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Evaluation of the effect of analgesic treatment on signs of nociception-related behaviors during physiotherapy in patients with disorders of consciousness: a pilot crossover randomized controlled trial

Estelle A.C. Bonin[a,b], Mariachiara L. Binda Fossati[a,c], Maria M. Filippini[a,d], Stephen Bornheim[e], Nicolas Lejeune[a,b,f,g], Anthony T. O'Brien[h], Olivier Bodart[a], Steven Laureys[a,b], Aurore Thibaut[a,b,*], Camille Chatelle[a,b]

Abstract

Neuro-orthopedic disorders are common in patients with disorders of consciousness (DOC) and can lead to potential pain. However, the patients' inability to communicate makes pain detection and management very challenging for clinicians. In this crossover randomized double-blind placebo-controlled study, we investigated the effects of an analgesic treatment on the presence of nociception-related behaviors. At baseline, the Nociception Coma Scale-Revised (NCS-R) was performed in 3 conditions: a non-noxious stimulation, a noxious stimulation, and during a physiotherapy session. Patients with a NCS-R total score during physiotherapy equal or above the score observed after the noxious stimulation could participate to the clinical trial, as well as patients with a score above 5. They received an analgesic treatment and a placebo on 2 consecutive days in a randomized order followed by an assessment with the NCS-R. Of the 18 patients, 15 displayed signs of potential pain during physiotherapy. Patients showed higher NCS-R scores during physiotherapy compared with the other conditions, suggesting that mobilizations were potentially painful. Of these 15 patients, 10 met the criteria to participate in the placebo-controlled trial. We did not find any effect of analgesic treatment on the NCS-R scores. This study highlights that physiotherapy may be potentially painful for patients with DOC, while analgesic treatments did not reduced NCS-R scores. Therefore, careful monitoring with appropriate assessment and treatment before and during mobilization should become a priority in clinical settings. Future studies should focus on the development of assessment tools sensitive to analgesic dosage to manage pain in DOC.

Keywords: Consciousness disorders, Pain management, Nociception Coma Scale-Revised, Physical therapy, Minimally conscious state, Unresponsive wakefulness syndrome/vegetative state, Randomized controlled trial

1. Introduction

Nociception is the neural process of encoding noxious stimuli. It includes physiological and behavioral aspects and does not require an access to consciousness.[16] *Pain* is defined as "an unpleasant sensory and emotional experience associated with potential or actual tissue damage".[18] Pain is therefore subjective and requires conscious processes. Severely brain-injured patients can suffer from disorders of consciousness (DOC) such as unresponsive wakefulness syndrome/vegetative state (UWS/VS; eye-opening periods and reflexive responses to stimuli[21,26]), minimally conscious state (MCS; reproducible but fluctuating signs of consciousness without communication[11]), and emergence from the MCS (EMCS; functional communication or use of objects[25]). These patients are unable or may have severe difficulties to reliably communicate and express their pain

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A. Thibaut and C. Chatelle contributed equally to this manuscript.

[a] Coma Science Group, GIGA-Consciousness, University of Liège, Liège, Belgium, [b] Centre du Cerveau (C²), University Hospital, Liège, Belgium, [c] Behavioral and Nervous System Sciences Department, University of Pavia, Pavia, Italy, [d] Neuromotor and Rehabilitation Department, AUSL-IRCSS of Reggio Emilia, Reggio Emilia, Italy, [e] Department of Sport and Rehabilitation Sciences, University of Liège, Liège, Belgium, [f] CHN William Lennox, Saint-Luc Hospital Group, Ottignies, Belgium, [g] Institute of Neurosciences, UCLouvain, Brussels, Belgium, [h] Independent Scholar, Aetna, CVS Health Company, Hartford, CT, United States

**Corresponding author. Address: GIGA-Consciousness, Coma Science Group CHU Sart Tilman, GIGA-Research B34-Quartier Hôpital Ave de l'Hôpital, 11 4000 Liège, Belgium. Tel.: +32 4 284 36 14. E-mail address: aurore.thibaut@uliege.be (A. Thibaut).*

