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MELODIC INTONATION THERAPY IN POSTSTROKE NONFLUENT APHASIA: A RANDOMISED PILOT TRIAL

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MELODIC INTONATION THERAPY IMPROVES COMMUNICATION IN POSTSTROKE NONFLUENT APHASIA: A RANDOMISED PILOT TRIAL

ABSTRACT

Objective: To collect data to estimate the sample size of a definitive randomised clinical trial to evaluate the effects of Melodic Intonation Therapy in poststroke nonfluent aphasia.

Design: A randomised, crossover, interventional pilot trial.

Setting: Departments of Neurology and Rehabilitation from a university general hospital.

Participants: Stroke survivors with poststroke nonfluent aphasia.

Interventions: Patients randomised to group 1 had treatment with Melodic Intonation Therapy first (12 sessions over 6 weeks) followed by no treatment; the patients in group 2 started active treatment between 3 and 6 months after their inclusion in the study, serving as waiting list controls for the first phase.

Main measures: The Communicative Activity Log (CAL) questionnaire and the Boston Diagnostic Aphasia Examination (BDAE) were evaluated at baseline, and at 6 and 12 weeks.

Results: Twenty patients were included. Four of the patients allocated to group 2 crossed over to group 1, receiving the treatment at first. Intention-to-treat analysis: after adjustment for baseline scores, the mean difference in the CAL evaluation from baseline in the treated group was 8.5 points (95% CI, 0.11–17.0; *P*=.043), with no significant change in any of the BDAE sections. Per protocol analysis showed similar results with a clear treatment effect (*P*=.043) on the CAL.

Conclusions: Melodic Intonation Therapy might have a positive effect on the communication skills of stroke survivors with nonfluent aphasia as measured by the CAL questionnaire. A full-scale trial with at least 27 patients per group is necessary to confirm these results.

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INTRODUCTION

According to a Cochrane meta-analysis, speech and language therapy for people with poststroke aphasia is beneficial in terms of improved functional communication, reading, writing and expressive language, compared with no therapy [1]. However, the supporting evidence is weak; two main challenges being the wide heterogeneity in the speech and language therapies used in clinical trials and the small sample size of the majority of them, thus preventing the recommendation of a specific therapy. In fact, at least 20 different therapeutic approaches were reported within the 74 randomised clinical trials included in the Cochrane meta-analysis, and the median sample size was 30 patients [1].

Melodic Intonation Therapy [2] is a language therapy proposed to improve aphasia after stroke; although evidence for its efficacy from randomised clinical trials is still scarce [1]. Melodic Intonation Therapy has been proposed for selected patients, particularly those with significant defects in language production, poor verbal agility, relatively preserved repetition and poor understanding (i.e., essentially patients with nonfluent aphasia) [2,3]. It is based on the use of musical elements of speech (rhythm and melody) to improve language production by engaging language-capable regions in the undamaged right hemisphere of the brain [4]. Patients with aphasia are trained to keep the beat of oral statements that are initially sung by the therapist; the patient then attempts to reproduce these statements whilst keeping the intonation and the beat. As the therapy progresses, the therapist eliminates the stimulation and the patient must produce the item independently and with their usual prosody.

It has been hypothesised that Melodic Intonation Therapy can promote both functional and structural brain plasticity, and the proposed mechanisms for its therapeutic effect are the activation of language-capable regions of the right cerebral hemisphere and the promotion of left perilesional activation. Some neuroimaging studies support both hypotheses [5–7].

To improve the generalised use of this speech therapy, adaptations to other languages, such as French, Italian and Portuguese (Brazil), have already been successfully completed [8–10]. We recently reported the development of a Spanish adaptation of Melodic Intonation Therapy that includes commonly used phrases in the patient's environment, and we explored its feasibility for use in a nonrandomised small study including four patients with nonfluent poststroke aphasia [11]. It is necessary, however, to perform a larger prospective study to demonstrate the benefits of this therapy in improving aphasia outcome. Due to the paucity of data on the effectiveness of this therapy, it appears necessary to conduct a pilot trial to collect data to estimate the sample size of a definitive randomised clinical trial [12].

METHODS

Design: This was a randomised pilot study developed by the Departments of Neurology and Rehabilitation (Speech Therapy Unit) of a stroke centre at a university general hospital, with the aim of collecting data to estimate the sample size of a definitive randomised clinical trial. The study was conducted according to the recommendations of the Helsinki Declaration and Good Clinical Practice guidelines and was approved by the La Paz University Hospital Ethics Committee for Clinical Research (Code HULP-PI 894). It has been registered at the Clinical Trials Government website with the trial number NCT3433495.

