Changes of somatosensory evoked potential and motor evoked potential after allogenic human neural stem cell (hNSC) transplantation in spinal cord injured patients

Jee-hyun Yoo

Department of Medicine

The Graduate School, Yonsei University

Changes of somatosensory evoked potential and motor evoked potential after allogenic human neural stem cell (hNSC) transplantation in spinal cord injured patients

Directed by Professor Ji Cheol Shin

The Master's Thesis

submitted to the Department of Medicine,

the Graduate School of Yonsei University

in partial fulfillment of the requirements for the degree

of Master of Medical Science

Jee-hyun Yoo

December 2008

This certifies that the Master's Thesis of

Jee-hyun Yoo is approved.

Thesis Supervisor : Ji Cheol Shin

Yoon Gil Park : Thesis Committee Member#1

Joong Woo Leem : Thesis Committee Member#2

The Graduate School

Yonsei University

December 2008

ACKNOWLEDGEMENTS

I would first like to thank professor Ji Cheol Shin, supervisor of this thesis. He was the source of inspirations in the field of rehabilitation, and he encouraged me to pursue subspecialty in spinal cord rehab. Becoming his student was a major turning point in my career. I would also like to thank professors Yoon Gil Park, Joong Woo Leem and Kook In Park. They also provided valuable guidance in writing of this thesis. .

Eternal gratitude goes out to my husband, my parents and inlaws, who have been very understanding of my busy schedule while writing the thesis. And to my brother Jee-ho: I wouldn’t have written this paper in English without your assistance.

And I am also appreciative of my fellow residents. Over our four years of residency, we've given each other courage and strength. And thanks to them, I was able to complete my residency successfully.

Finally, I want to thank God, who shows me the way in life. I believe that God will make a way for me.

Jee-hyun Yoo

<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

<ABSTRACT>

Changes of somatosensory evoked potential and motor evoked potential after allogenic human neural stem cell (hNSC) transplantation in spinal cord injured patients

Jee-hyun Yoo

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Ji Cheol Shin)

The aim of this study is to investigate whether somatosensory evoked potential (SEP) and motor evoked potential (MEP) are useful in assessing the efficiency of the stem cell transplantation.

A total of 11 patients received allogenic human neural stem cell transplantation. SEP and MEP studies were done before the transplantation, and then two months, six months, and twelve months after the transplantation.

Three patients who initially had no response to median nerve SEP revealed prolonged latency or normal response twelve months after the transplantation. In ulnar nerve SEP, five patients who initially had no response to ulnar nerve SEP noted prolonged latency or normal response to Rt. ulnar nerve SEP; and three of them noted prolonged latency or normal response to Lt. ulnar nerve SEP twelve months after the transplantation. One patient who initially couldn't obtain tibial, peroneal, and pudendal nerve SEPs had prolonged latency SEPs twelve months after transplantation.

Three of the five patients who initially couldn't obtain a right biceps MEP had a normal right biceps MEP and two of the five patients who initially couldn't obtain a left biceps MEP had a normal left biceps MEP twelve months after the transplantation. In case of right APB MEP, twelve months after the transplantation one more patient showed a prolonged latency and low amplitude of MEP. But we couldn't find any correlation between motor/sensory score and SEP/MEP changes. Some had no improvement of motor score or sensory score but showed improvement of SEP study. On the other hand, others had some

improvement of motor or sensory score but they still couldn't obtain SEP/MEP studies.

In conclusion, SEP and MEP studies may not be useful in assessing the efficiency of the stem cell transplantation.

Key words : cell transplantation, somatosensory evoked potential, motor evoked potential

Changes of somatosensory evoked potentials and motor evoked potentials after allogenic human neural stem cell (hNSC) transplantation in spinal cord injured patients

Jee-hyun Yoo

Department of Medicine or Medical Science

The Graduate School, Yonsei University

(Directed by Professor Ji Cheol Shin)

I. INTRODUCTION

Spinal cord injury (SCI) leads to complete or incomplete motor and sensory deficits at and below the level of injury and also to autonomic dysfunction. Severed axons don't spontaneously regenerate. Thus there are some non-pharmacological or pharmacological treatment options for SCI.[1, 2]

Non-pharmacological treatment options include surgery and rehabilitation. Pharmacological treatment options can be categorized into several groups: drugs that improve axonal conduction in the injured spinal cord, drugs that have neuroprotective/neuroregenerative effects, and cell-mediated repair of the injured spinal cord.[2, 3]

A number of electrophysiological studies, such as somatosensory evoked potential (SEP) study and motor evoked potential (MEP) study, have been used in acute SCI patients. Recording of lower extremity SEP could distinguish

between complete and incomplete lesions,[4] and changes of SEP components can precede clinically detectable improvements of motor or sensory function in the acute stage after SCI.[5] However, SEP is not always associated with motor recovery. That's because SEP shows the sparing of the sensory fiber in the posterior column-medial lemniscus pathway, whereas motor function is determined by the degree of the sparing of the corticospinal tract located in the cord's anterolateral portion.[6] Thereby, many studies have reported that SEP studies are no more effective for prognosticating outcome than a proper examination. But others still report SEP studies' prognostic benefits in predicting gait and hand function in patients with acute SCI.[6-8]

In contrast to SEP, MEP reflects the degrees of neural transmission of the corticospinal tract. Curt A et al reported that MEP was absent in muscles below the level of injury in complete tetraplegia and MEP which was obtained at abductor digiti quinti (ADQ) was highly predictive of the recovery of hand function. Also, MEP which was obtained at quadriceps femoris and tibialis anterior (TA) was highly predictive of the recovery of ambulatory capacity.[9]

Lately, many studies about cell transplantation to SCI rats or humans are being reported. In present studies, they use American spinal injury association (ASIA) scoring, behavioral testing for rats, Functional Independence Measure (FIM), Modified Barthel Index (MBI), or MRI to assess the efficiency of cell transplantation.[10, 11] It is the rare report that assesses efficiency of cell transplantation through electrophysiologic studies in human study.

Lee et al reported two studies with results of SEP and MEP from acute SCI rats which received O-2A cell[12] or human mesenchymal stem cell

transplantation.[13] They showed changes of SEP and MEP study, but SEP changes were not significantly different statistically. And they did not analyze the correlation between the changes in SEP and MEP and changes in motor function.

Moviglia et al[14] presented the results of tibial nerve SEP of two chronic SCI patients. They prepared to transplant neural stem cell by co-culturing bone marrow mesenchymal stem cell with patient's autoimmune T cell. They reported there were changes of SEP study but they didn't present one patient's SEP graph. While they reported changes to SEP and motor function, they did not realize the correlation between changes in SEP and changes in motor function.

Syková et al[15] published the results of SEP, MEP, MRI, and neurologic examination on 20 patients who have undergone autologous bone marrow transplantation before the procedure and three months, six months and twelve months afterward. But their work only included median and tibial SEP.

It is important that neurologic examination is done exactly for assessing the efficiency of stem cell transplantation. But to make up for inaccurate neurologic exam as a result of inexperience, there needs to be an objective method to assess efficiency of stem cell transplantation. Electrophysiologic study can be one such method.

Therefore, the aim of this study is to investigate whether there is any correlation between changes in motor function and sensory function and changes in SEP and MEP; and whether SEP and MEP are useful in assessing efficiency of cell transplantation.

