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# Higher nociception scores in minimally conscious state compared to unresponsive wakefulness syndrome and positive correlations among CRS-R, GCS-P and NCS-R in Patients with Disorders of Consciousness

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## Abstract

**Background**: One of the greatest challenges in understanding pain is the difficulty in assessing or recognizing it in patients with disorders of consciousness (DOC).

**Objective**: To compare the nociception using the Nociception Coma Scale Revised (NCS-R) in DOC. Methods: In the first phase, patients with DOC were evaluated using the Coma Recovery Scale-Revised (CRS-R) to diagnose the type of DOC, either Unresponsive Wakefulness Syndrome (UWS) or Minimally Conscious State (MCS). Subsequently, the Modified Glasgow Coma Scale-Pupils Score (GCS-P) was applied, and the occurrence of pain was assessed using the NCS-R.

**Main Outcome Measures**: Score of NCS-R from UWS and MCS patients and correlations among CRS-R, GCS-P and NCS-R. In the second phase, a subgroup of patients with a cutoff score of ≥5 on the NCS-R was selected to evaluate the analgesic effect.

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**Results**: The mean NCS-R scores were higher in the MCS group (n=42) compared to the UWS group, (n=14) with differences mainly attributed to the motor, verbal and facial components. Strong positive correlations were observed for the whole sample between NCS-R and GCS-P (r=0.788; p<0.001); between CRS-R and GCS-P (r=0.754; p<0.001) and between NCS-R and CRS-R (r=0.796; p<0.001). In the UWS group, a moderate positive correlation was also observed. In phase 2, in the NCS-R assessment, the two groups showed similar mean score.

**Conclusions**: We found that the UWS group had lower NCS-R scores than the MCS. In addition, across the entire sample and in the UWS group, the three scales used (CRS-R, GCS-P and NCS-R) showed positive correlations.

**Keywords:** Consciousness Disorders; Pain Management; Nociception Coma Scale-Revised; Minimally Conscious State; Unresponsive Wakefulness Syndrome/Vegetative State.

## 1. Introduction

Recognizing nociceptive experiences in patients with impaired consciousness is both difficult and frustrating. Nociception, a term coined by Sherrington (1900), is not synonymous with pain; it refers to the processing of a painful stimulus and its transmission to the subcortical and cortical structures. [1] After the coma period, many neurocritical patients may present in three stages of comorbidities of consciousness (DOC): Coma, Vegetative State or Unresponsive Wakefulness Syndrome (UWS) and Minimally Conscious State (MCS). Some patients may improve slowly, while others remain in these conditions for weeks, months, years, or decades[2]. When pain is experienced as a physical sensation or unpleasant emotion, it is typically expressed through the conscious experience of pain or externalized in the form of verbalizations, vocalizations, and/or behavioral responses such as grimacing, crying, or agitation. In neurologically compromised patients, pain – whether conscious perceived or not – may be accompanied by increased spasticity and autonomic activation (e.g., hypertension, tachycardia, tachypnea, sweating, pupillary changes etc.)[3].

The need for accurate diagnosis and standardized care for neurological abnormalities is especially necessary where care is performed. Many patients develop spasticity and pressure ulcers, require catheters for nutrition and prolonged airway monitoring, and numerous situations that imply the need for management in this complex domain, which generate pain in a scenario compromised by the inability to communicate[4]. The objective was to compare nociception scores as measured by the Nociception Coma Scale Revised (NCS-R) in patients with disorders of consciousness (DOC): 1) In the first phase, patients with DOC were evaluated using the Coma Recovery Scale-Revised (CRS-R) to diagnose the type of DOC, either UWS or MCS. Subsequently, the Modified Glasgow Coma Scale with Pupil Score (GCS-P) was applied, and the occurrence of pain was assessed using the NCS-R; 2) A subgroup of patients with a cutoff of ≥5 points in the NCS-R was selected in order to evaluate the analgesic effect. Vital functions were monitored throughout both phases. We hypothesized that UWS patients would have lower NCS-R scores than MCS patients reflecting a worse clinical context for their condition. In addition, we hypothesized that the three scales used would be positively correlated, and this is associated with the fact that, although they have different evaluation targets, they progressively indicate increasing levels of neurological impairment of the patient.

## 2. Methods

The study employs a hybrid design, at first phase observational and the second, interventional.

