An Exploratory Study of the Bilateral Bispectral Index for Pain Detection in Traumatic-Brain-Injured Patients With Altered Level of Consciousness

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ABSTRACT

Introduction: Many patients with a traumatic brain injury (TBI) cannot communicate because of altered level of consciousness. Although observation of pain behaviors (e.g., frowning) is recommended for pain assessment in nonverbal populations, they are attenuated and sometimes even suppressed in patients with TBI receiving high doses of sedatives. This study explored the potential utility of the bilateral bispectral index system (BIS) for pain detection in critically ill adults with TBI and altered level of consciousness. **Methods:** Using a repeated measure within-subject design, participants ($N = 25$) were observed for 1 minute before (baseline), during, and 15 minutes after two procedures: (a) noninvasive blood pressure (nonnociceptive) and (b) turning (nociceptive). At each assessment, BIS indexes (0–100) of the right (R) and left (L) hemispheres and pain behaviors were documented. **Results:** Compared with baseline, significant median increases ($p \leq .05$) in BIS-R (+4.93%) and BIS-L (+8.43%) and in the frequency of pain behaviors (+3.00) were observed during turning but not noninvasive blood pressure. Interestingly, increases in BIS-R were more pronounced in participants with left-sided TBI (+17.23%, $p = .021$) than those with right-sided TBI (+3.01%). BIS-R fluctuations in participants with left-sided TBI were also positively correlated ($r_s = .986$, $p \leq .001$) with the frequency of pain behaviors observed during turning. **Conclusions:** Overall, only increases in BIS-R were correlated with participants' pain behaviors and in those with left-sided TBI exclusively. Although further research is needed, our findings support the potential use of the bilateral BIS for pain detection in nonverbal patients with TBI who cannot behaviorally respond to pain, but only when they have a left-sided injury.

Keywords: altered level of consciousness, bispectral index, brain injury, pain

Many patients with a traumatic brain injury (TBI) are unable to communicate their pain verbally or with signs during their stay in the intensive care unit (ICU) because of mechanical ventilation, aphasia, or altered level of consciousness (LOC; Young, 2007). In this situation, pain assessment becomes a challenge for ICU nurses. In nonverbal populations, the use of pain behaviors such as grimacing, increased muscle tension, and protective movements is strongly recommended for pain assessment (Barr et al., 2013; Herr, Coyne, McCaffery, Manworren, & Merkel, 2011). Unfortunately, behaviors are often suppressed in critically ill patients with TBI who are under the effects of neuromuscular blockers or high

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doses of sedatives to prevent deleterious elevation of intracranial pressure. Although vital signs are readily available in the ICU, they are not recommended for pain assessment (Herr et al., 2011). Indeed, in several validation studies, fluctuations in vital signs were not associated with critically ill patients' self-reports of pain (Gélinas & Arbour, 2009; Gélinas & Johnston, 2007). They were also found to fluctuate similarly during nonnociceptive and nociceptive procedures (Young, Siffleet, Nikoletti, & Shaw, 2006). Given that behavioral responses cannot always be observed in patients with TBI and that the validity of vital signs for the purpose of pain assessment is not empirically supported, the time has come to explore the utility of other potential physiologic measures for pain detection in this vulnerable patient group.

Recently, fluctuations in electroencephalogram (EEG) patterns were found to be associated with self-report of pain in healthy subjects (Nir, Sinai, Raz, Sprecher, & Yarnitsky, 2010; Zhang, Hu, Hung, Mouraux, & Iannetti, 2012). Thus, some electrocortical variables could be explored as alternative and objective means of detecting pain in nonverbal patients with TBI. The bispectral index system (BIS), a processed EEG parameter, is one of them. So far, few studies have examined the utility of the BIS index for the detection of pain in critically ill adults with altered LOC. In a recent study by Li, Miaskowski, Burkhardt, and Puntillo (2009), fluctuations in the BIS index were examined in postoperative cardiac surgery ICU patients (N = 48) exposed to a nonnociceptive procedure (i.e., gentle touch) and a nociceptive procedure (i.e., endotracheal suctioning or turning). A significant mean increase in the BIS index (+10%; $p < .001$) was observed during the nociceptive procedure, compared with rest (or baseline) and the nonnociceptive procedure, supporting the discriminant validation of the BIS. Interestingly, a subsample of 10 patients who were able to self-report indicated that the nociceptive procedure was painful (by head nodding), but the association between BIS fluctuations and self-report of pain intensity could not be explored. In a similar study by Gélinas, Tousignant-Laflamme, Tanguay, and Bourgault (2011) with mechanically ventilated ICU patients (N = 9) with surgical, medical, and trauma diagnoses, a significant median increase in the BIS index (between +20% and +30%) was observed from rest to the nociceptive procedures (i.e., endotracheal suctioning and turning). Facial electromyogram (EMG) activity also increased (+10%) during the nociceptive procedures. Such results tend to support the potential utility of the BIS index for the detection of pain in nonverbal critically ill patients. Still, the validation of the BIS index for the purpose of pain assessment remains to be initiated in patients with TBI.

Because fluctuation in electroencephalogram (EEG) patterns have been associated at times with self-reports of pain in healthy subjects, the use of some electrocortical variables, such as the bispectral index system (BIS), may provide an objective means of detecting pain in nonverbal patients.