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experience.[11,14] Nevertheless, the IASP specified that "the inability to communicate verbally does not negate the possibility that an individual is experiencing pain".[18] Sources of pain can be heterogeneous and vary depending on the patient's condition. For instance, in the acute setting, pain can be a consequence of fractures, soft tissue injuries, and inserted tubes. On the other hand, during the subacute and chronic phases, pain is more likely to be caused by spasticity, myostatic contracture, arthrosis, or dystonia.[24] Therefore, pain and nociception management in this population is a clinical challenge and an ethical responsibility. The Nociception Coma Scale-Revised (NCS-R) was developed to assess pain and nociception in patients with DOC.[23] This behavioral scale comprises 3 subscales (motor, verbal, and facial expressions) respectively scoring from 0 (no response) to 3 (highest response level) with a maximal total score of 9. Several studies reported its good concurrent validity as well as sensitivity to nociception and level of consciousness.[2,7,8] The clinical value of the NCS-R in pain management for patients with DOC was evaluated in a study conducted in the acute setting (ie, intensive care unit). The results suggested that the NCS-R seems to be an appropriate tool to monitor analgesic administration and ensures that the provided analgesic treatment reduces signs of pain without influencing the level of consciousness.[6] However, there is currently no reliable guideline that has been defined regarding its use in a clinical setting.[7] Moreover, these studies showed some limitations regarding the analgesic administration (ie, lack of blinding and absence of placebo[6,7]).

In this study, we first aim to investigate whether mobilizations (ie, physiotherapy [PT]) are associated with increased signs of nociception-related behaviors in patients with DOC, as measured with the NCS-R. We expected that mobilizations would not induce as much of these signs as a noxious stimulation. However, if patients display NCS-R scores during PT equal or higher than those after a noxious stimulation, this may suggest that PT could potentially be painful. In a second phase, we wanted to assess the sensitivity of the NCS-R to analgesics treatment in the context of a potentially painful condition in a clinical setting by conducting a crossover randomized double-blind placebo-controlled study. We hypothesized that analgesic treatment administration would induce a decrease in the NCS-R scores during both PT and noxious stimulation.

2. Methods

2.1. Standard protocol approvals, registrations, and patient consents

The study was registered (NCT04330547) and approved by the Ethics Committee of the Hospital-Faculty Ethics committee of the University of Liege, and written informed consent was obtained from the patients' legal representatives in accordance with the Declaration of Helsinki.

2.2. Study design

This study is a 2-arm, 2-period crossover randomized double-blind placebo-controlled trial.

2.3. Participants and eligibility criteria

In this crossover randomized double-blind placebo-controlled study, patients were assessed as part of a week of diagnostic and prognostic assessment. Inclusion criteria were as follows: (1) age $\geq$ 16 years; (2) $>$ 28 days postinjury; (3) no administration of neuromuscular function blockers and no sedation 24 hours before assessment; and (4) a diagnosis of UWS/VS MCS, or EMCS based on the behavioral assessment performed using the Coma Recovery Scale-Revised (CRS-R[12]). Exclusion criteria were as follows: (1) documented history of previous brain injury; (2) premorbid history of developmental, psychiatric, or neurologic illness resulting in documented functional disability up to time of the injury; and (3) upper-limb contusions, fractures, or flaccid paralysis.

Note that medication was documented to control for drug effect on the central nervous system (Supplementary Table 1, available at http://links.lww.com/PAIN/B403).

2.4. Randomization and blinding

Each patient included in the clinical trial received once the placebo and once the analgesic treatment, in a randomized order. The medical doctor in charge of the randomization provided to the nurse the type and the dose of the analgesic treatment or the placebo to administrate (see Clinical trial section for more details). Investigators and patients were blinded to the treatment allocation.

2.5. Procedures

The study was performed within 3 days and was divided into 2 phases (baseline assessments at T0 and the clinical trial at T1 and T2).

2.6. Baseline (T0)

The level of consciousness was assessed using the CRS-R. This scale is the gold standard for the behavioral assessment of the level of consciousness and is widely used in patients with prolonged DOC.[12] It is composed of 6 subscales that assess the following domains: visual, motor, auditory, oro-motor or verbal functions, communication, and arousal. The score ranges from 0 to 23, in which the lowest score indicates coma and the highest score indicates the emergence from the minimally conscious state. The diagnosis is made according to the presence or absence of particular behavioral responses.[13] Then, the Modified Ashworth Scale (MAS[4]) was used to assess spasticity (ie, reflex contraction in response to passive stretching) at the main joints of upper and lower limbs. This scale ranges from 0 (no increase in muscle tone) to 4 (very strong increase in tone and stiffness). Spastic hypertonia, by definition, depends on the speed of execution of the movement (the faster the limb is mobilized, the more hypertonia increases). The evaluation should be performed at least 3 times for each joint. After that, patients' pain responsiveness was assessed using the NCS-R during a tactile stimulation (ie, 5 taps on the dorsal part of the hand) and during a noxious stimulation (ie, deep pressure on the nail bed of the left and right middle fingers for 5 seconds[23]). Then, the presence of potential pain was assessed with the NCS-R during 15 minutes of passive mobilizations of the upper and lower limbs performed by always the same trained physiotherapist (ie, PT[10]). The physiotherapist (ie, S.B.; see co-authors) stopped the movement when the articulation could no longer be mobilized and maintained that posture for a certain time (ie, between 30 and 90 seconds depending on the state of the stretched muscle and the patient's discomfort).