II. MATERIALS AND METHODS

1. Participants

Participants were eligible when they were admitted to Severance Hospital of Yonsei University College of Medicine if they were between 15 and 60 years old, had no motor or sensory function in the sacral segments S4-S5 (American Spinal Injury Association [ASIA] Impairment Scale A, 'ASIA-A'), or had sensory but not motor function below the neurological level including the sacral segments S4-S5 (ASIA-B). Also, the spinal cord injury had to be due to trauma with onset duration of less than six months by the time of this study.

Exclusion criteria included: multiple spinal cord injury; spinal cord injury due to spine or spinal cord tumor; progressive/nonprogressive disease of brain or spinal cord; major concurrent medical illness (i.e. cancer, diabetes mellitus); substance abuse; and psychiatric illness. Subjects who had received any type of cell transplantation for the treatment of spinal cord injury or who had concomitant skeletal fracture or peripheral nerve injury that could impact on neurologic evaluation were also excluded.

Selected participants were thoroughly informed of the trial and its accompanying risks. The trial was approved by the institutional review board of the Severance Hospital at Yonsei University.

2. Preparation of human embryonic neural stem cell and cell transplantation

We acquired hNSC (HFT13), which had been frozen inside a liquid nitrogen tank. In our cell therapy laboratory, we thawed one vial of hNSC before

transplantation. After performing a laminectomy, a neurosurgeon exposed a dura mater and these hNSC were directly injected into the injured spinal cord of 11 patients.

3mg/kg/day of cyclosporine, which is an immunosuppressant, were administered to patients starting four days before the transplantation to three weeks after the transplantation. Then, 2mg/kg/day of cyclosporine were administered for next three weeks and then 1mg/kg/day of cyclosporine for additional two weeks.

3. Neurological assessment

Before the transplantation, and eight weeks, six months and twelve months after the transplantation, neurologic assessments were performed. Neurologic assessments were done according to the reference manual for the International Standards for Neurological Classification of Spinal Cord Injury (2002 revised version).[16]

From the reference manual, five assessments were performed. First, ASIA pin prick scores (ASS-P) and ASIA light touch scores (ASS-L) were calculated by the summation of sensory scores of key points. In case of ASS-P, a three-point scale was used. Zero (0): Patient had no feeling of being touched with either the sharp or dull ends of the pin or couldn't distinguish between the sharp and dull ends of the pin; One (1): Patient was able to distinguish between the sharp and dull ends of the pin, but pin did not as sharp as on the face; Two (2): Patient was able to distinguish between the sharp and dull ends of the pin and pin felt as sharp as on the face. In case of ASS-L, a different three-point scale was used.

Zero (0): Patient did not correctly and reliably reported being touched; One (1): Patient correctly reported being touched, but but not so on the face; Two (2): Patient correctly reported being touched, including on the face. Therefore, the perfect score of each ASS was 112 points. [6, 16]

Second, ASIA motor scores (AMS) were calculated by the summation of motor scores of key muscles. Key muscles are: C5 - elbow flexors, C6 - wrist extensors, C7 - elbow extensors, C8 - finger flexor (distal phalanx of the 3rd finger), T1 - finger abductors (little finger), L2 - hip flexors, L3 - knee extensors, L4 - ankle dorsiflexors, L5 - long toe extensors, and S1 - ankle plantaflexors. Each muscle was tested by the traditional six-point manual muscle testing scale and was scored zero to five points. Therefore, the perfect score of AMS was 100 points. [6, 16]

Third, we determined the patient's ASIA impairment scale. ASIA impairment scale is as follows; A = Complete. No sensory or motor function was preserved in the sacral segments S4-S5; B = Incomplete. Sensory, not motor, function was preserved below the neurological level and included the sacral segments S4-S5; C = Incomplete. Motor function was preserved below the neurological level, and more than half of key muscles below the neurological level had a muscle grade less than 3; D = Incomplete. Motor function was preserved below the neurological level, and at least half of key muscles below the neurological level had a muscle grade greater or equal to 3.[16]

Neurologic assessments were performed by three specially trained physicians who had a minimum of four years' experience in treating SCI patients.

4. SEP study

Before the transplantation, and eight weeks, six months and twelve months after the transplantation, median, ulnar, peroneal, tibial, and pudendal nerves SEP studies were performed.

The stimulating electrodes were placed over the median nerve at the wrist for median nerve SEP studies, ulnar nerve at the wrist for ulnar nerve SEP studies, tibial nerve at the medial ankle for tibial nerve SEP studies, and peroneal nerve at the popliteal fossa for peroneal SEP studies. For pudendal nerve SEP studies, stimulating electrode was placed on the shaft of the penis by ring electrode in males or on the clitoris by bar electrode in females. Recording electrodes were placed on the C3'- Fz for median and ulnar nerve SEP studies. For tibial, peroneal, and pudendal SEP studies, recording electrodes were placed on the Cz'- Fz.

Stimulation frequency was 3Hz and stimulation duration was 0.1msec. And stimulation intensity was able to produce a visual contraction of abductor pollicis brevis (APB) for median nerve, abductor digiti quinti (ADQ) for ulnar nerve, abductor hallucis (AH) for tibial nerve, and extensor digitorum brevis (EDB) for peroneal nerve. Sweep speed was 5msec/division for median and ulnar nerve SEP and 10msec/division for tibial, peroneal, and pudendal nerve SEP. Sensitivity was 2μV/division.

With median nerve and ulnar nerve SEP, we obtained N20 latency by applying 250 repeated stimulations twice each. As for tibial, peroneal, pudendal nerve SEP, P40 latency was acquired through 250 repeated stimulations that were applied twice. SEP was performed using Synergy (Medelec Synergy-Oxford

Instruments, Surrey, UK).

Normal values are as below; median SEP 16.9~20.6ms; ulnar SEP 18.1~20.5ms; tibial SEP 32~46ms; peroneal SEP 32.3~36.3ms; pudendal nerve SEP 40.4~44.2ms for men and 38.5~41.1ms for women.[17]

5. MEP study

Before the transplantation, and eight weeks, six months and twelve months after the transplantation, MEP was obtained at biceps, APB and tibialis anterior (TA) muscles. First, to obtain a resting motor threshold that was the lowest transcranial magnetic stimulation (TMS) intensity could yield a MEP more than 50μV in amplitude in muscles at rest in at least five out of 10 stimulations. Then, we stimulated a motor cortex 10 times on 1.2 times the intensity of resting motor threshold and obtained a mean amplitude and latency of MEP. Then, we used normalized amplitude, which is gained by dividing mean amplitude by compound muscle action potential amplitude. MEP was performed using Magstim (Magstim Company Limited, Whitland, UK).

Normal values are as below; biceps MEP latency 9.1~14.7ms, amplitude 0.21~1.08; APB MEP latency 12.2~18.4ms, amplitude 0.25~1.10; TA MEP latency 20.2~32.5ms, amplitude 0.19~0.88.[18]

III. RESULTS

1. Patient population

A total of eleven patients underwent the transplantation and all of them finished their 12-month follow-ups. There were nine men and two women and their mean age was 37.2 years. The mean time from onset to hNSC transplantation was 57 days and the range was from ten days to 139 days. Ten were tetraplegic and one was paraplegic (Patient K). Before the transplantation, they were ASIA A except patient A who was ASIA B. Twelve months after the transplantation, patient A converted from ASIA B to ASIA D, patient B from ASIA A to ASIA C, and patient C from ASIA A to ASIA B (Table 1).

