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Transcranial Low-Level Laser Therapy May Improve Alertness and Awareness in Traumatic Brain Injured Subjects with Severe Disorders of Consciousness: a Case Series

ORIGINAL

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Abstract

Background: Transcranial low-level laser therapy (T-LLT) proved promising in acute stroke studies and in single traumatic brain injured subjects (TBI). It was assumed to increase cortical mitochondrial energy production and/or vasodilatation.

Objective: Within this case series the potential of transcranial low-level laser therapy in improving the alertness and awareness in TBI subjects with severe disorders of consciousness will be investigated.

Methods: Following a 21-day baseline, the forehead of five patients, four chronic in a state of unresponsive wakefulness or minimal consciousness, one subacute in the state of akinetic mutism, was stimulated with the T-LLT (785 nm, 10 mW/cm^2, CW mode, 21 emitting diodes) for 10 min every workday for six weeks. Follow-up was four weeks after end of intervention. Primary variable was the revised version of the Coma Recovery Scale (r-CRS, 0-23), blindly assessed by an external reviewer with the help of videos.

Results: The r-CRS, almost stable during baseline, improved in all patients during the intervention, from 3 to 12, 9 to 12, 8 to 12 and 5-12 in the chronic, and from 6 to 21 in the subacute patient. Follow-up revealed a sustained effect. The patient in the state of akinetic mutism improved her competence in the activities of daily living and mobility status. Single epileptic fits occurred in two patients during the intervention.

Conclusion: T-LLT improved the patients' alertness and awareness; epileptic fits were potential side effects. Sham-controlled studies including the quantitative assessment of awareness should follow the case series.

Keywords
Brain stimulation, traumatic brain injury, minimal conscious state, near-infrared light, transcranial low-level laser therapy, revised coma recovery scale.

Introduction

Patients with severe disorders of consciousness (DOC) are a major challenge to the health care systems worldwide. The reported prevalence was 2-10 per 100.000 inhabitants, the major etiologies are traumatic and anoxic brain lesions. [1]

DOCs can be clinically visualized on a functional continuum encompassing the level of vigilance and awareness. The MultiSociety Task Force on PVS (persistent vegetative state) introduced the terms of unresponsive wakefulness syndrome (UWS) and minimally conscious state (MCS). [2] UWS patients show arousal signs objectified by sustained eye opening and the presence of reflex behavior only. The MCS patients show first signs of awareness recovery, for instance by the visual pursuit of moving stimuli in the front of the patients' eyes or following simple verbal commands. [3] Akinetic mutism is regarded as another clinical entity.

Among the known therapeutic options to promote alertness and awareness in DOCs patients, e.g. multisensory stimulation, deep brain stimulation, and Amantadin, none has gained acceptance or, in case of the positively evaluated Amantadin, bears the risk of epileptic fits. [4]

Non-invasive brain stimulation may be a new therapeutic tool in improving the alertness and awareness in traumatic brain injured subjects with severe disorders of consciousness. In a double-blind sham-controlled crossover design, Thibuat et al delivered anodal and sham transcranial direct current stimulation (tDCS) in randomized order for 20 minutes over the left dorsolateral prefrontal cortex in acute UWS and MCS patients. [5] The authors concluded that tDCS transiently improved signs of consciousness in MCS patients, a notion supported by the case series of Angelakis et al. [6] By contrast, for chronic patients with severe traumatic brain injury, Lesniak et al., did not find sufficient evidence to support the efficacy of repeated tDCS of the left dorsolateral prefrontal cortex for enhancing rehabilitation of memory and attention as compared to sham stimulation. [7]

Transcranial low-level laser therapy (T-LLT) may be an alterantive to tDCS. Nawashiro et al. had applied 73 bilateral, transcranial near-infrared light-emitting diode (LED) irradiations to the forehead of a single chronic UWS patient. [8] The patient started to move his left hand to reach the tracheotomy tube at the end of the intervention, side effects did not occur. Further, mildly to moderately affected TBI patients, following repetitive self-adminstered T-LLT of the forehead, had reported positive effects on their attention and reaction times.

