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

Valentine Delmas

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UNIVERSITE DES ANTILLES
HYACINTHE BASTARAUD
2019

FACULTE DE MEDECINE
2019ANTI0449

**ASSESSING PAIN IN CRITICALLY ILL BRAIN-INJURED
PATIENTS:
A psychometric comparison of three pain scales and videopupillometry**

THESE

Présentée et soutenue publiquement à la Faculté de Médecine de Montpellier
Et examinée par les enseignants de ladite faculté pour le compte de la Faculté des Antilles

Le 13 septembre 2019

Pour obtenir le grade de

DOCTEUR EN MEDECINE

Par

DELMAS Valentine

Examineurs de la thèse :	Mr CARLES Michel	Professeur Président
	Mr JABER Samir	Professeur
	Mr PERRIGAULT Pierre-François	Professeur
	Mr CHANQUES Gérald	Professeur Directeur de Thèse

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LISTE DES ABREVIATIONS

AUCs	Areas Under the ROC Curves
BPS	Behavioral Pain Scale
CIBI	Critically Ill Brain Injured
CPOT	Critical Care Observation Pain Tool
CRS-R	Coma Recovering Scale Revised
ICU	Intensive Care Unit
NCS	Nociception Coma Scale
NCS-R	Nociception Coma Scale Revised
NCS-I	Nociception Coma Scale adapted for Intubated patients
NCS-R-I	Nociception Coma Scale Revised version adapted for Intubated patients
RASS	Richmond Agitation Sedation Scale
ROC	Receiving Operating Characteristic
SAPS II	Simplified Acute Physiology Score II

RESUME

INTRODUCTION : L'objectif de cette étude psychométrique était de valider et comparer trois échelles comportementales (Behavioral Pain Scale [BPS], Nociception Coma Scale adaptée au patient intubé [NCS-I], et sa version révisée [NCS-R-I]) et la vidéopupillométrie pour évaluer la douleur chez les patients intubés, cérébro-lésés et non communicants en réanimation.

MÉTHODES : L'évaluation de la douleur a été réalisée avant, pendant, juste après et 5 minutes après 3 procédures : une procédure de référence non douloureuse (évaluation du niveau de sédation par l'échelle d'agitation-sédation de Richmond) et 2 procédures douloureuses (le nursing et l'aspiration trachéale). Le critère de jugement principal était la validité discriminative de l'outil déterminée par la comparaison de différentes mesures de la douleur avec cet outil à différents temps et stimulations. Les critères de jugement secondaires étaient la consistance interne de l'échelle, la reproductibilité inter-observateur et la faisabilité pratique.

RÉSULTATS / DISCUSSION : Cinquante patients (54% de femmes, âgés de 63 [56-68] ans) ont été inclus, 13 [7-24] jours après une lésion cérébrale (76% d'AVC hémorragique ou ischémique). La validité discriminative a été démontrée pour tous les outils par une augmentation significativement plus importante de l'intensité douloureuse lors des procédures douloureuses que lors de la procédure non douloureuse ($p < 0,001$). Le BPS était le seul outil ne variant pas significativement au cours de la procédure non nociceptive ($p = 0.41$), suggérant qu'il était l'outil le plus discriminant. Le BPS, la NCS-I et la NCS-R-I permettaient de prédire les procédures douloureuses de manière performante (aires sous les courbes ≥ 0.96), contrairement à la vidéopupillométrie (aire sous la courbe = 0.67). Le BPS, la NCS-I et la NCS-R-I avaient une reproductibilité inter-observateur importante (kappa pondéré = 0.86, 0.82 et 0.84, respectivement). Le BPS, la NCS-I et la NCS-R-I avaient une consistance interne modérée (Cronbach $\alpha > 0.60$). L'analyse factorielle du composant principal montrait deux dimensions pour chacun des 3 outils cliniques : la première comprenant la majorité des informations et la deuxième représentant les items moteurs. La faisabilité de l'échelle paraissait meilleure pour l'équipe paramédicale pour la NCS-I et la NCS-R-I que pour le BPS.