If the NCS-R score observed during PT was higher or equal to the one observed during a noxious stimulation, or if it was higher or equal to the cut-off score of 5 defined in a previous study,[5] the patient was eligible for the second phase of the study, the clinical trial.

2.7. Clinical trial (T1 and T2)

This randomized double-blind placebo-controlled clinical trial was performed on the subset of patients identified on T0. Analgesic and placebo treatments were administered 24 hours apart (T1 and T2) by a nurse, at least a half-hour before each assessment. The placebo administered was Folavit capsules (folic acid, 0.4 mg). The nature and dose of the analgesic administered were chosen according to the patient's needs, based on the World Health Organization guidelines (ie, nonopioid as level 1, weak as level 2, and strong opioid as level 3[29]):

(1) If the patients had no analgesic treatment, they received a nonopioid analgesic (level 1).
(2) If the patient was already receiving pain medications, we added the lowest effective dose of the level above the level of the regular pain medications of the patient:
   - If they already had a level 1 drug, they received a level 2 drug.
   - If they already had a level 2 drug, they received a level 3 drug.
   - If the patient was already taking a level 3 drug, we increased the dosage by steps (reference: 5 mg oxycodone as first choice for level 3 drugs, also see supplementary Table 2 lists of the suggested medications (from first to last choice by category), available at http://links.lww.com/PAIN/B403).

The medication was administered by oral intake or gastrostomy feeding tube, according to the habits of the patient regarding his or her usual medication intake.

The same assessments were performed as described in T0 for T1 and T2 (ie, NCS-R during tactile, noxious, and PT; CRS-R; and spasticity assessment).

2.8. Statistical analyses

As our data (ie, NCS-R total scores and the CRS-R total scores) were ordinal and our sample was rather small ($n < 30$), we used nonparametric tests for analyses.

2.8.1. Baseline

A Kruskal–Wallis test was performed to test baseline differences (T0) between the 3 stimulations (ie, tactile, noxious, and PT). Then, a Dunn test was performed as a post hoc analysis to investigate differences in NCS-R scores between each stimulation.

2.8.2. Clinical trial

We investigated differences in NCS-R scores and subscores between each stimulation (ie, tactile, noxious, and PT) and each condition (ie, placebo and treatment) using Kruskal–Wallis and Dunn tests (post hoc analysis). Finally, we used Kruskal–Wallis and Dunn tests to investigate the effect of treatment and placebo administration on the level of consciousness (CRS-R scores).

Analyses were performed using R studio (version 4.0.2) and were considered significant at $P < 0.05$. For each of the Dunn tests, P values were adjusted using the Benjamini–Hochberg (BH) method.

3. Results

3.1. Baseline (T0)

From February 2018 to February 2019, 18 patients were included in the study (8 women; age 44 ± 15 years), of which 2 patients were UWS/VS, 14 were MCS, and 2 were EMCS according to the CRS-R assessment (refer to **Fig. 1** for the flow diagram). Etiology was traumatic (n = 8), ruptured aneurysm (n = 6), and postanoxic encephalopathy (n = 5) (refer to **Table 1** for demographic and clinical data).

During baseline, 15 of the 18 patients showed signs of potential pain (ie, NCS-R ≥ 5) during PT (15/18, 83.3%). Given the initial population, most of the patients with potential pain were MCS (13/15, 86.7%), only one was UWS/VS (1/15, 6.6%), and one EMCS (1/15, 6.6%). Of these 15 patients, 11 had a NCS-R total score during PT higher or equal to the one observed after a noxious stimulation (11/15, 73.3%) and 4 showed a NCS-R total score during PT higher or equal to the cut-off score of 5 (4/15, 26.6%).[5] All the patients who were considered as potentially painful were spastic, and 13 of them (13/15, 86.7%) were severely spastic with a MAS score higher or equal to 3 (ie, corresponding to a considerable increase in tone with difficulty to perform passive movement 13/15, 86.7%) for one or more of the tested joints (see Supplementary Table 3 for more details on the MAS scores, available at http://links.lww.com/PAIN/B403). Of the 18 patients included in the study, 8 of them received an antispastic treatment (ie, baclofen per os (n = 7) or intrathecal (n = 1); **Table 1**). Finally, two-thirds of these patients were not under any analgesic treatment before their inclusion in the study (10/15, 66.6%).

