Assessing pain in critically ill brain-injured patients

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Assessing pain in critically ill brain-injured patients: a psychometric comparison of 3 pain scales and videopupillometry

Christine Bernard[a], Valentine Delmas[a], Claire Duflos[b], Nicolas Molinari[b], Océane Garnier[a,c], Kévin Chalard[a], Samir Jaber[c], Pierre-François Perrigault[a], Gérald Chanques[a,c,*]

Abstract

Three clinical scales (the Nociception Coma Scale adapted for Intubated patients [NCS-I], its Revised version [NCS-R-I], and the Behavioral Pain Scale [BPS]) and videopupillometry were compared for measuring pain in intubated, noncommunicating, critically ill, brain-injured patients. Pain assessment was performed before, during, just after, and 5 minutes after 3 procedures: the reference non-nociceptive procedure (assessment of the Richmond Agitation Sedation Scale) and 2 nociceptive procedures (turning and tracheal suctioning). The primary endpoint was construct validity (discriminant and criterion validation), determined by comparing pain measurements between different times/procedures. Secondary endpoints were internal consistency, inter-rater reliability, and feasibility. Fifty patients (54% women, median age 63 years [56-68]) were included 13 [7-24] days after brain injury (76% hemorrhagic or ischemic strokes). All tools increased significantly more ($P < 0.001$) during the nociceptive procedures vs the non-nociceptive procedure. The BPS was the only pain tool that did not increase significantly during the non-nociceptive procedure ($P = 0.41$), suggesting that it was the most discriminant tool. The BPS, NCS-I, and NCS-R-I were good predictors of nociception with areas under the curves ≥0.96, contrary to videopupillometry (area under the curve = 0.67). The BPS, NCS-I, and NCS-I-R had high inter-rater reliabilities (weighted kappa = 0.86, 0.82 and 0.84, respectively). Internal consistency was moderate (>0.60) for all pain scales. Factor analysis represented a majority of information on a first dimension, with motor domains represented on a second dimension. Scale feasibility was better for the NCS-I and NCS-R-I than for the BPS. In conclusion, the BPS, NCS-I, and NCS-R-I are valid, reliable, and acceptable pain scales for use in intubated critically ill, brain-injured patients, unlike videopupillometry. Future research requires tool design centered on domains of observation adapted to this very specific population.

Keywords: Pain, Pain measurement, Brain injuries, Consciousness disorders, Behavior, Intubation, Intensive care unit, Critical care

1. Introduction

Over the past decade, great efforts have been made to better manage pain in critically ill patients.[32] In addition to ethical concerns, pain management has been associated with lower sedative use and improved patient outcomes.[8,18] However, the literature on pain management in critically ill, brain-injured (CIBI) patients remains scarce.[18,32] The recent American guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the intensive care unit (ICU) highlighted as an evidence gap and future direction of research that "[pain] scale revisions could enhance the validity of their use in ICU patients with brain injury and other neurologically critically-ill patients".[18] The validation study of the Nociception Coma Scale (NCS) was published in *PAIN* in 2010,[38] then later revised to a simpler version (NCS-Revised or NCS-R).[13] Based on behavioral observations taking into account 3 or 4 domains (facial expressions, visual, motor, and verbal responses), these scales were constructed for and validated in brain-injured patients. They demonstrated good psychometric properties and, considering that brain injury and neurological deficiencies significantly alter/diminish pain expression in this group, constituted a considerable step forward in this challenging branch of pain management.[3] However, the NCS(-R) includes a verbal observational domain and, thus, was not constructed for use in intubated patients, although invasive mechanical ventilation is the most critical period for pain/discomfort in ICU patients (regardless of brain injury).[29,31]

In this context, we obtained permission from Prof Schnakers to adapt the NCS to intubated patients, creating the NCS-I and NCS-R-I, and proceeded with their psychometric validation. Simultaneously, we also compared these new scales with the

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

[a] Department of Anesthesia and Critical Care Medicine, Montpellier University Hospital Gui de Chauliac, Montpellier, France, [b] Department of Medical Information and Statistics, Montpellier University Hospital La Colombière, Institut Montpelliérain Alexander Grothendieck (IMAG), University of Montpellier, CNRS, Montpellier, France, [c] Department of Anesthesia and Critical Care Medicine, Montpellier University Hospital Saint Eloi, PhyMedExp, University of Montpellier, INSERM, CNRS, Montpellier, France

**Corresponding author. Address: Département d'Anesthésie et de Réanimation, Hôpital Saint Eloi-CHU de Montpellier, 80 Ave Augustin Fliche, 34295 Montpellier Cedex 5, France. Tel.: 00 33 4 67 33 72 71; fax: 00 33 4 67 33 74 48. E-mail address: g-chanques@chu-montpellier.fr (G. Chanques).*

Behavioral Pain Scale (BPS)[10,30] which is one of the most validated and used pain scales in critically ill patients, but like the NCS(R)-I, still has some concerns for validity among CIBI patients.[18] Given that all the latter have subjective components, we also included videopupillometry as an objective measure of pain in nonverbal patients. Videopupillometry has been reported as more sensitive than behavioral observation in a population of critically ill patients without brain injury.[27] To summarize, we conducted the present psychometric study to compare 3 clinical tools (NCS-I, NCS-R-I, and BPS) and videopupillometry for pain assessment in a specific population of intubated CIBI patients.

2. Materials and methods

2.1. Ethics approval

The study was approved by a scientific/ethics committee (*Comité de Protection des Personnes Sud-Méditerranée-1* [ID-RCB: 2016-A00748-43]) according to French law[43] and registered on ClinicalTrials (NCT02830256).