Several considerations should be taken for the preliminary validation of the BIS index in patients with TBI. First, it is important to mention that the BIS technology was initially developed to optimize titration of anesthetic agents and limit the risk of intraoperative recall during surgery because conscious perception of pain was reported by patients receiving sedatives and paralytic agents during surgical procedures (Johansen & Sebel, 2000). Accordingly, the BIS index was found to be a good correlate of level of awareness (and a potential indicator of pain perception) in patients with altered LOC, although it remains quite stable and provides little clinical information in fully awake patients (Schnakers et al., 2008). Considering that the BIS index does not fluctuate in patients who are conscious/awake, the association between the BIS and patients' self-report of pain (the gold standard in pain assessment and the ultimate information in performing criterion validation) can hardly be examined. As an alternative, fluctuations in BIS can be described and compared during a nonnociceptive procedure and a nociceptive procedure for discriminant validation and then associated to other recognized indicators of pain such as pain behaviors for convergent validation (Barr et al., 2013; Herr et al., 2011). Another concern is the fact that lateralization of EEG activity can occur in patients with TBI (Zasler, Katz, & Zafonte, 2006). For this reason, the new version of the BIS monitor (called the bilateral BIS) could be better suited for patients with TBI because it enables recording of BIS and facial EMG parameters for the right (R) and left (L) hemispheres separately, something not possible with earlier BIS devices. Finally, several variables including TBI severity, level of sedation, and administration of analgesic and sedative agents could affect response to a painful stimulation of patients with TBI (Roulin & Ramelet, 2011). These variables should be

considered in the validation of the BIS index for the purpose of pain detection in patients with TBI.

Aim and Objectives

This study aimed to explore the potential utility of the bilateral BIS index for the purpose of pain detection in nonverbal adults with TBI in the ICU. The specific objectives were the following:

1. For discriminant validation, to describe and compare bilateral BIS index and facial EMG values for the R and L hemispheres recorded across different assessments (e.g., 1 minute before, during, and 15 minutes postprocedure) and procedures (e.g., nonnociceptive and nociceptive).
2. For convergent validation, to examine the associations between fluctuations in BIS index and the frequency of pain behaviors documented during the nociceptive procedure.

A secondary objective of the study was

3. to explore the potential influence of TBI severity, level of sedation, and administration of analgesic and sedative agents on bilateral BIS fluctuations observed during the nociceptive procedure.

Methods

Design, Sample, and Ethics

A repeated measure within-subject design was used. A convenience sample of patients with TBI admitted to a level I trauma ICU of the McGill University Health Center in Montreal, Quebec, Canada, was recruited. Because all patients were unable to consent for themselves, legal representative of patients meeting the following inclusion criteria were invited to participate: (a) aged 18 years and older, (b) admitted to the ICU after a TBI (with or without other injuries) for more than 24 hours and less than 30 days (corresponding to the acute stage of TBI recovery), and (c) have a score higher than 3 and lower than 13 on the Glasgow Coma Scale (GCS; Teasdale & Jennett, 1974) showing alterations in LOC but arousability at different degrees to external stimulation. Patients were excluded if they had any conditions potentially interfering with cortical integration of pain signals including (a) a documented history of chronic substance abuse in the medical chart, (b) a previous TBI, (c) a diagnosed cognitive deficit or psychiatric condition, and (d) a suspected brain death. Patients were also excluded if they could not be turned in bed as per medical order. Although the bilateral BIS could mostly be useful in nonverbal patients who cannot respond behaviorally to pain, patients with TBI with motor paralysis (because of spinal cord injury or neuromuscular blockers) were excluded as well, because the association between BIS fluctuations and pain behaviors was essential for the initial validation process of the BIS for pain detection in nonverbal patients with TBI. Finally, patients' initial GCS scores (i.e., gathered within the first few hours post-TBI) were not considered in the inclusion/exclusion criteria. Rather, only GCS scores obtained within minutes before data collection were considered.

The study was approved by the research ethics committee of the hospital. Legal representatives were approached by a doctoral student researcher (C. A.), written consent was obtained, and a copy was given to the representative.

Variables and Instruments

The BIS monitor is a noninvasive technology, which measures different electrocortical indices through electrodes placed on the patient's forehead (see the Figure, available as Supplemental Digital Content 1, at http://links.lww.com/JNN/A35). Its main variable, the BIS index, consists of a single number computed from a complex algorithmic equation based on the EEG data of a large sample of healthy adult subjects undergoing general anesthesia (Johansen & Sebel, 2000). Its value can range from 0 (complete EEG suppression) to 100 (fully awake), and it is expected to fluctuate within certain limits depending on patients' LOC. Specifically, a BIS value between 90 and 100 correlates with an awake state, values in the 70s–80s correlate with light-to-moderate conscious sedation, values in the 60s–70s correlate with deep sedation, and scores from 30s to 60s correlate with moderate-to-deep hypnotic states similar to the ones observed during general anesthesia (Olson, Chioffi, Macy, Meek, & Cook, 2003). The BIS index can also be affected by artifacts caused by muscle activity of the forehead (such as frowning and orbit tightening; Liu et al., 2005). For this reason, the BIS monitor provides simultaneous recording of frontal EMG, which reflects the electrical power of facial muscle activity and is a good indicator of artifacts. The BIS monitor also provides a signal quality index, which should be >80% to ensure good impedance of BIS electrodes and low probability of artifacts in BIS signal (Schnakers et al., 2008).

