The Efficacy of Early Cognitive-Linguistic Treatment and Communicative Treatment in Aphasia after Stroke - A Randomized Controlled Trial (RATS-2)

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TITLE PAGE

Title

The Efficacy of Early Cognitive-Linguistic Treatment and Communicative Treatment in Aphasia after Stroke – A Randomized Controlled Trial (RATS-2)

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ABSTRACT

Background: The two main approaches in aphasia treatment are cognitive-linguistic treatment (CLT), aimed at restoring the linguistic levels affected, semantics, phonology or syntax, and communicative treatment, aimed at optimizing information transfer by training compensatory strategies and use of residual language skills. We tested the hypothesis that CLT is more effective than communicative treatment in the early stages after stroke.

Methods: In this multi-center, randomized, parallel group trial with blinded outcome assessment, 80 patients with aphasia after stroke were included within three weeks post-stroke. Patients received six months of CLT, comprising semantic and/or phonological training, or communicative treatment for at least two hours per week. They were assessed before treatment and at three and six months with the Amsterdam-Nijmegen Everyday Language Test (ANELT-A, primary outcome) and semantic and phonological tests (secondary outcomes). The intervention effect was evaluated by means of analysis of covariance, with adjustment for baseline scores.

Results: There was no difference between the mean ANELT-A score of the CLT group (n=38) and the communicative treatment group (n=42), neither at three (adjusted difference: 1.5, 95% confidence interval: -2.6 to 5.6) nor at six months post-stroke (adjusted difference: 1.6, 95% confidence interval: -2.3 to 5.6). On two of six specific semantic and phonological tests the mean scores differed significantly, both in favor of CLT.

Conclusion: This study does not confirm our hypothesis that patients with aphasia after stroke benefit more from CLT, aimed at activation of the underlying semantic and phonologic processes, than from general, nonspecific communicative treatment (ISRCTN67723958 Current Controlled Trials).

INTRODUCTION

Aphasia is present in about 30% of all acute stroke patients and affects their daily communication and social participation. There are two main approaches in aphasia treatment: cognitive-linguistic treatment (CLT) and communicative treatment. The ultimate goal of both approaches is to improve patients' everyday communication. They differ fundamentally in how they achieve this: CLT focuses on the impairment and aims at improving the underlying linguistic processing at the linguistic levels affected, e.g. semantics (word meaning)[1], phonology (word sound)[2] or syntax (understanding and building sentences).[3] Communicative treatment focuses on the disability: patients are trained to use their residual language skills combined with compensatory strategies in order to optimize information transfer.[4]

It is unclear which of both approaches is best for which patients in which period of recovery. In the extensive literature about the efficacy of aphasia treatment there is more evidence for the efficacy of CLT - recommended as Practice Standard in 2005[5] - than of communicative treatment, which has been evaluated less frequently. However, a meta-analysis and recent reviews on cognitive rehabilitation have emphasized the need for well-designed trials on aphasia treatment in general and on specific treatments[5-8] with a sufficient sample size, a functional outcome measure and well-defined methods of intervention.[8] In the last three decades 11 randomized controlled trials (RCTs) were conducted on a specific treatment method for aphasic stroke patients delivered by a speech-language therapist (SLT). To date, no RCTs have been conducted in which the benefits of both approaches, in the form of individual treatment, are compared.

A factor that may influence the efficacy of treatment is timing. Meta-analyses of uncontrolled studies and RCTs suggested that the largest improvements after language treatment occur within one year post-injury[6, 9] and mainly when treatment was started within the first three months.[6] In these analyses the type of treatment was not controlled. It is very well possible that CLT and communicative treatment differentially interact with time post-onset.

Code[10] poses that treatment aimed at restoration of impaired cognitive processes is probably more appropriate in acute stages when natural recovery occurs. Addressing specific neural networks, involved in semantics and phonology, by specific treatment activities (CLT) might facilitate or speed up neural recovery processes. Hence, starting early may be crucial for the efficacy of CLT, but less important for communicative treatment. This view is reflected in the current preference in many centers to give CLT in the acute stage followed by communicative treatment when a plateau in improvement has been reached.

