Combining Physical Therapy with Dalfampridine in Patients with Multiple Sclerosis and Walking Limitations

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Background

- Walking limitations are a frequent consequence of MS, and have an impact on daily activities, employment, and quality of life[1]
- Dalfampridine extended release tablets (prolonged-release fampridine in Europe; sustained or modified release fampridine elsewhere), 10 mg twice daily, are available to improve walking in people with MS, based on an improvement in walking speed on the Timed 25 Foot Walk (T25FW) in two phase 3 clinical trials[2]
- Exercise and physical therapy (PT) were shown to improve gait and ambulation in MS[3,4]
- The main objective of this study was to measure the additive effect of PT and dalfampridine in individuals with MS and impaired ambulation, compared to adding a home exercise program (HEP) to dalfampridine

Specific Aims

Primary Aim 1: To evaluate the effect of adding PT to dalfampridine on *gait pattern*, compared to adding a HEP to dalfampridine.
Primary Aim 2: To evaluate the effect of adding PT to dalfampridine on walking endurance, compared to adding a HEP to dalfampridine.
Secondary Aim 1: To evaluate the effect of adding PT to dalfampridine on walking speed, compared to adding a HEP to dalfampridine.
Secondary Aim 2: To evaluate the effect of adding PT to dalfampridine on subject-reported walking performance, compared adding a HEP to dalfampridine.
Secondary Aim 3: To evaluate the safety of a combination of PT and dalfampridine, compared to dalfampridine alone.
Secondary Aim 4: To evaluate the carryover effect of PT up to 4 weeks after subjects are switched to a HEP.

Methods

Design: single blind randomized controlled 2-arm cross-over study ***(Figure 1)***.
Main Inclusion/Exclusion Criteria:
- Diagnosis of MS
- Age 18 to 70 years
- Score of 2 or greater on the Ambulation Index scale
- Able to safely complete all study procedures, particularly the 2-minute walk, and treatments (physical therapy and home exercise program)
- On dalfampridine for at least 2 weeks at screening visit

Interventions:
- PT: two 1-hour sessions per week over 4 weeks. Each session included stretching, strengthening, gait training, and balance training.
- HEP: daily stretching exercises (hip adductors, hamstrings, gluteus, gastrocnemius/soleus)

Statistical Analysis:
- A repeated measures ANOVA was used to test the hypotheses.

Outcome Measures

Blinded Evaluations:
- walking endurance (2-minute walk; 2MW)
- walking speed (T25FW)

Unblinded Evaluations:
- Spatiotemporal gait parameters (stride length, step width, double support time, Functional Ambulation Profile (FAP) score)
- MS Walking Scale 12 (MSWS-12)

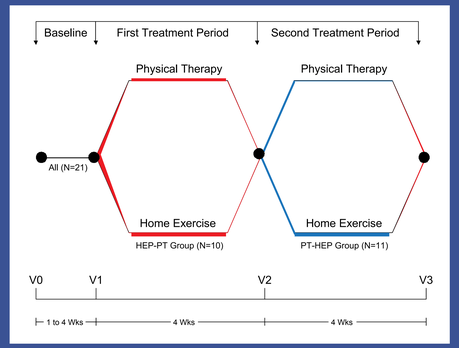
Safety Assessments:
- Numeric Pain Rating Scale (NPRS)
- Falls reported (recall at screening, diary for other visits)

Exploratory Variables:
- Strength on manual muscle testing (MMT)

Spasticity (Modified Ashworth Scale; MAS).

Descriptive Variable:
- Patient Determined Disease Steps (PDDS)

Figure 1 – Study Design



Results

Enrollment: 21 subjects were enrolled and randomized, and all subjects completed all study visits. The goal was to obtain complete data on at least 20 subjects.

Baseline: there were no statistically significant between-group differences ***(Table 1)***.

Results *(continued)*

Efficacy: a mixed effects model analysis showed a significant visit effect favoring PT for the following variables:
- Spatiotemporal gait parameters ***(Figure 2)***
  - **stride length** between the first and second visit for the PT-HEP group and between the first and third visits for the HEP-PT group.
  - **step width** between the first and second visit for the PT-HEP group.
  - **double support time** between the first and second visit for the PT-HEP group.
- Walking endurance (2-minute walk test) ***(Figure 3)*** between the first and second visit for the PT-HEP group, and between the second and third visits for the HEP-PT group.
- Muscle strength (MMT) between the first and second visit for the PT-HEP group

There was a trend for improvement of (decrease in) T25FW speed between visits 1 and 2 for the PT-HEP group (p=0.057), and between visits 2 and 3 for the HEP-PT group (P=0.076). ***(Figure 4)***

Subject-reported walking performance: significant differences in MSWS-12 scores in the HEP-PT group between the first and second visit, and between the first and the third visit.

