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ORIGINAL ARTICLE

Effect of verticalization with Erigo® in the acute rehabilitation of severe acquired brain injury

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Abstract
The recovery of the orthostatism after a severe acquired brain injury (sABI) is an essential objective to pursue in order to avoid the occurrence of secondary complications resulting from prolonged immobilization to which the patient is subjected during the acute phase. This randomized controlled trial aims to evaluate the effect of verticalization with the lower limb robot-assisted training system Erigo® versus conventional neurorehabilitation in 44 adult subjects affected by sequelae of sABI in the acute rehabilitation phase, related to cardiorespiratory signs and measures of impairment and activity. At the end of the study (20 treatment sessions, 5 sessions per week), in both groups of patients, there were no dropouts nor adverse events. In subject verticalized with *Erigo*®, there were no episodes of (pre)syncope from orthostatic hypotension nor postural orthostatic tachycardia and cardiorespiratory signs remained stable; moreover, there were no increase in muscle tone nor reduction in range of motion at lower limbs. Results obtained show improved outcomes on the whole and in a similar way in both groups; however, the improvement in scores of the National Institutes of Health Stroke Scale, the Tinetti scale, and the Functional Independence Measure from the enrollment to the end of the treatment cycle being equal, the evaluation performed at the 10th session allows to establish that the improvement appears earlier in the intervention group and later in the control group. The more rapid recovery of impairments and some activities in subjects treated with *Erigo*® could allow a "time-saver" to devote to the rehabilitation of sensory-motor functions which are more complex and subordinated to the preliminary reacquisition of elementary postures and motor strategies.

Keywords Severe acquired brain injury · sABI · Acute rehabilitation · Verticalization · Robotics · Erigo®

Introduction

The term "severe acquired brain injury" (sABI) indicates a brain injury, with traumatic origin (severe traumatic brain injury) or another nature (vascular ischemic or hemorrhagic, hypoxic-anoxic, neoplastic, infectious, toxic-metabolic), determining a more or less prolonged (generally lasting no less than 24 h) state of coma (Glasgow Coma Scale equal to or less

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than 8/15), and subsequent sensory-motor, cognitive or behavioral impairments, as to result in significant disability. From this condition are excluded situations of cerebral damage at prenatal, perinatal or immediately postnatal onset (defined as cerebral palsy), those resulting from chronic-degenerative diseases of the nervous system, those secondary to cerebrovascular diseases that do not determine a state of coma.

Regardless of the etiopathogenetic mechanism, the definition of sABI implies the presence of conditions immediately related to brain damage (coma), distant outcomes (multiple impairments) and functional alterations (disability). In general, sensory-motor impairments, together with cognitive-behavioral disorders, significantly influence all phases of the rehabilitation process. Since their recovery is greater and faster in the first weeks after the acute event and is reduced in the following months [1–11], also the rehabilitation is more effective if carried out as early as possible (starting from the period in which the patient is in the intensive care unit), in order to prevent secondary damages, minimize impairments, and restore awareness until the clinical stabilization [12–16].

Notably, the loss of the ability to maintain the orthostatism after an acute event in more or less rapid time triggers a series of homeostatic adaptations of neurovegetative, hemodynamic, respiratory, osteo-mio-articular nature; therefore, the recovery of the orthostatism is an essential objective to pursue—regardless of the extent of the sABI and the prognosis of rehabilitation—in order to avoid the occurrence of secondary complications resulting from prolonged immobilization due to the acute phase. The verticalization must be obtained with precocity, gradualness, and constant monitoring of blood pressure and heart rate, to avoid the occurrence of episodes of orthostatic hypotension, more frequent in the early stages of verticalization. It aims to recover the vasomotor control (contrasting the onset of orthostatic hypotension), improve the respiratory function, prevent pressure ulcers and osteoporosis and disuse hypotrophy, limit the establishment of spasticity and contractures of paretic limbs, enhance the trunk control.

