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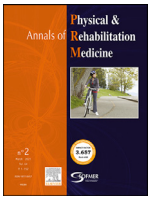

Original article

Short-term outcomes of early intensive neurorehabilitation for prolonged disorders of consciousness: A prospective cohort study

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ABSTRACT

Background: Advances in medical care have increased survival in people with severe brain injuries and with that the number of survivors with prolonged disorders of consciousness (PDOC) has increased. In the literature, early intensive neurorehabilitation (EIN) for people with PDOC is recommended to achieve the best possible outcomes.
Objectives: To evaluate the frequency and extent of recovery of consciousness, mortality, complications, pain and discomfort, and medication during a nationwide EIN programme in people with PDOC after acquired brain injury. We hypothesized that level of consciousness would improve in half of people with PDOC.
Methods: Prospective cohort study. People with PDOC aged 16 years and older admitted to the EIN department centralized in a single rehabilitation centre in the Netherlands (Libra Rehabilitation & Audiology) were included. The EIN delivers a subacute medical level of care and rehabilitation for a maximum duration of 14 weeks. The outcome measures were level of consciousness (CRS-R), mortality, number of complications, medication and pain/discomfort (NCS-R).
Results: Of the 104 people included, 68 % emerged to a minimal conscious state with command-following or higher during EIN and 44 % regained consciousness. Mortality during EIN was 6 %, and 50 % of deaths followed a non-treatment decision or withdrawal of life-sustaining treatment. Almost all participants had at least 1 medical complication, leading to hospital readmission for 30 %. 73 % showed no pain or discomfort. During EIN, cardiovascular medication and analgesics were reduced by 15 %.
Conclusions: During the EIN programme, a large percentage of people with PDOC regained at least a minimal conscious state or even consciousness. These outcomes and the frequent medical complications in these people suggest that intensive specialized care should be offered to all people with PDOC. The outcomes of this study might help health professionals to better inform the families of people with PDOC about the short-term prognosis of PDOC.
Protocol registration number: The Dutch Trial Register, NL 8138.

Introduction

Advances in emergency and neurosurgical procedures have increased survival in people with severe traumatic (TBI) and non-traumatic brain injuries (NTBI). Consequently, the number of survivors with disorders of consciousness (DOC) has also increased [1,2]. The absence of, or limited, signs of consciousness for at least 4 weeks after acute brain injury is indicative of a prolonged disorder of consciousness (PDOC) [3]. PDOC includes unresponsive wakefulness syndrome (UWS) and minimally conscious state (MCS). UWS is characterized by periods of eye-opening but no behavioural evidence of

Abbreviations: CRS-R, Coma Recovery Scale-Revised; DOCTOR, Disorders of Consciousness, Treatment and Outcome Registry; DRS, Disability Rating Scale; EIN, Early intensive neurorehabilitation; e-MCS, Emergence from minimal conscious state; ICF, International Classification of Functioning, Disability and Health; LOC, Level of consciousness; MCS, Minimally conscious state; NCS-R, Nociception Coma Scale-Revised; NTBI, Non-traumatic brain injury; PDOC, Prolonged disorder of consciousness; PSH, Paroxysmal sympathetic hyperactivity; TBI, Traumatic brain injury; TPI, Time post injury; UWS, Unresponsive wakefulness syndrome

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conscious awareness [4]. MCS is characterized by clearly discernible but inconsistent behavioural signs of conscious awareness [5]. MCS was later subcategorized based on the complexity of people's behaviours [6]. The term MCS minus (MCS-) describes people with low-level behavioural responses (ie, people with visual pursuit, localisation of noxious stimuli or contingent behaviours, such as appropriate smiling or crying to emotional stimuli). MCS plus (MCS+) is used to describe people with high-level behavioural responses (ie, able to follow commands, have intelligible verbalizations or intentional communication). Emergence from MCS (e-MCS), regaining consciousness, occurs when the person is able to communicate reliably through verbal or gestural yes-no responses, or is able to demonstrate the use of 2 or more objects in a functional manner [5].

Early intensive neurorehabilitation (EIN) is recommended for people with PDOC to achieve the best outcomes [7]. The aim of such a rehabilitation programme is threefold [8,9].

The first aim of EIN is systematic accurate assessment of level of consciousness (LOC) and facilitation of recovery of consciousness. Over the past decades, recovery of consciousness after intensive neurorehabilitation in people with PDOC has been demonstrated to occur in 44–69 % of people on average [10–16]. This wide range may depend on whether only people with UWS or both people with UWS and MCS are included, or on the aetiology of the brain injury. People with TBI [10,14,16] and people with MCS [11,13,14,16] have better LOC outcomes than people with a non-traumatic cause of brain injury and/or people with UWS. No literature is available on the spontaneous recovery of PDOC without delivery of specialized care and no randomized controlled trials have been conducted [17]. Therefore, it is impossible to state whether recovery of consciousness is the result of intensive neurorehabilitation treatment or spontaneous recovery. However, Aidinoff et al [10] demonstrated an improvement in survival and recovery of consciousness in people with UWS over the last 2 decades after EIN in a rehabilitation centre. This suggests that improvements in acute medical care and EIN have contributed to advances in UWS outcomes.