Accordingly , the authors intended to investigate the potential of frontal T-LLT to imimprove alertness and awareness in traumatic brain injured subjects with severe disorders of consciousness. A baseline treatment design was applied. Five DOC-patients participated, four in the chronic and one in the subacute stage. The Coma Recovery Scale (r-CRS), regarded as the most sensitive scale to detect signs of consciousness, was the primary variable. [9] The hypothesis was a positive effect of T-LTT on arousal and external awareness.

Methods

Subjects

Five DOC-patients were studied, tables 1-5 summarize their clinical data including the r-CRS score at trial onset. **(Table 1-5)** Inclusion criteria were a DOC, hospitalization in either a centre of neurological rehabilitation or a long-term care institution, a brain imaging MRI or CT excluding an acute intra- or extracerebral bleeding, or any condition requiring acute intervention, an EEG excluding a non-convulsive status, and stable medical and pharmacological conditions. Exclusion criteria were metal implants in the brain and pregnancy. A caregiver consented into the individual treatment with the CE-certified laser device. The clinic's ethical committee had approved the study.

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Table 1. Patient #1.

Diagnosis	**57-year old man, severe TBI with multiple frontal contusions, subdural hematoma, spastic dystonic tetrapresis**							
Lesion interval at baseline	**29 months**							
Measure points (in days)	Baseline			Intervention period				Follow-up
	-21	-14	-7	0	14	28*	42*	70*
Brain stem reflex	yes	yes	yes	yes	yes	yes	yes	yes
Sleep-wake-cycle	yes	yes	yes	yes	yes	yes	yes	yes
Awake –hours per day	3	2	3	3	4	5-6	5-6	5-6
Eye-opening	none	none	none	none	with stimulus	spontaneous	spontaneous	spontaneous
Non-verbal interaction	none	none	none	none	Minimal/adequate	Minimal/adequate	Minimal/adequate	Minimal/adequate
Best motor response	pain induced flexion withdrawl	pain induced flexion withdrawl	pain induced flexion withdrawl	pain induced flexion withdrawl	Voluntary reduced activity finger flexors	Voluntary reduced activity finger flexors	Voluntary reduced activity finger flexors	Voluntary reduced activity finger flexors
Visual pursuit	fluctuating	fluctuating	fluctuating	fluctuating	Visiual pursuit	Visiual pursuit	Visiual pursuit	Visiual pursuit
Rankin scale (0-5)	5	5	5	5	5	5	5	5
Barthel Index (0-100)	0	0	0	0	0	0	0	0
Revised Coma Recovery Scale, (0-23)	3	4	3	3	6	9	11	12
Breathing	C-PAP	C-PAP	C-PAP	C-PAP	Passive humidifier	Passive humidifier	Passive humidifier	Passive humidifier
Tracheal canula	blocked	blocked	blocked	blocked	un-blocked	none	none	none
nutrition	PEG	PEG	PEG	PEG	PEG	PEG/partial orally	PEG/partial orally	PEG/partial orally
mobility	Bed-bound	Bed-bound	Bed-bound	Bed-bound	Care wheel-chair	Care wheel-chair	Care wheel-chair	Care wheel-chair
*: intervention was interrupted for two weeks due to a focal epileptic fit with secondary generalisation after 14 days of intervention								

Table 2. Patient #2.