So far, the main use of the BIS index has been to quantify changes in the electrophysiological state of the brain during sedation and anaesthesia (see Rosow & Manberg, 2001, for a review). Most recently, however, the BIS was studied in relation to nociception in sedated patients undergoing various surgical interventions. In those studies, significant elevation in BIS values (between 5% and 20%) was found in anesthetized patients exposed to experimental nociceptive stimulations (transcutaneous electrical nerve stimulation

or ice pack), suggesting that those patients had increased LOC and higher risk of intraoperative recall of pain during the application of the nociceptive stimulation (Sandin et al., 2008; Takamatsu, Ozaki, & Kazama, 2006). Thus, the capacity of BIS index to fluctuate in response to nociception, even in deeply sedated patients, supports its potential usefulness for pain detection in patients with altered LOC, including those with a TBI.

Although the BIS technology is fairly recent, several versions of the BIS monitor were put on the market since its initial release in 1996. As mentioned, the latest version of the BIS monitor called the bilateral BIS (BIS VISTA; Aspect Medical Systems, Newton, MA) was used in this study according to manufacturer's instructions because of its capacity to record the BIS index and facial EMG for each hemisphere (R and L) separately. The BIS VISTA monitor provided a continuous output of the raw EEG and facial EMG patterns and converted the raw data into numerical values (at 5-second intervals) to be used for data analysis. All variables (i.e., bilateral BIS and facial EMG values) were transferred to a data collection computer connected to the BIS VISTA monitor with a port serial cable (e.g., Moberg-CNS monitor; Ambler, PA).

This study was part of a larger project aimed to validate the use of pain behaviors and vital sign fluctuations for pain assessment in critically ill patients with TBI with different LOCs (Arbour et al., 2014). For the purpose of this larger project, a behavioral checklist was created by combining 44 items from two behavioral pain scales that have undergone previous validation in critical care: (a) the Pain Behavioral Assessment Tool (Puntillo et al., 2004) and (b) the Critical-Care Pain Observation Tool (CPOT; Gélinas, Fillion, Puntillo, Viens, & Fortier, 2006). Six items were added to the checklist after pilot testing. The final checklist included 50 items with their descriptions. Behaviors were clustered into four categories: (a) facial expressions, (b) body movements, (c) muscle tension, and (d) compliance with the ventilator (for mechanically ventilated patients) or vocalization (for nonventilated ones). Information about the individual psychometric properties of the Pain Behavioral Assessment Tool and the CPOT and the development of the behavioral checklist with these two scales was published (Le, Gélinas, Arbour, & Rodrigue, 2013).

Procedure

Sociodemographic characteristics (gender, age, ethnicity, cause of TBI) and medical information such as severity of injury (Injury Severity Score; Baker, O'Neill, Haddon, & Long, 1974), predictor of prognosis (Acute Physiology and Chronic Health Evaluation II score; Knaus, Draper, Wagner, & Zimmerman, 1985), and LOC (according to GCS score; Teasdale & Jennett, 1974) were collected for each participant through their medical files. TBI localization (as determined by medical team through physical examination and CT-scan reading) was also gathered in medical files. In mechanically ventilated participants, LOC was recomputed with the adapted GCS (Rutledge, Lentz, Fakhry, & Hunt, 1996), which takes into account the inability of ventilated patients to express themselves verbally when estimating the LOC (which is not done in the original GCS). Information about TBI severity (i.e., mild, moderate, or severe) and variables related to the therapeutic regimen including level of sedation (Richmond Agitation Sedation Scale; Sessler et al., 2002) and administration of analgesic and sedative agents within 4 hours before data collection were also collected. The 4-hour time frame was selected because it mirrors the half time (i.e., the time it takes for the plasma concentration of a drug to reach half of its original concentration [American Pain Society, 2003]) of fentanyl and hydromorphone, the analgesics included in the pain management protocol of the ICU. Inversely, analgesics and sedatives administered more than 4 hours before data collection were not considered for data analysis because they were thought to have a limited impact on patients' reactivity to pain.

After skin preparation with isopropyl alcohol, a bilateral BIS sensor was placed in a standard frontal bipolar montage with a ground electrode placed at the inner junction of the left eyebrow and four electrodes placed symmetrically on the participants' forehead (two on each temporal area and two above each eyebrow) allowing recording of four EEG channels. Once the quality of BIS signal was ensured with signal quality index > 80%, participants were left unstimulated for 5 minutes, allowing them to grow accustomed to the BIS electrodes. Then, the bilateral BIS sensor was connected to the BIS VISTA monitor for data collection. During data collection, participants with TBI were exposed to two procedures commonly performed in the ICU: (a) noninvasive blood pressure (NIBP; known as a nonnociceptive procedure; Gélinas & Johnston, 2007) and (b) turning (known as a nociceptive procedure; Puntillo et al., 2001). For each procedure, participants were observed for 1 minute before (at baseline), during, and 15 minutes postprocedure for six assessment periods. The 15-minute time frame was selected for the postprocedure assessment because that amount of time is generally required by the human body for the elimination of stress hormones (including epinephrine and norepinephrine) after being exposed to a stressor such as pain (Berne & Levy, 1983). Video recording was performed during data collection using two video cameras (Sony HDRXR160 HD). One was installed at the foot of the bed on a tripod to record body movements, and the other was held by the

research assistant (M. R.) to capture patients' facial expressions. At each assessment, behaviors were documented at the bedside by the doctoral student researcher (C. A.) who was allowed to review the videos in the event that healthcare staff interfered with her observation of the participant during an assessment period.