In our previous RCT, RATS-1[11], semantic treatment (BOX)[12] was compared with phonological treatment (FIKS)[13], applied 4-12 months post-stroke. The two treatments appeared to be equally effective in improving verbal communication (Amsterdam-Nijmegen Everyday Language Test, ANELT-A).[14] In the current study, RATS-2, we therefore combined BOX and FIKS and compared this CLT with communicative treatment to evaluate their efficacy in an earlier stage of aphasia.

Our objective was to measure the efficacy of CLT, applied in the first six months starting within three weeks post-stroke, on everyday verbal communication and on semantic and phonological processing. We hypothesized that CLT would be more effective than communicative treatment and that its effect would be the largest in the first three months.

METHODS

Participants

All patients with aphasia after intracerebral hemorrhage or ischemic stroke of less than three weeks duration were screened for eligibility by the local speech-language therapist (SLT) of 15 hospitals in the Netherlands and Belgium. We included patients aged 18-85 with a life expectancy of more than six months.

Apart from a disorder in verbal communication as measured with the ANELT-A (score <44/50), a semantic and/or phonological disorder had to be present. A semantic disorder implied a score on Semantic Association Test-verbal[15] of less than 26/30 and/or a score on

Semantic Association (PALPA)[16] of less than 12/15. A phonological disorder implied a score on Nonword Repetition Task[16] of less than 20/24 and/or on Auditory Lexical Decision[16] of less than 76/80.

Exclusion criteria were severe dysarthria, developmental dyslexia or visual perceptual disorder; pre-existing aphasia, premorbid dementia and recent psychiatric disorder.

Interventions

Experimental treatment

Cognitive-linguistic treatment (CLT) consisted of BOX, a semantic treatment program, and/or FIKS, a phonological treatment program (paper and computer versions). BOX contains many semantic decision tasks using written words, sentences and texts that may also be presented orally. BOX aims to enhance semantic processing. FIKS has a similar structure but is directed at the phonological input and output routes. The SLT determined which treatment program(s) and which subparts the patient needed.

Control treatment

Communicative treatment aimed at improving communicative ability using all verbal and nonverbal strategies available to the patient, e.g. written choice communication and communication books. By definition, exercises are personally relevant and embedded in a communicative setting. Examples of methods used are PACE[17] (Promoting Aphasics' Communicative Effectiveness), role playing and conversational coaching.

Assessment

Baseline measures, including patient demographics and date and type of stroke, were recorded before randomization. The assessment at baseline and at three and six months post-stroke consisted of various linguistic measures and a measure of disability (Table 1).

Table 1 Reported assessments

Linguistics

Semantic measures

- Semantic Association Test (SAT)[15], verbal version. The SAT is based on the principles of the Pyramids and Palm Trees Test.[18] The patient chooses from four written words (three semantically related words and an unrelated word) the word that is semantically closest to the target word.
- Semantic Association with low-imageability words (PALPA).[16]
- Semantic Word Fluency: animals and professions.

Phonological measures

- Nonword Repetition Task (PALPA).
- Auditory Lexical Decision (PALPA). The patient decides if words are existing or nonexisting.
- Letter Fluency: D, A and T.

Other linguistic measures

- Amsterdam-Nijmegen Everyday Language Test (ANELT).[14] Verbal responses to ten everyday language scenarios are scored on a 5-point scale for informational content (scale A).
- Aachen Aphasia Test[19] (only at 6-8 weeks post-stroke).

Disability

- Modified Rankin Scale.[20]
-

The Amsterdam-Nijmegen Everyday Language Test (ANELT) consists of ten scenarios to which the patient has to respond verbally. For example: You are in a store and you want to buy a television. I am the salesperson here. "Can I help you?". Patients' verbal responses are rated for informational content on scale A "understandability", and for articulation on scale B (intelligibility). The scales are from 1 (bad) to 5 (good) so the total score on both scales ranges from 10 to 50. The ANELT is both a valid test (ecological validity is strong, criterion-related validity is .81, construct validity is good) and a reliable test (inter-rater reliability is .92, test-retest reliability is .92, goodness of fit is >0.91).[22]

Procedure

This trial was approved by the Ethical Committee of Erasmus MC and is registered (ISRCTN67723958). Written informed consent was obtained from all patients and their proxy before enrollment.

