Research Article
Volume 10:1, 2023

International Journal of Neurorehabilitation

ISSN: 2376-0281 Open Access

Therapy with a Free-Standing Robotic Exoskeleton in People with Advanced Multiple Sclerosis: A Feasibility Study

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Abstract

Background: Evidence for the use of lower limb robotic exoskeletons for people with advanced multiple sclerosis is in its early stages, and to date there have been no published studies into the use of free-standing exoskeletons in this population.

Objective: This study aimed to determine the feasibility of a course of therapy in a free-standing robotic exoskeleton with people with advanced multiple sclerosis.

Methods: Following a 12 week wait list control period participants with advanced multiple sclerosis (Kurtzke Expanded Disability Status Scale score of ≥6.0) completed 12 weeks of twice weekly therapy in a free-standing robotic exoskeleton. A battery of assessments was performed at participant enrolment including motor function, balance, strength, independence and health-related quality of life, commencement and conclusion of the intervention phase, and at 12 weeks follow-up.

Results: Ten participants were eligible to participate in the study, with eight completing the full duration of the study; two dropped out due to an exacerbation of their condition, unrelated to the intervention. A lack of symptom stability in the control phase made interpretation of outcomes difficult. Participants who completed the intervention demonstrated high acceptance and tolerance of the intervention. No adverse events occurred. Health-related quality of life improved within six weeks of commencing the intervention and was sustained. No other outcomes showed any consistent changes.

Conclusion: Therapy with a free-standing robotic exoskeleton is acceptable to people with advanced multiple sclerosis and can improve health-related quality of life, however clinical feasibility of this intervention is limited at this time.

Keywords: Multiple sclerosis • Lower limb • Robotic exoskeleton • Neuro-rehabilitation

Introduction

Multiple sclerosis (MS) is the most common non-traumatic cause of disability in younger people in the world affecting around 2.8 million people [1,2]. It has recently been shown that those with a Kurtzke Expanded Disability Status Scale (EDSS) score of less than 6.0, i.e. not dependent on a mobility aid, can benefit from physical rehabilitation, with exercise improving walking ability and decreasing the impact on health related quality of life (QoL) [3-5]. Approximately 41% of people with MS have difficulty with independent ambulation [6]. Weightbearing exercise is an important component of the management of condition progression and secondary complications throughout the disease course, and evidence is emerging of the benefits for people with more advanced MS [7]. However, once a person with MS is having difficulty walking, the need for mobility aids, environmental adaptations and healthcare support, can limit access to exercise in weightbearing [8]. Robotic technologies may offer solutions to address some of these barriers to treatment.

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Received: 02 February, 2023, Manuscript No. ijn-23-89237; **Editor assigned:** 03 February, 2023, PreQC No. P-89237; **Reviewed:** 15 February, 2023, QC No. Q-89237; **Revised:** 22 February, 2023, Manuscript No. R-89237; **Published:** 28 February, 2023, DOI: 10.37421/2376-0281.2023.10.507

Robotic technologies with therapeutic applications have been developing rapidly in the last two decades with devices such as the Lokomat® (Hocoma, Zurich, Switzerland) [9], an exoskeleton combined with bodyweight-supported treadmill training, and the Gait Trainer GTII® (Reha-Stim, Berlin, Germany) [10], an end-effector device, which combines bodyweight-supported training with a closed chain stepping device. These devices can achieve 10-20 times more steps in a treatment session, therefore providing greater treatment intensity than conventional therapy [11]. A 2020 systematic review which included 10 studies using both the Lokomat® and the Gait Trainer GTII®, with participants with an EDSS between 5.5-7.5, showed superiority over conventional therapy for fatigue, spasticity and global mobility, for those with severe disability [12]. This superiority was not demonstrated when a subgroup analysis of only studies using the Lokomat® was conducted, suggesting more benefit from the Gait Trainer GTII®. Neither device showed superiority over conventional training at three month follow up. The use of treadmill-based and end-effector robotic a technology has also been shown to be safe, feasible and acceptable to patients [12-14]. However, a lack of consistently improved outcomes for patients compared with conventional therapy, a lack of visuo-spatial variability in training, and a focus on gait over all other functional exercise, has led to the development of overground lower limb robotic exoskeletons with potential application in people with MS [15,16].