Table 1. Summary of patient demographics, time from injury onset to hNSC transplantation, and spinal cord injury level

Patients	Sex	Age (yrs) (mean : 37.2yrs)	Onset	Stem cell Transplant.	Duration[1] (days) (mean : 57days)	Neurologic level of injury	ASIA Preop[2]	ASIA POD 12mo[3]
A	F	41	2006-07-06	2006-07-31	25	C7	B	**D**
B	F	45	2007-02-15	2007-03-08	23	C3	A	**C**
C	M	24	2007-02-06	2007-03-26	50	C5	A	**B**
D	M	33	2006-10-01	2006-12-21	80	C7	A	A
E	M	36	2006-05-11	2006-06-26	45	C3	A	A
F	M	34	2006-04-24	2006-06-01	37	C3	A	A
G	M	26	2006-09-20	2007-01-29	139	C4	A	A
H	M	32	2007-04-23	2007-05-21	28	C3	A	A
I	M	56	2006-11-18	2007-02-01	73	C4	A	A
J	M	53	2006-12-10	2007-04-12	122	C3	A	A
K	M	40	2006-12-25	2007-01-05	10	T10	A	A

[1] Times from injury onset to hNSC transplantation.

[2] ASIA was evaluated before the transplantation.

[3] ASIA was evaluated twelve months after the transplantation

2. Neurologic assessment

We conducted neurologic assessment all of the patients before the transplantation, and eight weeks, six months and twelve months after the transplantation and calculated ASIA motor score (AMS, Table 2), ASIA sensory score of light touch (ASS-L, Table 3) and pinprick (ASS-P, Table 4). Patient A, who converted from ASIA B to ASIA D, had the greatest AMS changes and patient C, who converted from ASIA A to ASIA B, had the greatest ASS-L changes.

According to guidelines by International Campaign for Cures of Spinal Cord Injury Paralysis (ICCP) panel, to identify the efficacy of a therapeutic intervention for lower cervical ASIA-A patients, a 20-point AMS improvement might be considered a valid primary outcome end point. And for ASIA-B patients, a 50-pointAMS improvement might be required. [19]

Among our patients, there was only one lower cervical ASIA-A patient, and eight patients were high or middle cervical ASIA-A. And patient A, who was ASIA-B before the transplantation, showed a 49-point AMS improvement. Therefore, we used changes in percentage of AMS, ASS-L and ASS-P instead of guideline by ICCP panel. We calculated percentage change as below: changes of AMS = {improvement points of AMS/(perfect score of AMS - preoperation AMS)} x 100; changes of ASS-L or ASS-P = {improvement points of ASS-L or ASS-P/(perfect score of ASS-L or ASS-P - preoperation ASS-L or ASS-P)} x 100.

Table 2. Changes of AMS

Name	Right		Left		Total		Changes of AMS (%)[1]
	Preop	POD 12mo	Preop	POD 12mo	Preop	POD 12mo	
A	14	36	14	40	28	76	66.7
B	8	16	7	13	15	29	16.5
C	8	12	10	12	18	24	7.3
D	15	19	14	19	29	38	12.7
E	0	7	0	1	0	8	8.0
F	0	3	0	3	0	6	6.0
G	5	8	8	10	13	18	5.7
H	0	4	0	0	0	4	4.0
I	1	1	1	2	2	3	1.0
J	3	3	3	3	6	6	0.0
K	25	25	25	25	50	50	0.0

1 $\text{Changes of AMS} = \frac{\text{AMS POD12mo} - \text{AMS Preop}}{100 - \text{AMS Preop}} \times 100$

Table 3. Changes of ASS-L

Name	Right		Left		Total		Changes of ASS-L (%)[1]
	Preop	POD 12mo	Preop	POD 12mo	Preop	POD 12mo	
A	34	35	34	35	68	70	2.3
B	7	8	6	8	13	18	5.1
C	11	38	11	38	22	76	60.0
D	13	13	12	12	25	25	0.0
E	6	8	5	5	11	13	2.0
F	6	6	4	6	10	12	2.0
G	7	8	10	10	17	18	1.1
H	4	10	4	4	8	15	6.7
I	6	7	6	7	12	14	2.0
J	6	6	6	6	12	12	0.0
K	36	37	36	36	72	73	2.5

1 $\text{Changes of ASS-L} = \frac{\text{ASS-L POD12mo} - \text{ASS-L Preop}}{112 - \text{ASS-L Preop}} \times 100$

Table 4. Changes of ASS-P

Name	Right		Left		Total		Changes of ASS-P (%)[1]
	Preop	POD 12mo	Preop	POD 12mo	Preop	POD 12mo	
A	15	25	16	21	31	46	17.3
B	7	11	6	11	13	22	9.1
C	10	12	9	12	19	24	5.4
D	13	13	12	12	25	25	0.0
E	6	6	5	5	11	11	0.0
F	6	6	6	6	12	12	0.0
G	6	8	10	10	16	18	2.1
H	4	5	4	4	8	9	1.0
I	6	7	6	7	12	14	2.0
J	5	6	4	6	9	12	2.9
K	36	37	34	35	70	72	4.8

1 $\text{Changes of ASS-P} = \frac{\text{ASS-P POD12mo} - \text{ASS-P Preop}}{112 - \text{ASS-P Preop}} \times 100$

3. SEP study

Before the transplantation, four of the eleven patients had no response to median nerve SEP. Among these patients, three revealed prolonged latency or normal response to bilateral median nerve SEP twelve months after the transplantation (Table 5).

Median nerve is composed of fibers from spinal level C5~T1. Thereby we calculated AMS and ASS-L of C5~T1 (Figure 1, 2).

Table 5. Changes of median nerve SEP

Name	Rt				Lt			
	Preop	POD 2mo	POD 6mo	POD 12mo	Preop	POD 2mo	POD 6mo	POD 12mo
E	No[1]	No	**33.15**	**25.15**	No	No	**22.95**	**31.50**
F	No	No	No	**19.00**	No	No	No	**17.95**
H	No	**17.80**	**19.40**	**17.71**	No	**18.75**	**16.00**	**20.95**
J	No	No	No	No	No	No	No	No