Diagnosis	**57-year old woman, severe TBI with bifrontal contusions, SAB, akinetic mutism and mild tetraparesis, N. oculomotorius paresis left**							
Lesion interval at baseline	**4.5 months**							
Measure points (in days)	Baseline			Intervention period				Follow-up
	-21	-14	-7	0	14	28	42	70
Brain stem reflex	yes	yes	yes	yes	yes	yes	yes	yes
Sleep-wake-cycle	yes	yes	yes	yes	yes	yes	yes	yes
Awake –hours per day	3h	2-3h	3h	2-3h	5h	7-8h	8h	8h
Eye-opening	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous
Visual pursuit	fixation	fixation	fixation	Visual pursuit	Object-localisation	Object-localisation	Object-recognition	Object-recognition
Non-verbal interaction	none	none	none	none	minimal	Reduced/adequate	Reduced/adequate	Reduced/adequate
verbal interaction	none	none	none	none	Single words	Short sentences	Short sentences	Short sentences
Best motor response	pain induced flexion withdrawl	pain induced flexion withdrawl	pain induced flexion withdrawl	pain induced flexion withdrawl	Object manipulation	Automatic motor response	Functional object use	Functional object use
Rankin scale (0-5)	4	4	4	4	4	3	3	3
Barthel index (0-100)	0	0	0	0	0	0	15	15
Revised Coma Recovery Scale, (0-23)	7	7	8	8	14	18	20	21
Breathing	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous
Tracheal canula	no	no	no	no	no	no	no	no
Nutrition	PEG	PEG	PEG	PEG	PEG	Partially oral	Partially oral	Partially oral
Mobility	Care wheel-chair	Care wheel-chair	Care wheel-chair	Care wheel-chair	Functional wheel-chair	stance	Walking with rollator	Walking with rollator

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Table 3. Patient #3.

Diagnosis	**71 year-old man, severe TBI with traumatic SAB, intracerebral bleeding, spastic tetraparesis, N. oculomotorius paresis right**							
Lesion interval	**31 months**							
Measure points (in days)	Baseline			Intervention period				Follow-up
	-21	-14	-7	0	14	28	42	70
Brain stem reflex	yes	yes	yes	yes	yes	yes	yes	yes
Sleep-wake-cycle	yes	yes	yes	yes	yes	yes	yes	yes
Awake –hours per day	2-3	2-3	2-3	2-3	4	4	4-5	4-5
Eye-opening	with stimulus	with stimulus	with stimulus	with stimulus	with stimulus	spontaneous	spontaneous	spontaneous
Non-verbal interaction	none	none	none	none	Minimal/adequate	Minimal/adequate	Minimal/adequate	Minimal/adequate
Best motor response	pain induced flexion withdrawl	pain induced flexion withdrawl	pain induced flexion withdrawl	pain induced flexion withdrawl	pain induced flexion withdrawl	pain induced flexion withdrawl	pain induced flexion withdrawl	pain induced flexion withdrawl
Visual pursuit	fluctuating	fixation	fixation	fixation	Visiual pursuit	Visiual pursuit	Visiual pursuit	Visiual pursuit
Rankin scale (0-5)	5	5	5	5	5	5	5	5
Barthel Index (0-100)	0	0	0	0	0	0	0	0
Revised Coma Recovery Scale, (0-23)	8	8	8	8	12	11	12	11
Breathing	Passive humidifier	Passive humidifier	Passive humidifier	Passive humidifier	Passive humidifier	Passive humidifier	Passive humidifier	Passive humidifier
Tracheal canula	blocked	blocked	blocked	blocked	blocked	blocked	blocked	blocked
nutrition	PEG	PEG	PEG	PEG	PEG	PEG	PEG	PEG
mobility	Care wheel chair	Care wheel-chair	Care wheel-chair	Care Wheel-chair	Care wheel-chair	Care wheel-chair	Care wheel-chair	Care wheel-chair

Table 4. Patient #4.