The development of overground exoskeletons in the last ten years has provided a way to exercise in supported weightbearing, whilst in varying locations. This offers the opportunity to practice a gross motor task in different contexts, a key principle of neuro-rehabilitation [17]. Lower body exoskeletons such as the ReWalk, ExoAtlet and Ekso, and single joint devices such as Keeogo, have been investigated with MS populations [18-21]. Evidence of the potential benefit of these devices is emerging for outcomes such as walking speed and distance, endurance and stair climbing and QoL [19,21-24]. Whilst these studies are generally positive, one study found that two thirds of participants did not tolerate the treatment and another reported skin irritations [21]. Furthermore, all these

devices require the user to support themselves using upper limb support through a walking aid, which precludes many people [25]. A free-standing device may offer additional opportunity to a greater portion of the population.

To date there has been limited research into the use of free-standing exoskeletons in the rehabilitation of those with MS. Currently there is only device which can support the user without the need for walking aids, the REX (Rex Bionics, Auckland, New Zealand) [26]. The only published research into therapy with this device in the MS population found that participants did not significantly increase their VO_2 during a session of exercise in this device, and there was no change in this after 12 weeks of twice weekly robotic therapy, suggesting no effect on cardiovascular fitness [27]. A 2021 study found that a course of 12 weeks of therapy in the device with people with spinal cord injury was safe and acceptable, but that a small cohort of appropriate participants limited clinical feasibility [28]. A 2021 study of people with stroke found some benefit to levels of independence in activities of daily living after 12 weeks of therapy with the device [29]. To date no study has investigated the potential benefit to rehabilitation outcomes for people with MS after therapy with a free-standing exoskeleton. Given the numerous differences in features between free standing, mobility aid supported, and over-treadmill robotic devices, it is unreasonable to extrapolate the findings from previous research to free-standing devices. It is speculated that each type of device may have application in different sub-groups of the population. For example, it is surmised that free-standing exoskeletons would have higher clinical relevance in those with severe mobility impairment.

The aims of this research were to:

Evaluate the feasibility of delivering a course of therapy using a free-standing overground robotic exoskeleton in people with severe mobility impairment due to MS (i.e., EDSS≥6).

Determine any potential health related benefits of therapy using a free-standing overground robotic exoskeleton in people with severe mobility impairment due to MS.

Methods

Design

This 12-week pre-post intervention trial required participants to attend the University of Newcastle, Australia for twice weekly therapy in a free-standing lower limb robotic exoskeleton. A 12-week waitlist control phase was used to establish the level of symptom stability of each participant prior to the intervention. A 12-week follow-up determined whether any health-related benefits of the therapy were maintained upon completion of the intervention. Participants were screened for cognitive capacity to give consent, and written informed consent was obtained from all eligible participants prior to their involvement in the study. Participants continued routine activities and therapy for the duration of the study. Outcome measures were assessed upon enrolment into the study (week 0), at baseline (week 12), mid intervention (week 18), post intervention (week 24), and follow up (week 36).

Ethics approval was granted by the Hunter New England Human Research Ethics Committee and co-registered with the University of Newcastle. This study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617001316392). This manuscript was written in accordance with STROBE reporting guidelines.

Participants

As this was a pilot study, a convenience sample was recruited between November 2017 and June 2019. Data collection was completed in February 2020. Potential participants were identified by staff at the specialised Hunter New England MS clinic based on the following inclusion criteria 1) a diagnosis of MS with a score of ≥6 on the EDSS indicating severe mobility impairment with reliance on a mobility aid or other people for upright activities, 2) resident of the Hunter region, 3) over the age of 18 years, 4) discharged from inpatient rehabilitation services. Exclusion criteria were: 1) weight and height outside the range of 40-100kg and 4'8-6'4" (criteria set by the robotic manufacturer), 2) pregnancy, 3) unstable or severe cardiac or respiratory conditions, 4) recent fractures in lower limbs/pelvis/spine, 5) significant cognitive impairment (<19 on the Montreal cognitive assessment (MoCA)), 6) any medical condition which limits the ability to exercise in an upright position [30].

