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ORIGINAL ARTICLE

Trial of Contralateral Seventh Cervical Nerve Transfer for Spastic Arm Paralysis

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ABSTRACT

BACKGROUND

Spastic limb paralysis due to injury to a cerebral hemisphere can cause long-term disability. We investigated the effect of grafting the contralateral C7 nerve from the nonparalyzed side to the paralyzed side in patients with spastic arm paralysis due to chronic cerebral injury.

METHODS

We randomly assigned 36 patients who had had unilateral arm paralysis for more than 5 years to undergo C7 nerve transfer plus rehabilitation (18 patients) or to undergo rehabilitation alone (18 patients). The primary outcome was the change from baseline to month 12 in the total score on the Fugl–Meyer upper-extremity scale (scores range from 0 to 66, with higher scores indicating better function).

RESULTS

The mean increase in Fugl–Meyer score in the paralyzed arm was 17.7 in the surgery group and 2.6 in the control group (difference, 15.1; 95% confidence interval, 12.2 to 17.9; $P<0.001$). With regard to improvements in spasticity as measured on the Modified Ashworth Scale (an assessment of five joints, each scored from 0 to 5, with higher scores indicating more spasticity), the smallest between-group difference was in the thumb, with 6, 9, and 3 patients in the surgery group having a 2-unit improvement, a 1-unit improvement, or no change, respectively, as compared with 1, 6, and 7 patients in the control group ($P=0.02$). Transcranial magnetic stimulation and functional imaging showed connectivity between the ipsilateral hemisphere and the paralyzed arm. There were no significant differences from baseline to month 12 in power, tactile threshold, or two-point discrimination in the hand on the side of the donor graft.

CONCLUSIONS

In this single-center trial involving patients who had had unilateral arm paralysis due to chronic cerebral injury for more than 5 years, transfer of the C7 nerve from the nonparalyzed side to the side of the arm that was paralyzed was associated with a greater improvement in function and reduction of spasticity than rehabilitation alone over a period of 12 months. Physiological connectivity developed between the ipsilateral cerebral hemisphere and the paralyzed hand. (Funded by the National Natural Science Foundation of China and others; Chinese Clinical Trial Registry number, 13004466.)

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SPASTIC LIMB PARALYSIS DUE TO INJURY to a cerebral hemisphere from stroke, traumatic brain injury, or cerebral palsy is a cause of long-term disability.[1-3] It is estimated that 30 to 60% of stroke survivors are unable to use their paralyzed hand.[4] The spastic arm posture impairs activities of daily living, such as hygiene and dressing, and may cause pain.[5-9] Functional impairment in patients with damage to the motor region of the contralateral cerebral hemisphere is due to both the interruption of the inhibitory activity of upper motor neurons, which causes spasticity, and the weakness and loss of fractionated fine motor control of the hand.[6] During recovery from a hemispheral lesion, neural reorganization has been observed in both the ipsilesional and contralesional (i.e., the cerebral hemisphere ipsilateral to the side of paralysis) hemispheres. There is evidence for involvement of the contralesional hemisphere in the recovery of hand function after a stroke, particularly in the execution of tasks that require a high degree of accuracy or complexity.[10-13] However, direct connections between the ipsilateral hemisphere and the paralyzed hand are sparse in humans,[14] which limits this compensatory capacity.[15]

On the basis of our previous studies (a link to a video is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org), we postulated that the paralyzed hand could be functionally connected to the contralesional (ipsilateral) hemisphere by transferring a cervical spinal nerve from the nonparalyzed side to the paralyzed side. This approach has been used for the treatment of injuries to the brachial plexus.[16-24] Activation of a paralyzed arm with this technique requires both physiological connections of the anastomosed nerve to contralateral nerves and connectivity of the cerebral hemisphere ipsilateral to the injury to the grafted nerve.

Among the spinal nerves, the five that give rise to the brachial plexus (C5, C6, C7, C8, and T1) together contain approximately 40,000 to 69,000 nerve fibers and innervate the entire upper extremity.[25] The C7 nerve accounts for approximately 20% of these fibers. Because the motor function of the C7 nerve largely overlaps with that of the other four nerves that give rise to the brachial plexus, severing this nerve usually results in only transient weakness and numbness in the ipsilateral upper extremity.[16,18,19,26,27]

We performed a randomized trial of grafting of the C7 nerve from the nonparalyzed side to the side of a spastic paralyzed arm and assessed changes in clinical function and both central and peripheral neurophysiological activation with the use of transcranial magnetic stimulation and conventional nerve-conduction studies. We also used functional neuroimaging to assess changes in brain activation.

METHODS

TRIAL DESIGN

We conducted a randomized, controlled trial involving patients with cerebral injury at Huashan Hospital, Shanghai, China. Participants were eligible for inclusion if they had hemiplegia after a stroke, traumatic brain injury, or cerebral palsy, manifesting mainly as spasticity and weakness in the upper extremity contralateral to the cerebral lesion. We recruited patients who were between 12 and 45 years of age and had arm paresis that had ceased to improve after at least 5 years of rehabilitation. The muscle power and tactile sensitivity in the affected hand had to be decreased but not absent (the term “paralyzed” is used to denote this state in the remainder of the description of the trial). Transcranial magnetic stimulation had to have resulted in activation from the contralesional hemisphere to the unaffected arm and exclusive activation of the paralyzed hand by the ipsilesional hemisphere. Patients were excluded if they had systemic diseases such as diabetes mellitus or cardiopulmonary disease, developmental delay or poor cognitive ability, or severe, fixed contracture or joint deformity of the paralyzed arm (the complete list of inclusion and exclusion criteria is provided in the Supplementary Appendix). None of the patients from our previous studies of the nerve-grafting technique were included in this trial.[28,29]

The trial protocol was approved by the institutional review board of Huashan Hospital. Participants or their parents provided written informed consent. The first and last authors wrote the manuscript, and all the authors vouch for the accuracy and completeness of the results and analysis, the reporting of adverse events, and the adherence of the trial to the protocol, available at NEJM.org.

