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Thomas Bowman
Fondazione Don Carlo Gnocchi

Elisa Gervasoni
Fondazione Don Carlo Gnocchi

Amico Angelo Paolo
Policlinico di Bari

Roberto Antenucci
Azienda Unita Sanitaria Locale di Piacenza

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What is the impact of robotic rehabilitation on balance and gait outcomes in people with multiple sclerosis? A systematic review of randomized control trials

Thomas BOWMAN [1, 2] *, Elisa GERVASONI [1], Angelo P. AMICO [3], Roberto ANTENUCCI [4], Paolo BENANTI [5], Paolo BOLDRINI [6, 7], Donatella BONAIUTI [6], Angelo BURINI [8], Enrico Castelli [9], Francesco DRAICCHIO [10], Vincenzo FALABELLA [11], Silvia GALERI [1], Francesca GIMIGLIANO [12], Mauro GRIGIONI [13], Stefano MAZZON [14], Stefano MAZZOLENI [2, 15], Fabiola G. MESTANZA MATTOS [1], Franco MOLTENI [16], Giovanni MORONE [17], Maurizio PETRARCA [18], Alessandro PICELLI [19], Federico POSTERARO [20], Michele SENATORE [21], Giuseppe TURCHETTI [22], Simona CREA [1, 2], Davide CATTANEO [1], Maria C. CARROZZA [1, 2], CICERONE Italian Consensus Group for Robotic Rehabilitation[‡]

[1]IRCCS Fondazione Don Carlo Gnocchi ONLUS, Milan, Italy; [2]The BioRobotics Institute, Sant'Anna High School, Pontedera, Pisa, Italy; [3]Spinal Unit, Policlinico di Bari University Hospital, Bari, Italy; [4]Unit of Rehabilitation Medicine, Hospital of Castelsangiovanni, AUSL, Piacenza, Piacenza, Italy; [5]Department of Moral Theology, Pontifical Gregorian University, Rome, Italy; [6]Italian Society of Physical and Rehabilitation Medicine (SIMFER), Rome, Italy; [7]General Secretary European Society of Physical and Rehabilitation Medicine (ESPRM), Rotterdam, the Netherlands; [8]Humantech, Confapi, Milan, Italy; [9]Department of Intensive Neurorehabilitation and Robotics, Bambino Gesù Children's Hospital, Passoscuro Fiumicino, Rome, Italy; [10]Department of Occupational and Environmental Medicine, Epidemiology and Hygiene, INAIL, Rome, Italy; [11]Italian Federation of Persons with Spinal Cord Injuries (Faip Onlus), Rome, Italy; [12]Department of Mental and Physical Health and Preventive Medicine, Luigi Vanvitelli University of Campania, Naples, Italy; [13]National Center for Innovative Technologies in Public Health, Italian National Institute of Health, Rome, Italy; [14]Unit of Rehabilitation, ULSS (Local Health Authority) Euganea – Camposampiero Hospital, Padua, Italy; [15]Department of Electrical and Information Engineering (DEI), Polytechnic University of Bari, Bari, Italy; [16]Valduce Villa Beretta Hospital, Costa Masnaga, Lecco, Italy; [17]Santa Lucia Foundation IRCCS, Rome, Italy; [18]Department of Neurorehabilitation and Robotics, Movement Analysis and Robotics Laboratory (MARlab), Bambino Gesù Children's Hospital, IRCCS, Rome, Italy; [19]Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona, Verona, Italy; [20]Department of Rehabilitation, Versilia Hospital, AUSL Toscana Nord Ovest, Camaiore, Lucca, Italy; [21]Italian Association of Occupational Therapists (AITO), Rome, Italy; [22]Institute of Management, Scuola Superiore Sant'Anna, Pisa, Italy

[‡]Members are listed at the end of the paper

*Corresponding author: Thomas Bowman, Department of Neurorehabilitation, LaRiCE lab, Gait and Balance Disorders Laboratory, IRCCS Fondazione Don Carlo Gnocchi ONLUS, Via Capecelatro 66, 20148 Milan, Italy. E-mail: tbowman@dongnocchi.it.