Equipment

The REX (Rex Bionics, Auckland, NZ) is a free-standing lower limb robotic exoskeleton, classified as a class one medical device by the Therapeutic Goods Administration of Australia. It has actuated hips, knees and ankles, and does not require the user to support themselves with a walking aid. Movement is controlled *via* a joystick on the right arm of the device, by a physiotherapist trained in its operation. The device can walk on flat surfaces at a speed of 0.5m/s, and complete a range of exercises including sit to stand, squats, lunges and side-steps [26,31].

Intervention

Participants completed two sessions of exercise therapy per week for 12 weeks, with each session consisting of up to half an hour of individualised weight bearing therapy in the exoskeleton, as tolerated by the participant, prescribed and administered by a REX accredited physiotherapist. Participants were also provided with a home exercise program relevant to their treatment, which was updated throughout the trial as required.

Outcome measures

On initial assessment, medical screening was completed to determine eligibility for the study. Standard demographic information and MS status (including EDSS) were also collected. Leg measurements were taken so that the robotic device could be individually fitted. These data were not reassessed.

The primary outcome measure of interest was motor function as measured by items 1-5 of the motor assessment scale (MAS), with a score of 30/30 indicating maximum function [32]. A battery of secondary outcome measures was used to identify other potential health related benefits of this intervention. Balance was measured using the functional reach (FR) [33]. The five times sit to stand test (FTSST) was used to measure functional lower limb strength, along with dynamometer measurements of both quadriceps and grip strength [34]. Lean body mass was measured using the Biodynamic BIA 450 bioimpedance analyser (Washington state, USA) and reported as a percentage of total body mass. Functional independence was measured using the Barthel index (BI) where 100 indicates full independence [35,36]. Spasticity of the hamstrings, quadriceps and gastrocnemius muscles was measured with the Tardieu scale [37]. Fatigue was assessed out of 42 using the fatigue assessment scale (FAS), where a score of zero indicates no fatigue [38]. Health related QoL was evaluated on the short form 8 (SF-8) which is scored out of 50, with zero indicating full QoL. Mood was assessed using the hospital anxiety and depression scale (HADS) [39,40]. Anxiety and depression are each scored out of 21, with the total out of 42. Zero indicates no anxiety or depression. This research team designed a survey with a series of 16 Likert style questions to gauge the acceptability of exercising with this device. Five domains covered safety (three questions), likeability (four questions), comfort (five questions), usability (three questions), and desire to continue using the device (one question). Each question was scored out of five, with a maximum total score of 80 indicating high acceptance of the intervention. Two open ended questions asked participants' most liked and disliked features of this intervention.

Data analysis

Descriptive statistics, including medians and interquartile ranges (IQR), were calculated for demographic data. Outcome data that were collected bilaterally (FR, strength and spasticity) were reported as the average of both sides. Friedman's test was used to evaluate differences between outcome scores across the phases of the study. All analyses were conducted on an intention to treat basis, with missing data conservatively imputed using the last observation carried forward method.

Results

Participants

Sixteen participants were referred and assessed for eligibility, with ten meeting the enrollment criteria. The primary reason for ineligibility was not meeting the sizing criteria of the device (n =4). Two participants left the study during the intervention phase, both due to a worsening of their condition unrelated to the intervention. The remaining eight participants completed all 24 intervention sessions in a median of 12.5 weeks (IQR: 12, 13). Variation in the time to complete the intervention was due to researcher and participant illness,

and device malfunction. Figure 1 for flow of participants through the study. No adverse events were observed or reported throughout the duration of the study.

The median age of participants was 53, with a median time since diagnosis of 27 years. All except one participant had secondary progressive MS, and the median EDSS score was 6.5, indicating a need for bilateral support for mobility over short distances. Table 1 for participant demographic data.

Primary outcome – function

Participants had a median baseline MAS score of 21.5 (IQR: 19.25, 24.75). Between phases differences were not significant (Table 2).