In the most severe sensory-motor impairments, in which it is necessary to reach the upright position gradually or the patient is unable to load his body weight on the lower limbs, due to an altered state of consciousness, the use of the static tilting table is helpful. The restoration of the bodyweight load on the lower limbs stimulates the proprioception and increases the exteroceptive stimulation, facilitates the contact and interaction with the surrounding environment, and thus improves the awareness, preventing the complications deriving from prolonged bedridding at the same time [17–21]. A methodological and technological evolution of the traditional tilting table is constituted by its association with electronically controlled mechanisms of the movement of the lower limbs (steppers) [22–25], among which the most common is *Erigo*® (Hocoma AG, Volketswil, Switzerland), developed in 1998 at the Paraplegic Center of the Balgrist University Hospital in Zurich in collaboration with the Heidelberg University Orthopedic Clinic and marketed since 2005. This system can support and facilitate the mobilization of patients with little or no active motility, allowing the verticalization of the decubitus and simultaneously ensuring the loading and the alternate movement of the lower limbs based on biomechanically physiological movement patterns. Compared with the mobilization carried out with a traditional tilting table, with *Erigo*® verticalization (up to 80°) is coupled with the rhythmic passive movement of the lower limbs, the alternation of loading and unloading of the lower limbs is ensured (Fig. 1), and the movement is differentiable for each of the two lower limbs according to three different movement patterns (called "sinusoid", "gait", and "alternate legs").

Materials and methods

Subjects Since 2012, 72 subjects affected by sequelae of sABI (particularly, ischemic stroke, hemorrhagic stroke, and traumatic brain injury) have been admitted to the Neurorehabilitation Unit of "Quarenghi" Clinical Institute in San Pellegrino Terme (Bergamo).

We included subjects who had:

- acute event within 6 months prior to the admission to the Institute;
- cardio-pulmonary and circulatory stability.

Subjects were excluded if they had:

- acute event beyond 6 months prior to the admission to the Institute;
- previous experience of verticalization with *Erigo*® at other structure, relatively to the reference acute event;
- recovery of autonomous or with movable support orthostatism and/or of walking at the admission to the Institute;
- exclusive impairing of swallowing, speech, cognitive, and behavioral aspects;
- previous other sABI (with or without sequelae) or other previous diseases that had already affected subject's autonomy, considerably compromising the possibility of functional recovery (other stroke, advanced osteoarthritis, non-unions, vertebral instability);
- characteristics that affected the participation in the rehabilitation training with *Erigo*®, that is:

  – non-adaptable constitutions (leg length < 70 cm or > 102 cm, weight > 135 kg),
  – irreducible leg contractures or grade > 3 hypertonia according to the Modified Ashworth Scale,
  – bone diseases (delayed unions, non-unions, severe osteoporosis, osteomyelitis, vertebral instability),