CONCLUSION : Le BPS, la NCS-I et la NCS-R-I sont des échelles comportementales d'évaluation de la douleur valides, fiables et acceptables pour une utilisation chez les patients intubés cérébro-lésés contrairement à la vidéopupillométrie.

Mots-clés : Douleur, Mesure de la douleur, Lésions cérébrales, Étatde conscience altéré, Comportement, Intubation, Soins Intensifs.

ABSTRACT

INTRODUCTION: 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.

METHODS: 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.

RESULTS/DISCUSSION: 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-R-I had high interrater 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.

CONCLUSION: 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.

Key words: Pain, Pain measurement, Brain injuries, Consciousness disorders, Behavior, Intubation, Intensive care unit, Critical care.

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 lowersedative 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 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.

MATERIALS AND METHODS

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 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.

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.

4 Data recording

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.

4.1.1 Pain Scale

4.1.1.1 Behavioral Pain Scale (BPS)

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].

4.1.1.2 Nociception Coma Scale (NCS), 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.

Table 1: Description of the three clinical pain scales.

Behavioral Pain Scale (BPS)	Nociception Coma Scale <i>adapted for Intubated patients</i> (NCS-I)	Nociception Coma Scale -Revised version- <i>adapted for Intubated patients</i> (NCS-R-I)
FACIAL EXPRESSION	FACIAL EXPRESSION	FACIAL EXPRESSION
1 - Relaxed 2 - Partially tightened (= brow lowering) 3 - Fully tightened (= eyelid closing) 4 - Grimacing (=folded cheek)	0 - None 1 - Oral reflexive movement/Startle response 2 - Grimace 3 - Crying (tears)	0 - None 1 - Oral reflexive movement/Startle response 2 - Grimace 3 - Crying (tears)
UPPER LIMBS	MOTOR RESPONSE	MOTOR RESPONSE
1 - No movement 2 - Partially bent 3 - Fully bent with finger flexion 4 - Retracted, opposition to care	0 - None 1 - Abnormal posturing 2 - Flexion withdrawal 3 - Localization to noxious stimulation	0 - None 1 - Abnormal posturing 2 - Flexion withdrawal 3 - Localization to noxious stimulation
COMPLIANCE WITH VENTILATION	COMPLIANCE WITH VENTILATION	COMPLIANCE WITH VENTILATION
1 - Tolerating ventilation 2 - Coughing but tolerating ventilation most of the time 3 - Fighting ventilator but ventilation possible sometimes 4 - Unable to control ventilation	0 - Tolerating ventilation 1 - Coughing but tolerating ventilation most of the time 2 - Fighting ventilator but ventilation possible sometimes 3 - Unable to control ventilation	0 - Tolerating ventilation 1 - Coughing but tolerating ventilation most of the time 2 - Fighting ventilator but ventilation possible sometimes 3 - Unable to control ventilation
<i>Not applicable</i>	VISUAL RESPONSE	<i>Not applicable</i>
	0 - None 1 - Startle 2 - Eyes movements	

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.

4.2 Demographic and medical data

Patient characteristics were recorded from medical files including age, sex, height, weight, body mass index (kg/m²), Simplified 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.

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].

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.

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.

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].

5.2 Reliability

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].

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].

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).

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.

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 analyzed using SAS Enterprise Guide version 7.12 (2016) (SAS Institute, Cary, NC) and R software version 3.4.3 (November 30, 2017).

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.