[1] No response to SEP

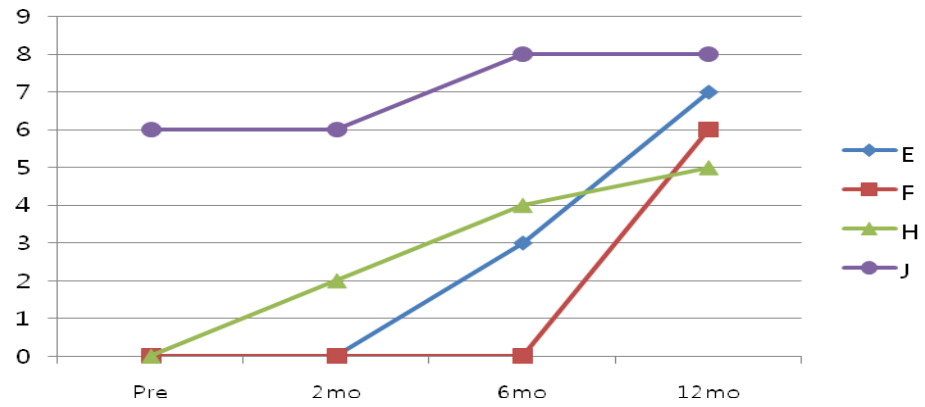

Figure 1. AMS of patient E, F, H, and J's C5~T1 levels

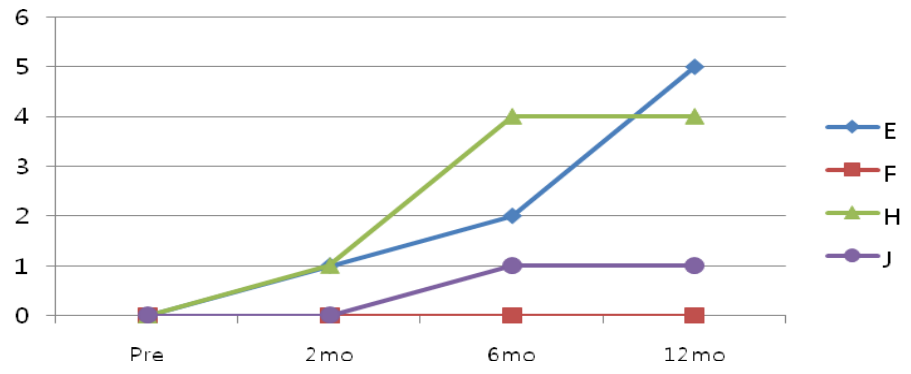

Figure 2. ASS-L of patient E, F, H, and J's C5~T1 levels

For ulnar nerve SEP, eight patients had no response to SEP before the transplantation. Five of them noted prolonged latency or normal response to Rt. ulnar nerve SEP; and three of them noted prolonged latency or normal response to Lt. ulnar nerve SEP twelve months after the transplantation (Table 6).

Ulnar nerve is composed of fibers from spinal level C7~T1. Thereby we calculated AMS and ASS-L of C7~T1 (Figure 3, 4).

Table 6. Changes of ulnar nerve SEP

Name	Rt				Lt			
	Preop	POD 2mo	POD 6mo	POD 12mo	Preop	POD 2mo	POD 6mo	POD 12mo
B	No[1]	No	No	**19.35**	No	No	No	**20.65**
E	No	No	**26.40**	**24.85**	No	No	No	No
F	No	No	No	**23.40**	No	No	No	**28.95**
I	No	**16.10**	**18.05**	**18.21**	No	No	No	No
H	No	**20.10**	**18.85**	**17.05**	No	**25.50**	**19.35**	**20.25**

[1] No response to SEP

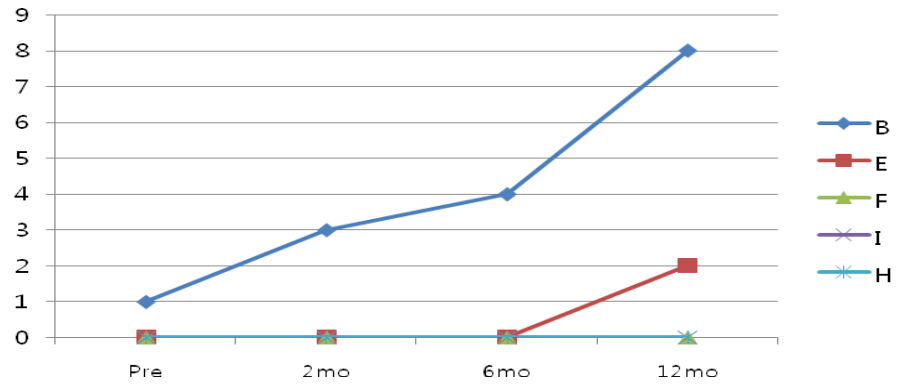

Figure 3. AMS of patient B, E, F, I, and H's C7~T1 levels

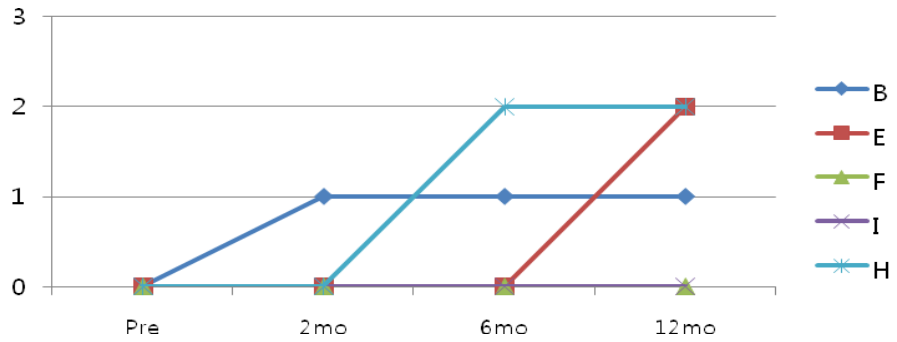

Figure 4. ASS-L of patient B, E, F, I, and H's C7~T1 levels

For tibial, peroneal, and pudendal nerve SEP, only one patient, patient A, had normal or prolonged latency of SEP, and the others revealed no response to SEP before the transplantation. Twelve months after the transplantation, we could obtain prolonged latency of bilateral tibial, peroneal, and pudendal nerve SEP of patient B, but not others who revealed no response of SEP initially (Table 7).

Tibial nerve is composed of fibers from spinal level L5~S2, peroneal nerve is composed of fibers from spinal level L4~S2 and pudendal nerve is composed of fibers from spinal level S2~S4. Thereby we calculated AMS of L4~S1 and ASS-L of L4~S4 (Figure 5). Patient B had only a two-point AMS improvement, but she revealed prolonged latency of tibial, peroneal, and pudendal nerve SEP. In case of ASS-L of L4~S4, patient A had no interval change and patient B revealed only one-point improvement.

Table 7. Changes of tibial, peroneal, and pudendal nerve SEPs

Name	Tibial nerve SEP		Peroneal nerve SEP		Pudendal nerve SEP	
	Preop (Rt/Lt)	POD 12mo (Rt/Lt)	Preop (Rt/Lt)	POD 12mo (Rt/Lt)	Preop (Rt/Lt)	POD 12mo (Rt/Lt)
A	36.2/36.1	42.40/41.00	36.3/36.7	41.80/41.10	34.67	40.30
B	No[1]	**61.90/43.10**	No	**44.80/44.60**	No	**61.80**

[1] No response to SEP

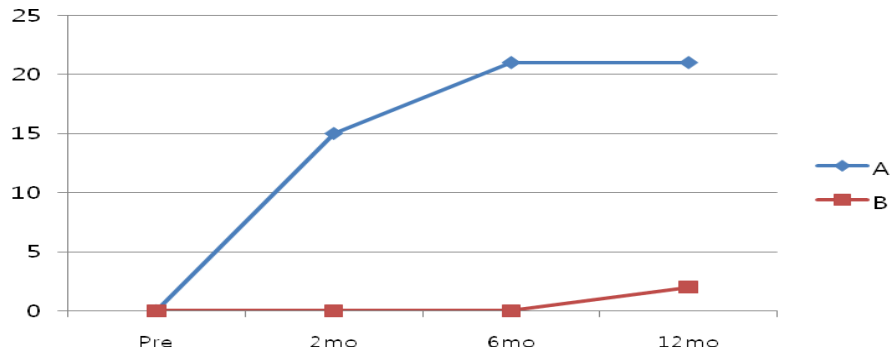

Figure 5. AMS of patient A, and B's L4~S1 levels

Patient B had improvement of AMS and ASS-P until twelve months after the transplantation and converted from ASIA A to ASIA C during that time. But her ASS-L didn't show improvement after six months following the transplantation (Figure 6). Initially, she had no response to ulnar, tibial, peroneal and pudendal nerve SEP, but twelve months after the transplantation, she revealed normal or prolonged latency of them (Table 8, Figure 7).