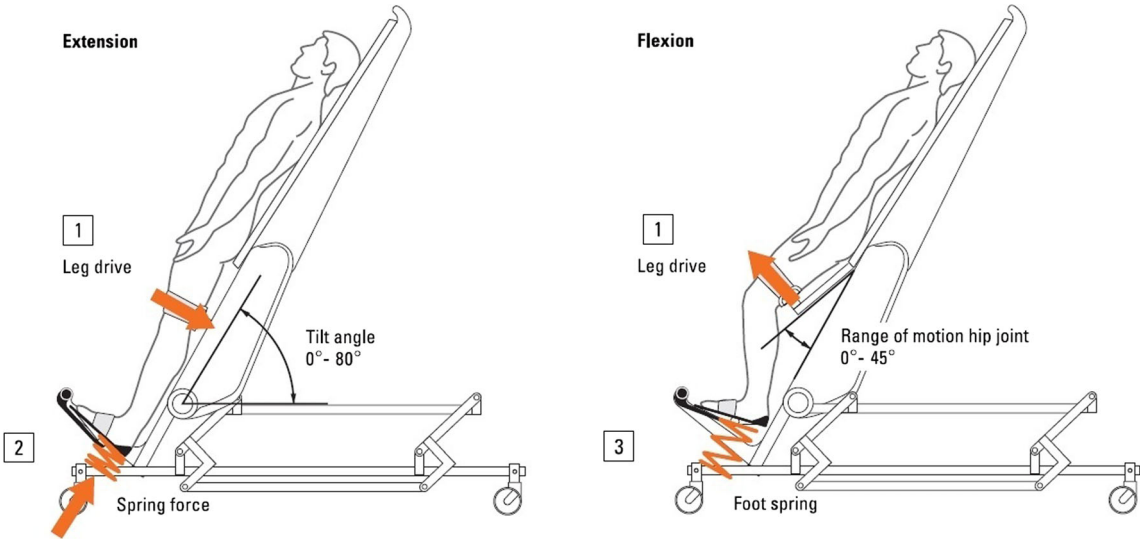

Fig. 1 In the *Erigo*® system, computer-controlled physiological movement of the lower limbs generates hip, knee and ankle extension and flexion (1), resulting in foot loading (2) and unloading (3), respectively

- pressure ulcers or other skin wounds on leg or back,
- severe heart failure and cardiovascular diseases,
- severe infectious or inflammatory diseases,
- opposition or aggressiveness.

Treatment protocol The treatment protocol was conducted during the first 30 days of admission to the Institute and included 20 treatment sessions (5 sessions per week), each comprehensive of 75 min of conventional neurorehabilitation (including traditional tilting table) with physiotherapist only (for subjects in the control group) or 45 min of conventional neurorehabilitation with physiotherapist and 30 min of verticalization with *Erigo*® (for subjects in the intervention group).

- The conventional neurorehabilitation consisted of passive and active joint mobilization, muscular stretching, exercises for proprioception, and trunk stabilization aimed at the achievement and maintenance of sitting position on the bed and wheelchair and the facilitation of transfers from bed to wheelchair and vice versa, according to standardized methods [26–29].
- The verticalization with *Erigo*® was set with 80° slope (reached within 5th session according to the following schedule: 60° in 1st session → 65° in 2nd session → 70° in 3rd session → 75° in 4th session → 80° from 5th session onwards) and with "sinusoidal" pattern of leg movement (since it is the most comparable to the one manually exerted by the physiotherapist). Moreover, at the beginning and the 5th minute of each session, the following cardiorespiratory signs were monitored: heart rate, blood pressure, and peripheral oxygen saturation. Indeed it is known that up to 20% of elderly people and—at the verticalization in the first phase of rehabilitation process (above all in those who are bedridden for a long time)—about 25% of subject with severe traumatic brain injury [30, 31] show orthostatic hypotension, maybe the most weakening aspect of autonomic dysfunction. This condition can cause a number of symptoms that include dizziness, weakness, blurred vision or blindness, pallor, palpitations, diaphoresis, nausea, hearing impairment, tachypnea, syncope, and can arise at the awakening, after a meal, with physical exercise, or more often with postural changes (particularly with the sudden transfer from clinostatism to the sitting position or from the sitting position to orthostatism). In this study, the criteria of verticalization and monitoring were so-set because a reduction in blood pressure up to 15 mmHg and an increase in heart rate up to 20 bpm during the first 6 min of verticalization represent a physiological adaptive response [32], whereas the syncope, though not univocally defined in literature, appears with a reduction in systolic blood pressure at least of 20 mmHg (30 mmHg in subjects with clinostatic hypertension) or in diastolic blood pressure at least of 10 mmHg compared to basal values within 3 min prior to the verticalization or to the at least 60° slope [33].

Evaluation and outcome measures At the enrollment (T0), the 10th session (T1) and the end of the treatment cycle (T2), each patient underwent a neurological and physiatric evaluation.

The clinical evaluation was completed with the administration of the National Institutes of Health Stroke Scale (NIHSS), which explores the level of consciousness, the sensation, eye and gaze movements, the presence of facial palsy, arm and leg motor drift, ataxia, aphasia, dysarthria, extinction, and inattention.