The second aim of EIN is the delivery of basic care, and management of secondary medical complications. People with PDOC can develop multiple complications. Within 6 months postinjury 80 –95 % of people with PDOC developed at least 1 medical complication [18,19], with musculoskeletal complications occurring most frequently. Complications can increase mortality and negatively influence cognitive and functional outcomes. Therefore, appropriate expertise in clinical management is warranted [20]. Whyte et al have shown that active and expert management accounts for a reduction of complications [18]. Pain perception must also be considered in individuals with PDOC as cortical activations have been shown, even in people with UWS [21]. Therefore, observation of pain-related behaviour and analgesic treatment is an important part of the management of people with PDOC [21].

The third aim of EIN is education, empowerment, and counselling of the family in their different roles, not only as legal representatives of the individual, but also as grieving loved-ones and contributors to the therapeutic process [22,23].

In the Netherlands, EIN for people with PDOC has been centralized within a single centre (Libra Rehabilitation) since 2019. This results in the unique situation that our study could include all the people with PDOC in the nation. This is a novelty in the field of studies on outcomes of EIN for PDOC. Centralization of care provides a better representation of the outcomes of EIN for PDOC as all individuals with PDOC have equal access to the rehabilitation programme. In addition, the outcomes are not confounded by potential variation in the content of the rehabilitation programme between centres. The close monitoring and systematic evaluation of people with PDOC may improve the quality of their care, which may also result in better quality of life for this challenging-to-manage group.

To examine all people with PDOC on a nationwide scale, a prospective cohort study with a 2-year follow-up was initiated: Disorders Of Consciousness, Treatment and Outcomes Registry (DOCTOR). This study reports the first results of the ongoing DOCTOR study. The aim of the current study was to evaluate the short-term outcomes, including the frequency and extent of recovery of consciousness, complications, pain and discomfort, medication, and mortality in people with PDOC after acquired brain injury during the EIN programme. We hypothesized that level of consciousness would improve in half of the people with PDOC during the EIN programme. We also expected that the results of this study would expand existing knowledge on the type and frequencies of complications, pain and discomfort experienced by people with PDOC, as well as changes in medication and circumstances of death during the EIN programme, which would be useful for health professionals and families taking care of people with PDOC.

Methods

Study design, settings, and participants

The DOCTOR study is a prospective, single-centre cohort study involving measurements at the start of EIN, at 5 and 10 weeks and at discharge from EIN (14 weeks), and at 28, 40, 52 and 104 weeks after the start of EIN. In addition, LOC and pain measurements are performed weekly during EIN, as part of the EIN programme [24]. The EIN programme ends as soon as the person has reached consciousness or, if they have not emerged from the disorder of consciousness, after a maximum of 14 weeks of EIN. Thereafter, people are discharged to standard medical rehabilitation, home, a specialized PDOC nursing home providing prolonged intensive neurorehabilitation, or to another institution, depending on the LOC and abilities of the individual and the preferences of their family. The current study describes the short-term outcomes, ie, the outcomes during and at discharge from EIN.

All consecutive people with PDOC admitted to EIN at Libra Rehabilitation in the Netherlands, were screened from April 2019 to March 2022. Inclusion criteria were ≥16 years at the time of injury, PDOC lasting at least 4 weeks and <6 months at admission, medically stable as judged by the treating rehabilitation physician, and first-time newly acquired non-progressive brain injury of any aetiology. Exclusion criteria were coma and uncontrollable epilepsy.

Ethical and regulatory considerations

Participants were included in the study within the first 2 weeks after admittance to EIN if written informed consent was obtained from their legally authorized representative. People who regained consciousness during the study trajectory were personally asked for their written informed consent to continue participation in the study.

The Medical Ethics Committee of Erasmus MC, University Medical Centre Rotterdam declared that the study was not subject to the Dutch Medical Research Involving Human Subjects Act, meaning that ethical approval for the study was waived under the national laws (MEC-2019–0127). This study reporting follows the STROBE guidelines for reporting observational studies (Appendix A).

EIN programme

After acute brain injury, people are referred to EIN if the disorder of consciousness lasts >4 weeks and if they are medically stable (eg, no ventilation and no intravenous medication). The EIN programme consists of a maximum of 14 weeks of treatment, or less if recovery of consciousness occurs earlier. EIN meets the American Academy of