Patients were assigned in a 1:1 ratio in a blinded fashion by means of simple, nonstratified randomization to undergo contralateral C7 nerve–transfer surgery followed by rehabilitation or rehabilitation only. The randomization sequences were computer-generated by an independent statistician and were not otherwise known to trial personnel until assignment.

TRIAL INTERVENTIONS

The procedure for C7 nerve transfer to the contralateral side has been described previously[28,29] and is shown schematically in Figure 1 and in an interactive graphic, available at NEJM.org, as well as in Figure S1 in the Supplementary Appendix. To limit surgical trauma and to shorten the gap between the distal end of the transplanted nerve and the recipient nerve, the procedure was modified from the original technique. In brief, an incision was made at the superior aspect of the sternum, and the donor C7 nerve on the nonparalyzed side was mobilized, sectioned as distally as possible but proximal to the point at which it combines with other nerves, and routed between the spinal column and esophagus; it was then anastomosed directly with the C7 nerve on the paralyzed side, which had been sectioned and mobilized as proximally as possible. No surgery was performed in the control group. The surgery and control groups received identical rehabilitation therapy four times per week for 12 months at one facility, administered by physiotherapists who were aware of the treatment assignments. Rehabilitation therapy included identical active exercise, passive range of motion, occupational therapy, functional training, physical therapy, acupuncture, massage, and the use of orthoses; the only between-group difference in rehabilitation therapy was the use of a special immobilizing cast during the postoperative period for patients who had undergone surgery (Fig. S2 in the Supplementary Appendix).