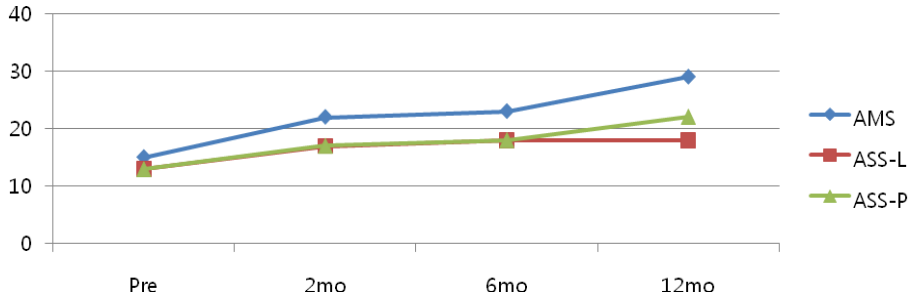

Figure 6. AMS, ASS-L and ASS-P graph of patient B

Table 8. SEP of patient B

	Preop (Rt/Lt)	POD 2mo (Rt/Lt)	POD 6mo (Rt/Lt)	POD 12mo (Rt/Lt)
Median SEP	20.00/18.55	21.40/27.60	21.05/23.15	18.10/16.70
Ulnar SEP	No[1]	No	No	**19.35/20.65**
Tibial SEP	No	No	No	**61.90/43.10**
Peroneal SEP	No	No	No	**44.80/44.60**
Pudendal SEP	No	No	No	**61.80**

[1] No response to SEP

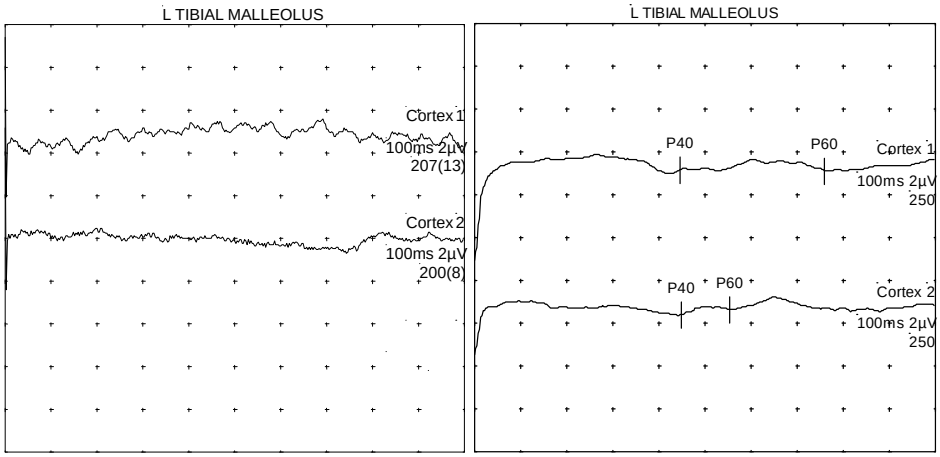

Figure 7. Left tibial SEP graph of patient B. Left one was obtained at preoperation evaluation and right one was obtained at twelve months after the transplantation.

In case of patient C, he had little improvement of AMS and ASS-P but after two months from transplantation, he had great improvements in ASS-L from 22 points to 76 points (Figure 8). But unlike patient B, patient C didn't show any interval changes of SEP studies compared to preoperation evaluations (Table 9).

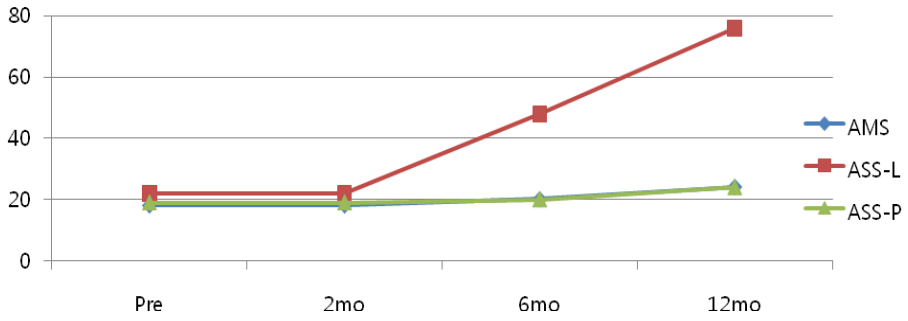

Figure 8. AMS, ASS-L and ASS-P graph of patient C

Table 9. SEP of patient C

	Preop (Rt/Lt)	POD 2mo (Rt/Lt)	POD 6mo (Rt/Lt)	POD 12mo (Rt/Lt)
Median SEP	20.50/20.60	26.40/26.70	20.20/20.00	20.60/20.25
Ulnar SEP	No[1]	No	No	No
Tibial SEP	No	No	No	No
Peroneal SEP	No	No	No	No
Pudendal SEP	No	No	No	No

[1] No response to SEP

4. MEP study

Three of the five patients who initially couldn't obtain a right biceps MEP had a normal right biceps MEP twelve months after the transplantation, and the remaining two of the five showed prolonged latency and low amplitude right biceps MEP (Table 10). Two of the five patients who initially couldn't obtain a left biceps MEP had a normal left biceps MEP twelve months after the transplantation, and one of the five showed prolonged latency and low amplitude left biceps MEP (Table 11). Patient I didn't show any improvement in right C5 motor score, but he revealed improvement in right biceps MEP (Figure 9). In case of left biceps MEP, patient E and H had improvement in left C5 motor score, but they could not obtain a left biceps MEP (Figure 10).