Additional physical outcomes

There were no consistent changes in FR FTSST, grip and quadriceps strength, spasticity or percentage of lean body mass throughout the study (Table 2).

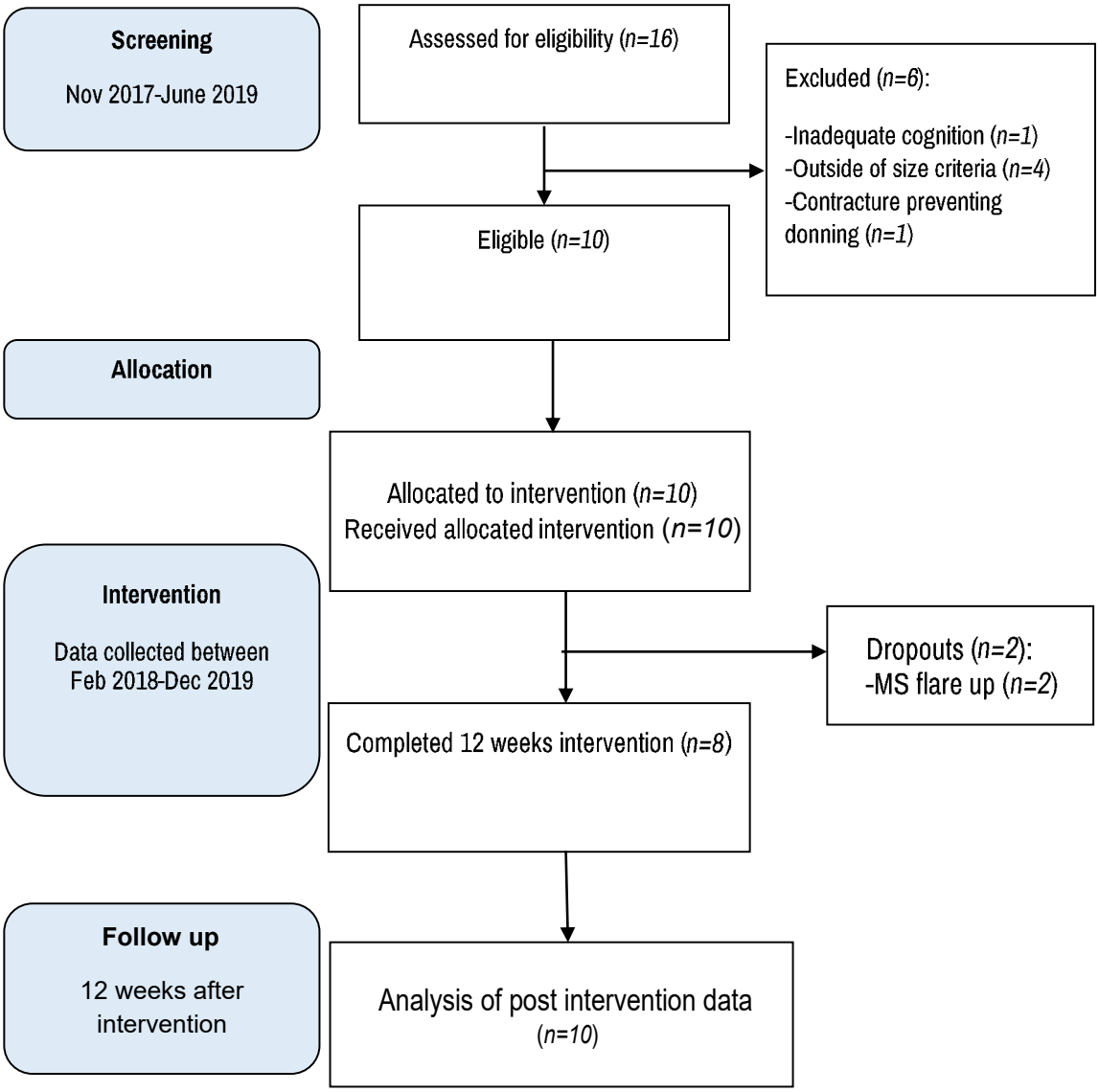

Figure 1. Flow of participants through the study.