ABSTRACT

INTRODUCTION: In recent years, robot-assisted gait training (RAGT) has been proposed as therapy for balance and gait dysfunctions in people with multiple sclerosis (PwMS). Through this systematic review, we aimed to discuss the impact of RAGT on balance and gait outcomes. Furthermore, characteristics of the training in terms of robots used, participants characteristics, protocols and combined therapeutic approaches have been described.

EVIDENCE ACQUISITION: As part of the Italian Consensus on robotic rehabilitation "CICERONE" a systematic search was provided in PubMed, the Cochrane Library and PEDro to identify relevant studies published before December 2019. Only randomized control trials (RCT) involving RAGT for PwMS were included. PEDro scale was used to assess the risk of bias and the

Oxford Center for Evidence-Based Medicine (OCEBM) was used to assess level of evidence of included studies.

EVIDENCE SYNTHESIS: The search on databases resulted in 336 records and, finally, 12 studies were included. RAGT was provided with Exoskeleton in ten studies (6-40 session, 2-5 per week) and with end-effector in two studies (12 sessions, 2-3 per week) with large variability in terms of participants' disability. All the exoskeletons were combined with bodyweight support treadmill and movement assistance varied from 0% to 100% depending on participants' disability, two studies combined exoskeleton with virtual reality. The end-effector speed ranged between 1.3 and 1.8 km/h, with bodyweight support starting from 50% and progressively reduced. In seven out of twelve studies RAGT was provided in a multimodal rehabilitation program or in combination with standard physical therapy. There is level 2 evidence that RAGT has positive impact in PwMS, reaching the minimally clinically importance difference in Berg Balance Scale, six-minute walking test and gait speed.

CONCLUSIONS: In available RCT, RAGT is mostly provided with exoskeleton devices and improves balance and gait outcomes in a clinically meaningful way. Considering several advantages in terms of safety, motor assistance and intensity of training provided, RAGT should be promoted for PwMS with severe disability in a multimodal rehabilitation context as an opportunity to maximize recovery.
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Key words: Rehabilitation; Robotics; Multiple sclerosis; Gait.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system (CNS) and it is the leading cause of non-traumatic disability in young and middle-aged adults.[1] People with multiple sclerosis (PwMS) present a wide range of neurological symptoms and different levels of disability related to the varying distribution of demyelization and axonal loss. Balance disorders and gait dysfunction are two of the main problems, with up to 85% of PwMS reporting difficulty in walking and over 50% fall at least once each year.[2]

Recent reviews reported that tailored rehabilitative interventions are essential for MS management.[3, 4] In particular, rehabilitation programs customized on the specific users' needs have been proven to lead to significant improvements in balance and gait functions, in people with mild to moderate disability as well as in people with severe disorders.[5-7] Gunn *et al*. reported that specific interventions explicitly aimed at improving balance outcomes show the greatest effect in comparison to unspecific interventions – not specifically focused to improve balance.[3, 8] Considering walking outcomes, Wiles *et al*. reported that conventional walking training (CWT) or traditional overground walking training, can be a specific and effective way to improve gait and mobility in PwMS.[9] Moreover, previous studies demonstrated that intense exercise practice leads to cortical reorganization and improved behavioral functions.[10] In line with this data, it has been found that in MS rehabilitation programs the greatest benefit has been achieved when practice reaches an intense level of challenging balance and gait exercise.[3]

In recent years, robotic devices have been proposed as tools to complement traditional therapy by means of novel rehabilitation programs, based on robot-mediated repeatable, intense, and motivating exercises, integrated with an enriched virtual environment that can feature improvements in movement quality.[11, 12]

Among all, Robot-Assisted Gait Training (RAGT) approaches have found relatively high success for the treatment of subjects with balance and gait dysfunctions. Two main design and control approaches can be undertaken to implement robot-mediated physical therapy, exoskeletal- or end-effector-based mechanisms. By acting in parallel with the human joints, exoskeletons can provide joint-specific movements and corrective actions, typically at the pelvis, hips, knees, and ankles, whereas end-effector robots can control the distal part of the leg with motor-driven footplates, delivering a synergistic action on the whole limb.[13]