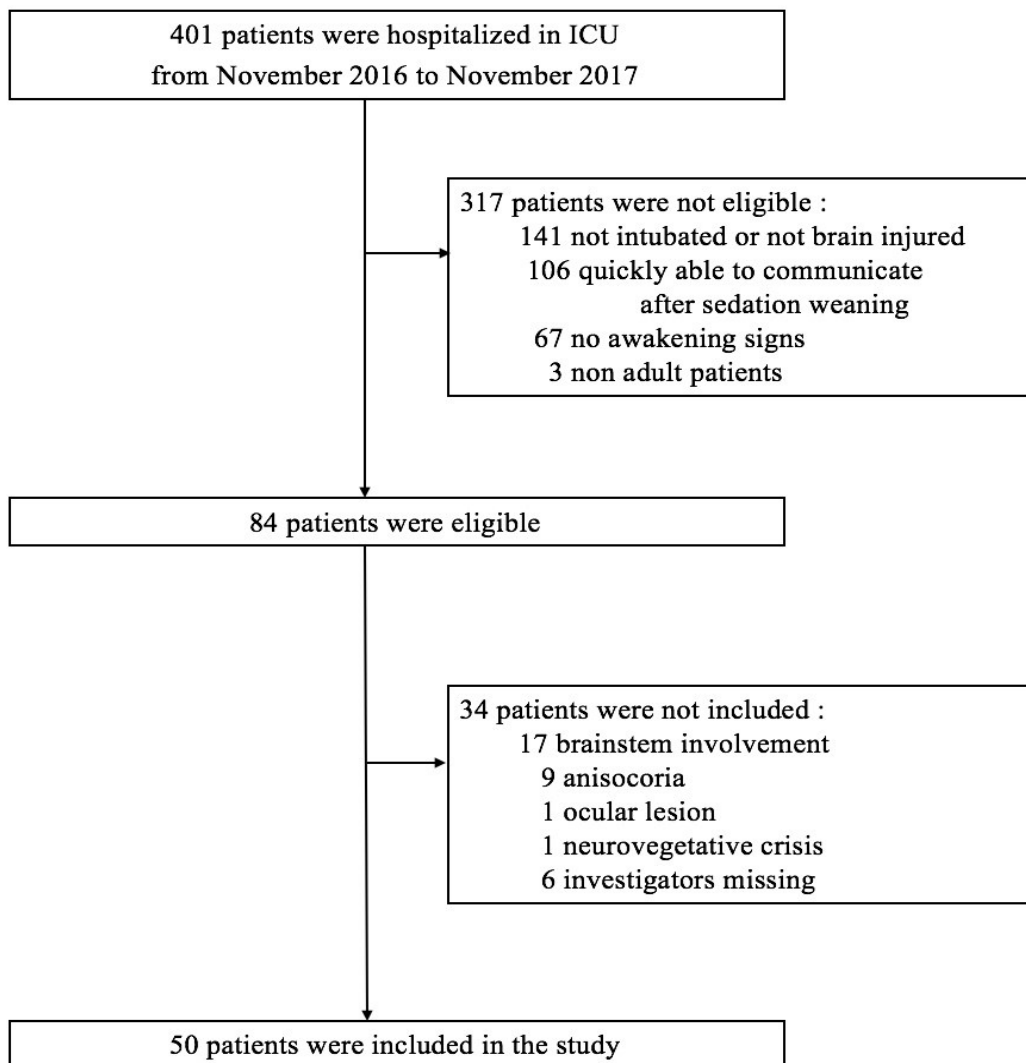


Figure 1: Study flowchart.

ICU, intensive care unit.

Table 2: Demographic and medical characteristics of the 50 patients included for analysis.

Age (years)	63 [56 - 68]
Sex (F/M)	27/23
Body Mass Index (kg/m ²)	26 [24 to 31]
Reason for admission, n (%)	
<i>Subarachnoid hemorrhage</i>	23 (46%)
<i>Intraparenchymal hematoma</i>	8 (16%)
<i>Ischemic stroke</i>	7 (14%)
<i>Traumatic brain injury</i>	4 (8%)
<i>Postoperative brain tumor</i>	3 (6%)
<i>Cardiac arrest</i>	3 (6%)
<i>Other</i>	2 (4%)
Time between brain injury and enrolment (days)	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 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

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.