Table 10. Changes of right biceps MEP

Name	Preop		POD 2mo		POD 6mo		POD 12mo	
	Latency (ms)	Amplitude	Latency (ms)	Amplitude	Latency (ms)	Amplitude	Latency (ms)	Amplitude
E	No[1]	No	No	No	**21.48**	**0.22**	**15.76**	**0.62**
F	No	No	No	No	**14.47**	**0.79**	**25.86**	**0.69**
G	14.65	0.67	14.05	0.65	12.93	0.72	14.09	0.72
H	No	No	No	No	**12.39**	**1.37**	**12.16**	**0.83**
I	No	No	No	No	**14.49**	**0.75**	**15.99**	**0.88**
J	No	No	**13.01**	**0.40**	**14.57**	**0.65**	**14.13**	**0.75**

[1] No response to MEP

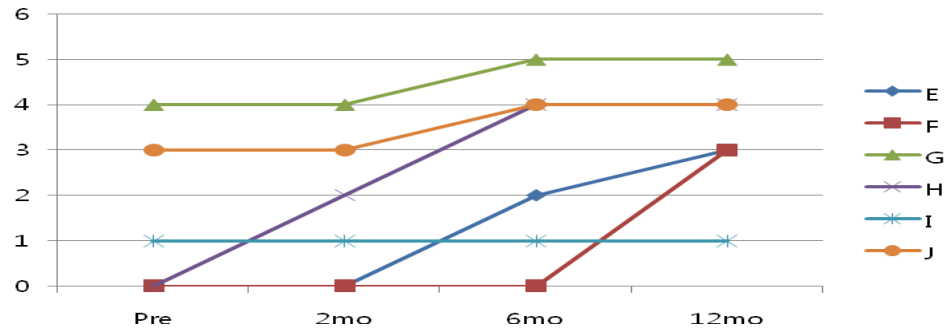

Figure 9. Right C5 motor changes of patient E, F, G, H, I, and J

Table 11. Changes of left biceps MEP

Name	Preop		POD 2mo		POD 6mo		POD 12mo	
	Latency (ms)	Amplitude	Latency (ms)	Amplitude	Latency (ms)	Amplitude	Latency (ms)	Amplitude
E	No[1]	No	No	No	No	No	No	No
F	No	No	No	No	**14.22**	**0.87**	**24.47**	**0.61**
G	13.46	0.46	13.98	0.74	14.04	0.81	15.33	0.92
H	No	No	No	No	No	No	No	No
I	No	No	No	No	14.31	1.25	17.37	0.53
J	No	No	**13.27**	**0.81**	**14.40**	**0.88**	**14.21**	**1.02**

[1] No response to MEP

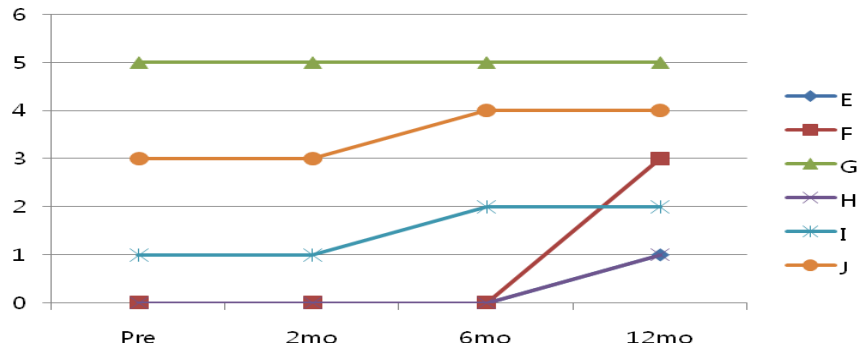

Figure 10. Left C5 motor changes of patient E, F, G, H, I, and J

In case of APB MEP, we could obtain a normal MEP from two patients before the transplantation, but twelve months after the transplantation patient D showed a prolonged latency and low amplitude of MEP on the right side (Table 12, 13). Patient D had no motor function of bilateral C8 and T1 key muscles before the transplantation, but patient D had an eight-point improvement in bilateral C8 and T1 key muscles at twelve months after the transplantation.

However, we couldn't obtain any TA MEP from all patients not only before

the transplantation but also after end of this study.

Table 12. Changes of APB MEP

Right	Preop		POD 2mo		POD 6mo		POD 12mo	
Name	Latency (ms)	Amplitude	Latency	Amplitude	Latency	Amplitude	Latency	Amplitude
A	22.20	0.59	22.29	0.67	20.92	1.33	19.80	1.34
D	No[1]	No	**24.85**	**0.39**	**25.95**	**0.07**	**28.59**	**0.18**
Left	Preop		POD 2mo		POD 6mo		POD 12mo	
Name	Latency (ms)	Amplitude	Latency	Amplitude	Latency	Amplitude	Latency	Amplitude
A	22.84	0.72	21.12	1.04	22.05	1.12	21.29	1.24
D	No	No	No	No	No	No	No	No

[1] No response to MEP

Patient F didn't show any improvement in AMS until six months after the transplantation but a six-point improvement in AMS was observed at twelve months after the transplantation. However, his ASS-P didn't show any improvement and ASS-L improved only two points at two months after the transplantation (Figure 11). At preoperation evaluation, we couldn't obtain all MEP study from him. At six months after transplantation, we could obtain a normal biceps MEP bilaterally and that preceded AMS changes (Table 14, Figure 12).

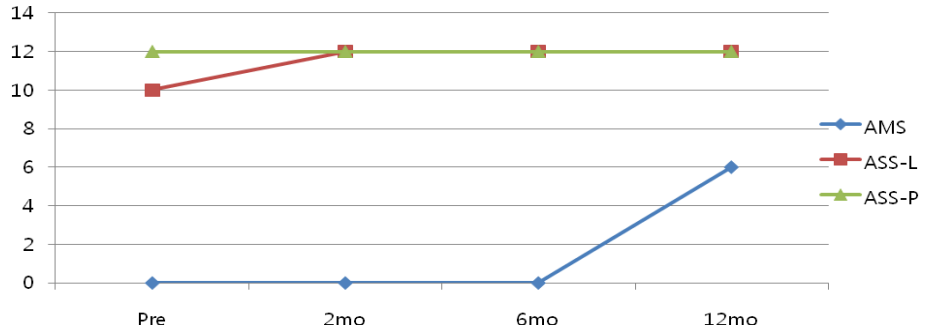

Figure 11. AMS, ASS-L and ASS-P graph of patient F

Table 13. MEP of patient F

		Preop		POD 2mo		POD 6mo		POD 12mo	
		Latency (ms)	Amplitude	Latency	Amplitude	Latency	Amplitude	Latency	Amplitude
Biceps	Right	No[1]	No	No	No	**14.47**	**0.79**	**15.76**	**0.62**
	Left	No	No	No	No	**14.22**	**0.87**	**24.47**	**0.69**
APB	Right	No	No	No	No	No	No	No	No
	Left	No	No	No	No	No	No	No	No
TA	Right	No	No	No	No	No	No	No	No
	Left	No	No	No	No	No	No	No	No

[1] No response to MEP

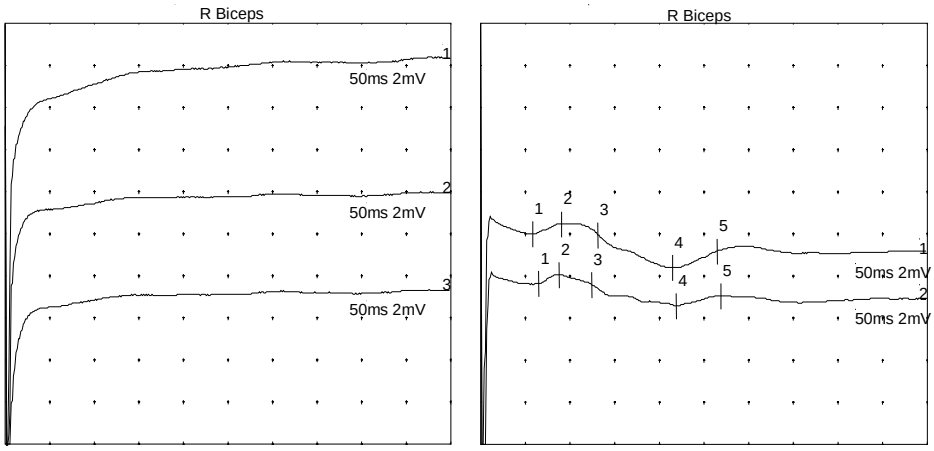

Figure 12. Right biceps MEP graph of patient F. The graph on the left was obtained at preoperation evaluation and the one on the right was obtained at six months after the transplantation.