Several studies focused on RAGT in patients with neurological diseases (*e.g.* Parkinson disease,[14] cerebral palsy,[15] spinal cord injuries[16] and stroke[17, 18]), whereas a growing number of RCTs aims at evaluating the effect of RAGT on balance and gait in PwMS compared to other approaches. Indeed, RAGT suggest promising results on PwMS, even if it is not yet clear which subjects will benefit most. To encourage evidence-based practice, this review aimed to collect and analyze the relevant information available on RAGT and to develop a pathology specific therapeutic approach for PwMS. More specifically, this review has the following objectives:

- describing the characteristics, in terms of age and disease severity of PwMS involved in RCTs studies using RAGT;
- reporting the types of robotic devices used for balance and gait rehabilitation in PwMS;
- showing the types of rehabilitation protocols using the robot devices and the combined therapeutic approaches;
- summarizing the quality of the studies and the level of evidence on the impact of RAGT compared to other rehabilitation approaches.

Evidence acquisition

The review protocol has been elaborated in the context of an Italian Consensus “CICERONE.” The goal of “CICERONE” was to establish the role of robots and electromechanical assisted devices for people with neurological disorders. The Italian Society of Physical and Rehabilitation Medicine (SIMFER) and the Italian Society of Neurological Rehabilitation (SIRN) are partners of the project. No funding has been provided.

Search strategies

The review has been performed according to the PRISMA statement.[19] The following databases were searched from inception to December 2019: PubMed, PEDro and, the Cochrane Central Register of Controlled Trials. Studies published in the English language were included. Relevant search terms were combined with Boolean operators (OR/AND). Specifically, the terms and keywords used were combined in the following search strategies:

- PubMed: (“robotics [mh]” OR “robot-assisted” OR “electric stimulation therapy/instrumentation [mh]” OR “electromechanical”) and (“rehabilitation [mh]” OR “training”) and “postural balance [mh];”
- Cochrane (CENTRAL): (“robotics” OR “robot-assisted” OR “electromechanical”) and (“rehabilitation” OR “training”) and “postural balance;”
- PEDro: “robotic.”

Selection criteria

Inclusion criteria were: 1) participants – adults with multiple sclerosis; 2) intervention – balance/gait rehabilitation using robotic devices; 3) comparators – no treatment, conventional rehabilitation/usual care, conventional/overground walking training and other; 4) outcomes – balance and gait; 5) study design – randomized controlled trials. Regarding the last point, RCTs have been selected as they represent the best study design to examine the effects of an intervention.[20] Studies written in languages other than English were excluded.

Study selection and data extraction

Titles and/or abstracts of studies retrieved using the search strategy were screened by three independent reviewers to identify studies in compliance with inclusion and exclusion criteria. The full text of eligible studies was further assessed for eligibility. Any disagreement has been resolved through discussion between reviewers. After inclusion, the study characteristics, research goals, and main findings were extracted and summarized according to the objectives of the review.

Quality assessment

Study quality was assessed using the PEDro scale. For each trial is given a total PEDro score, which ranges from 0 to 10.[21] Studies scoring 9-10 were classified as excellent, 6-8 as good, 4-5 as fair, and less than 4 as poor quality.[22] The possible risk of bias has been assessed together with the quality assessment of the included studies.

Level of evidence

The body of evidence is evaluated using a level of evidence framework for quantitative research on intervention studies “Oxford Center for Evidence-Based Medicine” (OCEBM).[23] In this framework, the highest level of evidence (level 1) is at least one systematic review or meta-analysis of RCTs, down to case series or pretest post-test studies without control (level 4). Randomized trials or observational studies with dramatic effects are considered as level 2. The level may be graded down based on the study quality and imprecision or because the absolute effect size is very small. The level may be graded up if there is a large or very large effect size. To consider that RCTs had level 1 evidence, we arbitrarily chose a cut-off score ≥9 by the PEDro scale, level 2 evidence for RCTs with a PEDro score ≥6 and, level 3 evidence has been considered for RCTs with PEDro scale <6 or very small sample size.