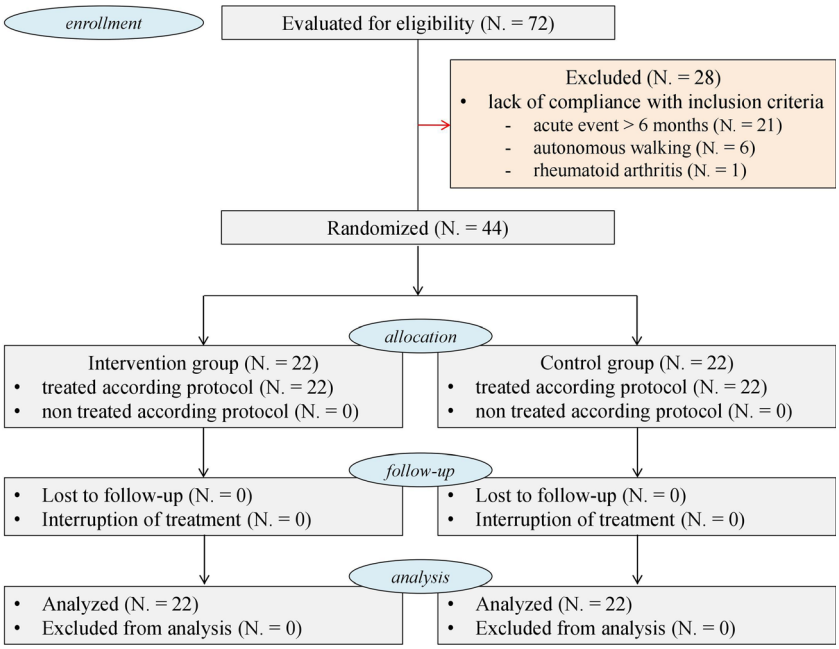

Fig. 2 Flow chart of the study according to the CONsolidated Standards of Reporting Trials (CONSORT) Statement

The evaluation of balance and gait was accomplished by administration of the Tinetti scale, which considers transfers, step length and symmetry, deviations, trunk sways, and has predictive value for risk of fall.

For a global evaluation of disability of each patient the Functional Independence Measure (FIM) was administered; it detects the level of autonomy in the performing activities of daily living (ADL)—self-care, sphincter control, transfers, locomotion, communication, and social cognition.

Statistical analysis Data obtained were analyzed with SigmaStat® 3.5 (Systat Software Inc., Point Richmond, CA). Since the distribution of the values was not normal, comparison between clinical scores was assessed with Wilcoxon test. Statistical significance was set to values of $p \leq 0.05$. Values are expressed as mean ± standard deviation (SD).

Results

Out of 72 patients evaluated for eligibility, 28 were excluded because of lack of compliance with inclusion criteria (21 because of chronic sABI, 6 because of autonomous walking, 1 because of deforming rheumatoid arthritis). The 44 enrolled were randomized in two clinically homogeneous groups, each composed of 22 subjects (the flow chart of the study is represented in Fig. 2).

The intervention group was composed of 14 males and 8 females, mean age 59.52 ± 22.16 years (range 16–86 years); the control group was composed of 15 males and 7 females, mean age 68.12 ± 16.60 years (range 26–90 years). In both groups, the time from the acute event was slightly shorter than 3 months (mean: 81.78 days), and the etiology was mostly represented by sequelae of ischemic stroke (demographic and clinical characteristics of enrolled subjects at T0 are shown in Table 1).

Table 1 Demographic and clinical characteristics of enrolled subjects at T0

		Intervention group ($N = 22$)	Control group ($N = 22$)
Age (years ± SD)		59.52 ± 22.16	68.12 ± 16.60
(range of age, in years)		(16–86)	(26–90)
Sex	Males	14	15
	Females	8	7
Time from acute event (days ± SD)		86.43 ± 23.91	77.12 ± 18.54
(range di time, in days)		(57–165)	(41–108)
Etiology	Ischemic stroke	11	13
	Hemorrhagic stroke	6	6
	Traumatic brain injury	5	3