Diagnosis	**30 year-old woman, severe TBI with multiple brain contusions and SAB, secondary pons infarction, severe spastic tetraparesis**							
Lesion interval	**50 months**							
Measure points (in days)	Baseline			Intervention period				Follow-up
	-21	-14	-7	0	14*	28*	42*	70*
Brain stem reflex	yes	yes	yes	yes	yes	yes	yes	yes
Sleep-wake-cycle	yes	yes	yes	yes	yes	yes	yes	yes
Awake –hours per day (h)	2-3	2-3	2-3	2-3	4	4	4-5	4-5
Eye-opening	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous
Non-verbal interaction	none	none	none	none	none	Minimal/adequate	Minimal/adequate	Minimal/adequate
Best motor response	pain induced flexion withdrawl	pain induced flexion withdrawl	pain induced flexion withdrawl	pain induced flexion withdrawl	pain induced flexion withdrawl	pain induced flexion withdrawl	pain induced flexion withdrawl	pain induced flexion withdrawl
Visual pursuit	startle response	startle response	startle response	startle response	fluctuating	fixation	visual pursuit	visual pusuit
Rankin scale (0-5)	5	5	5	5	5	5	5	5
Barthel index (0-100)	0	0	0	0	0	0	0	0
Revised Coma Recovery Scale, (0-23)	8	8	8	8	10	10	12	12
Breathing	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous
Tracheal canula	none	none	none	none	none	none	none	None
Nutrition	PEG	PEG	PEG	PEG	PEG	PEG	PEG	PEG
Mobility	Care wheel chair	Care wheel-chair	Care wheel-chair	Care Wheel-chair	Care wheel-chair	Care wheel-chair	Care wheel-chair	Care wheel-chair
*: intervention was interrupted for two weeks due to a focal epileptic fit with secondary generalisation after 14 days of intervention								

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Table 5. Patient #5.

Diagnosis	**21-year old woman, severe TBI with traumatic SAB, secondary hydrocephalus, shunt operation with multiple revisions, ethyl-toxic liver cirrhosis, borderline disease**							
Lesion onset	**26 months**							
Measure points (in days)	Baseline			Intervention period				Follow-up
	-21	-14	-7	0	14	28	42	70
Brain stem reflex	yes	yes	yes	yes	yes	yes	yes	yes
Sleep-wake-cycle	yes	yes	yes	yes	yes	yes	yes	yes
Awake –hours per day	2-3	3	3	3	4-5	4-5	4	4-5
Eye-opening	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous
Non-verbal interaction	none	none	none	none	none	Minimal/adequate	Minimal/adequate	Minimal/adequate
Best motor response	pain induced flexion withdrawl	pain induced flexion withdrawl	pain induced flexion withdrawl	pain induced flexion withdrawl	pain induced flexion withdrawl	pain induced flexion withdrawl	pain induced flexion withdrawl	pain induced flexion withdrawl
Visual pursuit	Startle response	Startle response	Startle response	Startle response	fixation	fixation	Visual pursuit	Visual pursuit
Rankin scale (0-5)	5	5	5	5	5	5	5	5
Barthel index (0-100)	0	0	0	0	0	0	0	0
Revised Coma Recovery Scale, (0-23)	5	6	6	6	9	9	11	12
Breathing	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous	Spontaneous
Tracheal canula	none	none	none	none	none	none	none	none
Nutrition	PEG	PEG	PEG	PEG	PEG	Partially oral	Partially oral	Partially oral
Mobility	Care wheel chair	Care wheel-chair	Care wheel-chair	Care Wheel-chair	Care wheel-chair	Care wheel-chair	Care wheel chair	Care wheel chair

Design

A baseline treatment design was chosen, it included a 21-day baseline with four measurement points (D-21, D-14, D-7, and D0), followed by an intervention period of six weeks, daily every workday for 10 minutes, i.e. an overall of 30 treatment sessions. The measurement points were D14, D28, and D42. Follow-up was four weeks after the end of the intervention (D70).

Intervention

A CE-certified softlaser ("Power Twin 21" by MKW Lasersystem) was used, with a wave length of 785 nm, 21 emitting diodes, 21 x 50 mW in the Nogier É mode.The current stimulation frequency of 36,5 Hz with an impulse length of 0,25 ms emitted 6 J in 10 minutes per emitting diode. The intensity was set to 10 mW/cm^2.

On the level of the superior crest of the fossa sphenoidale five points were marked on the forehead. During each of the 30 sessions, the therapist stimulated each point two times one minute by placing the stimulator onto the skin, i.e. the stimulation was 10 min in each of the 30 sessions. The patients wore safety glasses. In addition, all patients received ongoing physio-, occupational and speech therapy.