It is important to mention that the nociceptive procedure (i.e., turning) was performed by the nursing staff according to the participants' needs because this method is commonly used in validation studies of physiologic indicators of pain in critical care (Gélinas & Arbour, 2009; Gélinas & Johnston, 2007; Li et al., 2009; Payen et al., 2001). For each participant, however, nurses were instructed to perform the NIBP procedure before turning and to wait at least 15 minutes between both procedures to respect the pre–post design of the study. For NIBP, nurses were advised to take the blood pressure on the opposite side of the arterial line to not apply pressure on the cannula insertion site and potentially cause discomfort. Unless it was not medically approved, nurses turned participants on each side during the turning procedure in accordance with their ICU mobilization protocol to ensure that linen was dry and to stimulate blood flow for bedsore prevention. Finally, nurses were instructed to give usual care during data collection, and this included giving analgesic or sedative agents according to participants' conditions.

Data Analysis

On the basis of inspection of probability plots and Shapiro–Wilk tests with $p \leq .05$ (Samuel, Witmer, & Schaffner, 2012), BIS index and facial EMG data were not found to be normally distributed. To achieve the first research objective, median and quartiles were computed for BIS index and facial EMG values of the R and L hemispheres recorded across different assessments (1 minute before, during, and 15 minutes postprocedure) and procedures (NIBP and turning). Then, Friedman tests were performed to compare fluctuations in BIS index and facial EMG values of both hemispheres across the different assessments during NIBP and turning. Post hoc analyses using Wilcoxon paired-rank tests with Bonferroni correction were performed when appropriate (McHugh, 2011). Finally, Mann–Whitney *U* tests were performed to compare BIS index fluctuations on the R and L hemispheres in participants with right-sided TBI versus left-sided TBI.

To meet the second objective related to the association of bilateral BIS index with pain behaviors, a distinction was made between behavioral items on the checklist. Specifically, behaviors associated with a resting state and the absence of muscle activity (such as relaxed face and closed eyes) were considered as "neutral behaviors." Conversely, behaviors that showed a change in muscle activity or tone and that could be perceived as a reaction to a nociceptive procedure (like grimacing or guarding pain site) were considered as "pain behaviors." Although both neutral behaviors and pain behaviors were used for the computation of the descriptive statistics, only pain behaviors were used in the computation of comparative statistics (i.e., Wilcoxon paired-rank tests) and correlations. As such, frequencies of neutral behaviors and pain behaviors observed during NIBP and turning were computed. Then, Wilcoxon paired-rank tests were performed to compare the frequency of pain behaviors documented during both procedures. Finally, Spearman's rank-order correlations were performed to examine the association between fluctuations in BIS indexes (R and L) and the frequency of pain behaviors observed during turning in participants with right-sided TBI and those with left-sided TBI.

For the secondary objective of the study, Spearman's rank-order correlations were computed to explore the potential influence of TBI severity, level of sedation, and administration of analgesic and sedative agents on fluctuations in BIS index and facial EMG of the R and L hemispheres during turning. To facilitate data analysis, analgesic agents were converted into equianalgesic doses of morphine (e.g., doses that would offer the equivalent amount of morphine; American Pain Society, 2003). Sedatives were treated individually because no conversion chart was available.

Results

Sociodemographic Characteristics, Medical Variables, and Therapeutic Regimen

Twenty-nine participants with TBI recruited for the larger-scale study were eligible for BIS data collection because they were either unconscious (i.e., with GCS ≤ 8) or with altered LOC (i.e., GCS between 9 and 12). Among them, (a) $n = 2$ participants were excluded because the BIS electrodes did not stick to their skin because of diaphoresis, (b) one participant had signal quality index lower than 80% because of periorbital edema, and (c) another one had a bilateral bone flap (i.e., temporary removal of the R and L skull) impeding the placement of BIS electrodes on the forehead. Participants ($N = 25$) included in the final sample were mostly men ($n = 17$, 68.0%), with a median age of 56.5 years (min = 18.0 years, max = 85.0 years), and mainly admitted to the ICU after severe TBI ($n = 18$, 72.0%). In all participants, data collection occurred between the 2nd and 28th day after ICU admission (on the 12th day on average). Regarding localization of injury, almost half of the participants had right-sided TBI ($n = 12$, 48.0%), the other half had left-sided TBI ($n = 12$, 48.0%), and only one participant (4.0%) had bilateral TBI. Overall,

participants had a median Injury Severity Score of 9 (min = 9, max = 27) and a median Acute Physiology and Chronic Health Evaluation II score of 17 (min = 9, max = 25), which indicates that they experienced severe injuries but with low risk of complications. Moreover, they had a median adapted GCS of 10 (min = 9, max = 12), and most of them were mechanically ventilated (n = 19, 76.0%). Whereas 10 participants (40.0%) did not receive any analgesics or sedatives within 4 hours before data collection, 10 participants (40.0%) were receiving both. Although this was not an exclusion criterion, all participants were on a preventive treatment for seizure (using phenytoin) as per TBI protocol. Furthermore, at the time of data collection, participants with TBI were not receiving any drug known to interfere with BIS signal such as dexmedetomidine or ketamine (Paris et al., 2009). Information about participants' characteristics and therapeutic regimen is available in Tables 1 and 2, respectively.