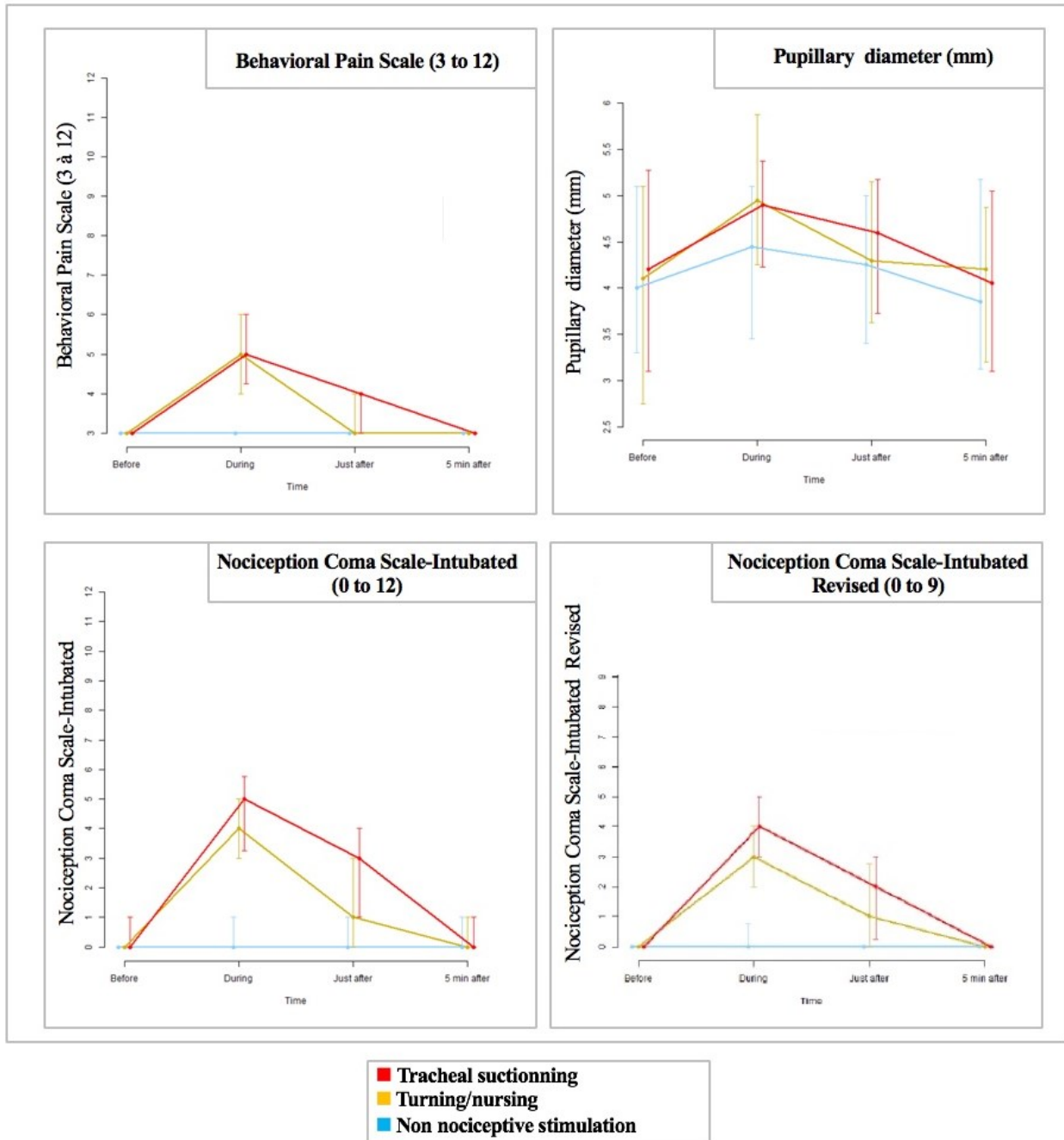


Figure 2: Variation of three clinical pain scales and videopupillometry at the different times of measurement, for each of the three care procedures.