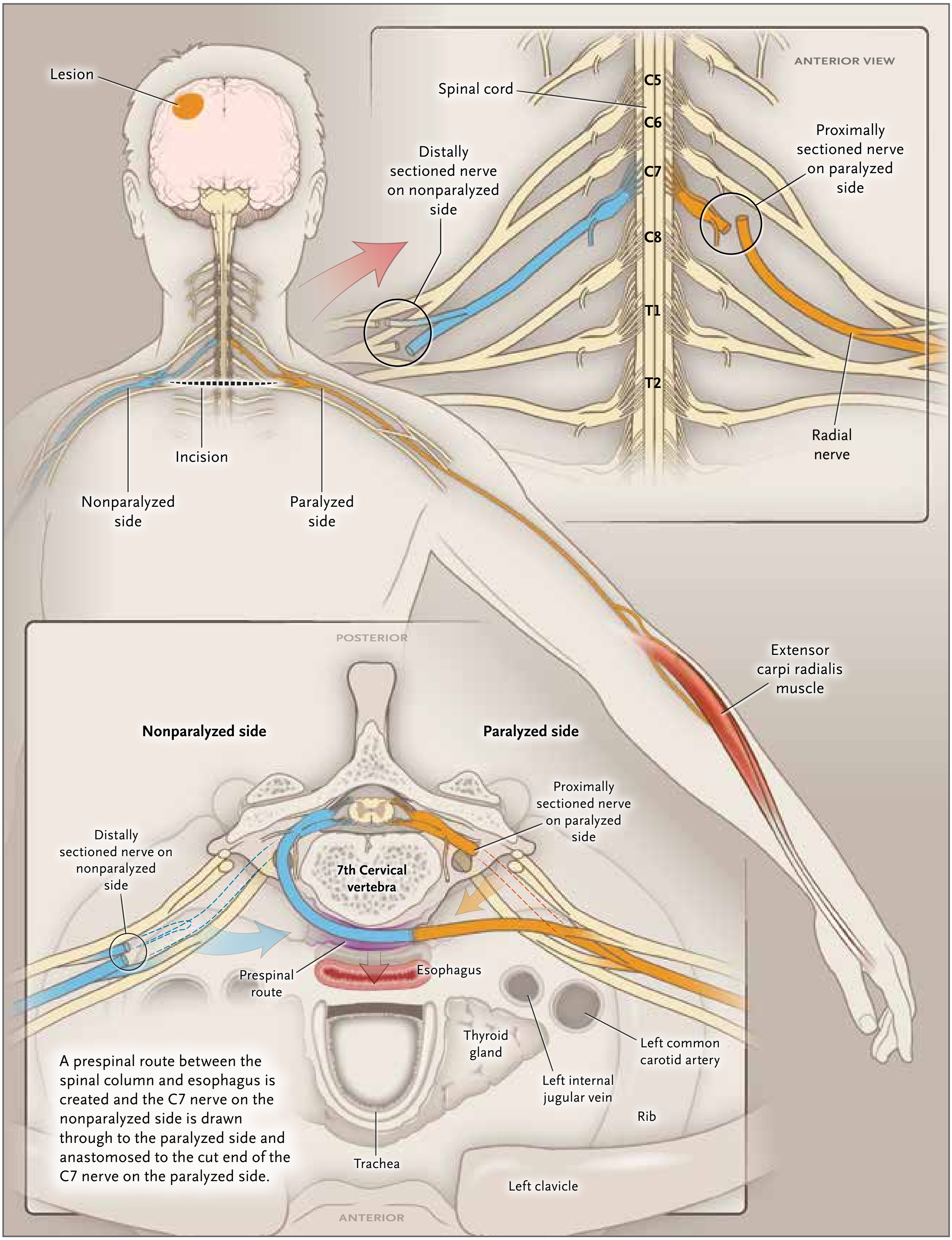
OUTCOMES

The primary outcome was the change in total score on the Fugl–Meyer upper-extremity scale from baseline to the end of month 12. The Fugl–Meyer scale is designed to assess recovery after stroke.[30] It measures 33 items, each scored from 0 to 2, with 0 indicating "cannot perform," 1 indicating "performs partially," and 2 indicating "performs fully"; the scale contains "shoulder and elbow" and "wrist and fingers" domains (total scores range from 0 to 66, with higher scores reflecting better function). Outcomes were assessed at baseline and at months 2, 4, 6, 8, 10, and 12 after recruitment.

The secondary outcomes included changes from baseline to month 12 in the Modified Ashworth Scale score for the elbow, forearm, wrist, thumb, and digits two through five, as well as active range of motion and functional use of the paralyzed arm. The Modified Ashworth Scale measures spasticity at each joint on a scale from 0 to 5, with higher values indicating more spasticity.[31] We considered a positive outcome to be a significant improvement from baseline in the score in at least one of the five joints tested. Evaluation of functional use of the limb included performance of activities such as dressing, tying shoes, wringing out a towel, and operating a mobile phone. The proportion of patients who accomplished at least three of the four tasks was a post hoc outcome.

An interactive graphic that includes videos is available at NEJM.org

Other secondary outcomes included neurophysiological and functional magnetic resonance imaging (MRI) assessments. Neurophysiological assessments were performed by means of electrical stimulation over the cervical nerves (Erb's point) of the unaffected side and recording over the extensor carpi radialis of the paralyzed arm and by means of transcranial magnetic stimulation over each hemisphere of the brain and recording over the extensor carpi radialis of the paralyzed arm (see the Supplementary Appendix). Functional MRI was performed while the patient was at rest and during active extension of the wrist on the paralyzed side (functional MRI methods are described in the Supplementary Appendix). Videos of the patients undergoing Fugl–Meyer scale assessment, Modified Ashworth Scale assessment, range-of-motion testing, and functional-use assessment were evaluated by two rehabilitation experts who were unaware of the treatment assignments, and functional imaging was assessed by investigators who were unaware of the treatment assignments; to mask identities and treatment assignments, the face of each patient and the area in which the incision would have been made in a patient who underwent surgery was obscured in the videos. Safety outcomes included adverse events and changes in muscle strength, tactile sensory threshold, and two-point discrimination of the arm and hand on the side of the severed, donor C7 nerve over a period of 12 months.



A prespinal route between the spinal column and esophagus is created and the C7 nerve on the nonparalyzed side is drawn through to the paralyzed side and anastomosed to the cut end of the C7 nerve on the paralyzed side.

Figure 1 (facing page). Contralateral C7 Nerve–Transfer Surgery.

A 15-cm transverse incision is made approximately 2 cm superior to the clavicle at the bottom of the neck. The brachial plexus nerves are exposed bilaterally, superior to the clavicle. The C7 nerve on the paralyzed side is severed near the intervertebral foramen, and the C7 nerve on the nonparalyzed side is severed as distally as possible, proximal to the point at which it combines with the fibers of other brachial plexus nerves. The anterolateral aspect of the C7 vertebral body is dissected bluntly, and the esophagus is exposed anterior to the vertebral body, which creates a conduit between the spinal column and the esophagus. The cut end of the C7 nerve on the nonparalyzed side is then drawn through the prespinal route to the paralyzed side and anastomosed directly (without a graft) to the cut end of the C7 nerve on the paralyzed side by means of microsurgical epineurium suturing. After surgery, the paralyzed upper extremity is immobilized with a head–arm brace for 4 weeks, after which the patients have the same rehabilitation therapy as they did before the surgery.

STATISTICAL ANALYSIS

On the basis of our preliminary study, we estimated that a sample size of 36 (18 per group), under the assumption of a 20% dropout rate, would provide 90% power to detect a mean (±SD) difference between groups of 6.6±5.2 on the Fugl–Meyer scale at an alpha level of 0.05. Descriptive statistics were used to report the characteristics of the patients at baseline. For continuous variables, Student's t-tests (or Satterthwaite's method) or Wilcoxon rank-sum tests were used for between-group comparisons, and paired t-tests or Wilcoxon matched-pairs signed-ranks tests were used for within-group comparisons between each follow-up visit and baseline. Intergroup comparisons of the continuous outcomes of changes from baseline to month 12 were performed by means of analysis of covariance to adjust baseline measures. For discrete variables, chi-square, Cochran–Mantel–Haenszel chi-square, or Fisher's exact tests were used for between-group comparisons and McNemar's chi-square tests were used for within-group comparisons. Differences between the groups in the changes from baseline in Modified Ashworth Scale score were compared by means of chi-square tests. Two-tailed P values of 0.05 were considered to indicate statistical significance. Boxcar analysis of functional MRI results was used for all sessions, with a t contrast (a statistical technique used to extract information about changes in functional MRI activity) and a corrected P value threshold of 0.05 for analyses involving a single patient. An analysis was performed for each session across patients with the use of a one-sample t-test, with a corrected P value threshold of 0.05 (family-wise error correction). The P values for changes assessed by means of functional MRI (Tables S8, S9, and S10 in the Supplementary Appendix) refer to comparisons between active movements and rest (detailed methods are provided in the Supplementary Appendix).[32]

