ERIGO: a possible strategy to treat orthostatic hypotension in progressive supranuclear palsy? A feasibility study

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Summary

Progressive supranuclear palsy (PSP) is a neurodegenerative disease of the central nervous system, presenting with different clinical phenotypes, all involving the extrapyramidal system. Orthostatic hypotension (OH) is a common symptom of cardiovascular autonomic dysfunction. OH is defined as a fall in systolic blood pressure of at least 20 mmHg and/or a fall in diastolic blood pressure of at least 10 mmHg on standing or head-up tilt. In this pilot study, we tested the feasibility and efficacy of the ERIGO® device in managing OH non-responsive to conventional treatments in a sample of patients with PSP. OH was chosen as the primary outcome, as the symptom is a serious complication in neurodegenerative disorders, challenging the rehabilitation treatment. Six patients received intensive training using ERIGO®, a robot-assisted tilt table with an integrated leg movement system that allows progressive verticalization of the patient, and application of functional electrical stimulation. In all the participants, OH improved after the training with the device, suggesting that robotic verticalization may be a feasible and effective tool in improving blood pressure stability in patients with PSP. Further studies in larger samples, also including patients with other neurodegenerative disorders associated with OH, are needed to confirm these promising results.

KEY WORDS: ERIGO, parkinsonisms, progressive supranuclear palsy, robotic neurorehabilitation, verticalization.

Introduction

Progressive supranuclear palsy (PSP) is a neurodegenerative disease of the central nervous system, presenting with different clinical phenotypes, including: i) Richardson syndrome, characterized by progressive gait disturbance with early, recurrent and frequent falls, supranuclear vertical ophthalmoplegia, rigidity, and dysexecutive syndrome (Richardson et al., 1963); ii) PSP-parkinsonism, manifesting with predominant asymmetric bradykinesia, rigidity, and moderate initial response to levodopa; this is a form often misdiagnosed as Parkinson’s disease (PD), particularly in the early stage (Williams, 2005); iii) “pure akinesia with gait freezing”, characterized by gradual onset of freezing of gait or speech disturbances, with no rigidity, tremor, supranuclear ophthalmoplegia, or cognitive decline (Williams et al., 2007); iv) primary non-fluent aphasia, a behavioral variant of frontotemporal dementia; and v) corticobasal syndrome (Josephs, 2006).

Progressive supranuclear palsy, like PD and atypical parkinsonism, can be associated with orthostatic hypotension (OH); prevalence rates of 7-26% have been reported in PSP and 9.6-58% in PD (Robertson, 2008; Peralta et al., 2007; Papapetropoulos et al., 2001; Low, 2008).

The prevalence of OH increases with age, leading to increased morbidity and mortality (Senard et al., 1997). In PD, OH mainly results from lesions of sympathetic efferent pathways and from dopaminergic therapies. The “consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome” (Freeman et al., 2011) defines OH as a decrease in systolic blood pressure (BP) of at least 20 mm/Hg and/or a decrease in diastolic BP of about 10 mm/Hg on moving from supine to upright position. Prior to measurement, the supine position should be maintained for 5 minutes or longer until BP and heart rate (HR) stabilization, after which 3 to 5 minutes in an upright position is suggested (Lahrmann et al., 2006; Freeman, 2008; Freeman et al., 2011). In patients with severe motor impairment who are unable to stand, passive head-up tilt is recommended.

In PD, the prevalence of OH correlates with disease duration and, as mentioned above, it can also be a result of PD medications; this situation leads to gait instability, generalized weakness, fatigue, a higher risk of falls, and reduced cognitive performance. Thus, this distressing symptom may worsen patient adherence to rehabilitation treatment, leading to worse outcomes.

OH treatment includes patient education and lifestyle approaches, together with symptomatic treatments, when possible (Ha et al., 2011). ERIGO® (Hocoma AG, Volketswil, Switzerland) is a well-tolerated method of patient mobilization and can be considered a safe early mobilization system for neurological patients. It consists of a robot-assisted tilt table with an integrated leg move-
ment system that allows progressive verticalization of the patient (from 0° to 90°), while applying continuous step-like movements, subjecting the patient’s lower limbs to a wide range of movement patterns and loads (Fig. 1). To date, ERIGO® has been applied to regain trunk control up to verticalization and to train lower limbs in preparation for resumption of gait. This serves to prevent the cardiopulmonary complications related to venous pooling in the lower extremities that can occur in patients affected by traumatic brain injury and stroke (Colombo et al., 2005; Calabrò et al., 2015). Moreover, it has been demonstrated that the device could be effective in improving OH in patients with brain and spinal cord injuries (Daunoraviciene et al., 2018), as well as in those with vegetative state (Taveggia et al., 2015). The aim of this pilot study was to test the feasibility and efficacy of ERIGO® in the treatment of OH non-responsive to conventional therapies — we considered the number of patients who were successfully treated, the number of adverse events (AEs) and the adverse reactions (ARs) in a sample of patients with PSP.