This figure shows the variation of the pain tools at different times of measurement (before, during, just after, and five 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).

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%).

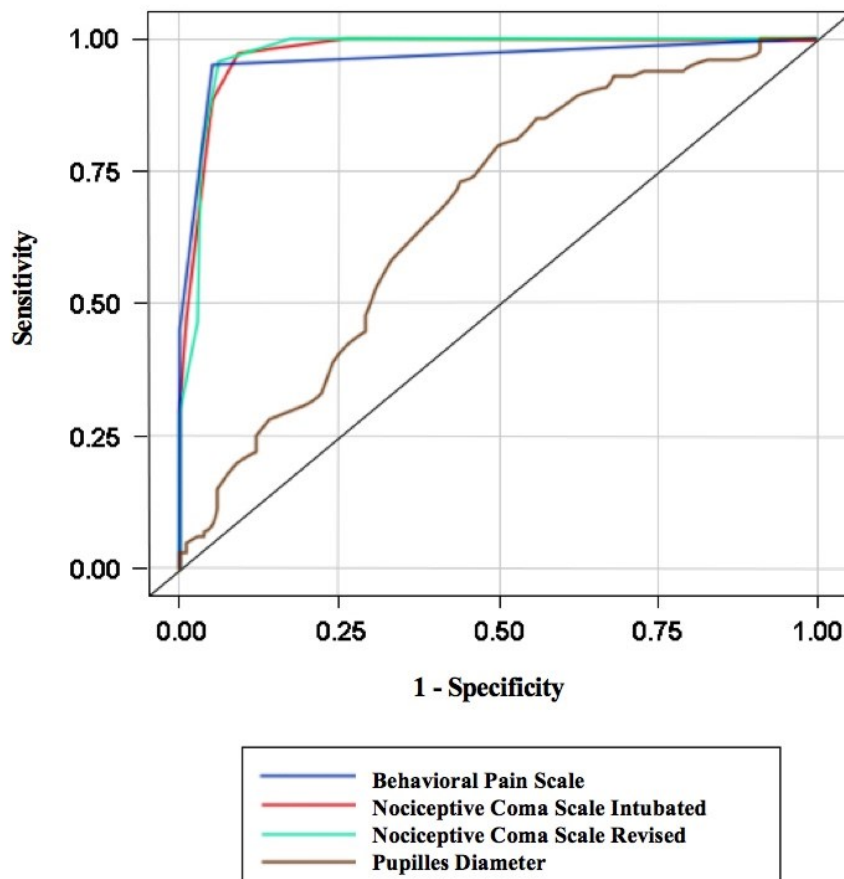


Figure 3: Receiver operating characteristic (ROC) curves of the three clinical pain scales and videopupillometry associated with pain (nociceptive procedures).

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.

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 ($p < 0.001$ 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.

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 ($p = 0.24$).

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%).

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, video pupillometry 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 5016 and 3736 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 led 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 non-intubated, 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, orbittightening, 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 limb [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 Appendix 1). 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].

CONCLUSION

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.

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APPENDICES

Appendix 1: Proposition of Psychometric Scoring for Pain Assessment Tools in Brain Injured Patients, According to the Method Developed in the 2018 Pain, Agitation/sedation, Delirium, Immobility and Sleep disruption (PADIS) guidelines [2].