RESULTS

PATIENTS

From July 2013 through December 2014, a total of 83 patients were screened; 45 were eligible for inclusion, and 36 were enrolled. The reasons patients were not enrolled were that they declined nonsurgical (4 patients) or surgical (3 patients) treatment or declined to undergo randomization (2 patients). A diagram of the enrollment of patients, randomization, and follow-up is shown in Figure S3 in the Supplementary Appendix.

The mean (±SD) interval from the original neurologic injury to the time of entry into the trial (i.e., baseline) was 15±9 years in the surgery group and 15±8 years in the control group; the durations of previous rehabilitation were 10±4 and 10±3 years, respectively, and the intervals between the most recent rehabilitation treatment and randomization were 5±7 and 5±6 years, respectively. The causes of cerebral injury included stroke, traumatic brain injury, cerebral palsy (congenital hemiplegia), and encephalitis (Table 1). There were no significant differences in the characteristics of the patients at baseline or in Fugl–Meyer or Ashworth scores at baseline between the groups, with the exception that 8 patients in the control group had cerebral palsy, as compared with 5 patients in the surgery group. At baseline, all patients were unable to perform reaching and grasping motions with their paralyzed hand and were unable to dress, tie shoes, wring out a towel, or operate a mobile phone with the affected arm and hand.

PRIMARY OUTCOME

The mean changes in the total Fugl–Meyer score from baseline to 12 months were 17.7±5.6 in the surgery group versus 2.6±2.0 in the control

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Surgery Group (N=18)	Control Group (N=18)
Male sex — no. (%)	18 (100)	18 (100)
Age — yr	27±9	26±8
Side of paralyzed hand — no. (%)		
Left	10 (56)	10 (56)
Right	8 (44)	8 (44)
Cause of injury — no. (%)		
Stroke	5 (28)	4 (22)
Traumatic brain injury	6 (33)	6 (33)
Cerebral palsy	5 (28)	8 (44)
Encephalitis	2 (11)	0
Time from original neurologic injury to entry into trial — yr	15±9	15±8
Duration of rehabilitation — yr	10±4	10±3
Interval between the end of rehabilitation and randomization — yr	5±7	5±6
Total Fugl–Meyer score†	29.0±3.0	29.1±3.5
Modified Ashworth Scale — score (no. of patients)‡		
Elbow extension	0 (1), 1 (4), 2 (13), 3 (0), 4 (0)	0 (1), 1 (7), 2 (10), 3(0), 4 (0)
Forearm rotation	0 (0), 1 (0), 2 (6), 3 (12), 4 (0)	0 (0), 1 (1), 2 (7), 3 (10), 4 (0)
Wrist extension	0 (0), 1 (1), 2 (10), 3 (6), 4 (1)	0 (0), 1 (0), 2 (12), 3 (6), 4 (0)
Thumb extension	0 (0), 1 (2), 2 (8), 3 (8), 4 (0)	0 (0), 1 (2), 2 (11), 3 (5), 4 (0)
Fingers 2–5 extension	0 (0), 1 (7), 2 (8), 3 (3), 4 (0)	0 (1), 1 (6), 2 (8), 3 (3), 4 (0)
Range of motion — degrees§		
Elbow	100±27	104±10
Forearm rotation	28±34	9±16
Wrist	31±27	32±9
Able to accomplish three or more functional tasks — no. (%)¶	0	0
Transcranial magnetic stimulation tests‖		
Ipsilesional hemisphere, paralyzed ECR		
Motor threshold — % of maximum output	39±2	39±2
Latency — msec	14.1±0.9	14.0±0.7
Amplitude — mV	0.82±0.21	0.82±0.18
Contralesional hemisphere, paralyzed ECR	NR	NR

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. NR denotes no response.

† The Fugl–Meyer upper-extremity scale is a measure of motor impairment; scores range from 0 to 66, with higher scores indicating better function.

‡ The Modified Ashworth Scale is a measure of spasticity (muscle tone) in the paralyzed arm; scores range from 0 to 5 at each of five joints, with higher scores indicating more severe spasticity. Data shown in these rows are the score (0 to 5) and the number of patients with that score (in parentheses).

§ Range of motion measures the range through which a joint could be actively moved. The Wilcoxon rank-sum test was used for analysis of between-group differences.

¶ Shown is the number and percentage of patients who could accomplish at least three of the following tasks: dressing, tying shoes, wringing out a towel, and operating a mobile phone.

‖ Transcranial magnetic stimulation measures the magnetic action potentials induced from the extensor carpi radius (ECR) on the paralyzed side while stimulating each cerebral hemisphere.

group, showing a significantly greater improvement in the surgery group (difference, 15.1; 95% confidence interval [CI], 12.2 to 17.9; P<0.001) (Table 2). A significant increase in score occurred at months 10 and 12 in the surgery group (Fig. S5 in the Supplementary Appendix). In a post hoc analysis, there were no significant differences between the two groups with respect to improvement in Fugl–Meyer scores and causes of cerebral damage (Table S1 in the Supplementary Appendix), but there were few patients in each group.