The influence of PT on NCS-R total scores was assessed with a Kruskal–Wallis test performed on the 18 patients included at baseline (T0). A difference in the NCS-R total scores was observed between the type of stimulation (ie, tactile, noxious, and PT; $\chi^2 = 32.11$, $P < 0.0001$). Additional analyses using Dunn tests corrected with the BH method showed a difference (**Fig. 2**) in the NCS-R scores between PT and tactile stimulation (Z score = 5.55, P value adjusted < 0.0001) as well as between tactile and noxious stimulation (Z score = 3.74, P value adjusted < 0.001). However, these additional analyses did not allow us to find a significant difference in the NCS-R scores between PT and noxious stimulation.

3.2. Clinical trial (T1 and T2)

Ten patients were included in the clinical trial (3 women, 5 TBI, 44.7 ± 12.6 years). Of the 15 patients identified as potentially

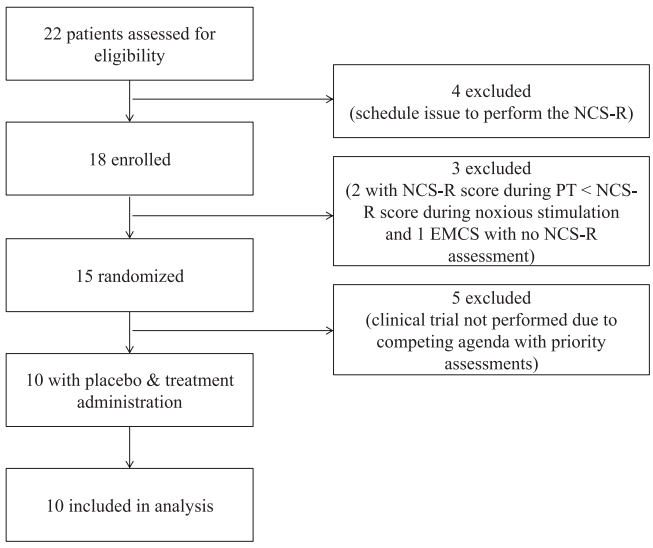

Figure 1. CONSORT flow diagram. NCS-R, Nociception Coma Scale-Revised; PT, physiotherapy.

Table 1

Demographics of patients included in the study.

Participants	Sex	Age	Etiology	Level of consciousness	Time since injury (d)	Tracheotomy	Inclusion phase 2	Reason of exclusion	Analgesic treatment			Antispastic treatment	
									Before the study	During the study	Dosage (per os)	Nature and administration mode	Dosage (per os)
1	M	23	Traumatic	UWS/VS	97	Yes	Yes	na	na	Paracetamol	1 g	No	
2	M	73	Postanoxia encephalopathy	MCS	645	No	No	NCS-R score during PT < NCS-R score during noxious stimulation	na	na	na	Lioresal (oral)	25 mg 3 × per day
3	M	37	Traumatic and hypoxia	MCS	2923	Yes	Yes	na	na	Paracetamol	1 gr	No	na
4	F	71	Ruptured aneurysm	MCS	412	Yes	No	Competing agenda with priority assessments	na	na	na	No	na
5	F	45	Ruptured aneurysm	MCS	1340	No	Yes	na	na	Paracetamol	1 gr	Lioresal (oral)	25 mg 3 × per day
6	F	50	Ruptured aneurysm	MCS	93	No	Yes	na	Yes (fentanyl and paracetamol)	Oxycodone	10 mg	Lioresal (oral)	25 mg 3 × per day
7	M	40	Traumatic	MCS	766	No	Yes	na	Yes (paracetamol and tramadol)	Tramadol	100 mg	Lioresal (oral)	25 mg 1 × per day
8	M	60	Postanoxia encephalopathy	MCS	341	Yes	Yes	na	na	Paracetamol	1 gr	No	na
9	M	30	Traumatic	EMCS	2412	No	Yes	na	Yes (tramadol)	Tramadol	50 mg	No	na
10	M	63	Traumatic	MCS	169	Yes	Yes	na	na	Paracetamol	1 gr	No	na
11	F	47	Ruptured aneurysm	MCS	124	Yes	Yes	na	Yes (paracetamol)	Tramadol	50 mg	No	na
12	F	33	Postanoxia encephalopathy	EMCS	7363	No	No	EMCS not assess with the NCS-R	Yes (paracetamol)	na	na	Lioresal (intrathecal)	ns
13	M	34	Traumatic	MCS	165	Yes	No	Competing agenda with priority assessments	na	na	na	No	na
14	F	40	Ruptured aneurysm	MCS	1290	No	No	Competing agenda with priority assessments	na	na	na	Lioresal (oral)	10 mg 3 × 2 per day
15	M	23	Traumatic	MCS	125	Yes	No	Competing agenda with priority assessments	na	na	na	No	na
16	M	52	Postanoxia encephalopathy	MCS	337	Yes	Yes	na	Yes (morphine and midazolam)	Oxycodone	5 mg	No	na
17	F	27	Traumatic	UWS/VS	765	No	No	NCS-R score during PT < NCS-R score during noxious stimulation	na	na	na	Lioresal (oral)	ns
18	F	39	Ruptured aneurysm	MCS	239	No	No	Competing agenda with priority assessments	na	na	na	Lioresal (oral)	15 mg 1 × per day