Evidence synthesis

After the database search, 336 potentially relevant papers were found. After the screening procedure following inclusion and exclusion criteria, 12 studies were included (Figure 1).

All RCT studies were included (6 RCT, 6 pilot RCT). The contents of the studies are summarized in Supplementary Digital Material 1: Supplementary Table I.[24-35]

Study and participants characteristics

The average age of the samples ranged from 35-73 years and the disease severity measured by the Expanded Disability Status Scale (EDSS) score ranged from 3 and 7,5 points. The sample size ranged from a minimum of 7 to a maximum of 72 subjects included. Drop-outs were reported in 8 studies with similar rates in the RAGT group and control group.

Type of robotic devices

Ten studies used an exoskeleton device (Lokomat, Hocoma; Volketswil, Switzerland) combined with body weight support treadmill training (BWSTT).[24-33] Two studies used an end-effector robot (Gait Trainer GT1 or GT2, Reha-Stim; Berlin, Germany).[34, 35]

Protocol characteristics and training specifications with robotic devices

The duration of the exoskeleton treatments varied from a minimum of 6 sessions to a maximum of 40 sessions, with a frequency between 2 and 5 sessions per week and a minimum duration of 3 weeks and a maximum of 8 weeks. Studies spanned a wide range of levels of movement assistance with the Lokomat device, going from 0% to 100%, the latter corresponding to the patient being completely passive and the robot providing the whole power. Considering the end-effector devices, a protocol of 12 sessions was performed with a 2 or 3 weekly frequency depending on the study protocol. The duration of the single session was from 40 to 50 minutes. The end-effector speed was selected to be comfortable for the patient, generally ranged between 1.3 and 1.8 km/h. In the study by Pompa *et al.*[34] bodyweight support started from 50% and was progressively reduced. Similarly, Gandolfi *et al.*[35] trained patients at 20% of supported bodyweight in the first session, reduced at 10% in the second session. Supplementary Digital Material 2: Supplementary Table II[24-35] provide training specifications (% body weight support, level of robotic guidance and gait speed) with robotic devices.

Therapeutic approaches combined with RAGT

In all the studies the exoskeleton was combined with BWSTT. The support was initially set at the 100-70% of bodyweight of every patient's weight and it was decreased in accordance with the load tolerance to a minimum of 20-0% at the end of rehabilitation. Similarly, treadmill speed was increased from 0.1 km/h to approximately 3 km/h or the maximum speed tolerated by the subjects.[28-30]

In Ruiz *et al*.[33] physical therapy was provided in the same session before and after 40 minutes of RAGT and BWSTT alone, while two studies[24, 31] combined virtual reality with an exoskeleton to boost the effect of RAGT. Moreover, 4 studies[24-27] reported that RAGT with exoskeleton was provided in the context of a multimodal rehabilitation program or in addition to standard physical therapy treatment.

Considering end-effector devices, Pompa *et al*.[34] performed standard inpatient rehabilitation sessions in addition to RAGT, while in Gandolfi *et al*.[35] 10 minutes of passive lower limb joint mobilization and stretching exercises were added in the same session immediately after the RAGT protocol.

Quality assessment

The average total PEDro score is 6.5 with a standard deviation of 1.2. Good to excellent quality is present in 66.5% of trial reports[24-26, 28, 30, 31, 34, 35] scoring ≥6/10 on the PEDro scale (Table I).[24-35] Fair quality is present in the rest of reports[27, 29, 32, 33] scoring 5 on the PEDro scale (Supplementary Table II).[24-35]

The possible risk of bias has been assessed together with the quality assessment of the studies (Supplementary Table II).[24-35] Four studies[27, 29, 30, 32] showed a possible selection bias because of inadequate concealment of allocated treatment. Other studies[24-26, 28, 31, 33-35] described an adequate method of randomization and concealment of allocate treatment. It is important to point out that the main drawback was the absence of proper blinding of participants and physical therapists providing treatment, that can lead to a performance bias in all the studies included. Conversely in most of the studies, an independent evaluator was in charge of clinical assessments but 3 studies[26, 29, 32] had no blind assessor leading to possible detection bias.