Table 1. Participant demographic data.

Participant	Sex	Age	Time since diagnosis (years)	MS type	Level of disability (EDSS)	Mobility status	Enrolment motor assessment scale score (/30)
1	M	50	5.5	PP	6	Stick	28
2	F	52	27	SP	6.5	Frame and assist	18
3	M	42	17	SP	6.5	Frame and assist	20
4*	M	54	30	SP	6	Stick	25
5	F	72	44	SP	6.5	Frame and supervision	19
6	F	57	27	SP	6.5	Transfers only	21
7	F	40	17	SP	7	Transfers only	10
8	F	59	31	SP	6.5	Frame	22
9	M	47	16	SP	6.5	Frame	24
10*	F	69	31	SP	6.5	Frame	25
Median (IQR)		53 (47.75, 58.5)	27 (17, 30.75)		6.5 (6.5, 6.5)		21.5 (19.25, 24.75)

Legend: * - denotes dropouts, IQR – interquartile range, M – male, F – female, MS – multiple sclerosis, PP – primary progressive, SP – secondary progressive, EDSS – Kurtzke expanded disability status scale

Other health related outcomes

A statistically significant difference in health related QoL was found, with the largest change in the first six weeks of the intervention (median improvement of -3.5, IQR: -4, -1, p = 0.01). Results for fatigue, mood and independence were not statistically significant and showed no clear trends, with inconsistency between participants across time (Table 3).

Survey

Responses to the closed survey questions were favourable throughout the study, with a median total of all scores of at least 70/80 at all timepoints. The domains of comfort and usability scored the lowest. The most liked features of the device can be grouped into two categories: physical or therapeutic benefits, and emotional and experiential benefits. *"I can move and stand up without having to*

Table 2. Results for physical outcomes.

	Enrolment (0 weeks)	Pre-intervention (12 weeks)	Mid-intervention (18 weeks)	Post-intervention (24 weeks)	Follow up (36 weeks)	Analysis	
Outcome	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Q statistic**	**p value**
Motor assessment scale (n=10)	21.5 (19.25, 24.75)	18 (15.25, 26)	20.5 (17.5, 23)	20 (15.25, 24)	20 (15, 25)	1.86	0.76
Functional reach (cm) (n=10)	6.6 (0, 16)	6 (0, 21.4)	12 (0, 19.6)	12 (0, 19.6)	10.5 (0, 21.5)	5.18	0.27
*Five times sit to stand test (secs) (n=8)	22.52 (17.3, 37.8)	23.7 (15.4, 27.9)	20.1 (18, 34.2)	22.7 (16.1, 32.2)	17.5 (16.1, 30.5)	1.37	0.85
Strength: Grip (kgs) (n=10)	20.5 (18, 23)	23.5 (16, 28)	21.8 (17.5, 27)	21.5 (17, 32)	21.8 (17.5, 24)	4.86	0.30
Strength: Quadriceps (kgs) (n=10)	22.5 (14, 33)	23.5 (14, 33)	24 (13, 36)	21.8 (10, 35)	24.3 (14, 31)	0.34	0.99
Tardieu: Hamstrings (◦) (n=10)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	8.00	0.09
Tardieu: Quadriceps (◦) (n=10)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	8.92	0.06
Tardieu: Gastrocnemius (◦) (n=10)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	1.33	0.86
% of lean body mass (n=10)	70.5 (66.7, 81.6)	72.8 (69.7, 83.7)	72.5 (64.2, 83.7)	72.3 (68.2, 83.7)	71.3 (65.5, 83.6	9.13	0.058

Legend: IQR – interquartile range
*Five times sit to stand test could not be completed by two participants

Table 3. Results for additional health related outcomes.