### 2.1. Determination of the sample size

To determine the sample size of this study, a pilot study of 25 patients with DOC was conducted and the score of NCS-R was considered as the sizing variable. Thus, an effective sample of at least 36 patients in the UWS group and 12 patients in the MCS group is required to identify, at a significant level of 5%, a difference of 2.5 points in the mean total score of NCS-R between the two groups, with a power of 90%, using the Student's t-test for independent samples. We used the software PASS 14[5].

- *Inclusion Criteria:* Patients aged 18 years or older; patients diagnosed with UWS or MCS, of different etiologies, hospitalized for at least one month; absence of infectious processes that would impair responses; absence of neuromuscular blockers.
- *Exclusion Criteria*: Patients with Locked-in syndrome; patients in the acute phase of coma; comatose patients due to causes that can be quickly reversed with surgical procedures or not.

### 2.2. Data collection

All selected patients were included after prior authorization from the legal representative. It was applied a questionnaire on demographic data (age, education, ethnicity, religion), health history and habits (smoking, alcoholism), cause of DOC. Data were recorded from four medical centers in Sao Paulo between August 2021 to July 2022.

*2.2.1. First phase: CRS-R Assessment*

The evaluation of each patient was performed by two observers trained and experienced in using the scales. In the first phase, the first baseline measurement of vital signs was initially performed: systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate (HR), respiratory rate (RR), and oxygen saturation (SaO2). Subsequently, the patients were assessed using the CRS-R[6]. The CRS-R comprises the evaluation of functions divided into auditory, visual, motor, oromotor/verbal, communication, and arousal domains. The total score is 23 points for people without disorders of consciousness. (Table 1). The evaluation of the scale enables diagnosis and classification of the sample into two groups; patients with a score of ≤9 classified as UWS, previously referred to as Persistent Neurovegetative State, and those with a score ≥ 10 as MCS. The classification was based on the study of Bodien et al.[7] The CRS-R is the most sensitive and reliable tool for recognizing consciousness transitions and it is the only scale able to distinguish between UWS and MCS[1].

**Table 1** Composition of the items from CRS-R, GCS-P, NCS-R applied in the study

| **CRS-R** | **GCS** | **NCS-R** |
|---|---|---|
| AUDITORY FUNCTION SCALE<br>4 – Consistent Movement to Command<br>3 – Reproducible Movement to Command<br>2 – Localization to Sound<br>1 – Auditory Startle<br>0 – None | | |
| VISION FUNCTION SCALE<br>5 – Object Recognition<br>4 – Object localization: Reaching<br>3 – Visual Pursuit<br>2 – Fixation<br>1 – Visual Startle<br>0 – None | EYE OPENING<br>4 – Opens eyes spontaneously<br>3– Opens eyes in response to speech<br>*2–- Opens eyes in response to painful stimulations*<br>1 - Does not open eyes in response to any stimulation | |
| MOTOR FUNCTION SCALE<br>6 – Functional Object Use<br>5 – Automatic Motor Response<br>4 – Object Manipulation<br>3 – *Localization to Noxious Stimulation**<br>*2 – Flexion Withdrawal*<br>*1 – Abnormal Posturing*<br>*0 – None* | MOTOR RESPONSE<br>6 – Follows commands<br>*5– Makes localized movement in response to painful stimulation*<br>*4– Makes non-purposeful movements in response to painful stimulation (withdraws from pain)*<br>*3 - Flexes upper extremities / extends lower extremities in response to painful stimulation*<br>*2 - Extends all extremities in response to painful stimulation*<br>*1- Makes no response to noxious stimuli* | MOTOR RESPONSE<br>3 – Localization to noxious stimulation<br>2 – Flexion withdrawal<br>1 – Abnormal posturing<br>0 – None/flaccid |
| OROMOTOR/VERBAL FUNCTION SCALE<br>3 – Intelligible Verbalization | VERBAL RESPONSE<br>5 – Is oriented to person, place and time<br>4 – Converses may be confused<br>3 – Replies with inappropriate words | VERBAL RESPONSE<br>3 – Verbalization (intelligible)<br>2 – Vocalization |

