Title Page:

Improvement of language function after C7 neurotomy at the intervertebral foramen in patients with chronic post-stroke aphasia: a phase I cohort study

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ABSTRACT

Background: Post-stroke aphasia is a common but intractable sequela which still needs new and more effective treatments. Evidence from follow-ups after contralateral seventh cervical nerve transfer surgery indicated that nerve transection leads to immediate language improvements in patients with right post-stroke aphasia.

Objective: Through a prospective cohort design, this study aims to prove that C7 neurotomy at the intervertebral foramen (NC7) combined with a 3-week intensive speech and language therapy (iSLT) can improve the language function in post-stroke aphasia patients.

Methods: In this study, patients aged over 18 years old and had been diagnosed with post-stroke aphasia for 1 year or longer were included. Primary outcomes were the change in the ability to retrieve personally relevant words in Boston Naming Test (BNT) with follow-up assessment after three-weeks' iSLT post-operatively. As well as several secondary outcome measures including the Western Aphasia Battery (WAB), daily communication abilities (measured by the Communication Activities of Daily Living Third Edition [CADL-3]) and Fugl-Meyer of upper limb part (UEFM).

Results: The average increase of BNT score was 11.2 points from baseline to 3 weeks post-operatively (P=0.001, 95%CI: 8.1-14.1). The WAB and CADL-3 assessment showed 9.4, 10.4 points increasing in average (P<0.005, 95%CI: 4.6 to 14.1; P<0.001, 95%CI:6.7 to 14.1) from baseline to 4-week follow-up, respectively. The mean difference from baseline to 3 weeks post-operatively in UEFM score decreased 0.8 points (95% CI: -3.2 to 1.6; p<0.405).

Conclusions: NC7 plus iSLT significantly improved the language function in patients with post-stroke aphasia, and did not significantly affect the motor function of the right limb. The mechanism of this surgery needs to be further explored.

Keywords: Post-stroke Aphasia, C7 neurotomy at the intervertebral foramen intensive speech and language therapy, Boston Naming Test, hemiplegia.

INTRODUCTION

Aphasia refers to a collection of acquired receptive and expressive language deficits [1]. It is a common sequela of stroke, frequently occurring in patients with left-sided hemiparesis [2, 3]. As a devastating condition to most stroke patients, aphasia affects nearly every social activity and interaction [4]. Current treatments focus on rehabilitation are reports of some improvement in language function, such as intensive speech and language therapy (iSLT) [5, 6], as well as low-frequency electrical stimulation therapy, repetitive transcranial magnetic stimulation (rTMS) [7], and transcranial direct current stimulation (tDCS) [8]. However, patients who reach the plateau stage have difficulty in further improving their language function [9].

We previously proposed that contralateral C7 transfer from the nonparalyzed side to the paralyzed side (contralateral C7 to C7 cross nerve transfer [CC7]) can effectively improve upper limb function [10, 11]. In the clinical follow-up of this surgery, post-stroke patients with complicated chronic aphasia surprisingly showed improvement in self-reported language function, not only in terms of fluency but also in terms of increased naming ability. This phenomenon was firstly found by patients' self-reports and then confirmed through cohort follow-up study (unpublished yet). Since the language function improvement occurs within a short period of time after surgery (mostly within half a day after surgery) and the nerve regeneration has not yet begun, we think this improvement is thought to be closely related to neurotomy. There is also previous literature on improved language function in patients after selective posterior rhizotomies (SPR) surgery reported [12, 13]. These evidences indicated that that the improvement in language function is more likely related to the severed cervical seventh nerve on the affected side. Therefore, we propose a modified procedure for the treatment of chronic post-stroke aphasia, which is severing only the affected (right) cervical seventh nerve (the same as the procedure on the paralyzed side in CC7) at the intervertebral foramen (NC7), and observe whether there is an improvement in language function.

To verify the safety and preliminary effectiveness of NC7 at the intervertebral foramen on

language impairment in patients with chronic post-stroke aphasia, we designed a prospective clinical small cohort study with BNT, WAB, Fugl-Meyer and other scales for language and motor function assessment.

METHODS

Study Design and Participants

This is a single center, prospective, explorative cohort study approved by the institutional review board (Institutional Review Board of Jing'an District Central Hospital Affiliated to Hua Shan hospital of Fudan University). Consents of the study were acquired for all patients participated in this study. In this study, we included five patients with post-stroke aphasia (> 1 year) who were planned to receive contralateral seventh cervical nerve neurotomy to improve the language function. The post-stroke aphasia is diagnosed by the Aphasia Quotient (< 93.8) calculated by the Western Aphasia Battery (WAB). The participants should be aged over 18 years old, right-handed, native Chinese speakers with adequate visual and auditory abilities to complete the assessments. Participants were excluded, if they had a speech and language disorder caused by other deficits or before the last disabling stroke (such as neurodegenerative diseases), if they were unable or unwilling to participant in the study, or if they were currently receiving intensive speech and language therapy within four weeks before screening.