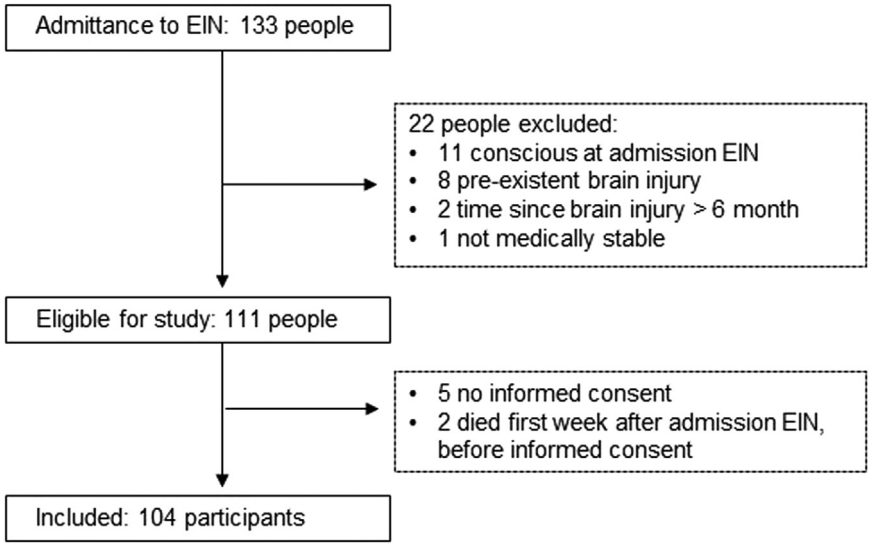

Fig. 1. Study flowchart illustrating participant enrolment.

Neurology guideline recommendations for people with prolonged disorders of consciousness [8].

PDOC people receive continuous skilled nursing (24/7) and medical care and a daily maximum of 150 min (5 × 30 min) of interdisciplinary rehabilitation to facilitate recovery of consciousness and prevent complications. The programme provides multimodal stimulation, pharmacological treatment, and mobilization therapies (eg, out of bed, physical interventions) to promote body function and reduce complications secondary to inactivity and deconditioning. A structured approach is used in which daily routines are built in together with a scheme of alternating therapy and rest. Further, diagnostic observation runs throughout the EIN program. In addition, an intensive parallel programme for families is provided with comprehensive education, counselling, and hands-on training and case management. A detailed description of the programme is provided in the protocol article of the DOCTOR study [24].

Evaluations

Outcomes reported in this paper are recovery from LOC (divided in subgroups: TBI/NTBI and UWS/MCS-/MCS+), physical disability, incidence and type of complications, level of discomfort or pain, medication, and mortality during EIN.

LOC was classified weekly by expert staff members using the Coma Recovery Scale-Revised (CRS-R) [25,26]. The CRS-R is a bedside assessment tool for differentiating levels of consciousness (UWS, MCS-, MCS+ and e-MCS) by observation of reactions to various stimuli. It is composed of 6 hierarchical subscales (auditory, visual, motor, oromotor/verbal, communication, and arousal function) with 23 dichotomously scored items. Total CRS-R score ranges from 0 (comatose state) to 23 (e-MCS).

Functional disability was evaluated with the Disability Rating Scale (DRS) [27] administered by the nursing staff of the EIN department at admittance, week 5, 10 and discharge from EIN. The DRS is an observational scale that evaluates residual functional abilities, with 8 items that assess 4 domains: arousability (3 items), dependence on others (1 item), cognitive abilities (3 items), and employability (1 item). The DRS score ranges from 0 (low level of disability) to 29 (high level of disability).

Medical complications and medications were recorded weekly by the medical staff of the EIN department for each participant and were classified according to the International Classification of Functioning, Disability and Health (ICF) in the domain of functions and structures [28]. Pain/discomfort was measured with the Nociception Coma Scale-Revised (NCS-R) [29,30]. The NCS-R includes 3 subscales assessing motor, verbal, and facial expression responses to pain, with a total score ranging from 0 to 9; a higher score indicates a higher level of possible discomfort/pain with a cut-off value of ≥4, indicating presence of pain/discomfort [31]. The NCS-R was performed during the administration of the CRS-R by the same experienced staff member administering the CRS-R. The score was determined by behaviour observations during the CRS-R, excluding the effect of the nociceptive stimulus of the CRS-R.

Demographic characteristics, clinical characteristics, medical history, length of stay at EIN and data on prior hospital admissions were obtained from the medical records by the researcher.

Statistical analysis

Descriptive statistics were used to present the outcomes of the study parameters and the socio-demographic data. Means and standard deviations and median and interquartile ranges (Q1; Q3) were calculated for variables on an interval scale and medians and Q1; Q3 for ordinal variables. Proportions were calculated for nominal variables.

Subgroup analyses were performed for participants with UWS versus MCS-, and MCS+ at baseline and for traumatic versus non-traumatic disorders of consciousness. For comparison of continuous variables, the independent *t*-test or Kruskal-Wallis test was used and the Chi-square test for categorical variables. A p-value <0.05 was considered statistically significant.

The proportions of participants transitioning from UWS to MCS and from MCS to e-MCS during EIN were calculated.

Results

Participants sample

In total, 133 people admitted with PDOC were screened for the study, 111 met the inclusion criteria and informed consent was provided for 104 (Fig. 1).

Table 1 shows the demographic and clinical characteristics of the participants. Mean (SD) age was 39 (16.5) years (range 16 to 74 years). Most participants had sustained TBI (n = 60, 58 %). Of the participants with NTBI, 20 (45 %) had anoxic brain injury. At admittance, 35 % had UWS, 35 % had MCS- and 30 % had MCS+. Median time

Table 1
Demographics, clinical findings and medical history at admittance to EIN.