| | | |
|---|---|---|
| 2 – Vocalization/Oral Movement<br>1 – Oral Reflexive Movement<br>0 – None | 2 – Makes incomprehensible sounds<br>1 – Makes no response | 1 – Groaning<br>0 – None |
| COMMUNICATION SCALE<br>2 – Functional: Accurate<br>1 – Non-functional: Intentional<br>0 – None | | |
| AROUSAL SCALE<br>3 – Attention<br>2 – Eye Opening w/o Stimulation<br>1 – Eye Opening with Stimulation<br>0 – Unarousable | | |
| | PUPILAR REACTIVITY<br>0: Both pupils<br>-1: One pupil<br>-2: Neither pupil | FACIAL EXPRESSION<br>3 – Cry<br>2 – Grimace<br>1 – Oral reflexive movement/startle response<br>0 – None |
| TOTAL SCORE | TOTAL SCORE | TOTAL SCORE |

*Items involving painful stimulation are rendered in italics.

GCS-P Assessment

Concomitantly with the evaluation of the CRS-R Scale, the GCS-P was used. The Glasgow Coma Scale (GCS), developed in 1974 by Teasdale and Jennett[8], is the most widely used behavioral measure to assess the severity of acute traumatic brain injury[9]. In 2018, the scale was updated adding pupillary reactivity to the assessment (GCS-P)[10] The results of both groups were compared.

NCS-R assessment

Next, the patients were assessed again for vital signs and then with the Nociception Coma Scale (NCS-R).[11] It is an observational inventory of nociceptive behavior. Initially it consisted of 4 items with scores ranging from 1 to 3. Later it was revised, and the visual item was removed[12]. It makes it possible to assess pain in patients with DOC. Nociceptive stimulation was applied to all patients to assess signs suggestive of pain based on the following items: motor and verbal reactions, and facial expressions (Table 1). During baseline, we observed the patient's spontaneous behaviors for 60 seconds. During the noxious condition, we applied pressure on the nailbed of the middle finger of the right hand for a minimum of 5 seconds and stopped as soon as a behavioral response was observed. Behavioral responses were recorded 10 seconds after each stimulation. To ensure a sufficient level of arousal, each condition was administered while patients showed spontaneous eye opening. The entire procedure lasted <5 minutes. The results of both groups were compared. Subsequently, vital signs were measured for the third time: at the beginning and after each evaluation with the NCS-R scale (Figure 1).

*2.2.2. Second phase*

In patients with NCS-R scores ranging from 5 to 9, a new evaluation NCS-R was applied. After re-measuring the reactions, patients were medicated with intravenous dipyrone (1000 mg) and/or morphine 2 (mg), drugs already prescribed during hospitalization, and the patients were reevaluated one hour after the drug procedure. This cutoff was based on neuroimaging data that determined a conservative NCS-R - score of 5 as specific to cortical pain processing, allowing the detection of covert consciousness[13]. Vital signs were measured before the evaluation with the NCS-R scale and immediately after nociceptive stimulation.

Ethical aspects

The research committee and the institutional review board of the Hospital das Clinicas, HCFMUSP approved the study protocol on April 9, 2021, CAAE 42626521.5.0000.0068.

### 2.3. Statistical analysis

Initially, the data were analyzed descriptively. For categorical variables, absolute and relative frequencies were presented, and for numerical variables, summary measures (mean, quartiles, and standard deviation). The existence of associations between two categorical variables was verified using Fisher's exact test. Comparisons between two means were conducted using the Student's t-test. Spearman's correlation was used to assess linear associations between scores, given the absence of normal distribution in some cases. A significant level of 5% was adopted for all statistical tests. Statistical analyses were performed using SPSS 20.0 and STATA 17[14].

## 3. Results

The study consisted of 56 participants. There were 33 men (58.9%). Ages ranged from 19 to 88 years (mean 52± 20 years). The UWS 42 group (75%) was significantly larger than the MCS group (n=14, 25%, p <0.001). There was no difference between UWS and MCS patients regarding age (51.8±20.0 vs 52.7± 20.2 years respectively) or BMI (26.3± 5.9 vs. 27.2± 5.7) respectively. No sociodemographic (ethnic, civil state, religion) or clinical factor (prevalence of diabetes mellitus, cerebrovascular, renal, cancer, liver, gastrointestinal diseases, alcohol or smoking) showed significant weight or statistically significant differences between patients in both groups. Traumatic etiology (39.3%) was significant as the predominant cause.