Discriminant Validation of Fluctuations in Bilateral BIS Index, Facial EMG, and Signal Quality Index Across Assessments and Procedures

Overall, significant fluctuations in BIS-L ($\chi^2(2)$ = 7.238, $p \leq .05$), facial EMG-R ($\chi 2(2)$ = 10.160, $p \leq .01$), and facial EMG-L ($\chi 2(2)$ = 10.160, $p \leq .01$) were found across assessments in participants during turning but not during NIBP (Table 3). In addition, a tendency toward significant fluctuations in BIS-R ($\chi 2(2)$ = 5.040, p = .080) was found across assessments during turning. Also worth mentioning, median values for signal quality index (R and L) were >80% across the different assessments and procedures suggesting good BIS signal quality during data collection. On the basis of post hoc comparisons, significant increases in BIS-R ($t(Z) = -2.093$, $p \leq .05$), BIS-L ($t(Z) = -2.549$, $p \leq .05$), and facial EMG-R ($t(Z) = -2.355$, $p \leq .05$) were observed between baseline (i.e., 1 minute preprocedure) and turning (Table 4). In contrast, significant decreases in BIS-L ($t(Z) = -2.256$, $p \leq .05$), facial EMG-R ($t(Z) = -3.081$, $p \leq .01$), and facial EMG-L ($t(Z) = -3.404$, $p \leq .01$) were observed between turning and 15 minutes postprocedure, whereas BIS-R remained elevated postturning ($t(Z) = -1.612$, p = .107). Interestingly, during turning, increases in BIS-R were found to be significantly less pronounced (U = 10.000, p = .021) in participants with right-sided TBI (median increase = 3.01%) compared with those with left-sided TBI (median increase = 17.23%). Conversely, no difference was observed (U = 23.000, p = .950) in BIS-L increases during turning between participants with right-sided TBI (median increase = 7.46%) and those with left-sided TBI (median increase = 8.76%).

TABLE 1. Sociodemographic Characteristics and Medical Variables of Study Participants (N = 25)

Variables	Study Sample (N = 25)
Age median (min–max)	56.5 (18.0–85.0)
Gender: n (%)	
Male	17 (68.0)
Female	8 (32.0)
Ethnicity: n (%)	
Caucasian	19 (76.0)
Black	2 (8.0)
Native American	2 (8.0)
Hispanic	1 (4.0)
Other	1 (4.0)
Cause of TBI: n (%)	
Fall	15 (60.0)
Motor vehicle accident: occupant	7 (28.0)
Struck by motor vehicle	2 (8.0)
Assault	1 (4.0)
TBI severity, n (%)	
Mild	1 (4.0)
Moderate	6 (24.0)
Severe	18 (72.0)
TBI localization, n (%)	
Right sided	12 (48.0)
Left sided	12 (48.0)
Bilateral	1 (4.0)
GCS score: median (min–max)	10 (9–12)
LOC category, n (%)	
Unconscious	6 (24.0)
Altered LOC	19 (76.0)
APACHE II score: median (min–max)	17 (9–25)
ISS score: median (min–max)	9 (9–27)
RASS score: median (min–max)	−4 (−4 to 0)

Note. APACHE II = Acute Physiology and Chronic Health Evaluation; ISS = Injury Severity Score; GCS = Glasgow Coma Scale; LOC = level of consciousness; RASS = Richmond Agitation Sedation Scale; TBI = traumatic brain injury.

Convergent Validation of Fluctuations in Bilateral BIS With Frequency of Pain Behaviors Exhibited During the Nociceptive Procedure

During data collection, pain behaviors were observed more often ($t(Z) = -3.741$, $p \leq .001$) during turning (median = 3, min = 0, max = 7) than during NIBP (median = 0, min = 0, max = 3; Table 5). Pain behaviors most frequently observed during turning were sudden eye opening (48.0%), eye weeping (48.0%),

TABLE 2. Analgesics, Equianalgesic Doses of Morphine, and Sedatives Administered Within 4 Hours Before Data Collection

	Study Sample (*N* = 25)
Analgesics	
Fentanyl infusion or I/V bolus (μg/h)	
Nb of infusion in place or bolus received (%)	10 (40.0)
Median dose (min–max)	112.50 (50.00–200.00)
Hydromorphone s/c bolus (mg)	
Nb of bolus received (%)	3 (12.0)
Median dose (min–max)	1.00 (0.50–2.00)
Total equianalgesic doses of morphine administered 4 hours before data collection (mg)	
Median (min–max)	40.00 (2.50–80.00)
Sedatives	
Diprivan infusion (mg/h)	
Nb of infusion in place (%)	11 (44.0)
Median dose (min–max)	225.00 (31.00–399.00)
Midazolam infusion (mg/h)	
Nb of infusion in place (%)	4 (16.0)
Median dose (min–max)	3.75 (3.00–5.00)

Note. I/V = intravenous; s/c = subcutaneous; Nb = number. Of note, administration frequency and percentages were computed on entire sample (i.e., *N* = 25), whereas median doses of analgesics or sedatives were computed on the number of participants who received that specific analgesic or sedative. Also of interest, 10 participants with TBI did not receive any analgesics or sedatives before data collection.

frowning (28.0%), flexion of lower limb (24.4%), and moaning (50.0%). In contrast, during NIBP, most observed behaviors were neutral and included closed eyes (96.0%), relaxed face (88.0%), immobility (80.0%), absence of muscle tension (92.0%), easy ventilation (94.7%), and no vocalization (83.3%). Regarding the association between bilateral BIS fluctuations and participants' behavioral responses during turning, a positive significant correlation (r_s = .986, $p \leq .001$) was found between BIS-R fluctuations and the frequency of pain behaviors exhibited during turning in participants with left-sided TBI only (n = 12; Table 6).

