective measures such as BIS as possible adjunctive measures of sedation in paralyzed patients, current NMBA guidelines make no recommendation regarding use, citing insufficient evidence because of the absence of outcomes data and the uncontrollable variability of BIS in the ICU setting.[1,2] The available data indicate some correlation with traditional sedation measures, with BIS readings of approximately 60 correlating with deep sedation[12]; however, some reports indicate inappropriate correlation with BIS[13] due to factors such as sepsis-associated encephalopathy, which leads to suppression of the electroencephalograph and environmental interference from nearby electromagnetic fields.[14]

For the primary outcome of sedation and analgesia exposure, we found no difference in daily sedation or analgesia exposure between patients with and patients without BIS-based titration. Daily sedation exposure in both groups was similar to that in previous studies of patients receiving an NMBA.[3] In addition, a reported daily morphine equivalent of 271 mg was similar to our study's daily analgesia dose.[3,8] Because sedation and analgesia doses are comparable to those used in similar populations of patients with ARDS, it is relevant that the use of BIS to determine titration did not seem to make a significant difference in overall sedation or use of analgesia. This result suggests that the use of BIS does not significantly affect the overall exposure to sedation and analgesia in unselected patients with ARDS. These findings are not surprising in light of a recent novel analysis of RASS scores in patients after neuromuscular blockade, which yielded a 35.7% positive predictive value for a BIS threshold of 60 to predict deep sedation, equating to a RASS score of -4 to -5.[15] We also did not find differences in any of the secondary clinical outcomes. With no significant difference in sedative and analgesia exposure, however, this finding is expected.

It is notable that our study groups had some differences in baseline characteristics, which may have affected sedation and analgesia exposure. At baseline, patients in the BIS group weighed significantly more than patients in the non-BIS group; this difference could affect NMBA doses and weight-based sedation with agents such as propofol. Also, medical ICUs used BIS-based titration more often than did surgical or cardiovascular ICUs, most likely because of practice differences between units. However, nursing training for BIS-based titration is similar in all these areas and is coordinated by a consistent group of clinical nurse specialists. Finally, we found a significant difference in the number of patients who received both propofol and benzodiazepine, and we accounted for this difference by calculating sedation exposure as midazolam equivalents. In addition, to account for all of these factors, we

performed a multivariable analysis and found that BIS monitoring did not influence sedation or analgesia exposure.

The use of BIS in detecting deep sedation in ICU patients was recently prospectively evaluated. With regard to the utility of BIS for detecting deep sedation, values of 50 in the careful absence of stimulation and 80 in stimulated patients were both useful for identifying patients who were deeply sedated. Importantly, this study excluded patients in whom various factors would probably have significantly interfered with BIS, including hypoxia, hypotension, and administration of muscle relaxants, making the utility of generalizing to patients with ARDS questionable. In addition, only 34% of enrolled patients received fentanyl.[4] Despite claims of the low resource requirements of BIS relative to traditional assessments, requiring a combination of both stimulated and unstimulated BIS in order to adequately identify inappropriately sedated patients questions resource requirements and the ability to adequately identify either BIS value without having a clinician at the bedside when it is recorded.

Although the method of titrating to BIS used in this study seems likely to be resource neutral, sparing assessment of baseline sedation before initiating an NMBA and resulting in no differences in sedation and analgesia exposure or measured clinical outcome, its use should be balanced with nursing workload. We did find a significant difference in the number of adjustments to both sedation and analgesia doses during the first 24 hours of NMBA administration, and more adjustments of both occurred in the group receiving BIS-based titration.

The observed increase in the number of analgesia adjustments in the BIS group may be explained by unmasking inadequate analgesia during routine procedures; these inadequacies could have been identified with adequate clinical resources and either bedside assessment or chart review. In addition, a significant difference was found in the absolute value of the change in sedation dose within the first 24 hours, with a larger change in the BIS group. This absolute change value did not correspond to an overall change in rate, suggesting that doses for patients in the BIS group were adjusted through both increases and decreases. We observed similar results in the subgroup of patients who were at high risk of inadequate sedation, as defined by a RASS score greater than -4 before an NMBA was initiated (data not shown). Even in that group, which was the most likely to have benefited from sedation management, BIS was not associated with an increase in sedation rate and as such was not an adequate replacement for clinical judgment.

We know of no studies in which the frequency of titration or bolus administration of sedatives or analgesics after NMBA was assessed. In critically ill patients, among whom the nursing workload is already significant, the additional time dedicated to BIS-based titration must be considered as a component of any prospective assessment of sedation management using BIS, especially when the utility of such practice is not well established.