Clinical Assessments

In this article, we presented the language and upper extremity function of the patients at baseline (T0) and T1 follow-up which were evaluated before-intervention, after the surgery and 3-week iSLT plan, respectively. The primary outcome is the change in total score of the Boston naming test (BNT) scale from baseline to 3 weeks after the surgery. WAB, Communication Activities of Daily Third Edition (CADL-3), Fugl-Meyer of upper limb part (UEFM) and Modified Ashworth Score (MAS) were used as secondary outcomes.

For the language function, BNT is a classic measurement tool for evaluating language function, which shows a high concurrent validity with other standard naming ability assessment tools, and it is particularly suitable in the post-acute/chronic phase after stroke aphasia. In this study, we chose the validated Chinese version of BNT [14, 15]. The WAB applied in this study is consisted of four subtests, spontaneous speech, auditory comprehension, naming and repetition [16], and CADL-3 scale contains 50 items assessing functional communication skills in seven areas of adults with neurogenic communication disorders [17]. The types of aphasia of these patients were classified according to WAB-Aphasia quotation calculated by the scores of the WAB scale.

For the motor function, we used the UEFM to evaluate the paralyzed upper limb function, of which higher score indicated better motor function of the upper limb [18]. The spasticity of elbow and finger on the paralyzed side were also evaluated with MAS, with higher values indicating more spasticity [19]. Safety outcomes include any incidence related to the surgery or irrelevant but occurred after the surgery during the study period, such as bleeding, Infection, pain, numbness and so on. Patients will receive study information containing explicit details on whom to contact in case of an adverse event. Investigators will record all descriptions of adverse events during each follow-up visit.

Structural Magnetic Resonance Image（MRI）evaluation was applied in all 5 patients to detect the lesion site of left hemisphere [20]. Functional magnetic resonance image (fMRI) was also acquired but not analysed in this article.

Interventions

NC7 at the intervertebral foramen. Make a 6-cm long longitudinal incision along the medial border of the sternocleidomastoid muscle on the right side after the cervical plexus under anaesthesia/general anaesthesia (depending on the patient's preference and the anaesthesiologist's risk assessment). Carefully separate the structure layer by layer and identify the brachial plexus by marking the C7 nerve with a vessel loop. Next, the C7 root is mobilized and sectioned as

proximally (at the intervertebral foramen) as possible. Afterwards, the distal cut-end of the right C7 root was sutured to subcutaneous soft-tissues.

iSLT Rehabilitation. A 3-week iSLT was performed one-week after the surgery. Speech and language therapy with a therapist for at least 45 minutes, twice a day, 5 days per week. Additional 1 hour/day self-administrated language-specific training. Patients receive rehabilitation treatment in Shanghai Jing'an District Central Hospital, where qualified rehabilitation therapists perform the therapy.

Statistics

For demographic data, function data and safety indicators at baseline and post-operative follow-up (week-4), descriptive statistics was performed. Categorical data are presented as frequency and percentage, and continuous data are described by standard deviation. A two-sample paired t-test was performed to compare within-group differences in BNT, WAB, CADL-3 and UEFM score, with 95% confidence intervals reported. P value is studied and $P < 0.05$ was considered statistically significant. The ratio of change in each scale were calculated as the mean change divided by the total score of the full scale or each subtest. SPSS 22.0 software was used for calculation.

RESULTS

The 5 patients' Demographic characteristics and baseline data was listed in Table 1. The lesion area of one slice from the MRI scanning was shown in Figure 1. In language function tests, we observed the BNT score showed significant increase from baseline to 4-week (mean change: 11.2, 95% CI: 8.1 to 14.3, $P<0.001$. The WAB and CADL-3 score both acquired significant increase from baseline to 4-week follow-up (mean change: 9.4, 95% CI: 4.6 to 14.1, $P<0.005$; mean change: 10.4, 95% CI: 6.7 to 14.1, $P<0.001$). In the motor function tests, the UEFM score showed decrease at 4-weeks follow-up (mean change: 0.8, 95%CI: -3.2 to 1.6, $P< 0.405$), but the difference did not meet the lowest significant level ($P<0.05$). The spasticity of the elbow, wrist and fingers decreased

at 3 weeks after the surgery (see Table 2 and 3). Table 4 displayed the safety outcome and the adverse reactions that arose in each patient during this study. All patients' tactile sensory threshold increased in thumb, index and middle fingers combined with numbness, and partial patients demonstrated pain, decreasing in muscle strength of the paralyzed side.

DISCUSSION

In this paper, we confirm the effectiveness of NC7 in enhancing language function by comparing the language improvement of five patients who received NC7 and iSLT in a prospective cohort study of NC7. For this result, our hypothesis included two possible mechanisms. The first one is the disruption of interhemispheric balance by NC7, altering efficacy in the right hemisphere. Research has shown that the left hemisphere of the brain is typically responsible for language processing in right-handed individuals [21]. However, the left hemisphere may become damaged for stroke, leading to aphasia. In some cases, the right hemisphere of the brain may be able to compensate [22, 23] for the loss of function by taking on some of the language processing tasks. It is thought that the enhanced function of the language network in the right hemisphere may be due to the increased activity and connectivity of the neurons in that hemisphere following the nerve transplant.