Materials and methods

Study population

We consecutively enrolled patients with a diagnosis of PSP attending our institute’s Movement Disorders Unit in the period January 2015 to December 2018. Six patients who met the following inclusion criteria were enrolled in this pilot study: diagnosis of PSP, according to the current guidelines (Höglinger et al., 2017); MMSE score > 15; absence of severe behavioral and psychiatric illness. The exclusion criteria were: internal carotid artery stenosis > 60%; severe cardiac diseases; severe medical conditions; contractures of the lower extremities; lower extremity thrombophlebitis or deep vein thrombosis; severe joint or bone pathologies; active epilepsy. The Ethics Committee of the IRCCS Centro Neurolesi Bonino Pulejo (Messina, Italy) approved the present study (IRCCSME 34/2014). All participants gave their written informed consent.

Intervention

Following the team assessment, an intensive four-week program of motor, speech and cognitive rehabilitation treatment was initiated (twice daily for six days a week). As the patients were in a chronic stage, we decided to apply two different approaches and compare their effects on BP control, which thus represented the main outcome measure. In this first phase, the patients were submitted to conventional physiotherapy (PT). After the first phase, we allowed a four-week interval before starting the next phase, to avoid cumulative effects. Then, the patients underwent phase 2, which consisted of a combined therapeutic approach that included robotic training with ERIGO®, and lasted for two months. However, the patients received the same amount of treatment in both phases; specifically, in the first phase they underwent 48 sessions of PT, whereas in the second phase they had 24 PT sessions and 24 sessions with ERIGO® combined with functional electrical stimulation (FES). Each patient’s entire rehabilitation treatment lasted about 4 months. The conventional treatment was provided according to the Bobath approach, aimed at improving trunk balance control in the sitting position, reducing spasticity and maintaining range of motion of single joints of the arms and legs. Verticalization obtained through gradual inclination of a simple tilt table, and BP variations were recorded (measured by means of a manual sphygmonanometer). The combined neurorehabilitation approach consisted of both robotic training, using ERIGO®, and the conventional rehabilitation approach (PT). The ERIGO® consists of a tilt table with an integrated robotic stepping device and it can be used in combination with FES. It is increasingly used for progressive verticalization. The system imparts cyclic leg movements in combination with step-synchronized leg muscle FES, and provides body weight loading to ensure safe stabilization in the upright position. The patient’s upper body is secured by a harness that fixes the chest and the shoulders to the table (Fig. 1). Leg movements are controlled by computer and are the result of passive thigh movements obtained by securing the distal thigh to the device; the feet are strapped to two footplates. The inclination of the tilt table can be continuously adjusted from the horizontal to the vertical position while applying continuous step-like movements subjecting the patient’s lower limbs to a wide range of movement patterns and loads. The speed of leg movement can be modified from 0 to 80 steps per minute.

Figure 1 - Training of a PSP by means of the ERIGO® device.
ERIGO-induced orthostatic hypotension

FES makes it possible to further increase the afferent stimulation of patients and thereby their cardiovascular stability (by improving orthostatic tolerance), even during early verticalization. During the robotic training, the patients were gradually tilted until they were in the vertical position, maintaining BP in normal range (Fig. 1). FES was applied bilaterally to the quadriceps, biceps femori, anterior tibialis and gastrocnemious muscles. During the first three training sessions, the patients were gradually verticalized from 10 to 30° over 15 minutes, and stepping was performed at a rate of 30 steps per minute. Loading of the legs was either passive or passive-active. By session 5, verticalization was increased to 60° over 15 minutes, and stepping to 35 steps per minute. By session 10, verticalization had reached 90° with 40 steps per minute. Whenever initial signs of intolerance were observed, at any angle of inclination, the protocol was interrupted, and patients were returned to their previous position. The process was then repeated until complete tolerance to 90° was reached.