### 3.1. PHASE 1: Initial evaluation of CRS-R, GCS-P and NCS-R scores

Table 2 presents the descriptive measures statistics for the CRS-R Scales scores, both for the total sample and for each group. In the CRS-R subscales, the values were higher in the MCS group compared to the UWS, a more significant difference in the auditory, visual and motor subscales.

**Table 2** Scores CRS-R according to diagnostic group (UWS vs. MCS)

| | **UWS** | | | **MCS** | | | **Total** | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | Mean | SD | N | Mean | SD | N | Mean | SD |
| CRS-R | | | | | | | | | |
| Auditory | 42 | 0.7 | 1.1 | 14 | 2.8 | 1.0 | 56 | 1.2 | 1.4 |
| Visual | 42 | 0.7 | 1.1 | 14 | 2.6 | 1.4 | 56 | 1.2 | 1.5 |
| Motor | 42 | 1.5 | 1.1 | 14 | 3.2 | 0.9 | 56 | 1.9 | 1.3 |
| Oro M/V | 42 | 0.4 | 0.6 | 14 | 0.7 | 0.7 | 56 | 0.5 | 0.6 |
| Communication | 42 | 0.0 | 0.2 | 14 | 0.1 | 0.4 | 56 | 0.1 | 0.3 |
| Arousal | 42 | 1.3 | 0.8 | 14 | 2.1 | 0.4 | 56 | 1.5 | 0.8 |
| CRS-R Score | 42 | 4.7 | 2.5 | 14 | 11.6 | 1.8 | 56 | 6.4 | 3.8 |

Table 3 also shows the GCS-P score. There were statistically significant differences in total scores between the groups (p<0.001). The differences were significant between the groups in Eye Opening (p=0.016) and Motor Reaction (p=0.007). MCS patients had higher total scores than UWS patients, both in the overall sample and in each individual item. According to Table 3, there were distinct distributions of the motor GCS-P items (p=0.039) and different means of the Glasgow score between the UWS and MCS groups (p<0.001). Thus, it was found that the MCS group had a higher percentage of pain localization and a higher mean score compared to the UWS group.

Regarding NCS-R as shown in Table 3, there were distinct distributions of the motor (p<0.001), verbal (p=0.043), facial (p=0.003) and distinct means of the NCS-R score between the UWS and MCS (p<0.001) groups. Thus, it was found that

the MCS group had higher percentages of presence of stimulus location and grimaces; lower percentage of verbal absence – "none" and higher mean NCS-R score compared to the UWS group (p<0.001).

**Table 3** Distribution of items from GCS-P and NCS-R and means score according to the diagnostic group

| | **Total (N= 56)** | **UWS (N=42)** | **MCS (N= 14)** | **p** |
|---|---|---|---|---|
| **GCS-P** | | | | |
| EG-ocular | | | | 0.160[a] |
| 1 | 11 (19.6) | 10 (23.8) | 1 (7.1) | |
| 2 | 6 (10.7) | 6 (14.3) | 0 (0.0) | |
| 3 | 4 (7.1) | 3 (7.1) | 1 (7.1) | |
| 4 | 35 (62.5) | 23 (54.8) | 12 (85.7) | |
| EG-verbal | | | | 0.096[a] |
| 1 | 51 (91.1) | 40 (95.2) | 11 (78.6) | |
| 2 | 4 (7.1) | 2 (4.8) | 2 (14.3) | |
| 5 | 1 (1.8) | 0 (0.0) | 1 (7.1) | |
| EG-motor | | | | 0.039[a] |
| 1 | 9 (16.1) | 8 (19.0) | 1 (7.1) | |
| 2 | 11 (19.6) | 10 (23.8) | 1 (7.1) | |
| 3 | 5 (8.9) | 5 (11.9) | 0 (0.0) | |
| 4 | 14 (25.0) | 11 (26.2) | 3 (21.4) | |
| 5 | 16 (28.6) | 8 (19.0) | 8 (57.1) | |
| 6 | 1 (1.8) | 0 (0.0) | 1 (7.1) | |
| Pupillary responsiveness | | | | 0.811[a] |
| -2 | 3 (5.4) | 2 (4.8) | 1 (7.1) | |
| -1 | 3 (5.4) | 3 (7.1) | 0 (0.0) | |
| 0 | 50 (89.3) | 37 (88.1) | 13 (92.9) | |
| Modified Glasgow Coma Scale | | | | <0.001[b] |
| Mean Score ± DP | 7.5 ± 2.2 | 6.8 ± 2.1 | 9.6 ± 0.8 | |
| Median Score (IIQ) | 8.0 (6.0 a 9.0) | 7.0 (5.0 a 9.0) | 10.0 (9.0 a 10.0) | |
| **NCS-R** | | | | |
| Motor response, n (%) | | | | <0.001[a] |
| None/flaccid | 10 (17.9) | 10 (23.8) | 0 (0.0) | |
| Abnormal posturing | 15 (26.8) | 15 (35.7) | 0 (0.0) | |
| Flexion withdrawal | 8 (14.3) | 7 (16.7) | 1 (7.1) | |
| Localization to noxious stimulation | 23 (41.1) | 10 (23.8) | 13 (92.9) | |
| Verbal response, n (%) | | | | 0.043[a] |
| None | 50 (89.3) | 40 (95.2) | 10 (71.4) | |
| Groaning | 3 (5.4) | 1 (2.4) | 2 (14.3) | |
| Vocalization | 3 (5.4) | 1 (2.4) | 2 (14.3) | |