EMCS, emergence from the minimally conscious state; F, female; MCS, minimally conscious state; M, male; UWS/VS, unresponsive wakefulness syndrome/vegetative state; na, not applicable.

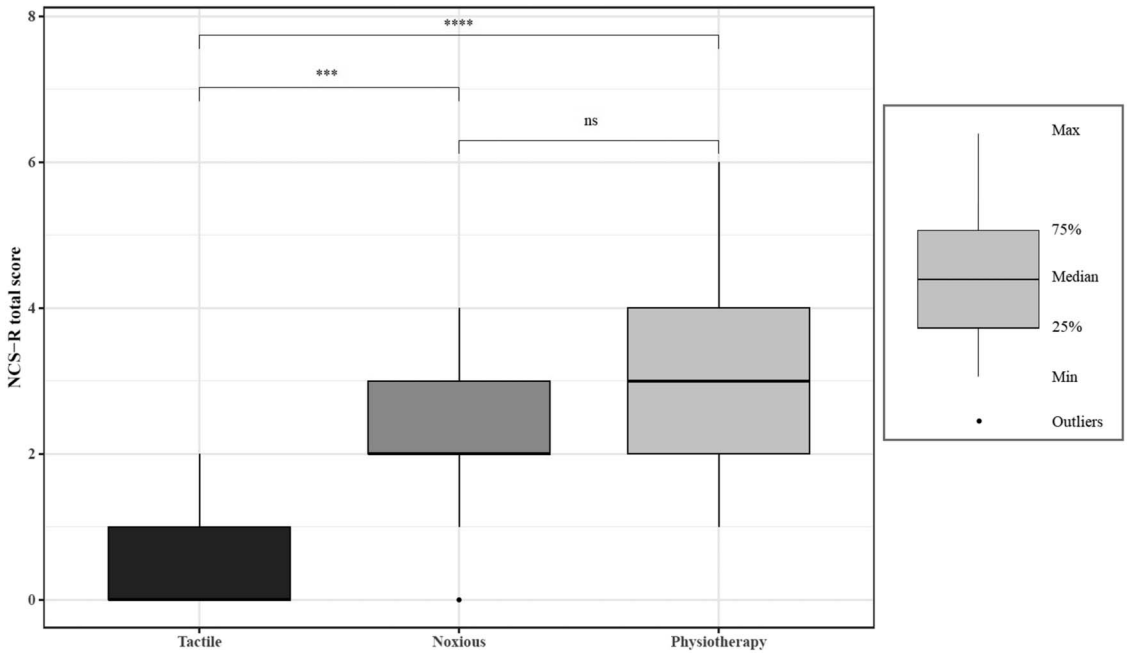

Figure 2. Changes in the NCS-R total score after tactile stimulation, noxious stimulation, and physiotherapy at baseline (T0; n = 18). NCS-R, Nociception Coma Scale-Revised; ns, not significant, ***$P < 0.001$, ****$P < 0$ 0.0001).

painful during baseline, 5 were not included in the clinical trial because of schedule issues (ie, the clinical trial could not be scheduled because of competing agenda with priority assessments).