Outcome measures

The primary objective of this trial was to assess feasibility. Thus, we evaluated the number of patients who were able to complete the trial, the number who showed better tolerance to postural changes, and the number of ERIGO® sessions correctly completed. The intervention was considered feasible if at least 60% of the planned sessions were completed. AEs and ARs were monitored during the trial, counting the number of occurrences. Causes of ARs were assessed daily.

With regard to clinical outcomes, the patients underwent BP recording in supine position and after tilting in the upright position (bedside Thompson test), before and after phase 1 (T0 and T1, respectively), and before and after phase 2 (T2 and T3, respectively). The primary endpoint was a reduction in the delta of variation in maximum (ΔPmax) and minimum blood pressure (ΔPmin). Moreover, as secondary endpoints, patients were evaluated for independence, using the Functional Independence Measure (FIM) (this is used to assess a patient’s level of disability as well as change in patient status in response to rehabilitation), and for trunk control, using the Trunk Control Test (TCT).

Table I - Clinical-demographic data of the six patients.

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>gender</th>
<th>dd (y)</th>
<th>bedside Thompson test (mmHg)</th>
<th>TCT (/100)</th>
<th>FIM (/126)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>max</td>
<td>min</td>
<td>max</td>
</tr>
<tr>
<td>68</td>
<td>F</td>
<td>6</td>
<td>145</td>
<td>90</td>
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<td>M</td>
<td>6</td>
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<tr>
<td>68</td>
<td>F</td>
<td>5</td>
<td>151</td>
<td>95</td>
<td>82</td>
</tr>
</tbody>
</table>

Abbreviations: dd, disease duration; TCT, Trunk Control Test; FIM, Functional Independence Measure

Statistical analysis

Clinical scores (ordinal measures) were analyzed using the Wilcoxon signed-ranks test. Parametric data were analyzed using a one-way ANOVA. A value of p ≤ 0.05 was considered statistically significant. A Bonferroni correction for multiple comparisons was applied.

Results

All the patients had a diagnosis of PSP and all were in a chronic phase. They presented with at least two of the following symptoms: anosmia, behavioral disorders, dysarthria, falls, gait impairment, and postural instability which appeared between the ages of 60-68 years and were followed, within 2-3 years, by one of more of the following: altered trunk alignment, inability to stand, anarthria, asymmetric bilateral hyp Bradykinesia, bilateral pyramidal tract syndrome, bilateral resting tremor, urinary incontinence, OH (positive bedside Thompson test, i.e. OH appearing after 3 minutes of upright position, with drowsiness up to syncope), cognitive decline, dysphagia, hypomimia, nystagmus, plastic hypertonia, and supranuclear gaze palsy. Other clinical-demographic data are reported in Table I.

All the patients were able to complete both the treatments, showed better tolerance to postural changes only after ERIGO® training, and correctly completed all the sessions. Moreover, none of the patients complained of AEs or ARs. After the conventional treatment, no improvement in BP control was found (p > 0.2). At the end of the combined approach, each patient showed a significant reduction in ΔPmax and ΔPmin variation (p < 0.0001) (Table II). Moreover, all the patients acquired the ability to sit, and accordingly their TCT score increased (p < 0.001) as did their FIM score (p=0.001) (Table II).

Discussion

To the best of our knowledge, this is the first time that ERIGO® has been used to improve functional outcomes (i.e. postural BP control, standing and trunk control) in PSP. Indeed, at the end of the combined training, the number and amplitude of OH episodes were reduced in all the patients, and all presented a stabilization of BP and HR, particularly in the sitting position. These results suggest a neurovegetative re-adaptation, probably in-
duced by daily and gradual robotized standing. We decided to focus on OH in patients with PSP, as this symptom may negatively affect patients’ quality of life, adherence to treatment and thus rehabilitation outcomes. Orthostatic hypotension is known to result from an inadequate physiologic response to postural changes in BP, and it is a common feature of patients with PSP. The prevalence of OH in atypical parkinsonian syndromes ranges from 0-7% in corticobasal degeneration, to 7-26% in PSP and it is as high as 81% in multiple system atrophy (Colosimo et al., 2010). The pathophysiology of OH is thought to be related to impairment of sympathetically vasomotor nerves due to the neurodegenerative process (Metzler et al., 2012). Treatments for OH include correction of reversible iatrogenic causes. All patients should be offered non-pharmacological treatments, e.g. physical activity, cautious postural changes from sitting or lying down to the standing position, increased intake of liquids and salt (in the latter case aiming at more than 8 grams daily), and the use of long compressive stockings. In those patients who do not respond adequately to non-pharmacological treatments, fluodrocortisone, midodrine, and pyridostigmine are pharmacological therapies that have proven beneficial (Lanier et al., 2011).