	Total sample	TBI	NTBI	*p*-value
n (%)	104 (100)	60 (58)	44 (42)	
Age (years), mean (SD)	39.0 (16.5)	34.9 (15.1)	44.5 (16.9)	0.003
Sex				0.011
Female *n* (%)	51 (49)	23 (38)	28 (64)	
Male *n* (%)	53 (51)	37 (62)	16 (36)	
Level of consciousness*				0.753
UWS *n* (%)	36 (35)	19 (32)	17 (39)	
MCS- *n* (%)	37 (35)	22 (36)	15 (34)	
MCS+ *n* (%)	31 (30)	19 (32)	12 (27)	
TPI (days), mean (SD) median (Q1; Q3)	71.7 (27.6) 66.0 (53.3; 86.8)	72.0 (28.2) 65.5 (53.3; 88)	71.3 (27.0) 67 (51; 86.8)	0.893
Time at ICU (days) mean (SD)	33.2 (23.1)	35.7 (22.7)	30.1 (23.5)	0.227
Tracheal tube n(%)	40 (38)	25 (42)	15 (34)	0.433
CRS-R total score mean (SD)	8.7 (4.3)	8.8 (4.1)	8.7 (4.8)	0.916
DRS total score mean (SD)	23.2 (3.2)	23.1 (3.6)	23.3 (2.6)	0.719

* 1 participant had no CRS-R data at admittance EIN because of agitation and was diagnosed with MCS+ based on clinical judgement.
CRS-R: Coma Recovery Scale-Revised, DRS: Disability Rating Scale, ICU: Intensive Care Unit, MCS: Minimally Conscious State, TPI: Time Post-Injury, UWS: Unresponsive Wakefulness Syndrome.

between brain injury and admission to EIN was 66 days (IQR 53.3; 86.8 days). There were no significant differences in clinical characteristics between participants with UWS and those with MCS at admittance. Participants with TBI were significantly younger than participants with NTBI and were more often male. There was no significant difference in level of consciousness between the TBI and NTBI subgroups at baseline.

Recovery of level of consciousness at discharge from EIN

Table 2 shows the outcomes at discharge from EIN. Of the 104 participants, 6 (6 %) died, 46 (44 %) were classified with e-MCS, 34 (33 %) with MCS+, 8 (8 %) with MCS- and 10 (10 %) with UWS at discharge from EIN. During EIN, 71 of 104 (68 %) participants evolved from either UWS (23 of 36 participants, 64 %), or MCS- (30 of 37 MCS- participants, 81 %) to a higher command-following level of consciousness (MCS+ or e-MCS) or from MCS+ (18 of 31 MCS+, 58 %) to e-MCS. For 25 of 104 (24 %) participants, no change in LOC occurred during EIN.

Of the participants with TBI, 50 % regained consciousness, against 36 % of the participants with NTBI (30 % of participants with anoxic brain injury). At discharge from EIN, 54 % of the participants with MCS and 25 % of the participants with UWS had e-MCS. Mean (SD) DRS score at EIN discharge was 18.3 (5.6) ('extremely severe disability'), with highest (most severe) DRS scores in participants with UWS at discharge from EIN: mean 25.0 (1.3) ('extreme vegetative state') and lowest in participants who were conscious at discharge, mean 14.5 (4.6) ('severe disability'). Participants who had UWS at discharge from EIN had a longer time post injury at EIN admittance. Participants with e-MCS at EIN discharge less often required a tracheal tube and had fewer hospital readmissions during EIN than participants with a lower state of consciousness.

After completion of the EIN programme, 52 of 104 participants (50 %) were referred to a nursing home, of which 29 (28 %) went to a nursing home specialized in PDOC care providing prolonged intensive neurorehabilitation. In total, 39 of 104 participants (38 %) were referred to a rehabilitation centre. Fig. 2 shows the proportions of each LOC during each phase of EIN.

Complications and medication administered

The incidence of complications during EIN is shown in Table 3. The most common complications included hypertonia/spasticity, contractures, diarrhoea, sleep disturbance and urinary tract infections. Abnormal blood test findings also occurred frequently (56 % of participants). Participants with TBI more often had a neurological complication such as hydrocephalus or paroxysmal sympathetic hyperactivity (PSH). For the other complications, there were no differences between participants with TBI and NTBI.

Participants with UWS sustained a higher total number of medical complications than those with MCS. Hydrocephalus, PSH, vomiting and pneumonia occurred more frequently in those with UWS than MCS, the same was found for hypertonia and contractures.

Five participants (5 %) had no complications during EIN. The median (Q1; Q3) number of complications per participant was 6 (4; 9). Most participants sustained 4 or 5 complications and one participant experienced 22 complications, mostly urinary tract infections.

Pain/discomfort was observed more frequently in participants with NTBI. In 2 participants, pain/discomfort was present throughout the entire EIN stay. Both these participants had a TBI and PSH that could not be controlled adequately with medication. Pain/discomfort was detected once or twice during the EIN stay in 21 participants (20 %) and 3 or 4 times in 5 participants (5 %). In 76 (73 %) participants, no discomfort or pain was observed during the CRS-R assessments.