Our first step, already published, was to develop a Spanish adaptation of Melodic Intonation Therapy that included commonly used phrases in the patient's environment and to explore the feasibility of the Spanish adaptation of this language therapy in a nonrandomised trial including four patients with nonfluent poststroke aphasia [11]. We then developed a randomised, crossover, interventional pilot trial in a different set of patients. Recruitment started in September, 2012 and ended in February, 2016.

Patients: The patients were recruited from the outpatient clinic at the Department of Neurology and Stroke Centre of La Paz University Hospital as well as the Speech Therapy Unit from the Department of Rehabilitation. We included patients diagnosed with nonfluent aphasia due to unilateral stroke in the left hemisphere, without neuroimaging evidence of lesions in the right hemisphere, who fulfilled the following criteria:

- The time elapsed since the stroke exceeded 6 months.
- The patient had received a standard program of conventional speech therapy after stroke.
- The patient had persistent nonfluent aphasia with the following characteristics [3]:
    - Severely restricted language, which might be limited to meaningless stereotypy; unlike that observed in verbal tasks, the patient might produce some real and relevant words when singing familiar songs.
    - Poor repetition, even for single words.
    - Moderately preserved language comprehension.
    - The nonstereotyped language was produced with a slurring of speech.

- The total score for the repetition did not exceed the 70th percentile in the Boston Diagnostic Aphasia Examination [13]. The score was obtained from the average score in two areas: repetition of words and phrases.
- Listening comprehension must exceed the 15th percentile of the Boston Diagnostic Aphasia Examination, from the average score obtained in another three areas: word comprehension, commands and complex ideational material.

- Signed informed consent was provided.

We excluded patients with a history of previous stroke other than the index event or with any clinical condition (e.g., short life expectancy, coexisting disease) or other characteristics that precluded appropriate follow-up in the study; those who were participating in any therapeutic interventional clinical trials evaluating poststroke recovery; and those using psychotropic drugs that interfere with patient evaluation.

Sample size: Given this was a pilot study, a formal sample size calculation was not required. However, by using the free online sample size and power calculator GRANMO tool (version 7.12, April 2012) developed by the Municipal Institute for Medical Research (Barcelona, Spain) [14,15], and the data obtained on the four patients evaluated in the prior nonrandomised feasibility study, we estimated a sample size of 20 patients, accepting an alpha risk of 0.05 and a beta risk of 0.2. The minimum difference to be detected was 0.1 and the standard deviation was 0.15.

Study groups: Upon signature of informed consent, the included patients were randomly allocated to one of the following groups according to the period in which they received the Melodic Intonation Therapy (Figure 1):

a) Group 1: For whom Melodic Intonation Therapy was planned to start within the first 3 months of their inclusion in the study, with a subsequent period of 3 months without therapy (washout period).

b) Group 2: Melodic Intonation Therapy was delayed to start between 3 and 6 months after their inclusion in the study, without receiving speech therapy treatment in the first 3 months, thus serving as controls for the first phase of the study (waitlist controls) and as the active intervention group in the second phase.

A computer-generated random list of numbers provided by an independent statistician was used for study allocation. Allocation was simple, with a 1:1 ratio. The patients were consecutively allocated to the next available number on the randomization list, as long as they were included in the trial.

Intervention

The duration of therapy was 12 sessions performed over a 6-week period. Each session lasted 30 minutes. They were performed individually by a speech-experienced therapist previously trained in Melodic Intonation Therapy. We used the Melodic Intonation Therapy protocol adapted to Spanish [11]; in brief, three levels with 20 items in each level were established. Within each level, the items were ordered such that intonation intervals alternated and the difficulty level was progressive. All the items were reinforced with images and hand tapping.

Assessment of treatment outcomes

A neuropsychologist blinded to the group to which the patient was allocated evaluated the Boston Diagnostic Aphasia Examination [13] three times for each patient: at baseline, and at 6 and 12 weeks, as shown in Figure 1. The Boston Diagnostic Aphasia

Examination was chosen to evaluate the effects of Melodic Intonation Therapy following the instructions in the Melodic Intonation Therapy manual [3]. In addition, the Communicative Activity Log questionnaire [16] was completed by the caregiver. This measurement was chosen to obtain information about the amount and quality of communication in the real-world setting and has been used in other randomised clinical trials evaluating speech therapies [17,18].