Furthermore, in 7 studies[27-29, 31-33, 35] the presented results were not analyzed as intention to treat. Finally, 6 studies[24-27, 30, 34] provided an a priori sample size calculation increasing the statistical power of their results.

Level of evidence

Among the 12 reviewed studies, no one was properly designed and sufficiently high-powered to be ranked as level 1 of evidence (Supplementary Table I).[24-35] Along with Pompa *et al.*,[34] seven other studies were ranked as level-2 evidence[24-26, 28, 30, 31, 35] while 4 studies were ranked as level-3 evidence.[27, 29, 32, 33]

Discussion

This review of studies focuses on robotic rehabilitation for gait and balance in PwMS and it revealed that exoskeleton-based robotic devices are the most frequently applied in robot-mediated physical therapy for PwMS. Participants' clinical characteristics are heterogeneous because there is a large variability in terms of disability and age of patients involved in the studies. Similarly, the sample size is very small in preliminary pilot studies and larger in RCTs. Moreover, rehabilitation protocols with different frequency and intensity have been employed. All the reviewed studies evaluated inpatient or outpatient rehabilitation programs having balance or gait as primary outcomes.

Implications for robotic rehabilitation and clinical practice

Within the selected studies for this review, the impact of RAGT compared to other rehabilitation interventions for balance and gait outcomes was assessed. RAGT can be considered as a specific treatment for balance and gait outcomes and has been compared to other specific or unspecific interventions. Specific interventions include also activities strictly related to balance and walking by altering the base of support, speed during movements, body and/or head turns, and by using external tasks (*e.g.* catching and throwing).[36] Conversely, unspecific interventions may include passive stretching and general muscle strengthening with optional exercises for coordination, balance, and gait. The results of a level 3 RCT[29] showed that subjects with moderate to severe disability who underwent RAGT improved significantly gait speed, walking endurance, and spatio-temporal parameters (cadence, step length, double support time) compared to a control group who underwent conventional unspecific training; improvements are maintained at 3 months follow-up. In the same study, minimal clinically important difference (MCID), defined as the smallest change in a treatment outcome that an individual patient would identify as important,[37] was achieved only by the RAGT group. In specific, a change of 14.0 to 30.5 meters in walking endurance measured by the 6-meter walking test (6MWT) is considered clinically important across multiple patient groups[38] while a pre-post treatment change score higher than 0.77 seconds is considered a relevant improvement in dynamic balance measured by timed up and go test (TUG).[39] These results should be cautiously interpreted since the lower efficacy of unspecific interventions was already known;[8, 40] however, RAGT with exoskeleton seems more effective compared to unspecific balance and gait interventions in PwMS with moderate to severe disability.

On the other hand, results from 4 level-2 RCTs revealed that RAGT provided the same benefit in terms of balance,[25, 26, 28, 35] gait speed,[25, 26, 28, 35] and walking endurance[25, 28, 34] compared to specific rehabilitation interventions, as conventional walking training (CWT)[25, 26, 28, 34] or sensory integration balance training (SIBT).[35] The same results were found by Straudi *et al.*[30] (level 2 RCT); however, the author showed statistically significant improvement in balance, gait speed, and walking endurance after only six treatment sessions (midterm assessment) in the RAGT group, suggesting short-lasting effects of RAGT in progressive PwMS with severe gait impairments compared to CWT. Considering MCID value, part of the level-2 RCTs showed that both RAGT and CWT led to 3 points improvements in the Berg Balance Scale (BBS)[28, 35, 37] assessing static balance, and 19 meters in walking endurance[25] at the end of the treatment. Conversely, in other studies only RAGT led to meaningful improvements in balance (BBS),[25, 30] walking endurance[30, 34] and, gait speed (0.11 m/s).[27, 39] These data highlight that RAGT provides the amount of therapy needed to reach clinically meaningful improvements in PwMS.