However, the coexistence of OH and supine hypertension raises some additional problems when treating OH in Parkinsonian Syndrome. Use of alpha-2 adrenergic blockers such as yohimbine, which increases the release of norepinephrine and dopamine, can worsen supine hypertension. The same issue also exists when an indirectly acting sympathomimetic amine such as tyramine is given with a monoamine oxidase inhibitor (Jain and Goldstein, 2012).

In our pilot study, since recommended therapeutic strategies, including behavioral and pharmacological treatments, were not effective or harmful to the patients’ general medical conditions. And PT with conventional verticalization gave only mild results, we decided to submit the patients to an intensive innovative combined approach.

We believe that the use, in these patients, of gradual postural reconditioning, associated with passive leg motion, may have induced a progressive reconditioning of BP control by potentiating the muscular pump and favoring venous return, thus treating their OH. Moreover, the fact that ERIGO® treatment was combined with FES may have further increased the afferent stimulation, and thereby the patients’ cardiovascular stability during the gradual verticalization. In fact, cyclic FES to the leg muscles can effectively potentiate venous return, thereby helping to maintain the patient’s BP stability under orthostatic stress.

A neurophysiological mechanism should also be taken into account. In fact, the association of verticalization with stepping may exert an effect on spinal reflexes, i.e. vestibulo-spinal reflexes, and on the central pattern generator (CPG) circuits. It can also be hypothesized that robotic training may affect vasomotor tone, also by boosting the pathways to the supraspinal centers that control the CPG circuits, with a consequent modification of the autonomic discharge. In particular, the circuits are influenced by the basal ganglia, including the striato-pallidal connections and their outputs to sub-thalamic (where baroceptors and chemoreceptors related to muscle afferents are located), mesencephalic and cerebellar locomotor regions (Castermans et al., 2013). Intensive training with this innovative device may have potentiated neural plasticity at these higher levels, in such a way as to improve BP control and avoid OH.

To our knowledge, robotic verticalization has never previously been applied to treat OH in PSP, although robotic verticalization is believed to be effective in different neurological disorders (Calabrò et al., 2015; Taveggia et al., 2015; Rocca et al., 2016; Daunoraviciene et al., 2018). Indeed, it has been demonstrated that robotic verticalization is both safe and effective in improving orthostatic tolerance and posture and in inducing positive emotional reactions in patients affected by stroke and spinal cord injury. As early mobilization of patients suffering from severe brain injuries by means of ERIGO® does not increase the production of catecholamines, this tool can be considered a well-tolerated and safe system to mobilize these patients. Moreover, Taveggia et al. (2015) have shown that, in hemodynamically unstable patients with disorders of consciousness, BP and HR can be stabilized better by using lower limb robotic passive movements.

It is known that robot-based rehabilitation improves motor performances by inducing brain plasticity (Pellegrino et al., 2012; Duret et al., 2014; Bastens et al., 2014). Calabrò et al. (2015), using a specific electrophysiological approach, found a positive influence of ERIGO® training on vestibular system and sensory motor cortex plasticity, with a consequent better improvement in motor and cognitive function than obtained with conventional verticalization.

Further studies in larger samples are needed to verify whether and to what extent postural reconditioning with ERIGO® could be an effective strategy for managing OH and other autonomic dysfunctions negatively affecting PSP patients’ quality of life.

Table II - Mean blood pressure variations and global functional recovery before and after each treatment (i.e. T0-T1, conventional and T2-T3 robotic).

<table>
<thead>
<tr>
<th></th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔPmax (mmHg)</td>
<td>96</td>
<td>93</td>
<td>92</td>
<td>13</td>
</tr>
<tr>
<td>ΔPmin (mmHg)</td>
<td>59</td>
<td>60</td>
<td>64</td>
<td>5</td>
</tr>
<tr>
<td>TCT</td>
<td>38</td>
<td>36</td>
<td>35</td>
<td>52</td>
</tr>
<tr>
<td>FIM</td>
<td>41</td>
<td>42</td>
<td>38</td>
<td>46</td>
</tr>
</tbody>
</table>

Abbreviations: FIM, Functional Independence Measure; TCT, Trunk Control Test; ΔPmax and ΔPmin, delta of variation in maximum and minimum blood pressure before and after tilting.
References