| | | | | |
|---|---|---|---|---|
| Verbalization (intelligible) | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Facial expression, n (%) | | | | 0.003[a] |
| None | 14 (25.0) | 14 (33.3) | 0 (0.0) | |
| Oral reflexive movement/startle response | 15 (26.8) | 13 (31.0) | 2 (14.3) | |
| Grimace | 26 (46.4) | 15 (35.7) | 11 (78.6) | |
| Cry | 1 (1.8) | 0 (0.0) | 1 (7.1) | |
| NCS-R Score | | | | <0.001[b] |
| Media ± DP | 3.2 ± 1.8 | 2.5 ± 1.5 | 5.3 ± 0.8 | |
| Median (IIQ) | 3.0 (2.0 a 5.0) | 2.0 (1.0 a 4.0) | 5.0 (5.0 a 6.0) | |

p – Descriptive level, Fischer's exact test and Student's t test ([b]).; IIQ - Interquartile Interval (P25 a P75).

*3.1.1. Correlation among CRS-R, GCS-P e NCS-R*

Figure 1 shows the scatter plots and respective Spearman's correlations between the scores for the total sample and by groups. As shown in Figure 1A, there were strong positive correlations for the entire sample between CRS-R and GCS-P scores (r=0.754; p<0.001); NCS-R and GCS-P scores (r=0.788; p<0.001); between and between NCS-R, and CRS-R scores (r=0.796; p<0.001). According to Figure 1B, there were moderate positive correlations for the UWS group between CRS-R and GCS-P scores (r=0.763; p<0.001); between NCS-R and GCS-P scores (r=0.771; p<0.001); and between NCS-R and CRS-R scores (r=0.624; p<0.001). According to Figure 1C, for the MCS group, there were no significant correlations between CRS-R and GCS-P scores (r=0.191; p=0.513); between NCS-R and GCS-P scores (r=0.222; p=0.446); and between NCS-R and CRS-R scores (r=0.251; p=0.329).

Vital signs are shown in Table 4. In a longitudinal model to evaluate the average behaviors of groups over time, the effects of three components are analyzed: time, group, and interaction between group and time. There was an effect of time and group interaction on DBP (p=0.012), indicating that the mean variations of the two groups were distinct. Thus, it was observed that the mean DBP in the UWS group was not different throughout the evaluations, differently from the MCS group, which presented a higher mean in the evaluation after the stimulus compared to the baseline and pre-stimulus moments, which were similar to each other. In addition, the mean SBP, HR, and RR values in the first two evaluations were similar and lower than those of the post-stimulus evaluation. There was no difference in mean values between groups across all evaluation time points; with respect to SaO2, there were no differences in mean times in each of the groups. However, the mean of the UWS group was higher than in the MCS group.