2.2. Patient population

A 16-bed, medical-surgical, neuro-ICU at the University Hospital of Gui de Chauliac participated in this observational study from November 2016 to November 2017. Because of the absence of guidelines regarding the use of pain tools in CIBI patients,[18] no pain tool was routinely used in noncommunicating patients hospitalized in the neuro-ICU before the study. Consecutive patients aged older than 18 years admitted to the ICU after a brain injury were eligible if they (1) required invasive ventilatory support (endotracheal or tracheostomy tube), (2) showed signs of awakening after the initiation of sedation weaning, and (3) were unable to self-report their pain using a numeric rating scale.[12] Exclusion criteria were brain-stem involvement, neurovegetative crisis, and ocular lesions that might alter the accuracy of videopupillometry (glaucoma, keratitis, conjunctivitis, cataract, and anisocoria); pregnant or lactating women; and vulnerable and protected persons. All patients were affiliated with the French Health Care System. According to French law concerning research based on routine care and entailing minimal risks and constraints,[43] the patient relatives' nonopposition to patient participation in the research was requested,[43] as well as the patient's approval as soon as he/she was able to communicate.

2.3. Conduct of the study

Patients were screened daily for eligibility by investigators and included in the study after consent from their relatives. When awakening signs appeared, defined in our study by increasing scores on the Richmond Agitation Sedation Scale (RASS), the start of spontaneous breathing or coughing during a tracheal suctioning, investigators were contacted by the bedside nurse to assess pain during 3 routine care procedures planned by the bedside nurse: (1) evaluation of the sedation level following a standardized approach using the RASS method,[7,39] consisting of calling the patient's name or gently touching the shoulders, defined as the reference non-nociceptive procedure,[6] (2) tracheal suctioning, and (3) turning onto the side, the 2 latter procedures being the 2 most frequent and recognized nociceptive procedures in ICU mechanically ventilated patients.[15,31,33,35] Pain was assessed 5 minutes before, during, just after, and 5 minutes after each of the 3 care procedures, which were spaced 20 minutes apart.

2.4. Data recording

2.4.1. Pain

Pain was assessed with pain scales and a videopupillometer. Pain scale descriptors and instructions for use were explained to the bedside nurses by the same investigator (C.B.) before the first procedure for each patient. Pain scales were used by the investigator and the nurse at the same time. Data were reported on separate sheets, the 2 assessors being blinded to each other. The videopupillometer was used by a second investigator, blinded to the first one, after the clinical assessment of pain had been performed to avoid any interaction between the videopupillometry and the pain scales.

2.4.1.1. Pain scales

2.4.1.1.1. Behavioral Pain Scale

Widely used in ICUs to assess pain in noncommunicating patients, the BPS consists of 3 subdomains (facial expression, upper limb movement, and compliance with mechanical ventilation), each containing 4 items rated from 1 to 4.[30] The total BPS score ranges from 3 (no pain) to 12 (maximal pain). In the general population of ICU patients, a value higher than 4 is considered clinically significant,[10,11] and a value higher than 5 is considered as representing severe pain.[5,15] (see **Table 1** for descriptions).[9,10]

2.4.1.1.2. Nociception Coma Scale, Revised Nociception Coma Scale (NCS-R), and Nociception Coma Scale for Intubated patients

The NCS was constructed to assess 4 behavioral domains in patients with disorders of consciousness who are not intubated (ie, facial expression, visual response, verbal response, and motor response).[38] Each domain contains 4 items, rating from 0 to 3. The total NCS score ranges from 0 (no pain) to 12 (maximal pain). The visual response was subsequently removed from the original NCS because it rarely changes during nociceptive procedures.[13] Also, eye-opening can be a sign of recovery from brain injury rather than a pain behavior. The NCS-R ranges from 0 (no pain) to 9 (maximal pain). Pain thresholds for both the revised NCS (NCS-R) and the original NCS were between 4 and 5.[13,38] To adapt the NCS and the NCS-R to intubated mechanically ventilated patients (NCS-I and NCS-R-I), we replaced the verbal domain that is unusable in these patients, with the mechanical ventilation domain from the BPS score, both domains having the same number of items (n = 4), from no pain to maximal pain.

2.4.1.2. Videopupillometry

The pupil size was measured using a handheld videopupillometer (Algiscan; IDMed, Marseille, France) with an acquisition of 67 images per second with an accuracy of 0.01 mm. Pupil size measurements have been reported to change more substantially than behavioral signs in a study of 48 mechanically ventilated patients.[27] Also, pupillometry was the most discriminant electrophysiological tool regarding pain assessment, compared with heart rate monitoring and bispectral index measurements. As specifically concerns the CIBI patients included in this study, brain-stem injuries and clinical anisocoria were considered as exclusion criteria because of an expected inaccuracy of pupillometry in this specific context.

2.4.2. Demographic and medical data

Patient characteristics were recorded from medical files including age, sex, height, weight, body mass index (kg/m^2), Simplified

Table 1

Description of the 3 clinical pain scales.

Behavioral Pain Scale (BPS)	Nociception Coma Scale adapted for Intubated patients (NCS-I)	Nociception Coma Scale-Revised version—adapted for Intubated patients (NCS-R-I)
Facial expression	Facial expression	Facial expression
1. Relaxed	0. None	0. None
2. Partially tightened (= brow lowering)	1. Oral reflexive movement/startle response	1. Oral reflexive movement/startle response
3. Fully tightened (= eyelid closing)	2. Grimace	2. Grimace
4. Grimacing (=folded cheek)	3. Crying (tears)	3. Crying (tears)
Upper limbs	Motor response	Motor response
1. No movement	0. None	0. None
2. Partially bent	1. Abnormal posturing	1. Abnormal posturing
3. Fully bent with finger flexion	2. Flexion withdrawal	2. Flexion withdrawal
4. Retracted, opposition to care	3. Localization to noxious stimulation	3. Localization to noxious stimulation
Compliance with ventilaton	Compliance with ventilaton	Compliance with ventilaton
1. Tolerating ventilation	0. Tolerating ventilation	0. Tolerating ventilation
2. Coughing but tolerating ventilation most of the time	1. Coughing but tolerating ventilation most of the time	1. Coughing but tolerating ventilation most of the time
3. Fighting ventilator but ventilation possible sometimes	2. Fighting ventilator but ventilation possible sometimes	2. Fighting ventilator but ventilation possible sometimes
4. Unable to control ventilation	3. Unable to control ventilation	3. Unable to control ventilation
Not applicable	Visual response	Not applicable
	0. None	
	1. Startle	
	2. Eyes movements	
	3. Fixation	

Acute Physiology Score II (SAPS II) calculated within 24 hours after ICU admission, type of ICU admission, and time between admission and inclusion. Sedation levels were measured using the RASS (performed by the investigator at baseline before enrollment). Physiological parameters (heart and respiratory rates, arterial blood pressure, and pulse oximetry) were measured through bedside monitoring and recorded by the second investigator.