Table 2. Primary and Secondary Outcomes at Baseline and Month 12.*

Outcome	Surgery Group (N=18)	Control Group (N=18)	Mean Difference (95% CI)	P Value
Primary outcome				
Change in total Fugl–Meyer score from baseline to month 12†	17.7±5.6	2.6±2.0	15.1 (12.2 to 17.9)	<0.001
Change in total Fugl–Meyer score according to cause of paralysis				
Stroke	18.4±2.9	3.3±1.1	15.2 (7.2 to 23.1)	0.004
Traumatic brain injury	18.8±2.1	3.2±1.0	15.7 (10.2 to 21.1)	<0.001
Cerebral palsy	17.0±2.9	1.9±0.5	15.1 (7.2 to 23.1)	0.006
Secondary outcomes				
Change in Modified Ashworth Scale score from baseline to month 12‡				
Elbow extension	−2 (2), −1 (11), 0 (5)	−1 (1), 0 (16), 1 (1)	NA	<0.001
Forearm rotation	−2 (3), −1 (10), 0 (5)	−1 (3), 0 (14), 1 (1)	NA	0.003
Wrist extension	−2 (3), −1 (11)	−2 (1), −1 (3), 0 (12), 1 (2)	NA	0.005
Thumb extension	−2 (6), −1 (9), 0 (3)	−2 (1), −1 (6), 0 (7), 1 (4)	NA	0.02
Fingers 2–5 extension	−2 (4), −1 (10)	−1 (5), 0 (11), 1 (2)	NA	0.008
Change in range of motion from baseline to month 12 — degrees§				
Elbow	24±19	0±3	23.6 (14.4 to 32.8)	<0.001
Forearm rotation	36±19	1±5	35.0 (25.6 to 44.4)	<0.001
Wrist	49±21	1±5	47.8 (37.6 to 58.0)	<0.001
Able to accomplish three or more functional tasks at month 12 — no. (%)¶	16 (88.9)	0	NA	NA
Neurophysiological outcomes at month 12‖				
Stimulation of cervical nerves on nonparalyzed side, recording over ECR on paralyzed side				
Latency — msec	9.9±0.9	NR	NA	NA
Amplitude — mV	1.38±0.38	NR	NA	NA
Stimulation of cervical nerves on nonparalyzed side, recording over ECR on nonparalyzed side				
Latency — msec	7.5±0.9	7.2±0.6	0.3 (−0.3 to 0.8)	0.32
Amplitude — mV	1.88±0.28	1.82±0.24	0.63 (−0.12 to 0.24)	0.49
Stimulation of ipsilesional hemisphere, recording over ECR on paralyzed side				
Motor threshold — % of maximum output	40±2	39±1	−1 (−5 to 4)	0.79
Latency — msec	14.3±0.8	14.0±0.6	−0.5 (−2.1 to 1.2)	0.59
Amplitude — mV	0.78±0.20	0.81±0.18	−0.08 (−0.24 to 0.76)	0.30
Stimulation of contralesional hemisphere, recording over ECR on paralyzed side				
Motor threshold — % of maximum output	51±3	NR	NA	NA
Latency — msec	19.2±0.7	NR	NA	NA
Amplitude — mV	1.28±0.23	NR	NA	NA

* Plus–minus values are means ±SD. NA denotes not applicable.

† The Fugl–Meyer upper-extremity scale is a measure of motor impairment; scores range from 0 to 66, with higher scores indicating better function. Scores for shoulder and elbow and for the wrist and fingers for each category of cerebral injury are provided in Table S1 in the Supplementary Appendix.

‡ The Modified Ashworth Scale is a measure of spasticity (muscle tone) in the paralyzed arm; scores range from 0 to 5 at each of five joints, with higher scores indicating more severe spasticity. Negative numbers indicate a decrease and positive numbers an increase in spasticity from baseline to month 12. In these rows, the first number indicates the change in score, and the number in parentheses indicates the number of patients with that change in score. Changes in Modified Ashworth Scale score from baseline to month 12 were evaluated with the use of a chi-square or Fisher's exact test.

§ Range of motion measures the range through which a joint can be actively moved.

¶ Shown is the number and percentage of patients who could accomplish at least three of the following tasks: dressing, tying shoes, wringing out a towel, and operating a mobile phone.

‖ Neurophysiological outcomes included the results of peripheral-nerve conduction testing (stimulation at the contralateral cervical nerves and recording over the ECR on the paralyzed side) and transcranial magnetic stimulation (stimulation of each hemisphere and recording over the ECR on the paralyzed side) to verify peripheral and central connections.

SECONDARY OUTCOMES

Changes in spasticity from baseline to month 12 as measured on the Modified Ashworth Scale significantly favored the surgery group at all joints (elbow extension, P<0.001; forearm rotation, P=0.003; wrist extension, P=0.005; thumb extension, P=0.02; and extension of fingers two through five, P=0.008) (Table 2). The mean changes in the active range of motion from baseline to 12 months in the surgery group were 23±13 degrees at the elbow, 36±19 degrees in forearm rotation, and 49±21 degrees at the wrist; the corresponding changes in the control group were 0±3, 1±5, and 1±5 degrees (P<0.001 for all between-group comparisons) (Table 2).