SD standard deviation

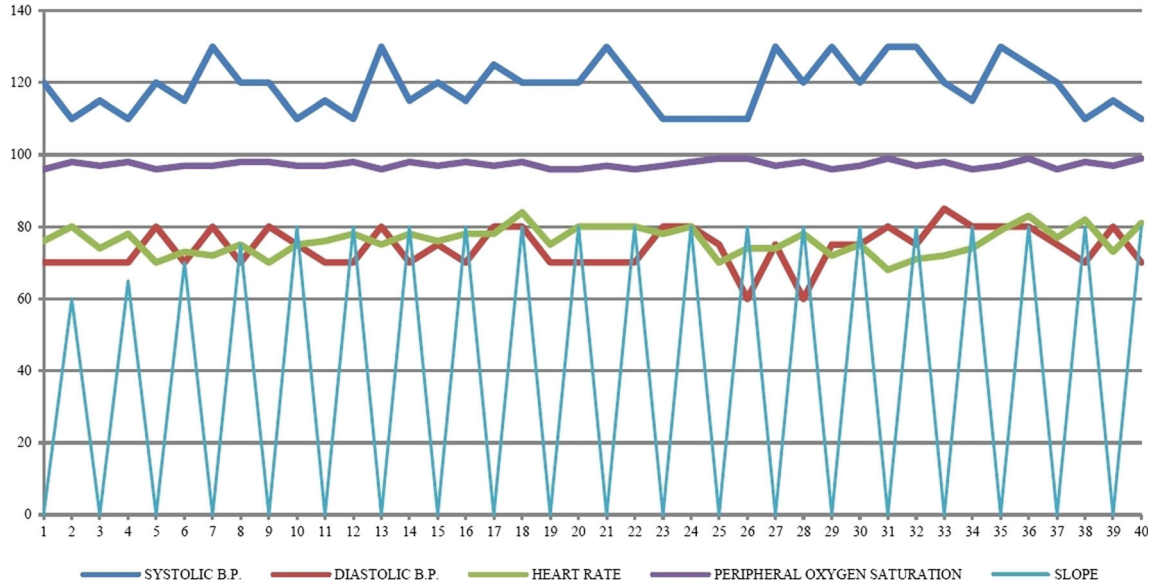

Fig. 3 Mean trends of cardiorespiratory signs (on the ordinate) in subjects in the intervention group, at the beginning (odd numbers on the abscissa) and the 5th minute (even numbers on the abscissa) of each session with *Erigo*®. Systolic and diastolic blood pressure are expressed in mmHg, heart rate is expressed in bpm, peripheral oxygen saturation is expressed in percent, slope is expressed in degrees

At the end of the study, in neither group, there were any dropouts or adverse events.

Notably, in subject verticalized with *Erigo*® there were no episodes of (pre)syncope from orthostatic hypotension nor postural orthostatic tachycardia; cardiorespiratory signs remained stable and showed the physiological response to standing from lying, with a slight reduction in systolic and diastolic blood pressure and a slight increase in heart rate (Fig. 3), in agreement with what is described in literature [34]. Moreover, there was no increase in muscle tone nor reduction in range of motion at lower limbs (data not shown), and in general, the robotic treatment resulted safe and well tolerated.

In the intervention group, a constant and significant improvement ($P < 0.001$) in scores of NIHSS (from 13.45 ± 4.00 to 12.50 ± 3.99 to 11.27 ± 3.48), Tinetti scale (from 2.73 ± 3.73 to 6.14 ± 4.06 to 8.50 ± 4.82), and FIM (from 52.82 ± 16.60 to 58.55 ± 18.71 to 62.59 ± 21.54) was observed from T0 to T1, from T1 to T2, and from T0 to T2.

In the control group, an analog trend was observed from T0 to T2 and from T1 to T2, with improvement in scores of NIHSS (from 13.27 ± 9.81 to 11.45 ± 9.76 and from 12.86 ± 9.51 to 11.45 ± 9.76), Tinetti scale (from 4.00 ± 4.04 to 7.77 ± 5.04 and from 5.68 ± 4.39 to 7.77 ± 5.04), and FIM (from 52.55 ± 23.92 to 61.23 ± 26.93 and from 55.64 ± 24.80 to 61.23 ± 26.93); instead, from T0 to T1 it was observed no significance in NIHSS and significance between $P < 0.05$ and $P < 0.001$ in Tinetti scale and FIM.