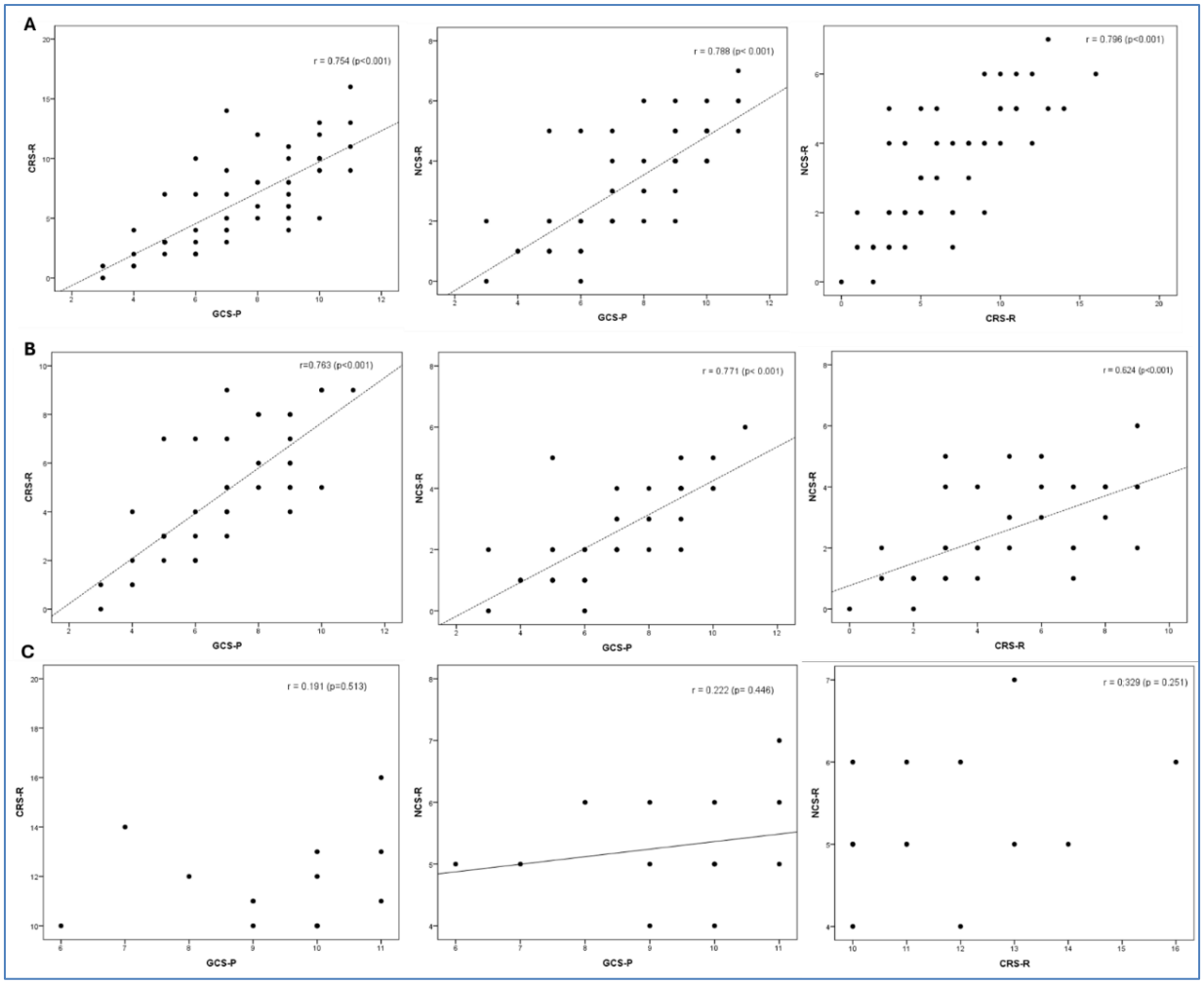


**Figure 1** Scatter plot from correlation among CRS-R, GCS-P and NCS-R scores in the entire sampling (A), in the UWS group (B) and in the MCS group (C).