Outcome variables

Primary variable was the revised version of the Coma Recovery Scale (r-CRS; 0-23). [9]. CRS-R consists of 23 items organized in 6 subscales that address arousal (0=unarousable - 3=attention), auditory (0=none – 4=consistent movement to command), visual (0= none – 5=object recognition), motor (0= none/flaccid – 6=functional object use), oromotor/verbal (0= none – 3=intelligible verbalization), and communication (0= none – 2=functional:accurate). Scoring is based on the presencce or absence of specific behavioral responses to sensory stimuli administered in a standardized manner. The lowest item on each subscale represent reflexive activity, whereas the highest item represent cognitively mediated behaviors.

The assessment of the r-CRS was recorded and in random order the videos were sent to an experienced external rater, who was unaware of the time points of each video and of the exact purpose of the study. She was on maternity leave and regularly assessed the r-CRS with the help of videos of all DOC patients of the clinic.

Second outcome parameter was the internationally known Barthel Index (BI, 0-100) to asssess the competence in the basic activities of living [10] .

Further, the caregivers answered the following questions at the end of the intervention: how do you rate his/her alertness in the sense of being awake during daytime? how do you rate his/her abilities to communicate (verbal, gestic, mimic) with you? how do you rate his/her emotional response to you? A six-scale ordinal (-3, -2, -1, 0 +1, +2; -3: worse than starting condition; 0: expectations were met; 2: were considerably exceeded) scale was used.

Statistics

The non-parametric Pettitt-test was chosen to detect the intraindividual differences over time in comprehension of the several measurepoints. Due to the small number of patients included in this case series, alpha was set to p=0.10 to increase the power.

Results

Patient # 1

The 57-year old male subject had suffered a severe TBI 2010. Brain images had revealed multiple intracerebral contusions, a subdural bifrontal hematoma, further the relatives reported that brain anoxia of unknown duration had complicated the clinical course initially. In 2013, he was admitted for ongoing neurological rehabilitation. Clinically he presented an UWS syndrome, a spastic-dystonic tetraparesis, wore a tracheal canula, was intermittently ventilated (CPAP mode) and fed via a percutaneous gastric tube. Brain stem reflexes were intact. Levitiracetam (3000 mg daily) had been prescribed due

to focal epileptic fits with secondary generalization occurring once a month. During the first four weeks, the medical situation was stabilized, weaning completed and he was seated in a wheelchair one hour a day. The EEG had shown signs of elevated cerebral excitability, accordingly Vimpat (2 x 100 mg daily) was additionally prescribed, the EEG improved. The relatives then agreed to participate in the evaluation.

The initial r-CRS (D-21) score was four, he presented oral reflexes and a strong flexor response to painful stimuli. During baseline, the r-CRS score ranged from 3 to four. The first two weeks of T-LLT increased the r-CRS score up to six, he could localize a sound, presented a blinking reflex and the eyes were open. Due to a focal epileptic fit with secondary generalization (it occurred 3 hours after the stimulation, lasted 1 minute approximately, and a lower urinary tract infection had required an antibiotic therapy at the same time), the T-LLT was interrupted for two weeks, and Vimpat medication was increased (2 x 150 mg daily), as the EEG again had showed signs of elevated cortical excitability. During the interruption, the r-CRS score dropped to its initial value of three.

Consented by the relatives, the T-LLT intervention was restarted for another four weeks, the r-CRS score increased again to a maximum score of 11 at D42. He became able to perform repetitively a visual pursuit with the help of a mirror moved in vertical and horizontal direction in front of his eyes, to protrude his tongue and to move his left hand on demand. Communication via lid closing and opening started but not consistently. The tracheal canula remained and his total dependency on external help did not change. The relatives rated the alertness +1, communication abilities 0, and the patients' emotional response +1. At follow-up, he reached a score of 12 in the r-CRS.

Patient #2

She was a 57 year old patient admitted for subacute neurological rehabilitation following severe TBI requiring an eight -week acute care and multiple neurosurgical interventions following epidural, traumatic sub-arachnoidal bleeding and multiple brain contusions in the bifrontal region. Due to focal epileptic fits, Levitiracetam (2500 mg daily) had been prescribed in the acute clinic. During the first six weeks of neurological rehabilitation, the patient was weaned, seated in a wheelchair, and the tracheal canula was removed, an EEG recordings had shown no signs of elevated cerebral excitability.