This study has several limitations. First, it was a retrospective review of medical records and thus is subject to the intrinsic shortcomings of such a design. Second, our study design defined BIS-based titration as occurring within 24 hours of initiating NMBA infusion. Because of this, some patients in the non-BIS group received BIS titration but only after 24 hours (Table 1). Notably, though, receipt of BIS monitoring by patients in the non-BIS group should not affect any of the 24-hour sedation outcomes, as their median time to BIS was greater than 24 hours; it may, however, have affected other clinical outcomes. In addition, initiation of BIS-based titration was delayed for a median of approximately 2.5 hours in the BIS group; this delay was probably a result of delayed documentation in the electronic medical records of acutely ill patients.

> Titration to BIS did not result in significant differences in sedation or analgesia exposure or clinical outcomes compared with traditional sedation monitoring in patients with ARDS on continuous NMBA.

Another limitation is that we were unable to review written or verbal orders to nursing staff other than medication orders placed within the electronic medical records. Although these are not used to determine titration parameters, they may include temporary instructions from providers to maintain current doses, limit down-titrations in response to a suppressed BIS, or limit dose increases because of an elevated BIS. The incidence of these communications at our institution is unknown, though they are probably rare. Finally, the decision to titrate to BIS was clinician dependent. Although we attempted to adjust for potential confounders that might affect our primary outcome through multivariable adjustment, this study may not account for differences that influence a clinician's decision to use BIS-based titration in order to manage sedation and analgesia during NMBA infusion.

Conclusion

In critically ill patients with ARDS who require continuous NMBA infusion, titrating sedation and analgesia on the basis of BIS did not result in significant differences in sedation or analgesia exposure and was not associated with differences in clinical outcomes when compared with an approach that did not titrate to BIS. Patients with titration to BIS, however, received more frequent and larger adjustments to infusion doses within the first 24 hours of NMBA administration. This supports guideline recommendations of BIS as adjunctive monitoring method to augment clinician assessment only until adequate prospective data are available, and it establishes an obligation to include workload assessments in any prospective assessment of BIS or similar objective sedation measures.

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CE 1.0 Hour Category A

Notice to CE enrollees:

This article has been designated for CE contact hour(s). The evaluation demonstrates your knowledge of the following objectives:

1. Describe the current approach to sedation and analgesia management in intensive care unit (ICU) patients who are on continuous infusion neuromuscular blockade.
2. Compare the recommendations for the use of bispectral index (BIS) monitors between the guidelines for pain/agitation/delirium and neuromuscular blockade.
3. Identify potential limitations to using BIS monitors for monitoring of sedation in ICU patients receiving neuromuscular blocking agents.

To complete the evaluation for CE contact hour(s) for this article #A1928051, visit www.ajcconline.org and click the "CE Articles" button. No CE evaluation fee for AACN members. This expires on September 1, 2022.

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Supplemental Table 1
Association of selected factors with sedation exposure, based on linear regression

Variable	Difference in sedative exposure, mean (95% CI), midazolam equivalents (mg) per patient per day	SE	*P*
In patients with or without BIS titration parameters at 24 hours	-41.20 (-86.30 to 3.95)	22.7	.07
Per kilogram of body weight	0.49 (-0.08 to 1.06)	0.29	.09
In patients transferred from other institutions	13.6 (-32.0 to 59.2)	22.9	.56
Per year of age	-1.25 (-2.72 to 0.23)	0.74	.10
By SOFA score	-7.5 (-13.8 to -1.2)	3.1	.02
In medical vs nonmedical ICU patients	21.6 (-31.8 to 74.9)	26.8	.42
By exposure to continuous benzodiazepine	20.0 (-32.8 to 72.9)	26.6	.45
In patients with stable RASS scores and deep sedation before NMBA infusion	-8.1 (-52.1 to 35.8)	22.1	.71

Abbreviations: BIS, bispectral index; ICU, intensive care unit; NMBA, neuromuscular blockade; RASS, Richmond Agitation-Sedation Scale; SOFA, Sequential Organ Failure Assessment.

Supplemental Table 2
Association of selected factors with analgesic exposure, based on linear regression

Variable	Difference in sedation exposure, mean (95% CI), morphine mg equivalents/patient/day	SE	*P*
In patients with or without BIS titration parameters at 24 hours	-88.6 (-203.3 to 26.0)	57.0	.13
Per kilogram of body weight	-0.42 (-1.87 to 1.03)	0.73	.57
In patients transferred from other institutions	28.7 (-84.7 to 142.1)	57.1	.62
Per year of age	-2.34 (-6.05 to 1.03)	1.87	.21
By SOFA score	-12.8 (-28.6 to 3.0)	8.0	.11
In medical versus nonmedical ICU patients	-98.1 (-225.3 to 29.2)	64.1	.13
In patients with stable RASS and deep sedation before NMBA infusion	-30.6 (-140.9 to 79.7)	55.5	.58

Abbreviations: BIS, bispectral index; ICU, intensive care unit; NMBA, neuromuscular blockade; RASS, Richmond Agitation-Sedation Scale; SOFA, Sequential Organ Failure Assessment.