At 12 months, 16 of the 18 patients who had undergone surgery were able to use the paralyzed hand to perform three or more of the tasks of dressing, tying shoes, wringing out a towel, and operating a mobile phone. In the control group, 7 of the 18 patients could perform two tasks, 3 could perform only one task, and 8 could perform none of the tasks (Table S3 in the Supplementary Appendix). An interactive graphic showing function at baseline and at month 12 in all 36 patients is available at NEJM.org.

NEUROPHYSIOLOGICAL ASSESSMENT

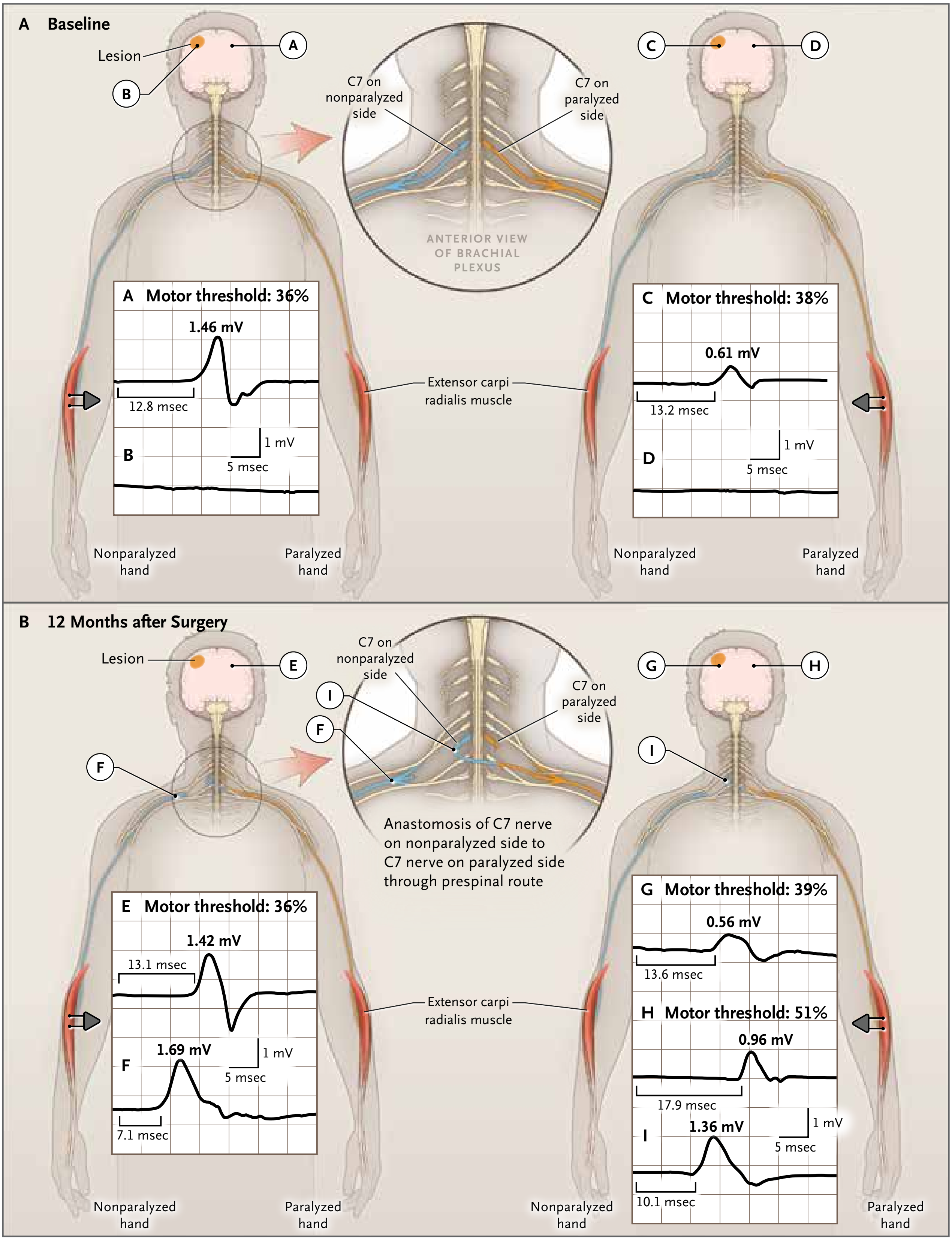
Motor-nerve action potentials could be recorded over the paralyzed extensor carpi radialis during stimulation of the contralateral C7 nerve in 8 patients in the surgery group at month 6, in 14 patients at month 8, and in all 18 patients at months 10 and 12. Transcranial magnetic stimulation elicited motor evoked potentials in the paralyzed extensor carpi radialis only during stimulation of the ipsilesional hemisphere at baseline in both groups (Table 2 and Fig. 2). In the surgery group, the paralyzed extensor carpi radialis responded to transcranial stimulation of the contralesional hemisphere at postoperative months 10 and 12. The mean latency of motor response at month 12 was 19.2±0.7 msec, and the mean amplitude was 1.28±0.23 mV (Table 2 and Fig. 2). A motor evoked potential from transcranial stimulation applied over the ipsilesional hemisphere could still be recorded over the paralyzed extensor carpi radialis at postoperative month 12; however, the amplitudes were decreased and the latencies were prolonged as compared with baseline measurements (Table 2 and Fig. 2). There was no response in the paralyzed hand to transcranial magnetic stimulation of the contralesional hemisphere at month 12 or at earlier points in the control group (Table 2). Patients in the control group had no response in the paralyzed limb to stimulation of contralateral cervical nerves or to stimulation of the contralesional hemisphere.