Statistical analysis

The analyses were performed using SAS 9.3 (SAS Institute, Cary, NC, USA). Data were expressed as median and interquartile range or mean and standard deviation for the continuous variables, or as absolute and relative frequencies for the categorical variables. To evaluate the benefit of Melodic Intonation Therapy on the Communicative Activity Log and Boston Diagnostic Aphasia Examination questionnaires, we used mixed effects linear regression models. A mixed effects linear regression model is a statistical model particularly useful for longitudinal studies in which repeated measurements are analysed. Because of their advantage in dealing with missing values, mixed effects models are usually preferred over other approaches, such as the repeated measures ANOVA, allowing for an adjustment of the treatment effects by the baseline values and the period effect in crossover trials.

Given this study has a crossover design with two treatment sequences (treatment-washout/waitlist-treatment) and two phases (phase 1 and phase 2) with a baseline evaluation of all the patients, we considered treatment and phase as principal fixed effects, the treatment*phase as interaction effect and the patient nested in the treatment sequence as random effect. The baseline evaluation was analysed as a covariant in the models. For pair-wise *post hoc* comparisons, we used the Bonferroni test. Finally, for

the calculation of the sample size needed for a definitive trial we used N Query advisor software (Statistical Solutions Ltd, Cork, Ireland).

RESULTS

A total of 36 patients were screened and evaluated by a specialist in neuropsychology, who administered the Boston Diagnostic Aphasia Examination. Twenty patients met the study criteria. All were right-handed, with ages ranging between 38 and 81 years. All were native Spanish speaking, and two also spoke another language (French). All the patients had had an ischaemic stroke in the territory of the left middle cerebral artery with persisting moderate-to-severe nonfluent aphasia or global aphasia.

Figure 1 shows the study flow diagram according to the Consolidated Standards of Reporting of Trials guidelines [11,14]. Four of the 10 patients allocated to group 2 crossed over to group 1, thus receiving the treatment at first, due to the inability of some patients to attend the treatment on the dates of the assigned group. For this reason, we are providing the results of the intention-to-treat (comparison of the treatment groups that includes all patients as originally allocated after randomization), as well as the per-protocol analysis (in which the four patients who crossed over to the first Melodic Intonation Therapy treatment and completed the treatment without any other deviation from protocol were analysed in the early treatment group) (Table 2). One patient allocated to group 1 dropped out of the study early due to a severe concomitant disease.

Intention-to-treat analysis

No differences were found in baseline characteristics between study groups (Table 1), nor in baseline scores in the neuropsychological evaluations (Table 2). Mixed effects linear models showed no significant treatment effects in the evaluation of either the

Boston Diagnostic Aphasia Examination-comprehension test (*P*=.925) or the Boston Diagnostic Aphasia Examination-repetition test (*P*=.727). Finally, the mixed effects linear regression models for Communicative Activity Log evaluation showed a clear treatment effect (*P*=.019) and period effects (*P*=.019) as well as a positive correlation with baseline values (coefficient=0.2; *P*=.006). After adjustment for baseline scores, the mean difference in the Communicative Activity Log evaluation from baseline in the treated group was 8.5 points (95% CI, 0.11–17.00; *P*=.048).

Per protocol analysis

No differences were found in baseline characteristics between study groups (Table 1), nor in baseline scores in the neuropsychological evaluations (Table 2). At the end of phase 1, however, group 1 (which received early Melodic Intonation Therapy) showed significantly higher values in the Communicative Activity Log, with no significant change in any of the Boston Diagnostic Aphasia Examination sections. At the end of phase 2, the values of the Communicative Activity Log test in group 2 also increased after Melodic Intonation Therapy, reaching values similar to those of group 1, which had been treated early. Fixed-effects linear models showed no significant treatment effect in the evaluation of the Boston Diagnostic Aphasia Examination-comprehension test (*P*=.460) nor in the Boston Diagnostic Aphasia Examination-repetition test (*P*=.995). Similarly to the intention-to-treat analysis, the fixed effect linear regression models for the Communicative Activity Log evaluation showed a clear treatment effect with a similar magnitude to that of the intention-to-treat analysis (mean difference 7.2 points (95% CI, 0.34–17.55; *P*=.043).

Sample size calculation for a definitive trial

Using the data on the standard deviation of the main change in the Communicative Activity Log evaluation after Melodic Intonation Therapy, for a definitive randomised, double-blind, parallel clinical trial we would need a sample size of 27 patients in each arm for an 80% power and a 0.050 two-sided significance level.