Q.1	Question	Scoring Legend	Score		
			BPS	NCS-I	NCS-R-I
	Scale Development: Item Selection and Content Validation				
1.1	Was the process of item selection described?	2: Scale was developed for a specific population, using a theoretical or conceptual framework, or a qualitative approach was used (e.g. consultation with clinicians or patients) 1: Scale was developed based on the literature review only 0: No information is provided about item selection	1	2*	2*
1.2	Was content evaluated by experts? (content validation)	2: Content was evaluated by experts in the field, a Delphi technique may have been used, and Content Validity Index (CVI) were calculated for each item included in the scale 1: Content was evaluated by experts, but no CVI is reported 0: No information is provided about content validation	0	1*	1*
1.3	Are limitations of some items presented or discussed?	1: No limitations or if any limitations, they are presented and item modifications have been made or precautions have been stated 0: No information is provided	1	1	1
Subtotal - Scale development (0-5)			2	4	4
Subtotal weighted score - Scale development (0-2)			0.8	1.6	1.6

* Taking into account other studies reporting the construction of NCS and NCS-R in non mechanically ventilated brain-injured patients.

Q.2	Question	Scoring Legend	Score		
			BPS	NCS-I	NCS-R-I
	Scale Testing - Reliability				
2.1	Was internal consistency of the scale calculated?	2: $0.70 < \alpha < 0.90$ 1: $0.60 < \alpha < 0.70$ or $\alpha > 0.90$ 0: $\alpha < 0.60$ or no information provided	1	1	1
2.2	Was interrater reliability calculated?	2: $\kappa > 0.60$ or $ICC > 0.80$ 1: $0.60 < \kappa < 0.40$ or $0.60 < ICC < 0.80$ 0: $\kappa < 0.40$, $ICC < 0.60$ or no information provided	2	2	2
2.3	Was interrater reliability tested with other raters besides research team?	1: Other raters then research staff members were involved 0: Only research staff members were involved	1	1	1
2.4	Was intrarater reliability tested? Optional-to be examined if $\kappa < 0.60$ or $ICC < 0.80$ for interrater reliability	2: $\kappa > 0.60$ or $ICC > 0.80$ 1: $0.60 < \kappa < 0.40$ or $0.60 < ICC < 0.80$ 0: $\kappa < 0.40$, $ICC < 0.60$ or no information provided	N/A	N/A	N/A
Subtotal - Scale development (0-5 or 0-7 if intrarater reliability testing required)			4/5	4/5	4/5
Subtotal weighted score - Scale development (0-6)			4.8	4.8	4.8

Q.3	Question	Scoring Legend	Score		
			BPS	NCS-I	NCS-R-I
Scale Testing: Construct Validity					
3.1	What is the total of participants for the purpose of testing the scale?	2: N>50 1: 20<N<50 0: N<20	2*	1	1
3.2	Criterion validation: Was the scale correlated with the “gold standard” measure renown in the field of interest (e.g. the patient’s self-report of pain)?	2: $r > 0.60$ with the “gold standard” measure 1: $0.40 < r < 0.60$ 0: $r < 0.40$ or no information provided	2	2	2
3.3	Criterion validation: Was the sensitivity of the scale calculated?	2: Sensitivity $\geq 80\%$ 1: $60\% < \text{Sensitivity} < 80\%$ 0: Sensitivity $< 60\%$ or no information provided	2	2	2
3.4	Criterion validation: Was the specificity of the scale calculated?	2: Specificity $\geq 80\%$ 1: $60\% < \text{Specificity} < 80\%$ 0: Specificity $< 60\%$ or no information provided	2	2	2
3.5	Discriminant validation: Was the scale able to discriminate between different situations, e.g. between pain and no pain (e.g. at rest and during a nociceptive procedure, before and after the administration of an analgesic)?	2: A clinically important difference was found 1: A difference was found but was not considered clinically important 0: No difference was found or no information is provided	2	2	2
Subtotal - Scale development (0-10)			10	9	9
Subtotal weighted score - Scale development (0-8)			8	7.2	7.2

* Taking into account other studies assessing BPS psychometrics in brain-injured intubated patients.