During EIN, cardiovascular medication and analgesics could be reduced by 15 % (Table 4). Stimulantia and laxantia administration increased during EIN, respectively from 14 to 34 % and 67 to 76 %.

Mortality

During EIN, 6 participants (6 %) died. Scenarios of dying were diverse: severe medical complications despite life-sustaining treatment (3 participants), severe medical complications after a non-treatment decision (1 participant) and death following withdrawal of life-sustaining therapy (2 participants). The aetiology of the brain injury was non-traumatic for all 6 participants, 5 of whom sustained an anoxic brain injury. Their mean age was 47.8 years (SD 15.8), ranging from 26 to 74 years.

Discussion

The DOCTOR-study, a prospective nationwide cohort study, investigates the outcomes of all people with PDOC in the Netherlands after early intensive neurorehabilitation. The proportion of participants who regained consciousness during EIN in our study was 44 %. This result is comparable with the findings of Noé et al [11]. Retrospective studies have reported higher proportions of recovery to a conscious state after PDOC (ie 53–69 %), but those studies only analysed people who completed the EIN program and excluded people who died [10,13,15,16]. We prospectively studied all participants who started

Table 2
Level of consciousness and mortality at discharge from early intensive neurorehabilitation in relation to A) baseline parameters and B) other outcomes

A

	Total	Discharge e-MCS	MCS+	MCS-	UWS	dead
n (%)	104 (100)	46 (44)	34 (33)	8 (8)	10 (10)	6 (6)
At admittance to EIN						
Etiology						
TBI n(%)	60 (100)	30 (50)	23 (38)	1 (2)	6 (10)	0 (0)
NTBI n(%)	44 (100)	16 (36)	11 (25)	7 (16)	4 (9)	6 (14)
Level of consciousness*						
UWS n(%)	36 (100)	9 (25)	14 (39)	2 (6)	8 (22)	3 (8)
MCS- n(%)	37 (100)	19 (51)	11 (30)	4 (11)	2 (5)	1 (3)
MCS+ n(%)	31 (100)	18 (58)	9 (29)	2 (7)	0	2 (7)
Age (years) mean (SD)	39.0 (16.5)	37.0 (15.8)	38.7 (16.7)	50.0 (19.9)	34.8 (14.3)	47.8 (15.8)
Sex						
Female n(%)	51 (100)	22 (43)	15 (29)	6 (12)	6 (12)	2 (4)
Male n(%)	53 (100)	24 (45)	19 (36)	2 (4)	4 (8)	4 (8)
CRS-R total score mean (SD)*	8.7 (4.3)	10.4 (4.5)	8.1 (3.8)	7.9 (2.5)	4.4 (2.3)	8.0 (4.6)
TPI (days), mean (SD) median (IQR)	71.7 (27.6) 66.0 (53.3; 86.8)	67.3 (28.5) 63.5 (46.5; 82)	76.2 (24.5) 76.0 (56.8; 94.3)	62.8 (23.9) 60.0 (50.3; 80.5)	88.1 (35.2) 83.5 (60; 102.8)	64.2 (17.5) 62.5 (48.8; 96.8)

B

	Total	Discharge e-MCS	MCS+	MCS-	UWS	dead
Discharge EIN						
DRS mean (SD)	18.3 (5.6)	14.5 (4.6)	20.2 (4.5)	21.9 (2.6)	25.0 (1.3)	
LOS (days), mean (SD) median (Q1; Q3)	91.0 (37.8) 96.5 (64.3; 114)	76.9 (34.8) 72 (51; 96.3)	103.5 (32.9) 105 (89; 128.5)	106.5 (8.7) 106.5 (99; 114)	125.3 (36.6) 110 (100; 142)	50.2 (35.7) 48.5 (13.8; 87.8)
Tracheal tube n (%)	13 (13)	2 (4)	4 (13)	2 (25)	3 (30)	2 (33)
Hospital readmission						
None n (%)	74 (71)	39 (85)	20 (59)	5 (63)	5 (50)	5 (83)
Once n (%)	14 (14)	3 (7)	6 (18)	2 (25)	2 (20)	1 (17)
Twice or more n (%)	16 (15)	4 (9)	8 (24)	1 (13)	3 (30)	0
Discharge destination						
RC n (%)	39 (38)	30 (65)	9 (27)	0	0	0
PIN n (%)	29 (28)	0	13 (38)	6 (75)	10 (100)	0
Nursh n (%)	23 (22)	13 (28)	8 (24)	2 (25)	0	0
Other n (%)	13 (13)	3 (7)	4 (12)	0	0	6 (100)

* 1 participant had no CRS-R data at admittance EIN because of agitation and was diagnosed with MCS+ based on clinical judgement.
CRS-R: Coma Recovery Scale-Revised, DRS: Disability Rating Scale, e-MCS: emerged from MCS (regaining consciousness), LOS: length of stay, MCS: Minimally Conscious State, NTBI: non-traumatic brain injury, Nursh: nursing home, PIN: prolonged intensive neurorehabilitation in nursing home, RC: rehabilitation centre, TBI: traumatic brain injury, TPI: time post injury, UWS: Unresponsive Wakefulness Syndrome.