Carryover: There was a significant improvement in 2-minute walk, stride length, and double support time between visits 1 and 3 in the PT-HEP group, suggesting a carryover effect of PT up to 4 weeks after the intervention was discontinued.

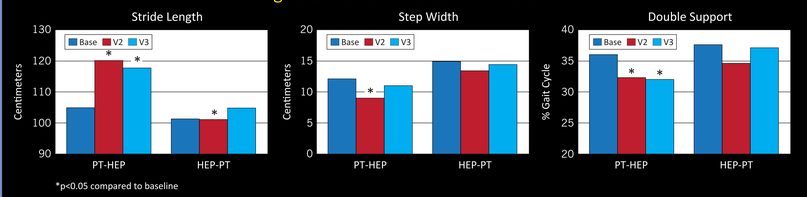
Safety:
- No significant difference in pain score between groups or within group over time.
- No significant between-group difference in thenumber of falls without injury reported
- Three subjects reported 4 other adverse events (UTI and fall with injury during HEP, increased difficulty walking and new intermittent low back pain during PT)

Table 1 - Patient Characteristics at Baseline

Parameters	All randomized (n=21)	HEP-PT Group (n=10)	PT-HEP Group (n=11)	P value
Age (years)	53.3 (7.4)	54.5 (9.5)	52.3 (5.1)	0.52*
Sex (%F)	71%	90%	55%	0.07**
Disease duration (years)	19.6 (6.1)	20.1 (5.4)	19.1 (7.0)	0.73*
Current disease course (RR / SP / PP)	43% / 48% / 9%	50% / 40% / 10%	36% / 55% / 9%	0.79**
Number of comorbidities	0.8 (1.2)	0.8 (1.2)	0.9 (1.2)	0.84*
BMI	25.8 (5.7)	27.2 (7.3)	24.6 (3.5)	0.32*
Disease-modifying therapy (% yes)	71%	80%	64%	0.41**
Number of concomitant medications	8 (4)	8 (4)	8 (4)	0.83*
Assistive device used (none / unilateral / bilateral)	14% / 43% / 43%	10% / 30% / 60%	18% / 55% / 27%	0.32**
AFO	48% yes	50% yes	55% yes	0.38**
Fall frequency (none / <1/month, ≤1 /month, ≤1/week)	33% / 33% / 14% / 20%	50% / 20% / 20% / 10%	18% / 45% / 9% / 28%	0.14**
Current exercise regimen (none / stretching only / other)	25% / 35% / 40%	33% / 33% / 34%	18% / 36% / 46%	0.72**
LE strength (MMT)	3.9 (0.7)	3.9 (0.7)	3.9 (0.7)	0.87*
LE spasticity (MAS)	0.8 (0.4)	0.8 (0.4)	0.7 (0.5)	0.43*
T25FW time	10.9 (6.9)	11.6 (7.4)	10.1 (6.7)	0.64*
2MW distance	97.2 (42.8)	90.6 (51.3)	103.2 (34.9)	0.53*
Stride length	103.2 (27.2)	101.3 (34.7)	104.9 (19.9)	0.78*
Step width	13.4 (5.0)	14.9 (5.7)	12.1 (3.9)	0.2*
Double support (% GC)	36.8 (11.3)	37.6 (12.5)	36.0 (10.6)	0.76*
FAP score	55.3 (12.2)	55.0 (10.9)	55.7 (13.8)	0.9*

* t-test ** Chi-square test

Figure 2 – Evolution of Gait Parameters



*p<0.05 compared to baseline

Figure 3 – Evolution of Walking Endurance on the 2-minute Walk Test

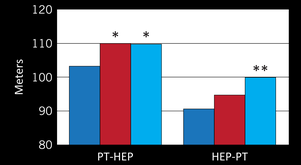
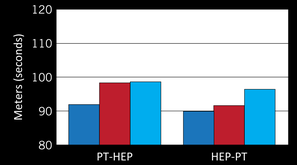


Figure 4 – Evolution of Walking Speed on the Timed 25 Foot Walk Test



*p<0.05 compared to baseline; **p<0.05 compared to V2

Conclusions

- Results from this study suggest that PT, compared to a home stretching program, has a greater effect in improving walking endurance and gait pattern in ambulatory patients with MS treated when associated to dalfampridine. The improvement noted on manual muscle testing suggests that the effect on ambulation was at least in part mediated by an improvement in lower extremity strength
- Subjects who started with stretching followed by PT reported a gradual improvement in perceived difficulty walking due to MS.
- There were no significant safety concerns with PT or HEP. The occurrence of falls throughout the study is a reminder that this population is at risk for falling, and for injury from falling.
- This data will be used to design larger studies of combined interventions with physical therapy and dalfampridine.

References

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Acknowledgements

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