Patient A had the greatest improvements in AMS and ASS-P among our patients and she converted from ASIA B to ASIA D as well. Most of the improvements occurred from preoperation to six months after the transplantation (Figure 13). But unlike patient F, patient A didn't show any interval changes in MEP studies compared to preoperation evaluations (Table 15).

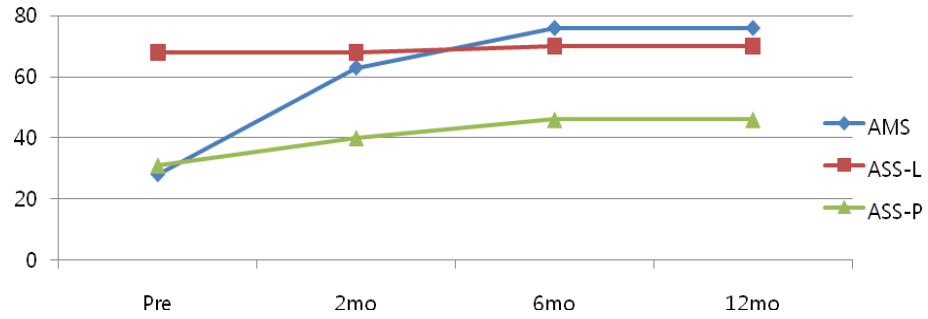

Figure 13 AMS, ASS-L and ASS-P graph of patient A

Table 14. MEP of patient A

		Preop		POD 2mo		POD 6mo		POD 12mo	
		Latency (ms)	Amplitude	Latency	Amplitude	Latency	Amplitude	Latency	Amplitude
Biceps	Right	14.02	1.84	14.19	1.86	15.33	1.42	12.62	1.70
	Left	12.58	1.23	12.58	1.10	15.06	2.33	12.86	1.53
APB	Right	22.20	1.07	22.29	1.21	20.92	2.59	19.80	4.55
	Left	22.84	0.72	21.12	1.46	22.05	1.57	21.29	2.79
TA	Right	No[1]	No	No	No	No	No	No	No
	Left	No	No	No	No	No	No	No	No

[1] No response to MEP

IV. DISCUSSION

In the present study, we could group our patients by their SEP and MEP results. In SEP study, there were three groups. The first one included those who had no response to any of SEP study at preoperation evaluation but had prolonged or normal response to that SEP study during follow-up period and through to twelve months after the transplantation. The second group included patients who had no response to any of SEP study at preoperation evaluation and had no interval change of that SEP study during follow-up period, or had a change during follow-up period but had it disappear at twelve months after the transplantation. Finally, the third group included those who had prolonged or normal response to any of SEP study at preoperation evaluation and maintained their response at twelve months after the transplantation.

In the first group, patient B had the greatest improvements in AMS and ASS-P and had the second largest improvements behind patient A among all patients. In case of ASS-L, patient J showed the greatest improvement. Also, patient B converted from ASIA A to C. Patient I's change of AMS was only 1.0%. All of them had improvement in ASS-L but patient F and B didn't show any improvement of ASS-P. The mean time from onset to hNSC transplantation was about 41 days and the range was from 23 days to 73 days.

In the second group, patient I had no improvements in AMS and ASS-L but others showed some improvements in AMS and ASS-L. Particularly, patient C had the greatest improvement in ASS-L among all patients and he converted from ASIA A to B. But patient G's change of ASS-L was only 1.1%. About ASS-P, all patients of the second group showed improvement. The mean time

from onset to hNSC transplantation was about 85 days and the range was from 28 days to 139 days.

In the third group, patient A had the greatest improvements in AMS and ASS-P among all patients and she converted from ASIA B to D. Patient D had improvement in AMS and had the third largest improvement among all patients but his ASS-L and ASS-P didn't change. The mean time from onset to hNSC transplantation was about 52 days and the range was from 25 days to 80 days.

As such, we couldn't find any common finding in each group. Among those who had improvements in SEP studies in the first group, one patient had the greatest improvement in AMS but another patient had smaller improvement in AMS than those of other patients in the second group. All of them had improvement in ASS-L but the greatest ASS-L changer was in the second group. Besides, two patients in the first group didn't show any improvement in ASS-P but all patients of the second group showed improvement of ASS-P.

There was no common finding in changes to ASIA. Patient B, who converted from ASIA A to C, was in the first group but patient C, who converted from ASIA A to B, was in the second group. And patient A, who converted from ASIA B to D, was in the third group.

Changes to AMS and ASS-L in each SEP are as follows. In case of median SEP, we calculated AMS and ASS-L of C5~T1 level. Patient J had little improvement in AMS and ASS-L of C5~T1 level, but he didn't show any change in median nerve SEP. On the other hand, patient F didn't show any improvement in ASS-L of C5~T1 level but his median nerve SEP showed normal response at twelve months after the transplantation. In case of ulnar SEP,

we calculated AMS and ASS-L of C7~T1 level. Patient B, E and H had improvement in AMS or ASS-L of C7~T1 level not patient F and I. But patient F and I showed improvement in ulnar SEP also. For tibial, peroneal, and pudendal nerve SEP, we calculated AMS of L4~S1 level and ASS-L of L4~S4 level. Patient B had only a two-point AMS improvement and only one-point ASS-L improvement, but she revealed prolonged latency of tibial, peroneal, and pudendal nerve SEP at twelve months after the transplantation.

The first group's mean time from onset to hNSC transplantation was shorter than the second group and patients whose mean time was longer than 100 days all fell in the second group.

In MEP study, there were three groups as well. The first one included those who had no response to any of MEP study at preoperation evaluation but had prolonged and low amplitude or normal response to that MEP study during follow-up period and through to twelve months after the transplantation. The second group included patients who had no response to any of MEP study at preoperation evaluation and had no interval change of that MEP study during follow-up period. Finally, the third group included those who had prolonged or normal response to any of MEP study at preoperation evaluation and maintain their response at twelve months after the transplantation.

In the first group, patient D had the greatest improvement in AMS and in case of ASS-L, patient J did. Patient I had the greatest improvement in ASS-P among these patients. But patient I didn't show any improvement in AMS, patient D and I didn't show any improvement in ASS-L, and patient F, B and D didn't show any improvement in ASS-P. The mean time from onset to hNSC

transplantation was about 64 days and the range was from 28 days to 122 days.

The second group included only patient K. He was paraplegic and his AMS and TA MEP didn't show any interval change. But he showed improvements of ASS-L and ASS-P. The time from onset to hNSC transplantation was ten days.