She then presented a severe akinetic mutism in combination with a mild tetraparesis and a left N. oculomotorius paresis, brain stem reflexes were intact, she was totally dependent on external help, fed via a percutaneous gastric tube, and smeared with stool. Amantadin (100 mg daily) successfully improved the patient's condition, but was stopped due to a severe epileptic fit of two minutes duration after 5 days of intake. Lamotrigine (100 mg daily) was additionally prescribed, the EEG showed no more definite signs of cortical excitability. The caregiver was informed about the pros and cons of another Amantadin or N-LLT therapeutic attempt and opted for brain stimulation.

During baseline, the r-CRS ranged from seven to eight, during N-LLT the score improved to 20 (D42), the Follow-up score (D 70) was 21. At the end of the intervention, she could stand with holding on, walk a few steps assisted by a physical therapist, grasped objects placed in her visual field, ate some food, spoke a few words within the context and became oriented with respect to personal data. Stool smearing had ceased and she helped with basic activities of daily living (the extended Barthel Index had improved from –125 to 15). All activities were executed with marked delay and on external demand only. Side effects had not occurred. The relatives rated the alertness 0, communication abilities +1, and the patients' emotional response +1.

Patients #3-5

Three patients were residing in a long-term nursing home. The latencies since brain trauma were at least

two years. All had suffered a severe traumatic brain injury resulting in an UWS and spastic tetraparesis (patient #3, #4 and #5), for further clinical information see table 3-5. The initial rCRS scores were eight (patients #3 and #4), and ranged from five to seven in case of patient #5.

During intervention, the r-CRS score improved in all three subjects, continuously from 8 (D0) to 12 (D42) in both subjects # 3 and #4, and from 5 (D0) to 11 (D42) in subject #5. Subject # 4 experienced a focal epileptic fit (one 1 min duration) after two days of stimulation, she had no history of epileptic fits, but was on antibiotic therapy after dental surgery. The external neurologist together with the research team decided to halt the stimulation for one week, no antiepileptic medication was given, after stopping the antibiotic therapy the protocol went one. No further epileptic fits occurred. At Follow-up (D70) the positive effects remained stable.

Subject # 5 started crying during the second half of the intervention when a large mirror was placed in front of her when sitting in a wheelchair.

The relative of subject # 3 rated the gain in alertness +1, communication abilities 0, and emotional response +1, she further noticed a better postural control of his head while sitting, a notion confirmed by the therapeutic team. The relative of subject #4 rated the alertness +2, communication abilities +1, and the patients' emotional response +1. For patient # 5, the corresponding values were +1, 0, and +1.

The dependency on external help in ADL activities did not change, the tracheal canula in patient # 2 could be removed, he started swallowing meshed food, nevertheless feeding via a gastric tube remained.

The statistical analysis over all patients revealed a breakpoint at D28 with a p-value of p=0.069.

Discussion

The case studies recommend to further investigate the potential of non-invasive, transcranial N-LLT to promote alertness and awareness in DOC patients following traumatic brain injury. During 30 sessions of 10 min frontal transcranial N-LLT, all patients improved their alertness and external awareness, as confirmed by the rCRS scores and the relatives' impression. One patient in the subacute stage, presenting an akinetic mutism, also improved her mobility and ADL competence.

No statement on the method's effectiveness is warranted, the chosen design did not include a sham therapy, patient # 2 was in the subacute stage, and no quantitative measurements of awareness were assessed. On the other hand, additional impairments of vision, communication and hearing due to focal brain lesions, limiting the ability to follow the test commands, could not be excluded.

Two patients presented an epileptic fit (focal with secondary generalization, and focal) during the intervention, the events did not occur in direct context with the stimulation, but a causal relationship could not be excluded. In one subject, it was a first time event, the other patient had a known history including an antiepileptic medication, and both patients received an antibiotic therapy at the same time with the stimulation, which additionally lowered the cortical excitability level.