Our findings are in line with previous meta-analysis[41, 42] concluding that RAGT is as effective as specific balance and gait rehabilitation (*e.g.* CWT or SIBT) in improving balance, gait speed, walking ability, and stride length among PwMS. Another meta-analysis by Xie *et al*.[43] reported a higher effect of RAGT in walking endurance. Since PwMS with severe disability and severe balance impairment are at higher risk of falls,[8] it is possible that they could benefit more from RAGT than CWT, in terms of safety as well as walking performance. Indeed, this promising approach offers the possibility to provide passive and assisted as needed motor activities and to regulate body weight support allowing better performance, reducing the fall risk, and reducing the effort of physical therapists. Moreover, RAGT should be promoted on subjects at a higher level of disability to reinforce the neuronal circuits that contribute to postural control, enabling wheelchair-bound PwMS to practice a walking-like movement with minimal assistance.

Considering combined therapeutic approaches to RAGT, two studies[24, 31] (level of evidence 2) combined virtual reality (VR) with an exoskeleton to boost the effect of RAGT. Russo *et al*.[31] showed that 6 weeks of RAGT coupled with VR preceding 12 weeks of conventional rehabilitation has earlier effects in gait and balance outcomes compared to 18 weeks of conventional rehabilitation alone. Moreover, Calabro *et al*.[24] showed a small effect size in balance outcome in favor of RAGT combined with VR if compared to RAGT without VR. Although these studies did not show a statistically significant difference between treatments, these findings support the hypothesis that robotic rehabilitation combined with VR may be a useful tool in promoting neuroplasticity and functional recovery in PwMS, increasing subjects' motivation and compliance.

Between the included RCTs, 2 studies[27, 34] provided multimodal rehabilitation while other 5 studies[24-26, 33, 35] provided conventional physical therapy in addition to RAGT. According to scientific evidence, multimodal rehabilitation is recommended for PwMS and includes daily physical therapy, occupational therapy, and neuropsychological therapy carried out by a team of experts.[44]

This evidence highlights the positive role of RAGT not as a substitute for physical therapy but as rehabilitation support, able to generate a more complex, controlled multisensory stimulation boosting the experience of movement and to better quantify the dosage of intervention.[45, 46] Thus, emerging robotic technologies could enhance balance and gait rehabilitation and should be considered an opportunity to maximize recovery.[47] In this perspective, RAGT should be promoted in combination with physical therapy or in a multimodal rehabilitation program for PwMS.

Limitations of the study

Some limitations related to this review deserved to be discussed. First, the risk of bias has been examined for every single study to provide information about the level of evidence. Among all the bias categories the performance bias, due to knowledge of intervention allocation, is evident in all the studies included. This severe limitation could lead to systematic differences in the provided care between groups (*e.g.* favoring one group more than the other).[48] Due to the intrinsic nature of interventions (*e.g.* consisting of using robotic devices) blinding of participants and physical therapists is not easily applicable in trials involving RAGT, leading to a distortion of treatment effects when compared with more conventional therapeutic approaches.

A second issue to be considered is related to the instruments used to assess the quality of the studies and the level of evidence. It could be argued that instruments as the Cochrane risk of bias (ROB)[48] and GRADE system[49] should have been preferred as the higher standard recommended by the Cochrane Group. However, the clinometric properties of the PEDro scale reveal acceptable reliability and validity,[50] and a recent review by Mosley *et al*.[51] concluded that there is a moderate agreement for some items between PEDro and ROB. Moreover, either instrument can be used to quantify risk of bias, but they cannot be used interchangeably.[51]

Conversely, the OCEBM level of evidence refrains from making definitive recommendations and is less accurate compared to GRADE, but it is considered a simple and efficient tool.[52, 53] Furthermore, these instruments (PEDro and OCEBM) have been promoted by the organizers of the Consensus Conference "CICERONE" as standard methods to ensure uniformity in the assessment by all the participating experts.