For both conditions (ie, placebo and treatment), we found a difference in NCS-R total scores between the type of stimulation (placebo: $\chi^2 = 14.01$, $P < 0.001$; treatment: $\chi^2 = 10.31$, $P < 0.01$; **Fig. 3**). During the placebo condition, additional analyses using Dunn tests corrected with the BH method showed a difference in the NCS-R total scores between PT and tactile stimulation (Z score = 3.74, *P* value adjusted < 0.001). During the treatment condition, we also found a difference between PT and tactile stimulation (Z score = 3.20, *P* value adjusted < 0.01).

Moreover, regarding the NCS-R subscales (ie, motor, verbal, and facial expression), we found a difference on the facial expression NCS-R subscores for both condition (placebo: $\chi^2 = 10.87$, $P < 0.01$; treatment: $\chi^2 = 7.65$, $P < 0.05$). Dunn tests corrected with the BH method showed a difference on the NCS-R facial expression subscores between PT and tactile stimulation for both condition (placebo: Z score = 3.28, *P* value adjusted < 0.01; treatment: Z score = 2.76, *P* value adjusted < 0.05; see Supplementary Fig. 1, available at http://links.lww.com/PAIN/B403). We did not find differences between conditions on the motor and verbal NCS-R subscores. Statistical analyses used to investigate the effect of treatment administration on the NCS-R total scores during noxious stimulation and PT did not show any significant difference between each condition (ie, placebo and treatment; see Supplementary Fig. 2, available at http://links.lww.com/PAIN/B403).

At the single-subject level, a decrease of the NCS-R total score after the treatment administration was observed in 2 patients during PT. Four patients showed a higher NCS-R total score after treatment administration than after placebo administration (see Supplementary Table 3, available at http://links.lww.com/PAIN/B403). The Kruskal–Wallis analysis did not show any effect of treatment administration on the level of consciousness (ie, CRS-R total scores). At the single-subject level, no changes were observed for diagnosis between placebo and treatment condition.

4. Discussion

The aim of this study was first to investigate the influence of PT on signs of potential pain in patients with DOC and then to determine the effects of an analgesic treatment on those signs using a double-blind randomized placebo-controlled study. We can highlight 2 main findings:

(1) PT could be potentially painful for patients with DOC. Patients displayed higher NCS-R total scores during PT than during tactile stimulation and we did not observe differences between NCS-R total scores during PT vs noxious stimulation.

Our findings support the hypothesis that PT could potentially be painful for patients with DOC and could be at least as painful as noxious stimulation. The presence of spasticity could partially explain these results because all the patients suffered from spasticity and most of them had severe spasticity (ie, MAS score ≥ 3, 13/15, 86.7%). A previous study showed that 89% of patients with chronic DOC develop spasticity.[27] Spasticity was also associated with increased signs of pain, particularly during nursing cares and mobilizations.[27] Intrathecal baclofen pump is frequently used as an antispastic treatment in patients with severe brain injury. In addition to reducing the signs of pain related to spasticity, several open-label studies have shown that intrathecal baclofen may also improve patient's behavioral responsiveness.[17,20,28] To the best of our knowledge, no such study achieved to show such results with oral baclofen. In our study, 7 of the 8 patients included in the clinical trial received baclofen per os; therefore, the risk that pain or behavioral responsiveness could be influenced by the administration of intrathecal baclofen is limited. Importantly, 15 of the 18 patients included during baseline showed signs of potential pain during PT (ie, NCS-R > 4), and only 5 of them (33%) were treated with analgesics before inclusion. These results are in line with a previous