2.5. Statistical analysis

The psychometric properties of the pain tools used were assessed using the recommended terminology and methods for the assessment of pain in critically ill, nonverbal patients.[18,21]

2.5.1. Construct validity (primary endpoint)

There is no existing gold standard for measuring pain in nonverbal, CIBI patients. The measurement of the psychometric properties of the 3 pain scales and the videopupillometry was consequently based on indirect validation.

2.5.1.1. Discriminant validation

A valid pain tool would be able to significantly change during a nociceptive procedure (tracheal suctioning and turning), but not during the non-nociceptive reference procedure (RASS measurement). The Mann–Whitney–Wilcoxon test for paired data was used to test the difference between 2 conditions (before and during a procedure) for each pain tool.

2.5.1.2. Criterion validation

Because validating a pain tool is very challenging in nonverbal patients, we used required procedures that were notoriously nociceptive in critically ill patients (ie, turning and tracheal suctioning)[15,31,33,35] as the reference procedures for assessing the ability of the pain tools to detect pain.[11] This was conducted to show and compare the performance of the pain tools. Receiving operator characteristic (ROC) curves were constructed using the nociceptive procedures as the reference. Pain measurements obtained before and during the 2 nociceptive procedures (tracheal suctioning and turning) were included for analysis. DeLong, DeLong, and Clarke-Pearson method was used to compare ROC curves.[17]

2.5.2. Reliability

2.5.2.1. Internal consistency

Internal consistency was measured for the pain scales using the Cronbach alpha method.[14] A Cronbach alpha coefficient between 0.6 and 0.7 reflects a moderate internal consistency, while values over 0.7 reflect high internal consistency (ie, the inter-relation between each domain of the tool).[18,21] Cronbach alpha coefficients were compared among the 3 scales using the Feldt method.[10,19] Pairwise comparisons of Cronbach alpha coefficients were made between 2 pain scales using the same method. Furthermore, the factor structure of the pain scales was extracted by performing exploratory principal component analysis to determine the contribution of each item of the scales.[24]

2.5.2.2. Inter-rater reliability

Inter-rater reliability of the pain tools was tested by the Cichetti-Allison weighted kappa coefficient.[25] Coefficients above 0.80, 0.60, and 0.40 are considered as measuring “near perfect,” “important,” and “moderate” agreement,[18,21,25] respectively. Comparisons of kappa coefficients between scales were made using the z test.[1,10]

2.5.3. Scale feasibility

After the completion of the study, a questionnaire was sent to all observers to rate how they appreciated the precision, usefulness, and feasibility of the pain scales. A 5-point Likert scale was used (ie, very positive, positive, moderately positive, negative, or very negative).

2.5.4. Number of patients necessary to include for analysis

The power calculation was based on the discriminant validation of the pain tools (primary endpoint). A sample of 50 patients was calculated as necessary to demonstrate a variation of the BPS from 3 to 5 (±2), of the NCS-I or NCS-R-I from 0 to 4 (±1), and of the pupil size from 3 to 5 mm (±2), with an α of 0.05 and a β of 0.20.

2.5.5. Presentation of data

Quantitative data are shown as medians and 25th to 75th percentiles. A *P*-value of ≤0.05 was considered statistically significant. Data were analysed using SAS Enterprise Guide version 7.12 (2016) (SAS Institute, Cary, NC) and R software version 3.4.3 (November 30, 2017).

3. Results

Among the 401 patients admitted to the neuro-ICU during the study period, 84 patients were eligible and 50 patients were included. **Figure 1** shows the study flowchart. The median age was 63 (56-68) years, and SAPS II was 47 (37-56). There were 54% women. The main reasons for admission were subarachnoid hemorrhage (46%), intraparenchymal hematoma (16%), ischemic stroke (14%), traumatic brain injury (8%), postoperative brain tumor (6%), and recovery after cardiac arrest (6%). **Table 2** shows the patients' medical and demographic characteristics. Each patient was assessed 4 times (before, during, just after, and 5 minutes after) relative to 3 different care procedures, accounting for 600 pain assessments.

3.1. Discriminant validation (primary endpoint)

Figure 2 shows the variation of the pain tools at the different times of measurement, for each of the 3 care procedures. Each of the 3 pain scales and the pupil size increased significantly ($P < 0.001$) during both tracheal suctioning and turning (nociceptive procedures). The increase in pain scales and pupil size was also significantly higher during the nociceptive procedures than during the reference non-nociceptive procedure. All pain evaluations except the BPS increased significantly during the reference non-nociceptive procedure ($P < 0.001$ for the NCS-I and pupil size; $P = 0.046$ for the NCS-R-I). The BPS was therefore the only pain tool that increased significantly during the nociceptive procedures ($P < 0.001$), but not during the non-nociceptive procedure ($P = 0.41$). This demonstrated that all pain tools reached the discriminant validation, but the BPS could be the most discriminant tool.