Patients were assessed as soon as possible as from day three. Subsequently, they were included in the study and the allocated treatment was started three weeks post-stroke at the latest. Treatment was provided for six months or shorter if the patient had completely recovered. Patients were retested at three and six months. The assessment and treatment took place in patients' subsequent treatment settings or at home.

Treatment was applied with a minimum of two and preferably for five hours per week, partly individual and partly as homework. The SLTs wrote down the content and amount of treatment their patients received on registration forms that were returned to us and discussed this with us every two to three weeks.

Outcomes

The primary outcome was the ANELT scale A (understandability) at six months. This scale measures functional verbal communication. The ANELT-A was scored from audiotapes by two independent, experienced SLTs, blinded to test moment and treatment allocation. The means of both raters' scores were used in the analyses. In case of a difference between two scores of ≥ 7 points, the raters were asked, without giving further information, to score the particular test again. In the few cases in which the difference was still ≥ 7 points, the scores were averaged with that of a third rater.

The secondary outcome measures were the ANELT-A at three months, three semantic tests: Semantic Association Test-verbal, Semantic Association with low-imageability words and Semantic Word Fluency; and three phonological tests: Letter Fluency, Auditory Lexical Decision and Nonword Repetition Task.

The primary effect measure was the difference between the two treatment groups in mean score on the ANELT-A at six months. This difference at three months was a secondary effect measure. The other secondary effect measures were the following: the difference in proportion of patients who improved ≥ 7 points, the clinically relevant change for individual patients on the ANELT (critical difference) according to the test manual[14]; the difference in proportion of patients who, after treatment, fell in the ANELT category "moderate" or "mild/no communication disorder", score 30-50; and finally, the difference in score on the three semantic and three phonological tests, all at three and six months.

The assessments were done by members of the research group, of a supporting aphasia team, trainees, or involved or uninvolved colleagues of the treating SLT. In the minority of cases it was unavoidable that the tests were administered by the treating SLT. One hundred of 158 follow up assessments were carried out by a person who was blind for treatment allocation. The assessors were instructed both orally and through a manual on how to administer the tests. In addition, they were trained specifically in administering the ANELT.

Statistical analyses

Analyses were performed on the basis of intention to treat. We also performed an on treatment analysis by limiting the analysis to patients who had completed treatment. We used ANCOVA and adjusted for baseline severity[21] to test group differences in score on the ANELT-A and on the semantic and phonological tests at three and six months, with 95%

confidence interval (CI). Beside baseline severity, we planned to adjust for age, gender, level of education, aphasia type, and intensity of treatment. The proportion of patients in each group who improved ≥ 7 points after three and six months, and the proportion of patients in each group who fell in the ANELT category “moderate” or “mild/no communication disorder” were compared by Odds Ratio with 95% CI by means of multiple logistic regression. All analyses were performed in SPSS 15.0 for Windows.

Sample size

We calculated that a sample of 70 patients would provide a power of 0.87 to detect a difference of seven points, the clinically relevant change for individual patients, on the ANELT between the two treatment groups at a 5% 2-sided significance level. To compensate for non-evaluable patients we randomized 80 patients.

Randomization and blinding

Treatment allocation was stratified by center. An independent statistician provided the computer-generated random allocation sequence per center. An uninvolved secretary put the assignments per center in sequentially numbered, opaque envelopes that were sealed and stored in a locked drawer. The research coordinator wrote the research number of the patient on the next appropriate envelop and then opened it to assign the intervention.

The patients and SLTs could not be blinded to individual treatment allocations, but the assessment of the primary outcome was blinded. Patients' responses on the ANELT were tape-recorded and scored by two independent raters, blinded to test moment and treatment allocation.