Figure 2 (facing page). Neurophysiological Assessment in the Surgery Group.

Shown is a schematic depiction of a representative patient (Patient 4 in the surgery group), with peripheral-nerve stimulation and transcranial magnetic stimulation used to assess peripheral and central connections before and after surgery. Recordings are from the extensor carpi radialis on the nonparalyzed and paralyzed sides. At baseline (Panel A), there is a response in the nonparalyzed arm only from transcranial motor stimulation of the contralateral hemisphere (from stimulation site A but not from site B). On the paralyzed side, there is a low-amplitude motor evoked potential only in response to transcranial magnetic stimulation of the ipsilesional hemisphere (from site C but not from site D). At postoperative month 12 (Panel B), a motor evoked potential is still present in the nonparalyzed arm in response to stimulation of the contralateral hemisphere (site E). Despite sectioning of the C7 nerve, a compound muscle action potential (CMAP) is still present on the nonparalyzed side in response to stimulation over the ipsilateral brachial plexus (site F). The main result is shown on the right: a motor evoked potential could be recorded from the extensor carpi radialis on the paralyzed side during transcranial magnetic stimulation of the contralesional (ipsilateral) hemisphere (site H). A response is preserved in the contralateral hemisphere (site G; compare with site C in Panel A). Stimulation of the cervical nerves of the nonparalyzed arm proximal to the site of sectioning shows a CMAP over the extensor carpi radialis on the paralyzed side (site I). This indicates the development of a physiological connection between the paralyzed arm and the ipsilateral hemisphere through the contralateral, anastomosed C7 nerve. In both panels, the motor threshold represents the percentage of maximum transcranial magnetic stimulation required to elicit a response in the limb. The nerve-conduction recordings represent the CMAP recorded over the extensor carpi radialis. The amplitude and latency from proximal stimulation are shown (sites F and I in Panel B).

FUNCTIONAL MRI ASSESSMENT

In the surgery group, voluntary extension of the paralyzed wrist generated weak activation in the ipsilesional hemisphere at baseline (Fig. 3). Weak activation started to appear in the contralesional hemisphere at postoperative month 8 and had increased in amplitude, as determined by the number of voxels activated in the motor region, at


A Baseline
Lesion
A
B
C
D
C7 on nonparalyzed side
C7 on paralyzed side
ANTERIOR VIEW OF BRACHIAL PLEXUS
A Motor threshold: 36%
1.46 mV
12.8 msec
B
1 mV
5 msec
C Motor threshold: 38%
0.61 mV
13.2 msec
D
1 mV
5 msec
Extensor carpi radialis muscle
Nonparalyzed hand
Paralyzed hand
Nonparalyzed hand
Paralyzed hand
B 12 Months after Surgery
Lesion
E
F
G
H
I
I
F
C7 on nonparalyzed side
C7 on paralyzed side
Anastomosis of C7 nerve on nonparalyzed side to C7 nerve on paralyzed side through prespinal route
E Motor threshold: 36%
1.42 mV
13.1 msec
F
1.69 mV
1 mV
5 msec
7.1 msec
G Motor threshold: 39%
0.56 mV
13.6 msec
H Motor threshold: 51%
0.96 mV
17.9 msec
I
1.36 mV
1 mV
5 msec
10.1 msec
Extensor carpi radialis muscle
Nonparalyzed hand
Paralyzed hand
Nonparalyzed hand
Paralyzed hand


A Paralyzed Wrist Extension
Baseline
Month 2
Month 8
Month 10
Month 12
B Nonparalyzed Wrist Extension
Baseline
Month 2
Month 8
Month 10
Month 12
Ipsilesional Hemisphere
Ipsilesional Hemisphere
10
0
0
10

Figure 3 (facing page). Functional MRI Assessment in the Surgery Group.

Shown are the changes in brain activation on blood oxygenation–level dependent (BOLD) functional MRI during the 12 months after surgery in the surgery group; images are based on a group analysis of all the patients in the surgery group (details are provided in the Supplementary Appendix). Panel A shows brain activation while the patient actively extends the paralyzed wrist. Before surgery, activation was observed in the ipsilesional hemisphere when patients extended the paralyzed wrist. Activation appeared in both the ipsilesional and contralesional hemispheres beginning at month 8. Contralesional activation was stronger and covered a larger area than ipsilesional activation by month 10. Contralesional activation was weaker at month 12 than at months 8 and 10. Panel B shows brain activation while the patient actively extends the nonparalyzed wrist. Before surgery, activation was observed in the contralesional hemisphere when patients extended the nonparalyzed wrist. Brain activation associated with wrist extension on the nonparalyzed (nonoperated) side did not change during the 12-month follow-up period. In both panels, t values (a statistic indicating the strength of brain activation in each voxel) in the analyses comparing extension of the wrist with resting of the wrist are indicated on a color scale (color intensity ranges from 0 to 10, with higher values indicating higher t values and stronger activation in a given voxel); blue is used for the nonparalyzed wrist, and yellow for the paralyzed wrist.

months 10 and 12. Activation of the ipsilesional hemisphere generated by extension of the wrist of the paralyzed arm was lower at postoperative month 12 than it was at baseline (Table S8 in the Supplementary Appendix). In the control group, extension of the paralyzed wrist generated weak activation in the ipsilesional hemisphere at baseline, a response that did not change during the 12-month period (Table S9 in the Supplementary Appendix).