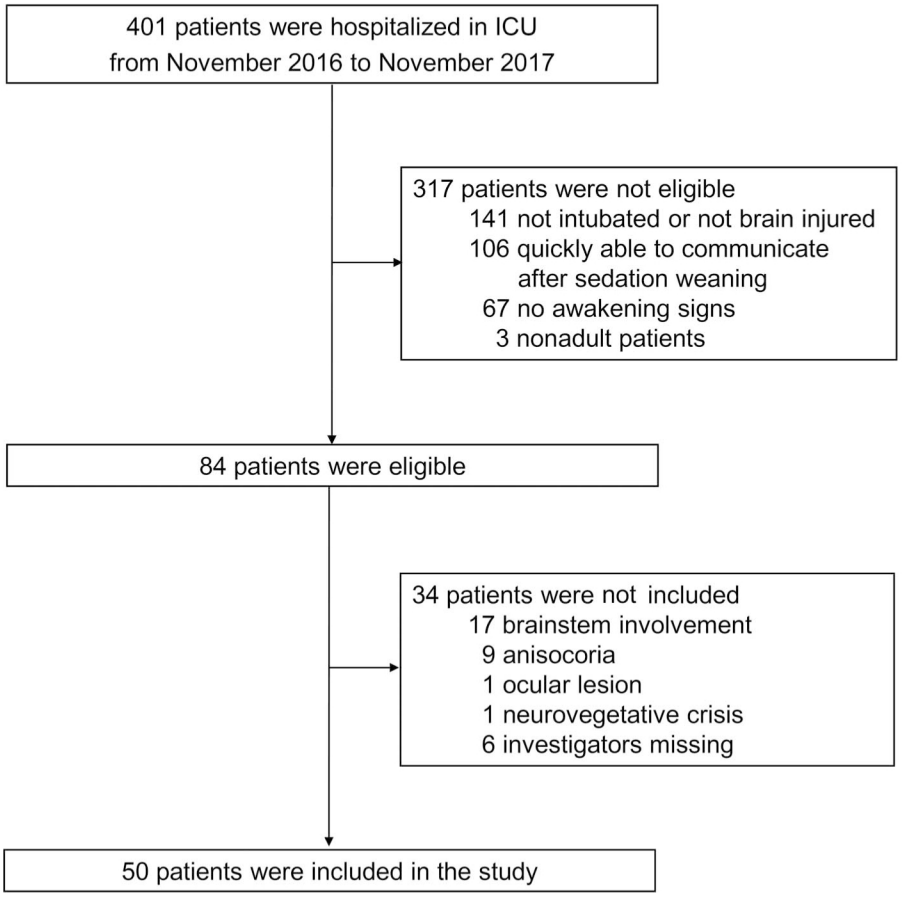

Figure 1. Study flowchart. ICU, intensive care unit.

Table 2

Demographic and medical characteristics of the 50 patients included for analysis.

Age (y)	63 (56 to 68)
Sex (F/M)	27/23
Body mass index (kg/m^{-2})	26 (24 to 31)
Reason for admission, n (%)	
Subarachnoid hemorrhage	23 (46%)
Intraparenchymal hematoma	8 (16%)
Ischemic stroke	7 (14%)
Traumatic brain injury	4 (8%)
Postoperative brain tumor	3 (6%)
Cardiac arrest	3 (6%)
Other	2 (4%)
Time between brain injury and enrolment (d)	13 (7 to 24)
Simplified Acute Physiology Score II (SAPS II)	47 (37 to 56)
Richmond Agitation Sedation Scale (RASS)	−3 (−4 to −2)
Glasgow level calculated without the verbal domain	5 (4 to 7)
Coma Recovering Scale-Revised (CRS-R)	6 (4 to 8)

Quantitative data are shown as medians and 25th to 75th percentiles.

3.2. Criterion validation

Figure 3 shows the ROC curves constructed according to the nociceptive procedures as the gold standard. The 3 pain scales (BPS, NCS-I, and NCS-R-I) had high areas under the curve (AUCs between 0.96 and 0.97) lacking detectable statistical differences among them, suggesting similar performances among the pain scales. The pupil size had a small AUC (0.67), significantly lower than the pain scales ($P < 0.001$ for each pairwise comparison between the pupil size and the pain scales). This suggests that measuring pupil size had a poor performance when assessing pain in this specific patient population. Analysis of monitored vital signs also showed small AUCs: 0.62 for heart rate, 0.75 for mean arterial blood pressure, and 0.76 for respiratory rate. Pulse oxymetry was very stable throughout the procedures: 98% (97%-99%).

3.3. Internal consistency

Cronbach alpha coefficients were significantly different among the 3 pain scales ($P < 0.001$), from 0.61 (95% confidence interval 0.56-0.66) for the BPS, through 0.69 (0.64-0.73) for the NCS-R-I and up to 0.70 (0.66-0.74) for the NCS-I. Even if the Cronbach alpha coefficient was significantly higher for the NCS-R-I and the NCS-I vs that for the BPS