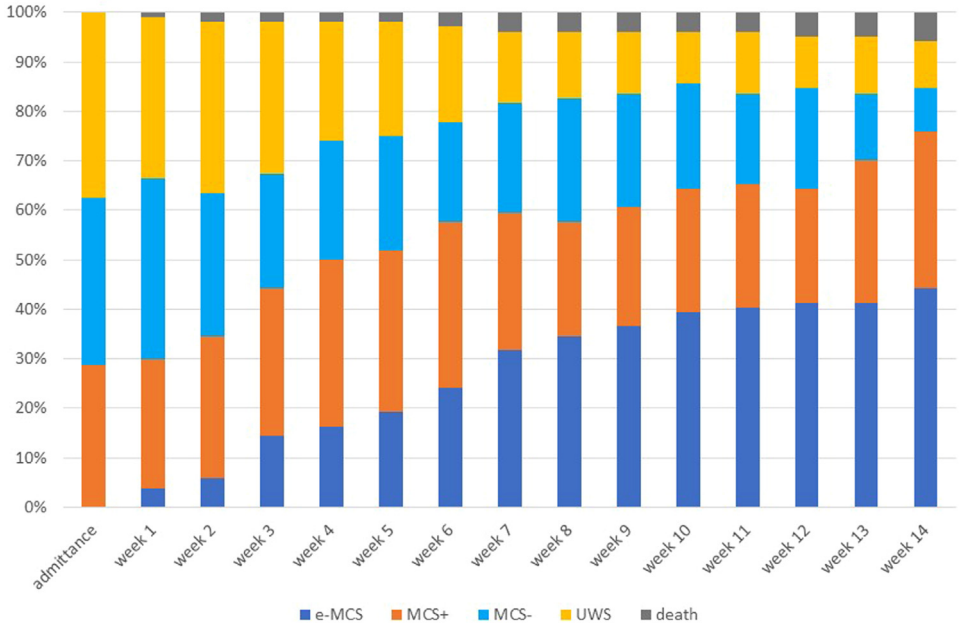

Fig. 2. Proportions of levels of consciousness for each week of the EIN programme.
e-MCS: emerged from MCS (regaining consciousness), MCS: Minimally Conscious State, UWS: Unresponsive Wakefulness Syndrome.

Table 3
Number of complications during EIN.