DISCUSSION

This small, randomised, clinical pilot trial suggests that Melodic Intonation Therapy could have a positive effect on the communication skills of stroke survivors with nonfluent aphasia as measured by the Communicative Activity Log questionnaire [16]. This effect appears early after therapy administration and remains at 3 months after the end of treatment. Few clinical trials have evaluated the efficacy of Melodic Intonation Therapy on poststroke aphasia. Conklyn et al. developed a pilot study in patients who had acute stroke, showing the feasibility of this therapy for in-hospital patients, as well as the significant improvements in responsiveness scores compared with controls [20]. Van der Meulen et al. conducted two randomised clinical trials evaluating the effect of Melodic Intonation Therapy: within the first 2–3 months after stroke [21] and after 1 year [22]. Within the first 2–3 months after stroke, Melodic Intonation Therapy improved repetition of trained and untrained tasks [21]. However, in patients with severe aphasia more than 1 year poststroke, despite Melodic Intonation Therapy having been associated with a significantly improved repetition of trained tasks, the effect did not remain stable at the follow-up assessment [22].

There is some heterogeneity in the outcome evaluations used in the various clinical trials published to date assessing the efficacy of Melodic Intonation Therapy in poststroke aphasia. Some have evaluated modified responsive and repetition subsections of the Western Aphasia Battery [20], whereas others [16,17] used the Sabadel story

retelling task, measuring information content in connected speech [23]; the Amsterdam Nijmegen Everyday Language Test, measuring verbal communication in daily life [24]; the Aachen Aphasia Test [25], with the repetition and naming subtests; and the Melodic Intonation Therapy repetition task [3]. The positive effects of Melodic Intonation Therapy have been shown in all except for the Sabadel task. Our study shows that Melodic Intonation Therapy is also useful for improving communication as measured by the Communicative Activity Log questionnaire [16]. This test has been shown to be useful for evaluating the effects of other speech therapies, such as constraint-induced aphasia therapy in clinical trials [16–18].

Our study has several limitations. First, the sample size was small and therefore underpowered to obtain firm conclusions. The study was designed as a pilot trial aimed to obtain data that could allow us to estimate the needed sample size for a further definitive randomised clinical trial focused on efficacy. Nevertheless, the total number of included patients is within the frame of prior randomised clinical trials published to date evaluating the efficacy of Melodic Intonation Therapy, ranging between 17 and 30 patients [20–22]. Although we achieved the precalculated sample size, one patient dropped out early due to the development of a severe concomitant disease and three other patients did not attend the final visit, resulting in a 20% dropout rate. An additional limitation was that four patients allocated to group 2 crossed over to group 1 due to the inability to attend the treatment on the dates corresponding to the assigned group. To prevent this from affecting the results, we provide the results of the ITT and the per-protocol analysis. In both analyses, the positive effect of Melodic Intonation Therapy on communication skills was suggested.

Another important problem was the long time required for the recruitment of patients, mainly due to the low prevalence of chronic severe nonfluent poststroke aphasia and to

the requirement of our study that patients should have completed the available standard speech therapy to avoid the ethical conflict of offering an investigational therapy with unknown efficacy, excluding them from the conventional speech therapy. Therefore our study was restricted to the inclusion of chronic aphasias resistant to standard speech therapy, therefore limiting the generalisation of our results. However, to progress to a definitive clinical trial, it would be feasible to modify that inclusion criterion allowing recruiting patients at earlier post-stroke stages, given Melodic Intonation Therapy has been shown to be feasible and beneficial in earlier stages, such as at acute stroke hospitalization [20], as well as within the first 2–3 months after stroke [21]. This modification would likely result in an easier recruitment of the needed sample size of 27 patients per group based on our calculations, as well in lower dropout rates.

Our main strength is the design as a crossover, randomised clinical trial, thus allowing more patients to be treated, and the ability to evaluate not only the early effect of Melodic Intonation Therapy, but also to assess the stability of the improvement in communication skills obtained by Melodic Intonation Therapy at 12 weeks after the baseline evaluation. In addition, we adjusted the models to evaluate the possible interaction with the period of treatment. Although all the included patients showed a clear improvement from baseline to the follow-up evaluations, our results suggest a treatment effect of Melodic Intonation Therapy on communication skills. With these results, we were able to calculate the sample size for a definitive randomised double-blind, parallel clinical trial to confirm the efficacy of this therapy in poststroke nonfluent aphasia.

In conclusion, this small, randomised pilot trial suggests that Melodic Intonation Therapy could have a positive effect on the communication skills of stroke survivors

with nonfluent aphasia as measured by the CAL questionnaire. A full-scale trial with at least 27 patients per group is necessary to confirm these results.