The analysis of scores of rating scales in subsets of patients showed improvements with a trend that reflects that of the two main groups, as illustrated in detail in Tables 2, 3, 4.

Table 2 Trend of NIHSS in subsets of patients

	Intervention group ($N = 22$)			Control group ($N = 22$)		
	T0	T1	T2	T0	T1	T2
Sex						
Males	12.93 ± 4,32	11.93 ± 3.95*	10.64 ± 3.10 *	14.33 ± 9.98	13.80 ± 9.56*	11.93 ± 9.91**
Females	14.38 ± 3.42	13.50 ± 4.11	12.38 ± 4.03*	11.00 ± 9.76	10.86 ± 9.84	10.43 ± 10.11
Etiology						
Ischemic stroke	14.09 ± 5.11	13.09 ± 5.22*	12.00 ± 4.31**	10.69 ± 8.98	10.54 ± 8.97	9.62 ± 9.08*
Hemorrhagic stroke	13.67 ± 1.86	13.17 ± 1.94*	11.83 ± 1.33	20.50 ± 11.10	19.33 ± 10.80	17.67 ± 11.41
Traumatic brain injury	11.80 ± 3.11	10.40 ± 1.82	9.00 ± 2.55*	10.00 ± 1.73	10.00 ± 1.73	7.00 ± 3.46

Values are expressed as mean ± standard deviation

$P < 0.05$; ** $P < 0.001$

Table 3 Trend of Tinetti scale in subsets of patients

	Intervention group ($N = 22$)			Control group ($N = 22$)		
	T0	T1	T2	T0	T1	T2
Sex						
Males	2.86 ± 4.02	5.86 ± 3.46**	7.64 ± 3.46**	3.80 ± 3.69	5.80 ± 4.43*	7.80 ± 5.19**
Females	2.50 ± 3.42	6.63 ± 5.18*	10.00 ± 6.39*	4.43 ± 5.00	5.43 ± 4.65	7.71 ± 5.12*
Etiology						
Ischemic stroke	3.45 ± 3.96	6.27 ± 4.41*	8.18 ± 4.53**	4.23 ± 4.00	5.92 ± 4.27	8.15 ± 4.65**
Hemorrhagic stroke	1.67 ± 3.61	6.17 ± 4.26	10.00 ± 5.93*	3.17 ± 3.97	4.17 ± 4.62	5.17 ± 5.08*
Traumatic brain injury	2.40 ± 3.78	5.80 ± 3.90*	7.40 ± 4.62	4.67 ± 5.69	7.67 ± 5.13	11.33 ± 5.69*

Values are expressed as mean ± standard deviation

*P < 0.05; **P < 0.001)

Discussion

Results obtained show improved outcomes on the whole and in a similar way in both groups. However, the improvement in scores of the rating scales from T0 to T2 being equal, the evaluation performed at T1 allows to establish that the improvement appears earlier in the intervention group and later in the control group. In the economy of the hospitalization, the more rapid recovery of impairments and of some activities in the subjects of the intervention group could allow a "time-saver" to devote (at least in theory) to the rehabilitation of sensory-motor functions which are more complex and subordinated to the preliminary reacquisition of elementary postures and motor strategies.

Indeed, the analysis of the scores of each rating scale in the whole groups, and even more in the subsets related to sex and etiology, shows that the recovery of neurological impairments, expressed through NIHSS, was significantly higher in the group of patients treated with *Erigo*® compared with the group of patients who performed only the conventional neurorehabilitation, in which the significance was observed only in male subjects and with sequelae of ischemic stroke. In both groups, however, male subjects and sABI from ischemic stroke showed a more significant recovery in all of the three rating scales compared with female subjects and sABI from hemorrhagic stroke (the datum relative to the etiological aspect is consistent with the stroke literature); on the one hand, this result can be explained in the light of the scores on average more favorable at T0 (conceivably because of slightly less clinical impairment at the time of access to the Neurorehabilitation Unit), on the other hand, it is definitely constant with the clinical/epidemiological aspect of the datum detected at the enrollment.