Medical complication	No of events	No (%) of participants with at least 1 event					
		All $N = 104$	TBI $n = 60$	NTBI $n = 44$	UWS $n = 36$	MCS- $n = 37$	MCS+ $n = 31$*
Neurological							
Epilepsy	23	18 (17)	11 (18)	7 (16)	9 (25)	7 (19)	2 (6)
Hydrocephalus	20	16 (15)	13 (22)	3 (7))	8 (22)	3 (8)	5 (16)
PSH	27	21 (20)	17 (28)	4 (9)	11 (31)	6 (16)	4 (13)
Sleep disturbance	39	28 (27)	18 (30)	10 (23)	11 (31)	9 (25)	8 (26)
Other (i.e. Apnoea, spinal cord injury, deterioration of consciousness)	21	19 (18)	11 (18)	8 (18)	7 (19)	7 (19)	5 (16)
Cardiac-vascular							
Thromboembolic disease	4	4 (4)	3 (5)	1 (2)	1 (3)	1 (3)	2 (6)
Tachycardia	33	31 (30)	17 (28)	14 (32)	11 (31)	10 (27)	10 (32)
Other (ie, hyper- and hypotension, bradycardia)	23	17 (16)	12 (20)	5 (11)	9 (25)	4 (11)	4 (13)
Gastrointestinal							
Vomiting	31	20 (19)	11 (18)	9 (20)	10 (28)	5 (14)	5 (16)
Diarrhoea	40	32 (31)	20 (33)	12 (27)	15 (42)	10 (27)	7 (23)
Obstipation	30	25 (24)	15 (25)	10 (23)	8 (22)	9 (25)	8 (26)
Gastric retention	3	3 (3)	2 (3)	1 (2)	1 (3)	2 (5)	0 (0)
Other (ie, diabetes, atypical gastrointestinal symptoms)	9	9 (9)	5 (8)	4 (9)	4 (11)	4 (11)	1 (3)
Renal							
Urinary retention	33	27 (26)	14 (23)	13 (30)	12 (33)	7 (19)	8 (26)
Other (kidney stones, haematuria)	13	12 (12)	7 (12)	5 (11)	6 (17)	4 (11)	2 (6)
Musculoskeletal							
Hypertonia/spasticity	64	62 (60)	37 (62)	25 (57)	27 (75)	20 (54)	15 (48)
Contractures	49	48 (46)	28 (47)	20 (45)	23 (64)	16 (43)	9 (29)
NHO	6	6 (6)	5 (8)	1 (2)	0 (0)	4 (11)	2 (6)
Hyperkinesia	17	15 (14)	7 (12)	8 (18)	6 (17)	4 (11)	5 (16)
Other (shoulder/mandibula dislocation, joint pain)	10	10 (10)	5 (8)	5 (11)	4 (11)	5 (14)	1 (3)
Skin							
Pressure ulcers	17	15 (14)	9 (15)	6 (14)	5 (14)	5 (14)	5 (16)
Rash	22	19 (19)	12 (20)	7 (16)	9 (25)	5 (14)	5 (16)
Other (ie, blister, pruritis)	11	11 (11)	7 (12)	4 (9)	4 (11)	6 (16)	1 (3)
Infection							
Upper respiratory tract infection	11	11 (11)	7 (12)	4 (9)	4 (11)	3 (8)	4 (13)
Pneumonia	26	23 (22)	13 (22)	10 (23)	14 (39)	8 (22)	1 (3)
Urinary tract infection	39	29 (28)	19 (32)	10 (23)	11 (31)	12 (32)	6 (19)
Brain/CSF	1	1 (1)	1 (2)	0 (0)	1 (3)	0 (0)	0 (0)
Wound/skin	14	12 (12)	6 (10)	6 (14)	3 (8)	4 (11)	5 (16)
Ear	3	3 (3)	3 (5)	0 (0)	2 (6)	1 (3)	0 (0)
Eye	9	7 (7)	7 (12)	0 (0)	6 (17)	0 (0)	1 (3)
Mouth/throat	4	4 (4)	2 (3)	2 (5)	2 (6)	0 (0)	2 (6)
Gastrointestinal	3	3 (3)	1 (2)	2 (5)	1 (3)	1 (3)	1 (3)
Sepsis	3	3 (3)	1 (2)	2 (5)	2 (6)	1 (3)	0 (0)
Fever of unknown cause	21	16 (15)	12 (20)	4 (9)	10 (28)	4 (11)	2 (6)
Other (ie, covid infection, abscess, central line infection)	13	13 (13)	6 (10)	7 (16)	3 (8)	6 (16)	4 (13)
Hematologic							
Abnormal blood test finding (hypo/hypernatria, liver function disturbance)	119	55 (53)	31 (52)	24 (55)	20 (56)	23 (62)	11 (35)
Agitation/aggression	18	14 (13)	8 (13)	6 (14)	3 (8)	6 (16)	5 (16)
Pain/discomfort NCS-R score≥4	77	28 (27)	13 (22)	15 (34)	11 (31)	10 (27)	7 (23)

* 1 participant had no CRS-R at admittance EIN because of agitation and was diagnosed with MCS+ based on clinical judgement.
CSF: cerebrospinal fluid, NCS-R: nociception coma scale-revised, NHO: neurogenic heterotopic ossification, PSH: paroxysmal sympathetic hyperactivity.

Table 4
Medication administered during EIN.

Medication	Admittance $N = 104$ n (%)	Discharge $N = 101$* n (%)
Stimulantia (i.e. amantadine)	14 (14)	34 (34)
Anti-epileptica	32 (31)	29 (29)
Anti-spastic	35 (34)	35 (35)
Anti-thrombotic agent	100 (96)	89 (88)
Cardiovascular$	68 (65)	50 (50)
Laxantia	70 (67)	77 (76)
Analgesics	52 (50)	35 (35)
Sedative/tranquillizers	20 (19)	21 (21)
Other#	14 (14)	20 (20)

* Missing data: $n = 3$.
$ The reason for cardiovascular medication prescription was paroxysmal sympathetic hyperactivity for 22 % at admission and for 18 % at discharge.
# ie, insulin, antibiotics, proton pomp inhibitor.

the EIN program. In addition, in our study, the mean time post injury (TPI) was 72 days, whereas in the other studies TPI was shorter with a mean between 22 and 57 days [10,13,15,16]. Furthermore, our study included only people with PDOC and excluded people with disorders of consciousness <28 days, whereas some studies included these people as well [10,13,15]. A shorter time post injury at admittance to EIN, especially within 28 days, is reported as a prognostic factor for better outcome [14,32,33].

Previous studies [10,16] showed differences between people with TBI and NTBI regarding level of consciousness at EIN discharge, with people with TBI regaining consciousness more often than people with NTBI. Although the proportion of people who regained consciousness was lower than in other studies, our study confirms this finding (emergence to a conscious state in 50 % of TBI versus 36 % of NTBI participants). The difference in consciousness outcome between participants admitted to EIN with UWS and MCS in our study (ie 25 %

versus 54 %) was consistent with previous studies that also reported that 50 % fewer people with UWS regained consciousness than people with MCS [11,13,16].