**Table 4** Phase 1: Vital signs by group and time of evaluation and results of mixed linear model analysis

| | **Basal** | **Pre-stimulus** | **Post stimulus** | **Multilevel model** | | | **N** |
|---|---|---|---|---|---|---|---|
| | | | | p | | | |
| | | | | Group | Time | Group x Time | |
| Systolic Blood Pressure | | | | | | | |
| UWS | 120.4 ± 23.1$^{A}$ | 122.2 ± 23.7$^{A}$ | 127.8 ± 27.0$^{B}$ | 0.175 | <0.001 | 0.084 | 42 |
| MCS | 117.7 ± 20.3$^{A}$ | 119.6 ± 20.7$^{A}$ | 131.6 ± 26.0$^{B}$ | | | | 14 |
| Diastolic Blood Pressure | | | | | | | |
| UWS | 71.6 ± 12.4 | 73.3 ± 13.6 | 75.2 ± 13.2 | 0.031 | <0.001 | 0.012 | 42 |
| MCS | 69.2 ± 11.3$^{A}$ | 72.2 ± 13.4$^{A}$ | 81.4 ± 16.9$^{B}$ | | | | 14 |
| Heart Rate | | | | | | | |
| UWS | 88.9 ± 18.8$^{A}$ | 91.3 ± 19.7$^{A}$ | 95.5 ± 19.1$^{B}$ | 0.921 | <0.001 | 0.922 | 42 |
| MCS | 85.6 ± 20.1$^{A}$ | 87.5 ± 21.8$^{A}$ | 92.7 ± 22.5$^{B}$ | | | | 14 |
| Rate Respiratory | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| UWS | 14.0 ± 3.2[A] | 14.2 ± 3.5[A] | 16.0 ± 4.2[B] | 0.855 | <0.001 | 0.834 | 42 |
| MCS | 13.6 ± 2.8[A] | 13.5 ± 2.7[A] | 15.2 ± 2.7[B] | | | | 14 |
| O2 Saturation | | | | | | | |
| UWS | 95.7 ± 2.3[§] | 96.0 ± 2.5[§] | 95.7 ± 3.0[§] | 0.020 | 0.195 | 0.063 | 42 |
| MCS | 94.4 ± 2.4[ٱ] | 93.7 ± 2.9[ٱ] | 94.9 ± 2.7[ٱ] | | | | 14 |

(A) and (B) present different mean values according to multiple comparisons using Bonferroni correction (comparison between evaluation moments).

§ and ٱ present different mean values according to multiple comparisons with Bonferroni correction (comparison between groups). DBP - Comparison between groups: baseline (p=1.000); pre (p=1.000) and post (p=0.374); Comparison across evaluation moments: UWS (baseline vs. pre: p=0.848; baseline vs. post: p=0.064 and pre vs. post=0.654), and MCS (baseline vs. pre: p=0.0.792; baseline vs. post: p<0.001 and pre vs. post=0.002).

### 3.2. Phase 2

A total of 16 patients (28.6%) were evaluated and underwent analgesic intervention, 4 (25.0%) from the UWS group and 12 (75.0%) from the MCS group, a statistically significant difference (X2=29.9; p<0.001). The two groups showed similar mean behaviors across evaluation moments pre or post intervention (p=0.896), with no effects of time (p=0.521) or group (p=0.830) on dipyrone use. There were no interaction effects on all vital signs, indicating that the mean variations between the groups were not distinct. However, a time effect was observed only in SBP (p<0.001). Thus, there was a similar mean increase in SBP after the use of dipyrone (p=0.481). Additionally, it was found that the mean saturation in the UWS group was higher compared to the MCS group across both evaluations.

## 4. Discussion

In this study, patients with DOC categorized as UWS and MCS showed distinct NCS-R scores, with the UWS group exhibiting lower values. Both were homogenized in numerous qualitative and quantitative sociodemographic variables. In addition, we found that in the whole sample and in the UWS group, the three scales used (CRS-R, GCS-P and NCS-R) were positively correlated. To our knowledge, this result is unprecedented in the literature.

Our sample may seem small, but other comparative studies involving these groups also had small sample sizes[15-17]. In spite of this, we carefully calculated the sample size, conducting a pilot study to obtain statistical power. It should be emphasized that sociodemographic factors were homogeneously distributed between both UWS and MCS groups, and that clinical aspects and comorbidities did not influence the classification, allowing the study to focus on the most relevant clinical scales.

In phase 1 we found that the proportion of patients in the UWS group was significantly higher than in the MCS group. This contrasts with previous comparative studies that assessed different variables in these groups, in which the MCS group was proportionally larger than the UWS group[18-20]. Therefore, our result of greater UWS than MCS is also original in the literature.

As expected, based on the definition of DOC, the CRS-R scale significantly discriminated between the groups, with higher values in MCS compared to UWS. Chatelle et al.[18] previously reported significantly higher CRS-R scores in MCS patient group compared to UWS patients (9.8 vs. 4.7 p < 0.001). Regarding the finding that the mean GCS-P score was higher in the MCS group than UWS, this was due to the ocular opening and motor reaction subscales.