Relationship Between Variables Related to TBI Injury or Therapeutic Regimen and Fluctuations in Bilateral BIS, Facial EMG, and Signal Quality Index During the Nociceptive Procedure

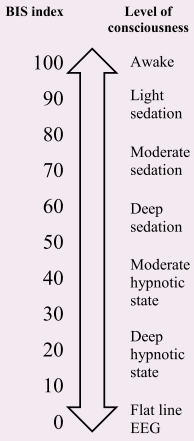
Regarding the potential influence of TBI severity and variables related to participants' therapeutic regimen (i.e., level of sedation, administration of analgesic and sedative agents) on bilateral BIS fluctuations during turning, a moderate negative correlation was found between BIS-L fluctuations during turning and TBI severity (r_s = −.577, $p \leq .05$). Moderate negative correlations were also found between BIS-L fluctuations and dosage of equianalgesic morphine received (r_p = −.409, $p \leq .05$) as well as dosage of Diprivan received (r_p = −.413, $p \leq .05$) within 4 hours before data collection (Table 7).

Discussion

Few studies have examined the potential utility of cerebral parameters for the purpose of pain detection in nonverbal critically ill patients. However, nonverbal patients with TBI are particularly vulnerable to untreated pain in critical care because the use of behaviors for pain assessment is not always possible. Unrelieved pain can lead to increased vascular resistance and rapid changes in cerebral blood flow, which can compromise neurological recovery of critically ill patients with TBI (Zasler et al., 2006). Accordingly, any effort toward the validation of alternative measures of pain is a step toward improved pain management in this highly vulnerable group. To our knowledge, this exploratory study was the first to validate the use of bilateral BIS index for the purpose of pain assessment in critically ill unconscious and altered-LOC patients with TBI.

Overall, compared with baseline, BIS-R (+4.93%) and BIS-L (+8.43%) increased significantly during turning, whereas BIS-R (+1.60%) and BIS-L (+1.29%) remained quite stable during NIBP. As these results suggest, the presence of pain induced by the turning procedure may have contributed to increased level of awareness of patients with TBI leading to an increase in the BIS index in each hemisphere. These results are similar to those observed in two previous studies (Gélinas et al., 2011; Li et al., 2009) where the BIS index significantly increased (of +10% and between 20% and 30%, respectively) during a noxious stimulation in sedated and mechanically ventilated ICU adults (mostly with surgical diagnosis), yet lower fluctuations in BIS-R and BIS-L were observed in our sample of participants with TBI during turning. Because the BIS response is sensitive to nociception and is mediated by the use of analgesic and sedative agents (Brocas et al., 2002; Guignard, Menigaux, Dupont, Fletcher, & Chauvin, 2000), lower BIS fluctuations in this study may be attributable to the use of higher doses of these medications in patients with TBI compared with other ICU populations. Indeed, whereas participants with TBI in this study received, on average, 124.00 (*SD* = 54.86) μg of fentanyl in the hour before the turning procedure, postoperative cardiac surgery

TABLE 3. Description and Comparison of Median Fluctuations in BIS Index and fEMG Values for Each Hemisphere Recorded Across Assessments Periods in Participants During NIBP and Turning Procedures



Variables	Assessment Periods: 1 Minute Before (Baseline) Median (Q_{25}–Q_{75})	During Median (Q_{25}–Q_{75})	15 Minutes Postprocedure Median (Q_{25}–Q_{75})	Friedman Tests: $\chi^2(2)$	p
NIBP					
BIS-R	45.80 (41.00–56.38)	47.40 (41.64–61.47)	49.16 (41.13–56.40)	0.347	.841
BIS-L	44.73 (40.80–56.38)	46.02 (40.18–57.45)	48.45 (41.30–58.14)	0.636	.727
fEMG-R	33.20 (30.62–38.25)	32.12 (28.93–38.30)	32.66 (29.75–39.50)	2.435	.296
fEMG-L	30.48 (28.02–35.15)	29.14 (27.71–35.45)	29.57 (28.60–40.57)	3.920	.141
Turning					
BIS-R	46.21 (39.63–64.26)	51.14 (44.09–78.88)	49.47 (43.32–70.71)	5.040	.080
BIS-L	48.55 (39.35–62.07)	56.98 (44.51–76.01)	49.34 (37.23–62.20)	7.238	.027*
fEMG-R	34.58 (29.50–43.76)	39.46 (35.98–46.50)	33.68 (29.14–41.11)	10.160	.006**
fEMG-L	31.95 (28.81–43.94)	38.68 (33.13–46.17)	29.13 (27.70–39.08)	10.160	.006**

Note. BIS-R = bispectral index right; BIS-L = bispectral index left; fEMG-R = frontal electromyogram right; fEMG-L = frontal electromyogram left; NIBP = noninvasive blood pressure.
*$p \leq .05$. **$p \leq .01$. ***$p \leq .001$.

adults in Li et al. (2009) study received 17 μg (SD = 47 μg). Supporting this hypothesis, significant moderate negative correlations were found between BIS-L fluctuations and dosage of equianalgesic morphine as well as dosage of Diprivan received before data collection. Nevertheless, our results suggest that larger doses of opioid administration do not impede bilateral BIS fluctuations during a nociceptive procedure.