The mortality rate in our study was 6 %. Mortality is not mentioned in other studies as an outcome of EIN because those studies were retrospective and included only people who completed the EIN programme. Studies evaluating outcome (including mortality) in people with PDOC 6 months post injury report mortality rates of 2−11 % [33−35]. These figures are comparable with those of our study, in which participants at the end of EIN were also approximately 6 months post injury. Estreano et al [36] found a mortality rate of 37 %, but the mean age of people with PDOC was higher and most people had UWS, which are both factors that have a negative impact on mortality [33,35]. In previous studies, all people died from severe medical complications despite life-sustaining treatments [33,35]. In contrast, in our study only 3 out of 6 participants died because of severe medical complications despite life-sustaining treatment, and the other 3 participants died following a non-treatment decision or withdrawal of life-sustaining therapy. This can be explained by the fact that the Netherlands is a country with a tradition of open discussion about quality of life and end of life. It is a legal option to withhold or withdraw life-sustaining treatment in people with PDOC, and this is always performed after extensive discussion with the person's representatives [37].

In the present study, the majority of participants (95 %) sustained at least 1 medical complication, in line with previous observations [18,19]. The most common medical complications in our study were hypertonia/spasticity, contractures, diarrhoea, sleep disturbances and urinary tract infections. Hypertonia/spasticity and contractures are consistent with previous studies [18,19,36]. Whyte et al [18] also mentioned urinary tract infections as a frequent complication. Estraneoet al [36] found a higher frequency of respiratory infections than in our study; 90 % of people in the study of Estraneo had a tracheostomy catheter versus 38 % in our study, which can explain the difference in frequency of respiratory infections. In general, comparing the frequency of complications between studies is difficult because of differences in case mix between studies (for example differences in mean age or the percentage of people with TBI) and differences in observation periods (varying from 6 weeks to >6 months). Moreover, diagnoses and classifications of medical complications were quite heterogeneous across studies.

Participants with UWS sustained more complications than participants with MCS, in particular pneumonia and PSH were more frequent with UWS. These findings are consistent with previous reports of respiratory complications [36] and PSH [19,36] as being frequent in people with UWS.

No pain was observed in 73 % of participants. This does not mean that participants did not experience pain at other moments. No other prospective studies are available on the occurrence of pain or pain-related behaviour in people with disorders of consciousness.

To our knowledge, no other prospective studies evaluated medication administered during neurorehabilitation in people with PDOC. Cardiovascular medication and analgesics could be reduced by approximately 15 % during EIN. At EIN discharge, 35 % of participants were still administered analgesics. The increase in the use of stimulants during EIN is in line with the American DOC guidelines [8], which advise to start amantadine in people with TBI. Laxantia use also increased during EIN, possibly because of the long-term immobility of the participants.

This study has several limitations. First, as EIN is standard care in the Netherlands, a randomised controlled design was not possible for ethical reasons. Therefore, conclusions about the effectiveness of EIN cannot be drawn from this study. Second, in agreement with the literature, we used the CRS-R as a diagnostic test/instrument for level of consciousness. Lately there has been some discussion about the CRS-R criteria. People may have difficulty achieving the operational threshold for e-MCS (eg, conscious people with aphasia cannot show functional communication [38]), and publications have suggested that the diagnostic criteria for emergence from MCS should be changed [39]. In the UK, the expert opinions of clinicians were established on how emergence of consciousness is determined in practice. The majority of the expert clinicians (79 %) reported that they worked with people who had emerged based on clinical judgement, but could not demonstrate this based on the current criteria [40]. Third, LOC determination in PDOC is difficult because of the lack of a gold standard. Recent guidelines advocate the use of additional diagnostic techniques such as EEG along with a behavioural assessment in the diagnostic process [8,41]. However, to date these are not implemented in daily PDOC care in the Netherlands. Assessment of LOC using the CRS-R should consider confounding factors such as motor, visual, auditory and/or cognitive impairments (eg, language, memory, flexibility and attention) [38], intubation, sedation and setting (eg, presence or absence of relatives) [42], as they may negatively influence the diagnostic evaluation [43]. Moreover, in the present study, only one CRS-R assessment per week was conducted as part of routine care whereas serial CRS-assessments (ie, 5 over 2 weeks) are recommended in order to optimize diagnostic accuracy [43]. Fourth, we used a general classification tool (ICF) for the assessment of complications, because a specific tool for their assessment in this challenging group was lacking. Recently, Estreano et al presented a structured, albeit not standardized, classification framework including complications frequently encountered in people with severe brain-injury [19,36]. In future research this framework could be used as a standard to enable comparison between studies.

Conclusions

This study shows that during the EIN programme, a large percentage of people with PDOC regain at least a minimal conscious state or even consciousness. These outcomes and the frequent medical complications in this group suggest that intensive specialized care should be offered to all people with PDOC. The findings of this study may improve the medical care/management of people with PDOC and might help health professionals to inform the families of people with PDOC about the short-term prognosis of PDOC. The outcomes might also be beneficial for societal stakeholders such as governmental institutions and insurance companies for informed decision-making. Future research into long-term outcomes, quality of life and cost-effectiveness is necessary for further improvement of care/rehabilitation following PDOC.

Data availability

Data will be made available on request.

Declaration of competing interest

The authors declare there is no conflict of interests.

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Data availability statement

The datasets that support the findings of this ongoing study are not yet publicly available but are available from the corresponding author upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.rehab.2024.101838.

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