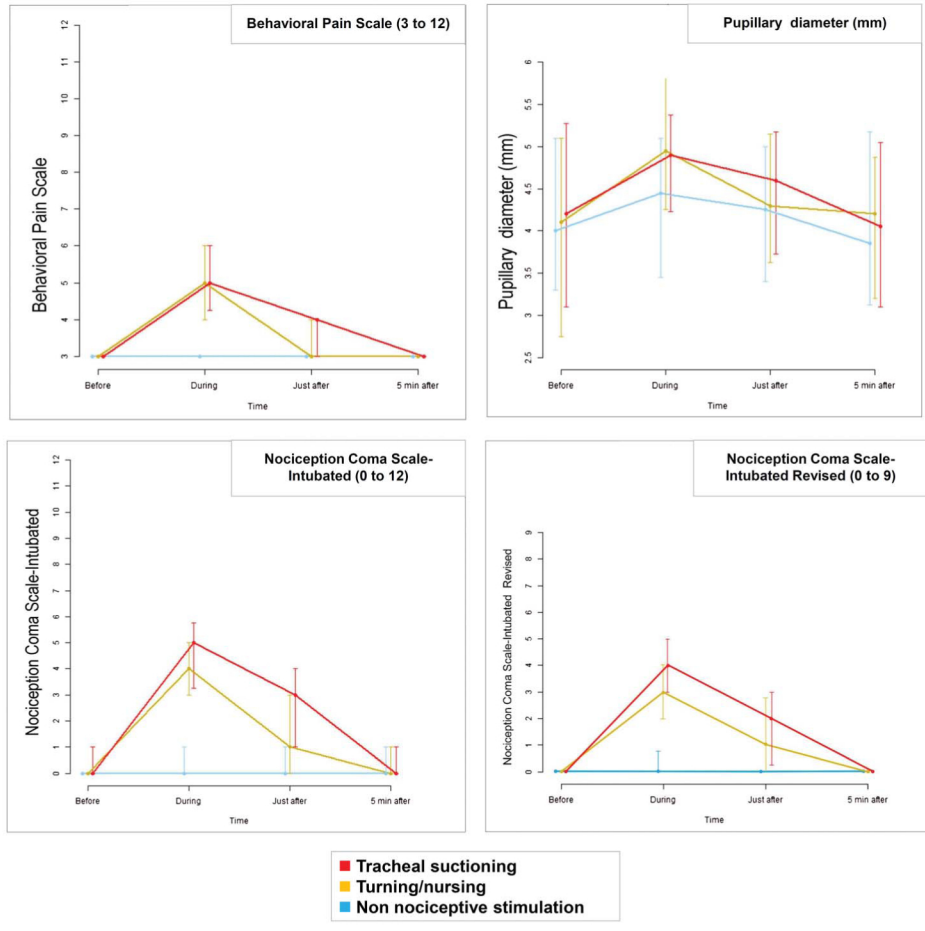

Figure 2. Variation of 3 clinical pain scales and videopupillometry at the different times of measurement, for each of the 3 care procedures. This figure shows the variation of the pain tools at the different times of measurement (before, during, just after, and 5 minutes after) relative to each of the 3 care procedures. The scores for the 3 clinical pain scales, and the pupillary diameter (mm), are shown as medians (points) and interquartile ranges (upper and lower bars).

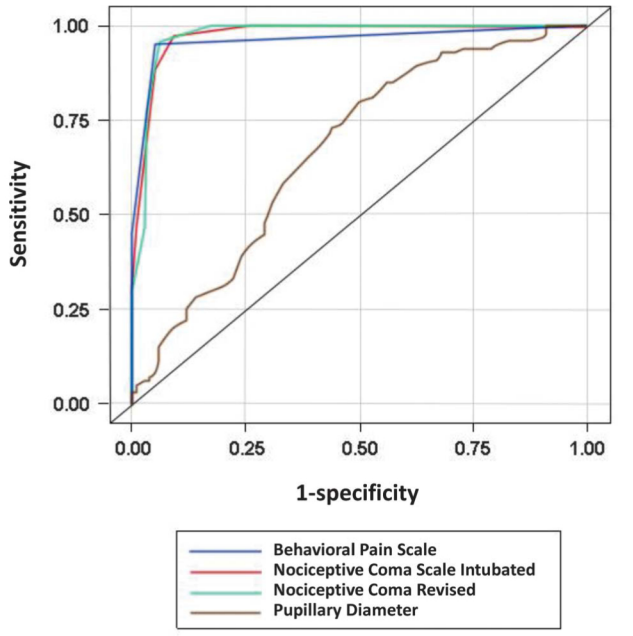

Figure 3. Receiver operating characteristic (ROC) curves of the 3 clinical pain scales and videopupillometry associated with pain (nociceptive procedures) Measurements of the BPS, NCS-I, NCS-R-I, and videopupillometry obtained before and during the 2 nociceptive procedures (tracheal suctioning and turning) were included for analysis. The 3 clinical pain scales (BPS, NCS-I, and NCS-R-I) were more predictive of pain (ie, the nociceptive procedures) than videopupillometry ($P < 0.001$). No significant differences were found among the 3 clinical pain scales. The areas under the curve (AUCs) were 0.96 (95th confidence interval 0.94-0.99) for the BPS and 0.97 (0.95-0.99) for the NCS-I and NCS-R-I. Thresholds determined by ROC analysis were 4 for the BPS and 2 for the NCS-I and NCS-R-I. BPS, Behavioral Pain Scale; NCS-I, Nociception Coma Scale adapted for Intubated patients; NCS-R-I, Revised version of the Nociception Coma Scale, adapted for Intubated patients.

($P < 0.001$ for each pairwise comparison), these results suggest that the internal consistency was only moderate for all 3 pain scales. The principal component analysis showed that all 3 pain scales were primarily two-dimensional with a principal dimension representing 56% of the variance for the BPS, 53% for the NCS-I, and 62% for the NCS-R-I. The motor domain for each of the 3 scales was poorly represented by the principal dimension and correctly represented by the second dimension.

3.4. Inter-rater reliability

The weighted kappa coefficient assessed the inter-rater reliability of the pain scales, with values between 0.82 (0.78-0.85) for the NCS-I, 0.84 (0.81-0.87) for the NCS-R-I, and 0.86 (0.83-0.89) for the BPS. These results suggest that the inter-rater reliability was high for all 3 pain scales. The weighted kappa coefficient was significantly higher for the BPS compared with the NCS-I ($P = 0.01$), but not for the NCS-R-I ($P = 0.24$).

3.5. Scale feasibility

Fifteen (71%) observers from among the 21 who participated in the study sent back the questionnaire. Regarding the proportion of ratings that were moderately to very positive, the BPS, NCS-I, and NCS-R-I were believed to be precise by 80%, 93%, and 93% of users, respectively. The usefulness of the scales was 87% for the BPS and 100% for the NCS-I/NCS-R-I. The easiness of learning was 67% for the BPS and 80% for the NCS-I/NCS-R-I. The scale that was found the most frequently easy or very easy to learn was the NCS-R-I (57%), compared with the others (NCS-I = 47%; BPS = 27%).

4. Discussion

The main finding of this psychometric study of pain assessment in mechanically ventilated brain-injured patients is that the BPS, the NCS-I, and the NCS-R-I are valid and reliable pain scales. The BPS is the most discriminant tool (ie, the only one that did not change significantly during the reference non-nociceptive procedure). However, it has the lowest internal consistency, although the latter is only moderate for all the tested pain scales. In addition, the BPS had the lowest user preference from among our participating neurocritical care givers. Contrary to the clinical pain scales, videopupillometry was not validated in this specific population of patients and had poor discriminant and criterion validation properties. These findings support the use of the BPS and NCS-I/NCS-R-I in CIBI patients. As concerns the latter scales, a detailed analysis of internal properties (consistency and factor analysis) suggests that there is room for future improvement in scale structure for this specific patient population.