Conclusions

Exoskeleton devices are the most frequently applied in robot-mediated physical therapy in PwMS. Moreover, it has been proved that RAGT improves balance and gait outcomes in a clinically meaningful way in this population. RAGT seems more effective if compared to unspecific rehabilitation, while it shows similar effects if compared to specific balance and gait training in studies with level 2 evidence. In spite of lack of firm conclusion on effect, RAGT has several advantages in terms of patient motor assistance, intensity of training, safety, and the possibility to combine other therapeutic approaches and should be promoted for PwMS with severe disability in a multimodal rehabilitation context as an opportunity to maximize recovery. Finally, the huge heterogeneity of the studies highlights the need for a growing number of well-designed RCTs with a larger sample size and able to customize the robotic treatment to PwMS.

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Group name.—CICERONE Italian Consensus Group for Robotic Rehabilitation: Alessio BARICICH (Health Sciences Department, University of Eastern Piedmont, Novara, Italy), Luciano BISSOLOTTI (Fondazione Teresa Camplani Casa di Cura Domus Salutis, Brescia, Italy), Marianna CAPECCI (Department of Experimental and Clinical Medicine, Neurorehabilitation Clinic, University Hospital of Ancona, Politecnica delle Marche University, Ancona, Italy), Loredana CAVALLI (Centro Giusti, Outpatient Recovery and Functional Rehabilitation Center, Florence, Italy), Giuseppina DI STEFANO (Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy), Johanna JONSDOTTIR (IRCCS Fondazione Don Carlo

Gnocchi ONLUS, Milan, Italy), Carmelo LENTINO (Unit of Recovery and Functional Reeducation, Primary Care Department ASL 2 SSRL, Santa Corona Hospital, Pietra Ligure, Savona, Italy), Perla MASSAI (Tuscany Rehabilitation Clinic, Montevarchi, Arezzo, Italy), Sandra MORELLI (National Center for Innovative Technologies in Public Health, Italian National Institute of Health, Rome, Italy), Antonio NARDONE (Neurorehabilitation and Spinal Unit, Department of Clinical-Surgical, Diagnostic and Pediatric Sciences, Centro Studi Attività Motorie, ICS Maugeri SPA SB, Institute of Pavia IRCCS, University of Pavia, Pavia, Italy), Daniele PANZERI (Scientific Institute, IRCCS Eugenio Medea, Bosisio Parini, Lecco, Italy), Elisa TAGLIONE (National Institute for Insurance against Accidents at Work [INAIL], Motor Rehabilitation Center, Volterra, Pisa, Italy).

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Figure 1.—Flowchart of study selection process.

Table I.—Quality of selected studies by the PEDro Scale.

PEDro Items	Beer *et al.*[27](2008)	Lo *et al.*[32](2008)	Schwartz *et al.*[28] (2012)	Vaney *et al.*[26] (2012)	Ruiz *et al.*[33](2013)	Straudi *et al.*[29] (2013)	Gandolfi *et al.*[35] (2014)	Straudi *et al.*[30] (2016)	Calabrò *et al.*[24] (2017)	Pompa *et al.*[34] (2017)	Russo *et al.*[31] (2018)	Straudi *et al.*[25] (2020)
Eligibility criteria*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Random allocation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Concealed allocation	No	No	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes
Baseline comparability	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Blind subjects	No	No	No	No	No	No	No	No	No	No	No	No
Blind therapists	No	No	No	No	No	No	No	No	No	No	No	No
Blind assessors	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Adequate follow-up	No	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Intention-to-treat analysis	No	No	No	Yes	No	No	No	Yes	Yes	Yes	No	Yes
Between-group comparisons	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Point estimates and variability	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
TOTAL SCORE	5	5	7	6	5	5	6	6	8	8	7	8

*Eligibility criteria item does not contribute to total score.

Figure 1. Flowchart of study selection process