The two rating scales of the activities showed both significant improvements to a greater extent in the subjects of the intervention group compared with the subjects of the control group, and to a greater extent for the Tinetti scale compared with the FIM. This can be attributed to the type of interventions provided as well as to the specificity of the two rating scales: the Tinetti scale is designed for the assessment of balance and gait, and also takes into account the stability of the trunk control and the transfer from the sitting position to orthostatism and vice versa; whereas, the FIM is built to assess the degree of autonomy in performing the ADL, but also includes cognitive items, not the subject of intervention in the present study (and nonetheless not sensitive to change [35]), which remained

Table 4 Trend of FIM in subsets of patients

	Intervention group ($N = 22$)			Control group ($N = 22$)		
	T0	T1	T2	T0	T1	T2
Sex						
Males	53.00 ± 13.99	59.29 ± 16.10**	64.14 ± 20.15**	49.80 ± 22.68	53.27 ± 23.72*	59.33 ± 26.60**
Females	52.50 ± 21.52	57.25 ± 23.77*	59.88 ± 25.00*	58.43 ± 27.24	60.71 ± 28.22	65.29 ± 29.31*
Etiology						
Ischemic stroke	55.91 ± 15.34	62.36 ± 17.11*	67.27 ± 19.95*	56.62 ± 23.97	59.85 ± 24.79*	65.31 ± 26.56*
Hemorrhagic stroke	47.50 ± 15.86	52.17 ± 18.63	55.00 ± 20.36	40.33 ± 25.81	40.83 ± 24.89	46.17 ± 29.94
Traumatic brain injury	52.40 ± 21.80	57.80 ± 23.87	61.40 ±27.84	59.33 ± 16.44	67.00 ± 16.09	73.67 ± 10.97**

Values are expressed as mean ± standard deviation

*P < 0.05; **P < 0.001

unchanged at the end of the study. The only exception are the subjects affected by sequelae of traumatic brain injury, for which the FIM score significantly increased in the control group compared with the intervention group; despite the limited relevance of this finding due to the small sample size (5 patients in the intervention group and 3 patients in the control group), two epidemiological aspects completely in line with literature [36–51] should be reported, i.e., that all of the eight subjects were male and that the mean age was 44.52 years.

In this regard, the relatively small number of patients in each subset prevented us from making a correlation of the outcomes in terms of impairment and activity (as well as, going beyond the aim of the present study, the etiology of the lesion) with the extent of cognitive deficits (even though evaluated by the neuropsychologist present within the multidisciplinary team), whose heterogeneity complicates the investigation of the sABI—each patient appearing unique in the combination of nature and magnitude of the acute event and severity of outcomes. In general terms, it should be emphasized that since 2005—the year of marketing of the *Erigo*® system—the numbers related to the treatment with this device of patients suffering from sequelae of sABI are still too small in literature (like an "orphan disease" by the research, despite the importance for patients and for the National Health Services). Notably, as far as we know, the present study appears to be the first conducted in the acute rehabilitation of patients affected by sequelae of sABI in which the outcomes in terms of impairment and activity following verticalization with *Erigo*® system were assessed compared with control group.

Conclusions

sABI are pathologies that share only the severity of the neurological pattern, but that the combination of multiple etiological and pathophysiological mechanisms, the presence and extent of secondary brain damage, the promptness of first aid and the appropriateness of treatment procedures in the acute phase make extremely varied on a therapeutic and prognostic level.

Despite the results achieved through verticalization with *Erigo*® system, the limits of this study and the absence of sufficiently uniform and consolidated data in the specialized literature make clear that further studies are needed to evaluate the utility of robotic treatments in the rehabilitation of sABI and also their impact on the different groups of patients, each one special in its own sensory-motor, cognitive-behavioral, and human dimension.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval and consent to participate The study was carried out according to the 1964 Declaration of Helsinki and the ethical standards of the institutional research committee. Each patient or, in the case of impossibility for the patient to sign because of the neurological status, legal guardian or family member signed an informed consent before enrollment.

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