	Enrolment (0 weeks)	Pre-intervention (12 weeks)	Mid-intervention (18 weeks)	Post-intervention (24 weeks)	Follow up (36 weeks)	Analysis	
Outcome (n=10)	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Q statistic**	**P value**
Fatigue assessment scale	25.5 (21.5, 31.25)	26 (23, 28)	22 (17.75, 26)	21 (20, 25.25)	22 (18.5, 25.75)	7.45	0.11
SF8	18.5 (17, 19)	19 (17.3, 22.3)	16.5 (14.5, 19.5)	18 (15.3, 19.8)	16.5 (15.3, 19.3)	2.5	0.01**
Hospital anxiety and depression scale	6.5 (5.3, 9.5)	7.5 (3, 9.8)	4 (4, 8)	9 (4.8, 13)	5.5 (3.3, 9)77.5	4.09	0.39
Barthel index	77.5 (70, 92.5)	75 (71.3, 85)	75 (66.3, 83.8)	75 (75, 83.8)	80 (67.5, 87.5)	5.54	0.24

Legend: IQR – interquartile range, ** - statistically significant

Table 4. Participant perceptions of the intervention.

	Pre-intervention (12 weeks)	Mid-intervention (18 weeks)	Post-intervention (24 weeks)	Follow up (36 weeks) *n=10*
n=10	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**
Perceived Safety /15	14 (13.25, 15)	15 (15, 15)	15 (15, 15)	15 (14.25, 15)
Likeability /20	18.5 (17.25, 19)	20 (18.25, 20)	20 (19, 20)	20 (19, 20)
Comfort /25	19.5 (18.25, 21)	20.5 (19.25, 23)	22.5 (21, 24.75)	22 (20.5, 24)
Usability /15	12.5 (12, 14)	14 (11.25, 15)	13.5 (12, 15)	14.5 (11.5, 15)
Continue use /5	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (4.25, 5)
Total score /80	70.5 (67, 71.75)	75.5 (63, 77.75)	75.5 (70.5, 78.25)	74 (69, 78)

Each question scored out of 5; perceived safety – 3 questions, likeability – 4 questions, comfort – 5 questions, usability – 3 questions, continue to use – 1 question

Table 5. Open ended survey questions.

n=10	"Liked"		"Disliked"
1. Physical/therapeutic benefits: a) Standing b) Therapeutic benefit	a) Stood for over 5 minutes Ability to stand (n=3) I can move and stand up without having to hold onto anything Standing rather than sitting Felt so tall Standing up straight Being vertical and able to exercise in standing b) Working muscles otherwise can't	1. Logistics: a) Transfers in and out b) Device design c) Study limitations	a) Awkward to get into it Anxiety about needing toilet and being stuck in the device Time it took to get in

	Believe it's toning muscle and increasing strength Exercise can't do otherwise Felt like a workout Felt like I'd done something Made muscles work which hadn't in years Muscle soreness from activity Exercise without having to sit down and rest Experience sensation of walking Good stretch		b) Cumbersome Slow Arms banging the device during upper limb exercises c) When the trial finished
2. Emotional and experiential benefits: a) Feeling of safety b) Feeling of freedom c) Sense of participation in a novel, enjoyable intervention	a) Felt safe Ability to move around without having to hold onto stuff Confident in standing as not worried about falling b) Freeing Freedom of standing up c) Gives me something constructive to do Participation The research Trying something new Enjoyed it	2. Therapeutic aspects:	Sometimes felt like the device is doing all the work Muscle soreness (delayed onset) like going to the gym
Comments from the post-intervention and follow up assessments combined			

hold onto anything", and experiencing "*exercises* [participant] *can't do otherwise"* were some positive comments. The least liked features related to the logistics of transferring in and out of the device, the device design, and one participant commented that they *"sometimes felt like the device was doing all the work"* (Tables 4 and 5).

Discussion

The high completion rate of the intervention, absence of adverse events, along with positive responses to the survey questions, indicate that this treatment modality is acceptable to people with severe mobility impairment because of MS. However, the lack of change for physical and health related outcomes throughout the study, cast doubt on the clinical feasibility of this intervention. Of the range of outcomes measured, only health related quality of life revealed a statistically significant between phase differences.