RESULTS

From September 2006 to April 2008, 85 patients were enrolled in 27 treatment centers in The Netherlands and Belgium. In 3 of 41 patients assigned CLT and in 2 of 44 patients assigned communicative treatment only baseline assessment was obtained and no follow-up due to serious concomitant illness, death or refusal to further participate. Because no outcomes could be determined in these five patients, we do not report on them. The intention-to-treat group therefore consisted of 80 patients who had received at least one follow-up assessment and in whom outcomes could be determined. For the on-treatment analyses we excluded 5 of 80 patients who prematurely aborted treatment (see details in Figure 1).

Baseline characteristics were well balanced (Table 2), except for gender: there were more men in the control group (57% versus 37% in the CLT group).

Table 2 Baseline characteristics of enrolled patients

	CLT (n=38)	Communicative treatment (n=42)
Age $\pm$ SD, y	68 $\pm$ 13	67 $\pm$ 15
Gender , n: male	14 (37%)	24 (57%)
Handedness (EHI), n:		
right	31 (82%)	36 (86%)
left	5 (13%)	2 (5%)
ambidexter	2 (5%)	4 (9%)
Level of education , n:		
no/unfinished elementary school	0 (0%)	1 (2%)
elementary school	7 (18%)	9 (21%)
unfinished junior secondary vocational education	1 (3%)	2 (5%)

junior secondary vocational education	17 (45%)	18 (43%)
senior vocational education	9 (24%)	8 (19%)
higher education	4 (10%)	2 (5%)
university	0 (0%)	2 (5%)
Type of stroke, n:		
ischemic	33 (87%)	38 (90%)
hemorrhagic	5 (13%)	4 (10%)
Location of lesion, n:		
left hemisphere	36 (95%)	39 (93%)
right hemisphere	2 (5%)	3 (7%)
Time post stroke to start of treatment, mean in days (range)	22 (11-37)	23 (9-49)
Rankin score (0-5), median (range)	3 (0-5)	3 (2-5)
ANELT A-scale (10-50), mean $\pm$ SD	21.4 $\pm$ 11.0	21.0 $\pm$ 11.1
Severity category ANELT-A, n		
very severe-severe (score 10-29)	27 (71%)	30 (71%)
moderate-mild-normal (score 30-50)	11 (29%)	12 (29%)
Disorder at inclusion, n		
semantic	3 (8%)	2 (5%)
phonological	4 (10%)	4 (9%)
semantic and phonological	31 (82%)	36 (86%)
AAT classification at 8 weeks, n:		
residual aphasia	5 (13%)	2 (5%)
not classifiable	4 (10%)	3 (7%)
global	2 (5%)	4 (9%)
Wernicke's	8 (21%)	16 (38%)
Broca's	4 (11%)	2 (5%)
Anomic	12 (32%)	12 (29%)
unknown	3 (8%)	3 (7%)

EHI indicates Edinburgh Handedness Inventory.

ANELT indicates Amsterdam-Nijmegen Everyday Language Test.

AAT indicates Aachen Aphasia Test.

Primary outcome

In both treatment groups the average ANELT-A scores improved. There was no significant difference in the mean ANELT-A scores of the two treatment groups, neither at three nor at six months post-stroke (Table 3). Almost all improvement occurred in the first three months. In total, four ANELT scores were lacking, two in the CLT group and two in the control group, due to loss of the audiotape, death, residence abroad and refusal. We replaced these lacking scores by the sum of the patient's ANELT-A score on the previous assessment and the mean improvement of the whole group in the previous period.

There was also no difference in improvement of ≥ 7 points on the ANELT-A. At three months 22/38 patients (58%) in the CLT group improved ≥ 7 points, compared with 26/42 (62%) in the communicative treatment group (OR=0.85, 95% CI=0.35 to 2.07). At six months 27/38 patients (71%) in the CLT group improved ≥ 7 points, compared with 31/42 (74%) in the communicative treatment group (OR=0.87, 95% CI=0.33 to 2.33).

At three months there was a trend regarding the proportion of patients in each group who fell in the ANELT category “moderate” or “mild/no communication disorder”: 27/38 patients (71%) from the CLT group, versus 23/42 (55%) in the communicative treatment group (OR=2.0, 95% CI=0.80 to 5.13). But this trend was not present anymore at six months (29/38 [76%] in the CLT group versus 30/42 [71%] in the communicative treatment group, OR=1.3, 95% CI=0.47 to 3.52).