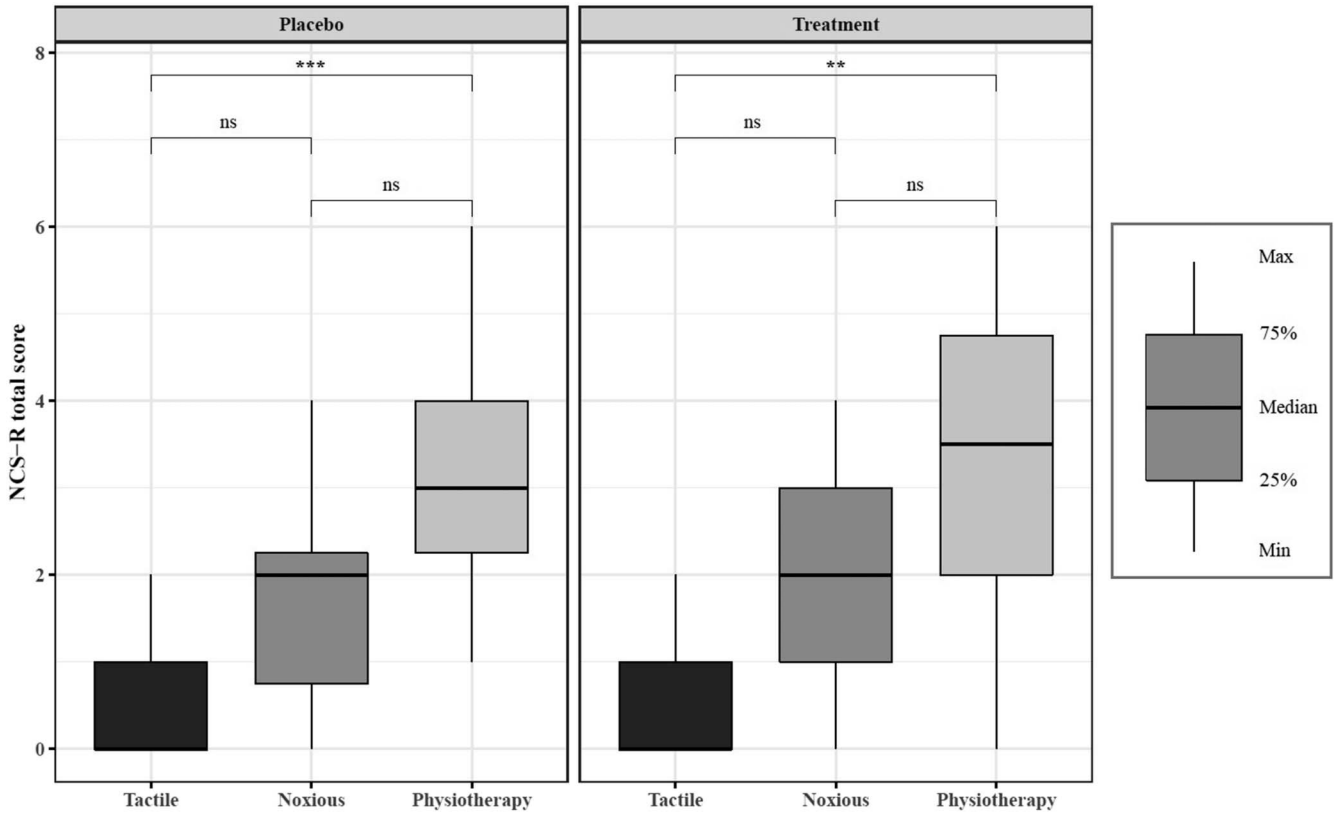

Figure 3. Changes in the NCS-R total score after tactile stimulation, noxious stimulation, and physiotherapy during the clinical trial (T1 and T2 n = 10) after the placebo or treatment administration. NCS-R, Nociception Coma Scale-Revised; ns, no significance, $^{**}P < 0.01$, $^{***}P < 0\ 0.001$).

clinical study which showed that 59% of patients with an identified potentially painful condition (polytrauma and wounds) did not have analgesic treatments during care.[6]

We also found that the facial expression subscale was particularly important, being the only one showing higher scores during PT compared with tactile stimulation. Spasticity and motor limitations can explain the absence of difference on the motor subscale. For the verbal subscale, 60% of the patients included in the clinical trial had a tracheotomy, which severely limits verbal interactions and could influence this subscore.[15]

These results highlight the fact that behavioral tools such as the NCS-R should be used more routinely to monitor potential pain during PT or other potentially painful care. This may allow the implementation of appropriate pain treatment and potentially also facilitate the management of spasticity in patients with DOC. In addition, future studies will need to focus on the definition of objective indicators of facial responses reflecting pain-related response in these patients because it seems to be a key behavior in the assessment of pain.[1]

(2) Analgesic treatment did not decrease signs of nociception during PT. During the double-blind randomized placebo-controlled study, no effect of analgesic treatment on NCS-R total scores and subscores was found. Surprisingly, at an individual level, we observed an increase in the NCS-R total score during PT after treatment administration for 4 patients and a decrease in only 2 patients.