Clinical messages:

- This small, randomised pilot clinical trial suggests that Melodic Intonation Therapy could have a positive effect on the communication skills of stroke survivors with nonfluent aphasia as measured by the Communicative Activity Log questionnaire. A full-scale trial with at least 27 patients per group is necessary to confirm these results.

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Genny Lubrini: Acquisition of data.

Rosario Madero-Jarabo: Study concept, analysis and interpretation, critical revision of manuscript.

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Blanca Fuentes: Study concept, analysis and interpretation, preparation of manuscript.

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Figure Legend

Figure 1. Flow diagram.

Table 1. Baseline characteristics. Per-protocol population.

	*Intention-to-treat population**			*Per-protocol population***		
	Group 1 *N=10*	***Group 2*** *N=10*	*P-value*	**Group 1** N=14	**Group 2** N=6	*P-value*
Demographic characteristics and time from stroke						
Age, mean (SD)	66.9 (14.7)	61.1 (14.1)	.364	65.2 (15.1)	61.7 (13.3)	.659
Male sex, N (%)	6 (60)	6 (60)	.675	10 (71.4)	2 (33.3)	.137
Educational level, N (%)			.392			.627
No education	2 (20)	1 (10)		3 (21.4)	0 (0)	
Primary school	7 (70)	5 (50)		8 (57.1)	4 (66.7)	
High school	1 (10)	2 (20)		2 (14.3)	1 (16.7)	
University	0 (0)	2 (20)		1 (7.1)	1 (16.7)	
Bilingual, N (%)	0 (0)	2 (20)	.237	2 (14.3)	0 (0)	.479
Time from stroke onset (months), median (IQR)	21.8 (17.5)	27.7 (18)	.462	16 (9, 36.5)	20.5 (14.7, 37)	.966
Prior standard speech therapy						
Time from prior standard speech therapy (months), median (IQR)	0 (0, 0)	1.5 (0, 7.7)	.085	0 (0, 0)	5 (0, 11.5)	.800
Duration (weeks), mean (SD)	49.7 (37.1)	87.2 (80.6)	.480	72.6 (68.3)	57.8 (55.8)	.633

IQR: interquartile range; SD: standard deviation. *Intention-to treat population: all the patients are included in the group as originally allocated after randomisation regardless of whether they crossed over to the other group. ** Per-protocol population: includes the four patients who crossed over in the early treatment group (group 1).

Table 2. Outcome evaluations.

	Boston Diagnostic Aphasia Examination - Comprehension, mean (SD)			**Boston Diagnostic Aphasia Examination – Repetition, mean (SD)**			**Communicative Activity Log**		
	Baseline	End of Phase 1 (6 weeks after baseline)	End of Phase 2 (12 weeks after baseline)	Baseline	End of Phase 1 (6 weeks after baseline)	End of Phase 2 (12 weeks after baseline)	Baseline	End of Phase 1 (6 weeks after baseline)	End of Phase 2 (12 weeks after baseline)
Intention-to-treat analysis*									
Group 1 (Sequence: treatment/washout) (N=10)	39.6 (20.7)	41.4 (23.9)	51.6 (31.5)	35 (25.4)	45.5 (35.4)	48.9 (26.6)	122 (30.1)	141 (20.4)	142 (23.2)
Group 2 (Sequence: waiting list/treatment) (N=10)	36.1 (32.1)	36.1 (19.2)	39.4 (26.9)	47.1 (28.5)	53.9 (27)	62.8 (28.2)	112.2 (20)	117 (23.3)	123.6 (14)
P-value‡	.391	.925		.326	.727		.736	**.048**	
Per-protocol analysis **									
Group 1 (Sequence: treatment/washout) (N=14)	33.6 (20.6)	38.1 (21.6)	43.8 (31.5)	37.7 (26.2)	50.4 (32.5)	57.7 (29.5)	122.1 (28.5)	141.5 (19.3)	142 (23.2)
Group 2 (Sequence: waiting list/treatment) (N=6)	46.9 (37.2)	40 (22.3)	48.6 (26.4)	49.1 (29.6)	48.3 (30.2)	52.5 (25.7)	106 (12.3)	111.2 (20.7)	123.7 (16.2)
P-value‡	.861	.460		.429	.995		.460	**.043**	

SD: standard deviation. *Intention-to treat analysis: all the patients are included in the group as originally allocated after randomisation regardless of whether they crossed over to the other group. ** Per-protocol population: the four patients who crossed over to the early treatment group are analysed as belonging to Group 1. ‡ P-value in cells of end of phase 1 and 2 corresponds to the treatment effect adjusted by the baseline values and the treatment period.

Figure 1. Flow diagram.