Pain assessment is challenging in critically ill, mechanically ventilated patients because these patients are often unable to communicate their pain, which is the gold standard of pain assessment in human beings.[12] Over the past decade, the implementation of clinical behavioral pain scales in ICU settings has been beneficial for pain recognition and patient outcomes.[18] However, a recent international, multicenter, neuro-ICU audit showed that although a majority of patients received analgesics during their ICU stay, pain assessments were almost never provided due to the absence of pain protocols in the studied ICUs.[45] Subsequently, the applicability of pain scales for patients without brain injury to those with brain injuries emerged as a knowledge gap of interest. To start answering this question, the inter-rater reliability of the BPS was measured in 151 intubated patients with diverse brain injuries and showed a similar agreement to that demonstrated in this study (kappa coefficient of 0.83).[44] More recently, the inter-rater reliability and discriminant validation were tested for the BPS in 2 studies including 50[16] and 37[36] traumatic brain-injured patients, respectively, and with good psychometric properties. However, the BPS increased significantly during the reference "non-nociceptive" procedure, ie, an eye-care procedure in both studies. By contrast, this study is the only one that uses an absolutely non-nociceptive procedure, thus enabling a robust discriminant validation. This is due to recent data that showed that even a priori non-nociceptive procedures such as dressing changes, that have been used as reference non-nociceptive procedure in previous studies,[9,11] could be painful in some patients.[4,6] This lead to the decision to use the RASS procedure as the reference non-nociceptive procedure that absolutely prevents pain contamination.[6,34] This study is also the first to assess the psychometric properties of the NCS and NCS-R specifically for intubated patients. Previous studies in nonintubated, brain-injured patients with diverse brain injuries included 48 patients to test the NCS[38] and 64 patients to test the NCS-R.[13] The inter-rater reliability was tested only for the NCS and was moderate (kappa = 0.61), while the discriminant validation demonstrated very good properties for both the NCS and the NCS-R. Internal consistency was not tested for the NCS and NCS-R. Previous studies in traumatic brain injuries reported a good internal consistency for the BPS (Cronbach alphas between 0.7 and 0.9),[16,36] better than in this study (Cronbach alpha between 0.6 and 0.7 for all pain scales). This might be

explained by the differences in patient populations, the present study including diverse brain injuries with a majority of vascular disease (76%) and a minority of trauma or surgeries (14%). A study of 80 noncommunicating ICU patients with nontraumatic brain injuries[37] reported that the most frequent behaviors were facial reactions (eg, brow lowering, orbit tightening, and eye movements), ventilator asynchrony, and muscle rigidity, but body movements were less present. The latter is consistent with this study where the motor domain was less represented by the first principal component, explaining a moderate internal consistency. In traumatic brain-injured patients, pain behavior might be different. A study of 45 ICU patients with traumatic brain injury reported that behaviors were mostly "untypical," including uncommon responses such as flushing, sudden eye opening, eye weeping, and flexion of limbs.[2] In any case, the BPS demonstrated globally good psychometric properties (discriminant and criterion validation, and inter-rater reliability), allowing its use in both traumatic[16,36] and nontraumatic (this study) brain-injured patients. In the same way, the Critical Care Observation Pain Tool (CPOT), that, along with the BPS, is the most validated and used tool in ICU settings throughout the world, has also been validated in ICU brain-injured patients with diverse brain injuries.[23,26,41,42] The CPOT was not tested in this study to make the study more feasible for the bedside nurses, to avoid potential bias related to performing too many scales in contrast with routine care, and because previous studies had already shown that the BPS and CPOT were very similar.[10,40]

Our study has several limitations. First, we were not able to perform a convergent validation of the pain scales (correlation coefficients) because, contrary to previous reports in non–brain-injured ICU patients,[27,28] videopupillometry poorly performed in our patient population, even if injuries potentially associated with pupillary response were considered as exclusion criteria (brainstem injuries and clinical anisocoria). This is a major finding of this study. Recently, the electrophysiology of pain based on heart rate variability has shown promising results in ICU patients, regardless of brain injury status.[11,22] Also, due to the study purpose, the patients were unable to self-report their pain intensity, and thus, the correlation between self-reported pain intensity and the behavioral pain scales could not be measured. However, this is also part of the reason why behavioral pain scales have been developed as surrogate markers of pain in the first place. When patients are able to self-report their pain intensity, even if significant, the correlation between self-reported pain scales and behaviors is poor, making the use of behavioral pain tools possibly inappropriate.[12] Second, the item selection and content validation of the pain scales were not performed before this study. Rather, this study deals with pre-existing pain scales adapted to a more-specific type of population (brain-injured patients). However, the modification of the NCS(-R) for intubated patients was made by expert clinicians in intensive and neurointensive care. Moreover, the content validation is supported by recent data in brain-injured patients, as previously discussed.[37] Finally, the psychometric properties of the pain scales assessed in this study can be quoted within the range of well-validated pain scales in the general ICU population, following the method used in the recent guidelines regarding pain management in ICU patients[18] (see eTable 1 in the electronical supplementary material, available at http://links.lww.com/PAIN/A834). However, the principal component analysis of the pain scales highlighted that some items could be modified to better fit with this specific population, contrary to what has been reported for non–brain-injured patients (for the BPS).[9,10] In the same way, a greater proportion of neurocritical caregivers preferred the NCS-I/NCS-R-I over the BPS in this study. This may be because the NCS was specifically constructed for brain-injured patients. Recent data on brain-injured patients reported several different and new types of behavior when assessed by video recording.[20] New pain tools specifically designed for CIBI patients will be developed in the future. These tools will need to be assessed for psychometric validity and feasibility in regards to pre-existing, routinely used tools such as the BPS, NCS, and CPOT. Finally, the next step in pain research will be to assess the impact of analgesia protocols using specifically validated pain scales for improving the pain management and related outcomes in CIBI patients, as demonstrated in non–brain-injured patients.[8,18]

5. Conclusions

In contrast to videopupillometry, the BPS, NCS-I, and NCS-R-I are valid, reliable, and acceptable pain tools for use in mechanically ventilated brain-injured patients. In ICU settings where the BPS is commonly used for assessing pain in nonverbal patients, the BPS can also be used in the specific subgroup of brain-injured patients. In neurological settings where the NCS or NCS-R are commonly used for assessing pain in brain-injured patients, the NCS-I or NCS-R-I can now also be used in the specific subgroup of intubated patients. Future pain scales that will be constructed specifically for brain-injured ICU patients should be tested against these widely used tools.