The two chronic UWS patients gained nine and six, the two chronic MCS patients gained six and three points on the rCRS after six weeks of stimulation. Thibaud et al. assessed the effects of a single session of left dorsolateral prefrontal cortex transcranial direct current stimulation (tDCS). [5] Patients with MCS improved for two points and patients with UWS for one point after a single session of tDCS.

Nawashiro et al. had applied 73 bilateral, transcranial near-infrared light-emitting diode (LED) irradiations to the forehead. [8] The patient started to move his left hand to reach the tracheotomy tube at the end of the intervention, side effects did not occur. Mildly affected TBI patients reported that a self-administered repetitive frontal transcranial sti-

mulation during the night time had consistently increased their attention and reaction times. Concerning healthy subjects, beneficial cognitive and emotional effects had been reported following frontal N-LLT. [11, 12]

Regarding the issue of skull penetration, Jagdeo et al. had reported that near infrared measurably penetrated soft tissue, bone and brain parenchyma in the formalin preserved human cadaveric model. [13] With the transfrontal application one should keep in mind the variable size of the frontal sinus, the bone around the sinus is thicker, and not seldom a sinusitis affects severely affected chronic patients. A thick bone and fluid, however, decrease the speed and thus the power of the near-infrared laser light. [8, 14]

Positive sham-controlled studies in acute stroke patients included the single T-LLT stimulation of 20 points according to the 10-20 system for one minute each, the wave length was 808 nm and the intensity 10 mW/cm^2. [15,16,17] In embolized rabbit's brain, Lapchak and De Taboada successfully showed that T-LLT (wave length 808 nm, intensity 10 mW/cm^2) significantly increased the cortical ATP, the penetration depth was 20 – 30 mm. [18] Accordingly the authors of the acute stroke studies speculated that the transcranial laser could have activated the respiratory chain, namely the complex IV, thus increasing the ATP production and helping cell recuperation. [14,19] Regarding the radiation parameters, Drochioiu recommended a wave length of 818 nm to best activate the NADH pathway of the respiratory chain [19] , the device used in the current series emitted a wave length of 785 nm, no other CE-certified laser with a radiation of either 818 or 808 nm was readily available on the market. With the lower radiation, one may have speculated that the FADH2 pathway of the respiratory chain had been more activated. However, in the electron transport chain, NADH + H+ containing 52.52 kcal/mol is used to produce three moles of ATP (17.51 kcal for each mol of ATP), whereas FADH2 with 35.94 kcal/mol will produce only two moles of ATP. Local heating and vasodilatation by T-LLT could have been another explanatory effect. [8]

The exclusive frontal application followed the previous clinical reports on the beneficial effects of N-LLT. [15,20] Further N-LLT was assumed to improve the cell metabolism of the stimulated brain areas. In the tDCS trials, the authors stimulated the left dorsolateral prefrontal cortex (DLPF) which is said to receive visual and and somatosensory input from the parietal heteromodal association cortices regarding vision, motion, spatial orientation and tactile sensations, and projects to subcortical monoaminergic and cholinergic sources. [5] . The current protocol also included the stimulation of the right DLPF, which has been linked to maintenance of sustained arousal and attention, which is similarily relevant for patients with DOC. Further safety issues in N-LLT protocols so far recommended to stimulate several points for shorter periods of time (1-2 minutes per site) and not stationary over a longer period of time, as in tDCS.

Limitations of the study were the absence of a control group, the absence of MRI-based mapping of the stimulated area, given the presence of focal damage and atrophy, and no quantitative assessment of attention and awareness. Profound clinical implications are thus not warranted, future clinical trials could concentrate on patients with an akinetic mutism after TBI. Ethically, team members raised the issue whether the promotion of awareness was beneficial to the patients; subject #5, for instance, started crying when seeing herself in a large mirror during the second half of the intervention period.

Conclusions

In summary, 30 sessions of 10 min of frontal T-LLT increased the alertness and awareness in five traumatic brain injured subjects with severe disorders of consciousness. Epileptic fits were potential side

effects. No statements on the effects of the non-invasive intervention are warranted, future studies including sham therapy and quantitative assessment of awareness are needed.

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