In the on-treatment analyses, with five patients less than in the intention to treat group, the treatment effects were much the same. Adjustment for neither the baseline characteristics age, gender, and level of education, nor for the variables aphasia type and intensity of treatment changed the results of the main outcomes.

The intraclass correlation coefficients between the two independent raters of the ANELT indicated excellent agreement (at baseline 0.95, at three months 0.97 and at six months 0.96).

Table 3 Primary outcome measure: mean ANELT-A scores for the CLT and the communicative treatment group

	CLT (n=38)	Communicative treatment (n=42)	Difference (95% CI)	Adjusted difference (95% CI)*	P value
3 months post- stroke	33.4	31.6	1.8 (-3.8 to 7.4)	1.5 (-2.6 to 5.6)	0.48
6 months post- stroke†	35.2	33.2	1.9 (-3.4 to 7.3)	1.6 (-2.3 to 5.6)	0.42

* Adjusted for baseline score; † Primary effect measure

Secondary outcome measures

Both treatment groups improved on all secondary tasks. There was a statistically significant difference between the groups on the fluency tasks, in favor of CLT: on Semantic Word Fluency at three months (adjusted difference=3.2, 95% CI=0.4 to 6.0) and on Letter Fluency at six months (adjusted difference=3.1, 95% CI=0.3 to 6.0). On the remaining secondary tasks, Semantic Association Test-verbal, Semantic Association with low imageability words, Auditory Lexical Decision and Nonword Repetition Task, there was no significant difference in improvement between the groups (Figure 2).

Treatment intensity

The mean intensity of treatment was 2.1 hours. The mean number of hours of therapy was 45.4 hours of which 33.8 hours were face-to-face with an SLT and 11.6 hours were spent on homework. More details are given in Table 4.

Table 4 Data on treatment intensity for both treatment groups

	0 – 3 months		3 – 6 months	
	CLT (n=38)	Communicative (n=41)	CLT (n=38)	Communicative (n=41)
Mean intensity (SD)	2.4 (0.9)	2.0 (1.0)	2.1 (1.2)	2.0 (1.2)
Number of patients	25 (66%)	21 (51%)	21 (55%)	15 (37%)

who had ≥ 2 hours of therapy				
Number of patients who had ≥ 5 hours of therapy	2 (5%)	1 (2%)	2 (5%)	2 (5%)

Intensity did not differ significantly between the two treatment groups (0-3 months: $p=0.2$; 3-6 months: $p=0.5$). A smaller percentage of patients in the communicative treatment group received the minimum treatment intensity of two hours compared with patients in the CLT group. However, this difference was not statistically significant (0-3 months: $\chi^2=1.7$, $p=0.2$; 3-6 months: $\chi^2=2.8$, $p=0.1$).

DISCUSSION

We compared the efficacy of CLT (semantic and phonological treatment) and communicative treatment, applied in the first six months post-stroke. The two groups showed an equal improvement on the ANELT-A at three and six months with the largest increase in the first three months. The proportion of patients who fell in the ANELT category “moderate” or “mild/no communication disorder” showed a trend in favor of CLT at three months, but not at six months. This difference at three months might be due to chance: more patients in the CLT group than in the control group scored near the cut-off and thus were more likely to shift from the severe to the moderate category. The scores on nearly all specific semantic and phonological tests were higher after CLT than after communicative treatment, but the difference was only significant for the semantic and letter fluency tasks.

This treatment effect in favour of CLT could be meaningful. Both fluency tasks are explicitly related to the aim of CLT, i.e. to improve semantic and phonological processing, which has a positive influence on word finding. The fluency tasks are productive tasks that require self generation of words, a stage in the pursuit of adequate verbal communication in general, measured by the ANELT. Although there was no significant overall treatment effect on our primary outcome measure, nearly all differences between groups were in favour of the CLT group and therefore the efficacy of CLT remains to be evaluated in future studies.