This study did not support the hypothesis that analgesic treatment could decrease signs of pain during PT (ie, NCS-R scores) because it was suggested in a previous open-label study showing a decrease of the NCS-R total score after administration of an analgesic treatment in acute patients.[6] However, the difference in terms of the methodology (eg, open-label vs double-blind, treatment) and the population (eg, acute vs chronic) should be investigated in the future.

The absence of analgesic effect in our study could be explained by the fact that either the NCS-R is not sensitive enough to detect the effect of the analgesic treatment or the medication administered did not efficiently reduce pain. Indeed, most of the patients received, as analgesic treatment, a nonopioid agent (ie, paracetamol). The use of such nonopioid medication may not have been strong enough to induce a noticeable effect on pain and therefore on the NCS-R. Hence, an optimal pain management should account for a titration period to adapt the medication to the patient's needs and condition. Future studies should also take into consideration the duration of the presence of signs of nociception during care to better detect the change after the administration of the treatment. Optimal pain management involves that the nature and the dose of the treatment are appropriate to the patient's needs to avoid a reduction in vigilance and a slow down in the recovery of consciousness.[20] Our results suggest that analgesic treatment did not have a negative influence on the level of consciousness of patients included in the study. However, our results could not support the case study suggesting that an appropriate analgesic treatment may promote behavioral responsiveness.[14] The absence of a titration allowing for optimal medication for each patient may explain this result.

Our findings must be interpreted despite several limitations. First, the sample size of this study is small (n = 18 and 15 for the clinical trial). Second, this study falls within the field of translational research and needed to be adapted to the clinical context.

Consequently, the nature of the analgesic treatments already in place for these patients was not controlled and heterogeneous. Moreover, the administration of the analgesic was provided through the gastrostomy feeding tube for 87% of the patient. However, it was performed at a distance from the enteral feeding, diminishing the risk of malabsorption that could be caused by the formation of complexes between the medication and molecules contained in the enteral feeding (eg, proteins or ions). These factors could have influenced the results and could explain the absence of difference between placebo and treatment. Another limitation is the possible variability in amplitudes of the movement during PT at baseline and after treatment administration because analgesic may have influenced the patients' range of motion. Finally, the presence of dysautonomia may be a limitation. However, according to the medical files of each patient included in this study none of them showed any signs of this syndrome such as paroxysmal hypertension, tachycardia, or hyperthermia. Therefore, it is unlikely that signs of dysautonomia would appear during the duration of our protocol. Moreover, based on demographical information, the shorter time since injury in our sample was about 97 days, which decreases the risk of dysautonomia. To the best of our knowledge, there is only one validated tool that allows to assess dysautonomia[3] and the NCS-R does not evaluate the same clinical signs, so the risk of misdiagnosis is rather low.

In the future, administration of treatments should be better controlled (ie, control of premedication and use of titration method, intravenous administration) and these results should be repeated in a multicenter study with a larger number of patients. In addition, we only used the NCS-R to assess pain responsiveness. However, the use of physiological measures of pain such as skin conductance[9,30] or heart rate[22] could have provided additional information on pain-related physiological metrics, which should not be neglected in a clinical setting. Moreover, at baseline, pain was only assessed once, whereas in a clinical setting pain and nociception assessments would have to be repeated on a daily basis to be able to detect fluctuations in pain responsiveness.

Finally, the CRS-R was performed on the day of the assessment for each condition, but not simultaneously with the NCS-R, and we know that patients with DOC may fluctuate during the day which could have an influence on pain sensitivity or responsiveness.[19] However, we did not find any significant change regarding the CRS-R total score at each day of assessment, suggesting that the level of consciousness assessment of these patients was relatively stable.

In conclusion, this study highlights that (1) PT is associated with potential pain in most of the patients with DOC and only a few of them were receiving an analgesic treatment before the study. (2) The study did not allow us to show an effect of a first-intention analgesic treatment on the NCS-R scores, suggesting that either the NCS-R score lacks sensitivity or the NCS-R responsiveness to analgesics should be evaluated with different levels of analgesic drugs. Our results highlight a lack of clear guidelines for (1) the implementation of such behavioral scales (eg, assessments frequency) and (2) the administration of optimal treatment in this population. Indeed, appropriate assessment (eg, systematic NCS-R assessment during care and mobilizations) and treatment (eg, titration allowing for optimal treatment for each patient) of pain before and during mobilizations should become a priority in clinical settings.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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The data related to this study can be made available upon reasonable request.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B403.

Supplemental video content

A video abstract associated with this article can be found at http://links.lww.com/PAIN/B404.

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