Interestingly, our results also suggest that fluctuations in BIS-R during nociceptive exposure could be significantly attenuated in patients with right-sided TBI (+3.01%) compared with those with left-sided TBI (+17.23%). In contrast, the occurrence of a left-sided TBI does not seem to affect BIS-L fluctuations during nociceptive exposure because similar increases in BIS-L were observed in participants with right-sided TBI (7.46%) and left-sided TBI (8.76%). Etiologically, the occurrence of a TBI often leads to the formation of cerebral edema on the affected hemisphere (Mindermann, Reinhardt, & Gratzl, 1992). Cerebral edema can lead to decreased cortical arousability in the affected area (Young, 2007). Considering this, milder increases in bilateral BIS-R values in participants with right-sided TBI during the nociceptive procedure are not surprising. Yet, in patients with left-sided TBI, even if a more pronounced increase in BIS-R was found (+17.23%) during the nociceptive procedure, a substantial increase in BIS-L (+8.76%) was also noted. This suggests that handedness and hemispheric dominance could play a role in the integration of nociceptive stimuli, especially in the presence of a brain injury (Pud, Golan, & Pesta, 2009).

TABLE 4. Pairwise Comparisons of Median BIS and fEMG Fluctuations in Each Hemisphere During Turning

Assessments	Post Hoc Wilcoxon Paired-rank Tests (With Bonferroni Correction[a]): $T(Z)$	p
1 minute before → turning		
BIS-R	−2.093	.016*
BIS-L	−2.549	.011*
fEMG-R	−2.355	.014*
fEMG-L	−1.870	.061
Turning → 15 minutes postturning		
BIS-R	−1.612	.107
BIS-L	−2.256	.017*
fEMG-R	−3.081	.002**
fEMG-L	−3.404	.001**
15 minutes postturning → 1 minute before		
BIS-R	−0.644	.520
BIS-L	−0.198	.843
fEMG-R	−0.646	.518
fEMG-L	−1.467	.142

Note. BIS-R = bispectral index right; BIS-L = bispectral index left; fEMG-R = frontal electromyogram right; fEMG-L = frontal electromyogram left.
[a]Adjusted Bonferroni p values: *$p \leq .017$, **$p \leq .003$, ***$p \leq .000$.

TABLE 5. Description and Comparison of Neutral Behaviors and Pain Behaviors Observed in Participants During NIBP and Turning

Behavioral Category	NIBP	Turning	Wilcoxon Paired-rank Test, *T*(*Z*)
Facial expression			
Eyes closed	24 (96.0%)	11 (44.0%)	
Relaxed face	22 (88.0%)	14 (56.0%)	
Sudden eye opening	–	12 (48.0%)	
Eye weeping	–	12 (48.0%)	
Frowning	–	7 (28.0%)	
Body movements (BMs)			
Absence of BM	20 (80.0%)	14 (56.0%)	
Flexion lower limb	–	6 (24.0%)	
Muscle tension			
No resistance	23 (92.0%)	21 (84.0%)	
Compliance with the ventilator[a]			
Easy ventilation or vocalization for nonintubated patients[b]	18 (94.7%)	16 (84.2%)	
No vocal	5 (83.3%)	3 (50.0%)	
Moaning	–	3 (50.0%)	
Frequency of behaviors suggestive of pain exhibited[c]			
Median (min–max)	0 (0–3)	3 (0–7)	−3.741***

Note. NIBP = noninvasive blood pressure.
[a]As n = 19 participants with TBI were mechanically ventilated at the time of data collection, percentages of behaviors within compliance with the ventilator category were computed on 19 participants. [b]As n = 6 participants with TBI were not intubated at the time of data collection, percentages of behaviors within vocalization category were computed on six participants. [c]Of note, behaviors suggestive of pain were considered in the computation of Wilcoxon rank test, whereas neutral behaviors associated with a resting state (i.e., relaxed face, eyes closed, absence of body movement, no resistance to passive movements, easy ventilation, and no vocal) were not.
*$p \leq .05$. **$p \leq .01$. ***$p \leq .001$.

Indeed, in this study, 92% of participants (n = 23) were right handed. Given that right-handed individuals usually have left hemispheric dominancy, this could explain why the BIS-L increased noticeably in participants during turning, even in the presence of a left-sided TBI.

Significant increases in facial EMG-R (+4.88 dB) were also observed during turning but not during NIBP. In addition, significant decreases in facial EMG-R (−5.78 dB) and facial EMG-L (−9.55 dB) were observed postturning. These results suggest that participants with TBI had increased facial reactions during the nociceptive procedure, whereas their facial expression remained mostly neutral during the nonnociceptive procedure and 15 minutes postprocedure. Significant increases in the frequency of pain behaviors (median increase of 3) were also observed in participants with TBI during turning, supporting the significant fluctuations in facial EMG-R observed during turning. Concomitant fluctuations in facial EMG and pain behaviors were also obtained in another study (Gélinas et al., 2011) in which increases of 10% in facial EMG and of 3 points in the CPOT score (Gélinas et al., 2006) were observed in mechanically ventilated ICU patients (with various diagnoses) during nociceptive procedures. Specifically, in our exploratory study, ≥28.0% of

TABLE 6. Spearman's Rank-order Correlations Between Frequency of Pain Behaviors and Median Changes in BIS Index for Each Hemisphere in Participants With Right-sided and Left-sided TBI[a]

	Right-sided TBI, n = 12		Left-sided TBI, n = 12	
	r_s	p	r_s	p
Pain behaviors: changes in BIS-R	−.213	.529	.986	.001***
Pain behaviors: changes in BIS-L	−.024	.955	.294	.571

Note. BIS-R = bispectral index right; BIS-L = bispectral index left; TBI = traumatic brain injury.
[a]One participant was not included in the computation of this table because he had bilateral TBI.
*$p \leq .05$. **$p \leq .01$. ***$p \leq .001$.