Regarding the finding of a significantly higher mean NCS-R score in the MCS group compared to the UWS group, our first working hypothesis was confirmed. This was due to differences in motor, verbal and facial items. Chatelle et al.[18] reported differences in the subscales that were reported and the NCS-R total score of the MCS group was significantly higher than in the UWS group. In another study by Shen et al.[20], investigated whether patients with DOC experience pain during physical therapy and noxious stimuli. They did not find differences in the NCS-R score at baseline only during physical therapy and under noxious stimuli.

With respect to the vital functions assessed, we found differences that had not been previously reported. Among these, only the O2 saturation was significantly different between the patients in the UWS and MCS groups, regardless of evaluation time. The mean of UWS group was higher than in the MCS group at all evaluation moments; however, this difference is not clinically significant, as the saturation levels in both groups remained adequate (>90%). In the healthy

individual, the cardiorespiratory autonomic response to pain induces acute and transient increases in heart rate (HR), blood pressure (BP), and ventilation[21]. Such a reaction involves a complex neural network, including the dorsal spinal and trigeminal horns, brainstem, hypothalamus, thalamus, and insular cortex[22]. Thus, the reflex autonomic response to a painful stimulus may be altered after a severe brain injury, with the severity and location of the brain injury affecting the autonomic pain reflex[23]. Surprisingly, the evaluation of pain response has been considered of minor importance in the clinical assessment of consciousness disorders[24], probably due to the limited descriptions of responses to noxious stimuli in MCS and UWS patients.

Regarding our main hypothesis, our study found that in the entire sample of DOC patients, the three rating scales CRS-R, GCS-P, and NCR-R had a strong positive correlation. Even in the majority UWS group, a moderate positive correlation between the three scales remained was observed. Previously, two studies had reported correlations between CRS-R and NCS-R, but GCS-P was not included. [18, 25]

We hypothesize that the correlations we found may be associated with worse neurological impairment in the UWS group. This is associated with the fact that, although they have different evaluation targets, they would progressively represent a greater neurological impairment of the patient.

Regarding the Phase 2 interventional study evaluating the analgesic effect performed in a smaller subgroup of patients, the MCS group represented the majority compared to the UWS group; no differences were observed in the NCS-R score. Two similar studies have been previously reported with discordant results. [15, 26]

The absence of any difference in the analgesic effect between UWS and MCS patients could be partially attributed to the residual sample size in Phase 2. In this phase, the sample calculation allowed us to find differences in the NCR-S score, but the size in the phase decreased significantly, with a decrease of approximately 90 percent in the UWS group and 15 percent in the MCS group. Perhaps a greater n could reveal some difference under such a study design. Another possible explanation could relate to the type and dosage of analgesic medication used.

### *Limitations*

1. In Phase 1, the observational study does not allow the establishment of causal relationships. 2. Although both groups consist of DOC patients, the UWS group, by definition, has a greater impairment of the level of consciousness and this could be associated with a lower nociceptive response expressed in the NCS-R score. 3. Another limitation is that the study was not blinded because the evaluators were aware of the DOC categories of the patients. According to the sequence and design of the study, this would be inevitable.

### *List of abbreviations:*

- CRS-R: Coma Recovery Scale-Revised
- DBP: diastolic blood pressure
- DOC: disorders of consciousness
- GCS-P: Modified Glasgow Coma Scale-Pupils
- HR: heart rate
- MCS: Minimally Conscious State
- NCS-R: Nociception Coma Scale Revised
- r: Pearson correlation coefficient
- RR: respiratory rate
- SaO2: oxygen saturation
- SBP: systolic blood pressure
- UWS: Unresponsive Wakefulness Syndrome

## 5. Conclusion

In this study, in patients with DOC categorized into UWS and MCS, we found that the UWS group had a lower NCS-R score compared to the MCS group. Both groups were homogenized in several sociodemographic and clinical variables. In addition, in the entire sample and in the UWS group, the three scales used (CRS-R, GCS-P, and NCS-R) were positively correlated, and this was associated with the fact that, although they have different evaluation targets, the lower score of them would progressively represent a lower neurological condition of the patient.

## Compliance with ethical standards

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*Disclosure of conflict of interest*

No conflict of interest to be disclosed.

*Statement of informed consent*

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