Q.4	Question	Scoring Legend	Score		
			BPS	NCS-I	NCS-R-I
Scale Feasibility					
4.1	Was the feasibility (i.e. ease of usage with which clinicians can apply the instrument in the clinical setting) of the scale examined?	1: Scale is considered to be feasible to use by more than 80% of the clinicians 0: Scale is considered to be complex to use by more than 20% of the clinicians or no information is provided information is provided	0	1	1
4.2	Are directives of use of the scale clearly described?	1: Yes, directives of use including the scoring method are described 0: No information about directives of use is provided	1	1	1
Subtotal - Scale development (0-2)			1	2	2
Subtotal weighted score - Scale development (0-2)			1	2	2

Q.5	Question	Scoring Legend	Score		
			BPS	NCS-I	NCS-R-I
Scale Relevance or Impact of Implementation in ICU patient outcomes					
5.1	Was the relevance of the scale or impact of its implementation in ICU patient outcomes examined?	1: Scale is considered to be useful and relevant to practice by more than 80% of the clinicians; use of the scale yielded a significant change into practice (e.g. better use of medication, increase in patients' assessments) 0: Scale is not considered to be useful and relevant to practice by more than 20% of the clinicians; use of the scale did not yield to a significant change into practice or no information provided	1	1	1
Subtotal - Scale development (0-1)			1	1	1
Subtotal weighted score - Scale development (0-2)			2	2	2
Total Score (0-23*)			18	20	20
Weighted Score (0-20)			15.7	17.4	17.4
Quality of Evidence			M	M	M

*Total score is 23 instead of 25 because Q2.4 is not required.

BPS: Behavioral Pain Scale; NCS-I: Nociception Coma Scale for Intubated patients; NCS-R-I: Revised Nociception Coma Scale for Intubated patients.
Quality of evidence: Low (L), Moderate (M), High (H).

Methods:

The method of psychometric scoring for behavioral pain scales constructed for assessing pain in critically ill non communicant adult patients was developed for the Pain, Agitation and Delirium guidelines from the American College of Critical Care Medicine (ACCM) in conjunction with the Society of Critical Care Medicine (SCCM) in 2013 [1,3], and updated in 2018 [2].

Among the 13 behavioral pain scales scored in the 2018 guidelines, the scores ranged from 6 to 21 (weighted scores from 4.5/20 to 16.7/20), with a mean score of 12.1/25 and a weighted score of 9.8/20 [2].

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SERMENT D'HIPPOCRATE

Au moment d'être admis à exercer la médecine, en présence des maîtres de cette école et de mes condisciples, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité qui la régissent.

Mon premier souci sera, de rétablir, de préserver ou de promouvoir la santé dans tous les éléments physiques et mentaux, individuels collectifs et sociaux. Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions.

J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou dignité.

Même sous la contrainte, je ne ferai usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients de décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer leurs consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera.
Je ne me laisserai influencer ni par la recherche du gain ni par la recherche de la gloire.

Admis dans l'intimité des personnes, je tairai les secrets qui me sont confiés.

Reçu à l'intérieur des maisons, je respecterai les secrets des foyers.

Et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances, sans acharnement.

Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission.

Que je sois modéré en tout, mais insatiable de mon amour de la science.

Je n'entreprendrai rien qui ne dépasse mes compétences ; je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses,

Que je sois déshonoré et méprisé si j'y manque.

DELMAS Valentine

**ASSESSING PAIN IN CRITICALLY ILL BRAIN INJURED PATIENTS:
A psychometric comparison of three pain scales and videopupillometry**

THESE: MEDECINE

Qualification: Médecine Spécialisée ⊕ Anesthésie Réanimation

ANNEE: 2019

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

ABSTRACT

INTRODUCTION: 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.

METHODS: 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.

RESULTS/DISCUSSION: 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-R-I had high interrater 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.

CONCLUSION: 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.

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Juges: Pr JABER Samir

: Pr PERRIGAULT Pierre François

: Pr CHANQUES Gérald