TABLE 7. Relationship Between TBI Severity, Variables Related to Therapeutic Regimen (e.g., Level of Sedation, Administration of Analgesics/Sedatives), and Participants' Fluctuations in Bilateral BIS and fEMG During Turning

	Spearman's Rank-order Correlations (r_s)			
	TBI Severity (n = 25)	**Level of Sedation: RASS Score (n = 25)**	**Equianalgesic Dose of Morphine (n = 12)**	**Dose of Diprivan (n = 11)**
Bilateral BIS value				
BIS-R	.069	−.108	−.027	−.285
BIS-L	−.577*	.314	−.409*	−.431*
Facial electromyogram				
fEMG-R	−.084	.262	.020	−.246
fEMG-L	−.181	−.259	.022	−.089

Note. TBI = traumatic brain injury; BIS-R = bispectral index right; BIS-L = bispectral index left; fEMG-R = frontal electromyogram right; fEMG-L = frontal electromyogram left.
*$p \leq .05$. **$p \leq .01$. ***$p \leq .001$.

participants with TBI showed sudden eye opening, eye weeping, and frowning during turning. Although behaviors such as sudden eye opening and eye weeping may seem to be atypical pain responses to nociceptive exposure, it is important to highlight that they were observed in 22.2%–66.7% of conscious participants (n = 9) who reported pain during turning in the larger-scale project. However, fluctuations in BIS index were only found to be significantly correlated with the frequency of pain behaviors during turning in participants with left-sided TBI and for BIS-R exclusively. Although right hemispheric dominance in the processing of painful stimuli has been recently documented (Ji & Neugebauer, 2009; Prochnow et al., 2013), use of BIS-R fluctuations for the detection of pain may only be possible in patients with left-sided TBI because the occurrence of a right-sided TBI seemed to attenuate BIS-R responses to nociceptive exposure. Another possible explanation of the lateralization in BIS values observed during turning is the fact that fluctuations in BIS-L seem to have been attenuated by the administration of analgesics and sedatives and the presence of more severe TBI. Thus, whereas increases in BIS-R could be indicative of pain perception in left-sided TBI, absence of fluctuations in BIS-L could be indicative of proper analgesia and sedation and could also indicate the presence of more severe brain lesions in patients with right-sided TBI exposed to nociceptive procedures.

Limitations

This exploratory study was not without limitations. First, because of the small sample size, the results cannot be generalized to all unconscious and altered-LOC patients with TBI in the ICU. Results may also not be applicable to patients with mild TBI because our sample was composed of almost exclusively patients with moderate and severe TBI. In addition, because participants in the study were not able to self-report and confirm the presence or absence of pain, it is not clear whether changes observed in the bilateral BIS were caused by pain and/or increased awareness after sensorial arousing during the turning procedure. Adding to this concern, fluctuations in bilateral BIS were not always correlated with the frequency of pain behaviors observed in participants with TBI during turning. A randomized application of an auditory stimulus (some before and some after the procedures) may have contributed to better understanding the variability in the bilateral BIS index induced by nociceptive versus by nonnociceptive sensorial stimulation. Furthermore, although participants were turned on both sides during the nociceptive procedure, they were either positioned on the back or on the right side or the left side at 15 minutes postturning. Considering that BIS values are influenced by cerebral blood flow, this element should be considered in further validation studies because it may influence fluctuations in BIS postturning. Finally, participants' behavioral responses could also have influenced BIS reactivity during turning. Although median facial EMG values were lower than 55 dB in each participant throughout data collection (suggesting low interferences with BIS values), it is impossible at this point to estimate how suppression of behaviors could influence BIS fluctuations during nociceptive procedures and, consequently, to fully appreciate the potential utility of bilateral BIS for pain detection in patients with TBI with motor paralysis.

Conclusions and Implications for Practice

In the ICU, patients with TBI are often under heavy doses of sedatives, limiting their capacity to react behaviorally to external stimulation such as pain.

Similarly to patients under anesthesia, dissociation between cortical integration of nociceptive input and behavioral reactivity has been reported in brain-injured patients with altered LOC (Laureys, 2005). In that sense, the BIS technology could provide insightful information about patients' analgesic needs in a context where other observational signs for pain assessment are not available. Specifically, findings from this exploratory study suggest that the bilateral BIS device could be useful for the detection of pain in unconscious and altered-LOC critically ill patients with left-sided TBI. Although future research is warranted to further examine the validity of the bilateral BIS in brain-injured populations (especially those with motor paralysis), this technology could eventually be considered as a complementary method to help clinicians in regards to detecting pain during nociceptive procedures and evaluating the effectiveness of pain management interventions. However, clinicians must keep in mind that the BIS monitoring system used in this study was the BIS VISTA. Other commercially available BIS monitoring systems may employ different mathematical algorithms (Paul & Umamaheswara Rao, 2006). Given that a tool is considered valid within the population and context it has been tested with exclusively (Streiner & Norman, 2008), BIS devices other than the BIS VISTA may lead to different results in critically ill patients with TBI. Still, the bilateral BIS may be an interesting technique to further study in the pain assessment process of patients with TBI because of its noninvasive nature and its suitability for use at the bedside.

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