SAFETY

Adverse events that were related to treatment (as determined by the principal investigator [the last author]) included limb or shoulder pain in 13 patients in the surgery group and in 8 patients in the control group, foreign-body sensation while swallowing in 12 patients in the surgery group, and fatigue in 15 patients in the surgery group. The adverse events that occurred on the side of the donor nerve were numbness in the hand in 16 patients, decreased power of elbow extension in 15 patients and of wrist extension in 16 patients, and attenuated sensory function in 16 patients (Table 3, and Table S5 in the Supplementary Appendix). Power in the arm on the side of the donor nerve became normal in 13 patients, and numbness was no longer present in 15 patients within 3 months. Sensorimotor deficits were not found on the side of the donor nerve in any patients at month 6. There were no significant differences in sensorimotor functions, as determined by means of neurologic examination, between baseline and postoperative month 12 in the nonparalyzed limb, with the exception of a decrease in sensory function in the index finger, as indicated in Figure S4 and Table S4 in the Supplementary Appendix.

DISCUSSION

We tested the effects of grafting the C7 nerve from the side of a normally functioning arm to the C7 nerve on the side of an arm that was paralyzed as a result of chronic cerebral injury. The paralyzed arm showed improved power, function, and reduced spasticity at month 12 in the surgery group, whereas there was significantly less improvement in the control group, in which patients received only physical therapy.

There was an initial phase of recovery after surgery that was characterized by the release of spasticity; in some patients, this phase started as early as the first postoperative day. This release of spasticity may have been a result of sectioning of the proximal C7 nerve, which contains nerve fibers from gamma motor neurons that innervate muscle spindles and maintain muscle tone. The scores on the Modified Ashworth Scale, a measure of spasticity, correspondingly started to decrease in the paralyzed elbows and wrists immediately after surgery. The second phase of recovery was characterized by improvements in muscle power and motor function, which were most evident beginning at approximately month 10, possibly reflecting the time course of the regeneration of nerve fibers through the gap between the distal end of the transplanted nerve, and more distally, on the side of the paralyzed hand. However, the release of spasticity may also have contributed both directly to improvements in hand and arm function and indirectly, by facilitating physical therapy. Nevertheless, the majority of clinical improvements coincided with physiological evidence of connectivity between the hemisphere on the side of

Table 3. Adverse Events.

Event	Surgery Group (N=18)							Control Group (N=18)						
	Baseline	Month 2	Month 4	Month 6	Month 8	Month 10	Month 12	Baseline	Month 2	Month 4	Month 6	Month 8	Month 10	Month 12
Complications related to treatment — no. of events*														
Any	0	56	4	0	0	0	0	0	0	0	0	0	0	0
Bleeding	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Infection	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pain	0	13	1	0	0	0	0	8	6	0	0	0	0	0
Foreign-body sensation while swallowing	0	12	0	0	0	0	0	0	0	0	0	0	0	0
Fatigue	0	15	2	0	0	0	0	0	0	0	0	0	0	0
Numbness	0	16	1	0	0	0	0	0	0	0	0	0	0	0
Changes in sensorimotor function†														
Decrease in muscle strength — no. (%)‡	0	15 (83)	1 (6)	0	0	0	0	0	0	0	0	0	0	0
Increase in tactile sensory threshold — no. (%)§	0	16 (89)	2 (11)	0	0	0	0	0	0	0	0	0	0	0
Increase in two-point discrimination — no. (%)¶	0	16 (89)	2 (11)	0	0	0	0	0	0	0	0	0	0	0

* The principal investigator determined whether a complication was related to the study treatment. A complication on either side of the body is included.

† Detailed data on sensorimotor function during the 12 months of follow-up are shown in the Figure S4 and Tables S4 and S5 in the Supplementary Appendix.

‡ The power of bilateral elbow, wrist, and finger extension was evaluated at baseline and at months 2, 4, 6, 8, 10, and 12, in accordance with the Medical Research Council grading system on a scale of 0 to 5, with higher scores indicating greater muscle power (details are provided in the Supplementary Appendix).

§ The tactile sensory threshold is the weakest stimulus that an organism can detect. The tactile sensory threshold was measured in both thumbs, index fingers, and middle fingers with Semmes–Weinstein monofilaments.

¶ Two-point discrimination is the ability to discern that two sharp objects that are touching the skin close to one another are truly two distinct points rather than one; this ability is assumed to reflect how finely innervated an area of skin is. Two-point discrimination was evaluated in both thumbs, index fingers, and middle fingers.

the donor nerve and the paralyzed arm. Over the 12 months of the trial, the ability to reach and to open the hand improved in patients who had undergone surgery, such that they were able to dress, wring out a towel, tie their shoes, and operate a mobile phone with the assistance of the paralyzed hand. Surgery-related adverse events occurred on the side of the donor nerve, including weakness at the elbow and in wrist extension, as well as numbness in the thumb and index and middle fingers and pain after surgery.

The underlying causes of the cerebral lesions underlying arm paralysis among patients in the present trial were diverse, and the patients were men of varying ages. These factors limit the generalizability of the findings. A larger cohort, followed for a longer period, would be necessary to determine whether cervical nerve transfer results in safe, consistent, and long-term improvements in the function of an arm that is chronically paralyzed as a result of a cerebral lesion.

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