Conflict of interest statement

In contexts unrelated to the present work, G. Chanques has consulted for and received honorarium from Orion Pharma and Aspen Medical France. S. Jaber has consulted for and received honorarium from the following companies: Dräger, Hamilton, Maquet, and Fisher Paykel. C. Bernard and G. Chanques report a National Grant from the Direction Générale de la Santé (DGOS): Projet Hospitalier de Recherche Infirmière et Paramédicale. The remaining authors declare that they have no conflicts of interest or financial supports to disclose.

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References

[1] Altman DG, editor. Practical statistics for medical research. London: Chapman and Hall, 1991.

[2] Arbour C, Choiniere M, Topolovec-Vranic J, Loiselle CG, Puntillo K, Gelinas C. Detecting pain in traumatic brain-injured patients with different levels of consciousness during common procedures in the ICU: typical or atypical behaviors? Clin J Pain 2014;30:960–9.

[3] Arbour C, Gélinas C. Behavioral and physiologic indicators of pain in nonverbal patients with a traumatic brain injury: an integrative review. Pain Manag Nurs 2014;15:506–18.

[4] Ayasrah S. Care-related pain in critically ill mechanically ventilated patients. Anaesth Intensive Care 2016;44:458–65.

[5] Chanques G, Conseil M, Roger C, Constantin JM, Prades A, Carr J, Muller L, Jung B, Belafia F, Cisse M, Delay JM, de Jong A, Lefrant JY, Futier E, Mercier G, Molinari N, Jaber S. Investigators of SOS-ventilation trial. Immediate interruption of sedation compared with usual sedation care in critically ill postoperative patients (SOS-ventilation): a randomised, parallel-group clinical trial. Lancet Respir Med 2017;5:795–805.

[6] Chanques G, Delay JM, Garnier O, Berra J, Prades A, Carr J, de Jong A, Molinari N, Jaber S. Is there a single non-painful procedure in the intensive care unit? It depends! Intensive Care Med 2018;44:528–30.

[7] Chanques G, Jaber S, Barbotte E, Verdier R, Henriette K, Lefrant J, Eledjam J. Validation of the French translated Richmond vigilance-agitation scale. Ann Fr Anesth Reanim 2006;25:696–701.

[8] Chanques G, Jaber S, Barbotte E, Violet S, Sebbane M, Perrigault PF, Mann C, Lefrant JY, Eledjam JJ. Impact of systematic evaluation of pain and agitation in an intensive care unit. Crit Care Med 2006;34:1691–9.

[9] Chanques G, Payen JF, Mercier G, de Lattre S, Viel E, Jung B, Cissé M, Lefrant JY, Jaber S. Assessing pain in non-intubated critically ill patients unable to self report: an adaptation of the Behavioral Pain Scale. Intensive Care Med 2009;35:2060–7.

[10] Chanques G, Pohlman A, Kress JP, Molinari N, de Jong A, Jaber S, Hall JB. Psychometric comparison of three behavioural scales for the assessment of pain in critically ill patients unable to self-report. Crit Care 2014;18:R160.

[11] Chanques G, Tarri T, Ride A, Prades A, De Jong A, Carr J, Molinari N, Jaber S. Analgesia nociception index for the assessment of pain in critically ill patients: a diagnostic accuracy study. Br J Anaesth 2017;119: 812–20.

[12] Chanques G, Viel E, Constantin JM, Jung B, de Lattre S, Carr J, Cissé M, Lefrant JY, Jaber S. The measurement of pain in intensive care unit: comparison of 5 self-report intensity scales. PAIN 2010;151:711–21.

[13] Chatelle C, Majerus S, Whyte J, Laureys S, Schnakers C. A sensitive scale to assess nociceptive pain in patients with disorders of consciousness. J Neurol Neurosurg Psychiatry 2012;83:1233–7.

[14] Cronbach L. Coefficient alpha and the internal structure of tests. Psychometrika 1951;16:297–334.

[15] de Jong A, Molinari N, de Lattre S, Gniadek C, Carr J, Conseil M, Susbielles MP, Jung B, Jaber S, Chanques G. Decreasing severe pain and serious adverse events while moving intensive care unit patients: a prospective interventional study (the NURSE-DO project). Crit Care 2013;17:R74.

[16] Dehghani H, Tavangar H, Ghandehari A. Validity and reliability of behavioral pain scale in patients with low level of consciousness due to head trauma hospitalized in intensive care unit. Arch Trauma Res 2014;3: e18608.

[17] DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837–45.

[18] Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, Watson PL, Weinhouse GL, Nunnally ME, Rochwerg B, Balas MC, van den Boogaard M, Bosma KJ, Brummel NE, Chanques G, Denehy L, Drouot X, Fraser GL, Harris JE, Joffe AM, Kho ME, Kress JP, Lanphere JA, McKinley S, Neufeld KJ, Pisani MA, Payen JF, Pun BT, Puntillo KA, Riker RR, Robinson BRH, Shehabi Y, Szumita PM, Winkelman C, Centofanti JE, Price C, Nikayin S, Misak CJ, Flood PD, Kiedrowski K, Alhazzani W. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and Sleep disruption in adult patients in the ICU. Crit Care Med 2018;46:e825–73.

[19] Feldt LS. A test of the hypothesis that Cronbach's alpha reliability coefficient is the same for two tests administered to the same sample. Psychometrika 1980;45:99–105.

[20] Gelinas C, Boitor M, Puntillo KA, Arbour C, Topolovec-Vranic J, Cusimano MD, Choiniere M, Streiner DL. Behaviors indicative of pain in brain-injured adult patients with different levels of consciousness in the intensive care unit. J Pain Symptom Manage 2019;57:761–73.