Another possible mechanism is that transection of the right C7 nerve root, especially near the intervertebral foreman which is close to the dorsal ganglion for delivering sensory input to the left hemisphere, will largely induce the functional plasticity of the left sensorimotor cortex. Since the sensorimotor cortex, especially the premotor cortex, is very close and even overlapped with the Broca's area, which is an essential area for the language production, this large functional plasticity may interact with the left Broca's area and induce benign plasticity which is beneficial to the language function.

Both of these two mechanisms could be a possible candidate after NC7, or were contributing simultaneously for the improvement of language function. To elucidate the underlying mechanism

of language improvement after NC7, further exploration with functional MRI or electroencephalograph is needed. A preliminary exploration through event-related functional are performed in this cohort but not analysed in this article. Further research is needed to confirm both mechanisms to fully understand the mechanisms by which NC7 surgery improves language function in patients with aphasia.

CONCLUSION

C7 neurotomy at the intervertebral foramen as a novel surgical approach, can improve the language function in adult patients with post-stroke aphasia. The underling mechanisms of the cortical reorganization still need further investigation.

LIMITATION

The major limitation of this study is the study design as a preliminary observation. Randomized controlled clinical trial should be performed and more clinical evaluations as well as clinical neurophysiological studies should be added in further studies.

Table 1. Demographic characteristics and baseline data of the patients included.

Patient ID.	Sex	Type of stroke	Time post stroke , years	Type of Aphasia*
1	M	Infarct	2.6	Broca's aphasia
2	M	Infarct	2.8	Global aphasia
3	M	Hemorrhage	7.5	Broca's aphasia
4	M	Hemorrhage	2.2	Global aphasia
5	M	Hemorrhage	1.9	Broca's aphasia

*The type of stroke was evaluated through WAB-AQ.

Table 2. Changes of the language and motor function evaluations from baseline to each follow-up.

Patient ID / Outcomes		1	2	3	4	5	Average (Mean±SD)
BNT-60	Baseline	13	4	39	1	6	12.6±15.4
	Week-3	25	13	54	10	17	23.8±17.8
	Change	12	9	15	9	11	11.2±2.5
WAB-AQ	Baseline	41.8	27.2	57.8	11.0	52.0	38.0±19.0
	Week-3	51.2	31.8	69.8	17.8	66.1	47.3±22.2
	Change	9.4	4.6	12.0	6.8	14.1	9.4±3.8
CADL	Baseline	42	57	34	40	51	51.4±20.5
	Week-3	49	67	39	48	59	61.8±22.9
	Change	7	10	5	8	8	10.4±3.0
UEFM	Baseline	9	15	19	11	23	15.4±5.7
	Week-3	11	15	17	10	20	14.6±4.1
	Change	2	0	-2	-1	-3	-0.8±1.9
MAS-Elbow	Baseline	1	2	1+	1	2	1(2),1+(1),2(2)
	Week-3	0	1+	1+	0	1	0(2), 1+(2),1(1)
	Change	1	0.5	0	1	1	0(1),0.5(1),1(3)
MAS-Wrist	Baseline	1	2	1+	2	1+	1(1),1+(2),2(2)
	Week-3	1	2	1	0	1	0(1), 1(3), 2(1)
	Change	0	0	0.5	2	0.5	0(2),0.5(2),2(1)
MAS-Thumb	Baseline	1	2	1	1+	1	1(3),1+(1),2(1)
	Week-3	1	2	1	1	0	0(1),1(3),2(1)
	Change	0	0	0	0.5	1	0(3),0.5(1),1(1)
MAS-Fingers	Baseline	1	1+	1	1+	2	1(2),1+(2),2(1)
	Week-3	1	1+	0	1+	2	0(1),1(1),1+(2),2(1)
	Change	0	0	1	0	0	0(4),1(4)

Table 3. Statistics of the changes of the primary and secondary outcomes.

	BNT-60	WAB	CADL-3	UEFM
Average difference	11.2	9.4	10.4	-0.8
95% CI	8.1 to 14.3	4.6 to 14.1	6.7 to 14.1	-3.2 to 1.6
P value	0.001	0.005	0.001	0.405

This table compared the differences of the primary and secondary outcomes between the week-4 follow-up
and baseline. P<0.05 is considered statistically significant. 95% CI: 95% confident interval.

Table 4. Safety outcomes and side-effects.

Events	1	2	3	4	5	Total %
Complications related to treatment – no. of events						
Bleeding	N	N	N	N	N	0
Infection	N	N	N	N	N	0
Pain	Y	Y	N	Y	Y	80%
Transient palsy of the phrenic nerve	N	N	N	N	N	0
Changes in sensorimotor function – no. of events						
Numbness	Y	Y	Y	Y	Y	100%
Decrease in muscle strength-paralyzed side						
Elbow	Y	Y	N	Y	Y	80%
Wrist	Y	N	Y	N	N	40%
Fingers	N	N	N	N	N	0
Tactile sensory threshold increases in thumb, index and middle fingers	Y	Y	Y	Y	Y	100%

Y refers to the presence of the incident in this patient, while N refers to the opposite.

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