Some methodological aspects of our study should be discussed. To our knowledge, RATS-2 is the first RCT that has evaluated aphasia treatment started in the acute stage, with everyday language use as primary outcome. Other strengths were the relatively large sample size ($n=80$), very good compliance and minimal loss to follow-up.

In line with recommendations for efficacy research on cognitive rehabilitation[5], we used a functional communication measure as primary outcome. In the Netherlands, the ANELT, in origin Dutch, was the only adequate test available. It has a high ecological validity[22] and is increasingly applied as primary outcome in treatment studies, both in the Netherlands[11, 23, 24] and elsewhere.[25] It is considered a weakness if, as in most studies, the outcome measure is trained material. Fewer studies considered generalisation to untrained material. The ultimate result is generalisation of the intervention to everyday communication, which we aimed to show. Therapy-specific findings in our previous trial[11] support the view that improving the underlying linguistic processing results in improved verbal communication.

Although we could not avoid that about one third of the outcome assessments was non-blinded, the final judgement of all ANELT samples, the primary outcome measure, was blinded.

A limitation is that we did not include a control group without language treatment. Therefore, we are not able to specify the potential effect of treatment over natural recovery. Because our aim was to measure the efficacy of a 6-months treatment period, we considered it both unethical and impracticable to withhold treatment from patients with a recent stroke for such a long period. Also, one may question whether the contrast between both treatments

was large enough. Although only one patient in our study received less than 75% of treatment according to protocol, it is obvious that in any communicative exercise, semantic and phonological processes are implicitly addressed. Therefore, we cannot exclude that overlap between the two treatments may have played a role. Finally, treatment intensity is currently an important issue in efficacy research and is assumed to be vital for the efficacy of treatment.[5, 6, 26] Possibly, the intensity in our study did not reach the threshold necessary to exceed natural recovery and find potential treatment effects[27] as we did not succeed in achieving the preferred intensity of five hours per week (the mean was 2.1 hours). A meta-analysis[28] suggested that 8.8 hours of treatment per week is needed to obtain a treatment effect and that two hours per week is insufficient. Recommendations in the remaining literature on treatment intensity range from 1.5 to two hours per week as being too little[6, 29], to two or three hours as the minimum to obtain positive results.[6, 30, 31]

Of the few well-designed RCTs on the efficacy of aphasia treatment, the one of Wertz et al.[32] is most comparable to ours. These authors compared treatment of specific language deficits with communicative treatment, started at four weeks post-onset, and found that the two were equally effective. Communicative treatment, however, was provided in a group instead of individually. In most other studies, conventional treatment was used, so approaches were mixed. Constraint-induced Aphasia Therapy[33], a treatment that is to date evaluated best, also combines a cognitive-linguistic and communicative approach. Elman&Bernstein-Ellis[4] examined the efficacy of group communication treatment separately, and found higher scores on communicative and linguistic measures compared to no treatment. CLT directed to semantic and phonological processing, which are crucial to word finding, has not been contrasted with no treatment in an RCT.

Our study does not support the widespread notion that CLT is more appropriate in an early stage and that communicative training is more suitable at a later stage.[10] Nor do the results support the recommendation that, in cognitive rehabilitation, clinicians should focus on training cognitive skills directly rather than broad interventions with the expectation of subsequent generalization to broader use in daily life.[9] The results also do not support the hypothesis that treatment of communication via the activation of the underlying processes, i.e. semantics and phonology, would be more effective in early aphasia, when natural recovery takes place, than a direct training of the communication itself. Because of the possible overlap between the two treatments and the low treatment intensity, the question whether CLT is efficacious particularly in the acute stage remains open. Therefore, in our next study, RATS-3, we aim to compare the effect of intensive CLT in aphasia patients very early post-stroke, with deferred treatment.

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Competing interests

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FIGURE LEGENDS

Figure 1 Flow chart of enrolled patients

Figure 2 Difference between the mean improvement on the secondary outcome measures of the CLT (n=38) and the communicative treatment group (n=42)

Differences in improvement between CLT & communicative treatment group

* indicates significant difference ($P < 0.05$)

Between brackets: the maximum score on the test