[21] Gelinas C, Puntillo KA, Joffe AM, Barr J. A validated approach to evaluating psychometric properties of pain assessment tools for use in nonverbal critically ill adults. Semin Respir Crit Care Med 2013;34: 153–68.

[22] Jendoubi A, Abbes A, Ghedira S, Houissa M. Pain measurement in mechanically ventilated patients with traumatic brain injury: behavioral pain tools versus analgesia nociception index. Indian J Crit Care Med 2017;21:585–8.

[23] Joffe AM, McNulty B, Boitor M, Marsh R, Gélinas C. Validation of the critical-care pain observation tool in brain-injured critically ill adults. J Crit Care 2016;36:76–80.

[24] Kline P. A psychometrics primer. London: Free Association Books, 2000.

[25] Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–74.

[26] Lee K, Oh H, Suh Y, Seo W. Patterns and clinical correlates of pain among brain injury patients in critical care assessed with the critical care pain observation tool. Pain Manag Nurs 2013;14:259–67.

[27] Li D, Miaskowski C, Burkhardt D, Puntillo K. Evaluations of physiologic reactivity and reflexive behaviors during noxious procedures in sedated critically ill patients. J Crit Care 2009;24:472.e9–413.

[28] Lukaszewicz AC, Dereu D, Gayat E, Payen D. The relevance of pupillometry for evaluation of analgesia before noxious procedures in the intensive care unit. Anesth Analg 2015;120:1297–300.

[29] Oddo M, Crippa IA, Mehta S, Menon D, Payen JF, Taccone FS, Citerio G. Optimizing sedation in patients with acute brain injury. Crit Care 2016;20: 128.

[30] Payen JF, Bru O, Bosson JL, Lagrasta A, Novel E, Deschaux I, Lavagne P, Jacquot C. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med 2001;29:2258–63.

[31] Payen JF, Chanques G, Mantz J, Hercule C, Auriant I, Leguillou JL, Binhas M, Genty C, Rolland C, Bosson JL. Investigators ftD. Current practices in sedation and analgesia for mechanically ventilated critically ill patients: a prospective multicenter patient-based study. Anesthesiology 2007;106:687–95.

[32] Puntillo K, Gélinas C, Chanques G. Next steps in ICU pain research. Intensive Care Med 2017;43:1386–8.

[33] Puntillo KA, Morris AB, Thompson CL, Stanik-Hutt J, White CA, Wild LR. Pain behaviors observed during six common procedures: results from Thunder Project II. Crit Care Med 2004;32:421–7.

[34] Puntillo KA. Procedural pain in intensive care: translating awareness into practice. Anaesth Intensive Care 2016;44:444–6.

[35] Puntillo KA, Max A, Timsit JF, Vignoud L, Chanques G, Robleda G, Roche-Campo F, Mancebo J, Divatia JV, Soares M, Ionescu DC, Grintescu IM, Vasiliu IL, Maggiore SM, Rusinova K, Owczuk R, Egerod I, Papathanassoglou ED, Kyranou M, Joynt GM, Burghi G, Freebairn RC, Ho KM, Kaarlola A, Gerritsen RT, Kesecioglu J, Sulaj MM, Norrenberg M, Benoit DD, Seha MS, Hennein A, Periera FJ, Benbenishty JS, Abroug F, Aquilina A, Monte JR, An Y, Azoulay E. Determinants of procedural pain intensity in the intensive care unit. The Europain(R) study. Am J Respir Crit Care Med 2014;189:39–47.

[36] Ribeiro CJN, Lima A, de Araujo RAS, Nunes MDS, Alves JAB, Dantas DV, Ribeiro M. Psychometric properties of the behavioral pain scale in traumatic brain injury. Pain Manag Nurs 2019;20:152–7.

[37] Roulin MJ, Ramelet AS. Behavioral changes in brain-injured critical care adults with different levels of consciousness during nociceptive stimulation: an observational study. Intensive Care Med 2014;40: 1115–23.

[38] Schnakers C, Chatelle C, Vanhaudenhuyse A, Majerus S, Ledoux D, Boly M, Bruno MA, Boveroux P, Demertzi A, Moonen G, Laureys S. The Nociception Coma Scale: a new tool to assess nociception in disorders of consciousness. PAIN 2010;148:215–9.

[39] Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O_Neal PV, Keane KA, Tesoro EP, Elswick RK. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002;166:1338–44.

[40] Severgnini P, Pelosi P, Contino E, Serafinelli E, Novario R, Chiaranda M. Accuracy of Critical Care Pain Observation Tool and Behavioral Pain Scale to assess pain in critically ill conscious and unconscious patients: prospective, observational study. J Intensive Care 2016;4:68.

[41] Shan K, Cao W, Yuan Y, Hao JJ, Sun XM, He X, Li GY, Wang YM, Zhou JX. Use of the critical-care pain observation tool and the bispectral index for the detection of pain in brain-injured patients undergoing mechanical ventilation: a STROBE-compliant observational study. Medicine (Baltimore) 2018;97:e10985.
[42] Topolovec-Vranic J, Gelinas C, Li Y, Pollman-Mudryj MA, Innis J, McFarlan A, Canzian S. Validation and evaluation of two observational pain assessment tools in a trauma and neurosurgical intensive care unit. Pain Res Manag 2013;18:e107–114.
[43] Toulouse E, Masseguin C, Lafont B, McGurk G, Harbonn A, JAR, Granier S, Dupeyron A, Bazin JE. French legal approach to clinical research. Anaesth Crit Care Pain Med 2018;37:607–14.
[44] Yu A, Teitelbaum J, Scott J, Gesin G, Russell B, Huynh T, Skrobik Y. Evaluating pain, sedation, and delirium in the neurologically critically ill-feasibility and reliability of standardized tools: a multi-institutional study. Crit Care Med 2013;41:2002–7.
[45] Zeiler FA, AlSubaie F, Zeiler K, Bernard F, Skrobik Y. Analgesia in neurocritical care: an international survey and practice audit. Crit Care Med 2016;44:973–80.