Our study revealed that this overground robotic therapy is acceptable to participants. A previous study evaluating the perceptions of robotic therapy in people with MS where participants reported high usability and perceived achievement of goals and improved QoL, concluded that this type of intervention can be useful for motivation and commitment to therapy [14]. Those who participated in our study had high compliance and reported positively about their experience. However, recruitment was low with only 16 participants referred over a two year period and of these only eight completed the intervention. As referral was made through a secondary provider, it is possible participants were not all identified, but as this was supplemented by strong local media interest in the study, and local therapist awareness, we can presume participant numbers would not have changed significantly with different recruitment strategies. Therefore, eligibility for this type of therapy appears to limit the clinical relevance of wide scale implementation, and our research does not support the notion that free-standing exoskeletons offer greater clinical feasibility than devices requiring upper limb support.

There was no consistent change in motor function over the course of the study. This is a unique study investigating a range of outcomes rather than just gait parameters, which other studies have focused on [19,21-23,25]. We are therefore unable to compare our findings for motor function with other studies. We chose not to evaluate gait parameters, as they were not expected to change in people already dependent on mobility aids or unable to walk. The measure of motor function used in this study has not been validated for people with MS, however the multiple sclerosis functional composite uses the 10m walk test to evaluate lower limb function, which is not appropriate with people with an EDSS of ≥6.0 [41].

Similarly, no benefits were revealed for the remaining physical outcome measures. It is possible that a higher dosage and/or intensity of intervention may have led to more positive changes. Our participants completed 30 minutes of exercise in standing, twice a week, for 12 weeks. This pragmatic dosage was chosen based on what could be realistically offered in the clinical setting. A previous study investigating the use of high intensity therapy (60 minutes, three times a week for three weeks) delivered using a mobility aid supported robotic device (Ekso) reported improved gait speed [22]. Future studies investigating dose parameters are required to ensure the full potential of these devices is explored.

This study showed an improvement in health related QoL in the first six weeks of the intervention. With low QoL commonly reported amongst those with MS, this finding merits further exploration [6]. A 2017 robotics study of six people with MS found improved QoL and mental health in almost all participants, which was maintained at three month follow up [23]. Similar results were found in a 2020 case study but with small sample sizes, these results lack external validity [24]. This study did not find a change in levels of independence, which is in contrast to a recent study using a mobility aid supported robotic device (ExoAtlet), however the change they found of 0.26 on the EDSS is unlikely to be clinically relevant as it would not represent a change in level of ability [3,19]. The results for other health related outcomes showed no trends. Future studies with increased dose parameters should still include these types of measures, in order to fully evaluate the potential impact of this intervention on the lives of people with MS.

We evaluated a range of physical and health related outcomes which is a strength of this study, as MS is a multifaceted condition with many symptoms which impact QoL [5]. This study had a control phase to determine condition stability, as it can be difficult to evaluate rehabilitation outcomes for people with MS due to the condition's fluctuating and degenerative nature. However, with changes found during the control phase in most outcomes, and wide IQRs, our participants did not have symptom stability. This makes interpretation of the results difficult, which is further compounded by a small sample size, both of which are considerations for future research with the MS population.

Conclusion

This study has shown that therapy with a free-standing overground robotic exoskeleton can improve health related QoL and is highly acceptable to participants, results which provide some support for therapy with a free-standing robotic exoskeleton. However, clinical feasibility may be limited by a small proportion of people with MS being eligible for participation. Few studies evaluate options for physical activity in those with severe mobility impairment as a result of MS, and as the disease progresses, these options are warranted to mitigate the secondary complications of inactivity and immobility. Further research with a powered sample is indicated to further explore the potential benefits of this type of intervention.

Acknowledgement

This research team would like to acknowledge and thank the Australian Institute of Neuro-rehabilitation, for loaning the REX for the duration of the study.

Data Availability

Data can be accessed by contacting the corresponding author.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of Interest

The Authors declare that there is no conflict of interest.

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How to cite this article: Postol, Nicola, Jessica Grissell, Caitlyn McHugh and Andrew Bivard, et al. "Therapy with a Free-Standing Robotic Exoskeleton in People with Advanced Multiple Sclerosis: A Feasibility Study." *Int J Neurorehabilitation Eng* 10 (2023): 507.