In the third group, patient A had the greatest improvements in AMS and ASS-P and patient C had the greatest improvements in ASS-L. The mean time from onset to hNSC transplantation was about 49 days and the range was from 23 days to 139 days.

As such, we couldn't find any common finding in each group as well as SEP study. In the first group, patient I didn't show improvement in AMS but he had improvement in MEP. Unlike patient I, patient K who was in the second group didn't show improvement of AMS and no interval change of MEP either.

We compared biceps MEP with C5 AMS and APB MEP with C8~T1 AMS. Some patient showed MEP improvement corresponding to AMS improvement, but another patient didn't show any MEP improvement despite AMS improvement.

These results do not match those from a previous study[15]. They concluded that they could observe an improvement of ASIA scores and it was accompanied by enhanced MEP and SEP. But they didn't mention the group who had no response to SEP study at preoperation evaluation and had a change during follow-up period but saw it disappear at twelve months after the transplantation. Also, they didn't compare AMS, ASS-L and ASS-P scores to SEP or MEP change.

V. CONCLUSION

We could find AMS, ASS-L and ASS-P changes after the cell transplantation and also some changes to SEP and MEP studies. But there wasn’t clear common finding between the groups. Therefore, SEP and MEP studies may not prove in assessing the efficiency of the stem cell transplantation.

REFERENCES

1. Fawcett JW. Overcoming inhibition in the damaged spinal cord. J Neurotrauma 2006;23:371-83.

2. Baptiste DC, Fehlings MG. Update on the treatment of spinal cord injury. Prog Brain Res 2007;161:217-33.

3. Coutts M, Keirstead HS. Stem cells for the treatment of spinal cord injury. Exp Neurol 2008;209:368-77.

4. Cheliout-Heraut F, Loubert G, Masri-Zada T, Aubrun F, Pasteyer J. Evaluation of early motor and sensory evoked potentials in cervical spinal cord injury. Neurophysiol Clin 1998;28:39-55.

5. Li C, Houlden DA, Rowed DW. Somatosensory evoked potentials and neurological grades as predictors of outcome in acute spinal cord injury. J Neurosurg 1990;72:600-9.

6. Delisa J, Gans B, Walsh N, Bockenek W, Frontera W, Geiringer S et al. Physical medicine & rehabilitation : Principles and practice. 4th ed. Philadelphia: LWW; 2005.

7. Curt A, Dietz V. Ambulatory capacity in spinal cord injury: significance of somatosensory evoked potentials and ASIA protocol in predicting outcome. Arch Phys Med Rehabil 1997;78:39-43.

8. Curt A, Dietz V. Traumatic cervical spinal cord injury: relation between somatosensory evoked potentials, neurological deficit, and hand function. Arch Phys Med Rehabil 1996;77:48-53.

9. Curt A, Keck ME, Dietz V. Functional outcome following spinal cord injury: significance of motor-evoked potentials and ASIA scores. Arch Phys

Med Rehabil 1998;79:81-6.

10. Iwanami A, Kaneko S, Nakamura M, Kanemura Y, Mori H, Kobayashi S et al. Transplantation of human neural stem cells for spinal cord injury in primates. J Neurosci Res 2005;80:182-90.

11. Chernykh ER, Stupak VV, Muradov GM, Sizikov MY, Shevela EY, Leplina OY et al. Application of autologous bone marrow stem cells in the therapy of spinal cord injury patients. Bull Exp Biol Med 2007;143:543-7.

12. Lee KH, Yoon DH, Park YG, Lee BH. Effects of glial transplantation on functional recovery following acute spinal cord injury. J Neurotrauma 2005;22:575-89.

13. Lee KH, Suh-Kim H, Choi JS, Jeun SS, Kim EJ, Kim SS et al. Human mesenchymal stem cell transplantation promotes functional recovery following acute spinal cord injury in rats. Acta Neurobiol Exp (Wars) 2007;67:13-22.

14. Moviglia GA, Fernandez Vina R, Brizuela JA, Saslavsky J, Vrsalovic F, Varela G et al. Combined protocol of cell therapy for chronic spinal cord injury. Report on the electrical and functional recovery of two patients. Cytotherapy 2006;8:202-9.

15. Sykova E, Homola A, Mazanec R, Lachmann H, Konradova SL, Kobylka P et al. Autologous bone marrow transplantation in patients with subacute and chronic spinal cord injury. Cell Transplant 2006;15:675-87.

16. Association ASI. International standards for neurological classification of spinal cord injury. Chicago: ASIA; 2002.

17. Liveson J, Ma D. Laboratory reference for clinical neurophysiology. 1st ed. Philadelphia, Seoul: F.A. Davis company, Yeong mun publishing company;

1992.

18. Dumitru D, Amato AA, Zwarts M. Electrodiagnostic medicine. 2nd ed. Philadelphia: Hanley & Belfus, INC.; 2002.

19. Steeves JD, Lammertse D, Curt A, Fawcett JW, Tuszynski MH, Ditunno JF et al. Guidelines for the conduct of clinical trials for spinal cord injury (SCI) as developed by the ICCP panel: clinical trial outcome measures. Spinal Cord 2007;45:206-21.

< ABSTRACT>

척수손상 환자에서 동종인간신경줄기세포 이식 후 체성감각유발전위와 운동신경유발전위 검사 소견의 변화

<지도교수 신지철>

연세대학교 대학원 의학과

유지현

본 연구에서는 체성감각유발전위 검사와 운동신경유발전위 검사가 신경줄기세포 이식술의 효과를 판정하는데 유용하게 이용될 수 있는지에 대해 살펴보고자 하였다.

총 11 명의 환자들에게 동종인간신경줄기세포를 이식하였고, 신경줄기세포 이식술 이전과 이후 2 개월, 6 개월, 12 개월에 각각 신경학적 검사 및 체성감각유발전위 검사, 운동신경유발전위 검사를 시행하였다. 시술 전 양측 정중신경 체성감각유발전위 검사에서 반응을 보이지 않았던 4 명의 환자 중 3 명의 환자, 시술 전 척골신경 체성감각유발전위 검사에서 반응을 보이지 않았던 8 명의 환자 중 5 명의 환자가 시술 후 12 개월에 우측 척골신경에서 정상 잠시 또는 느려진 잠시의 반응을 보였고, 3 명의 환자가 좌측 척골신경에서 정상 잠시 또는 느려진 잠시의 반응을 보였다. 시술 전 양측 경골신경, 비골신경, 음부신경 체성감각유발전위 검사에서 반응을 보이지 않았던 10 명의 환자 중 1 명의 환자가 시술 후 12 개월에 느려진 잠시의 반응을 보였다.

시술 전 양측 이두근에서 측정한 운동신경유발전위 검사 상 반응을 보이지 않았던 5 명의 환자 중 우측 이두근에서 3 명, 좌측 이두근에서 2 명, 단무지외전근에서 반응을 보이지 않았던 9 명의 환자 중 우측 단무지외전근에서 1 명의 환자가 시술 후 12 개월에 반응을 얻을 수 있었다. 전경골근의 운동신경유발전위는 모든 환자에서 시술 전, 시술 12 개월 후에 반응을 보이지 않았다. 신경줄기세포 이식술 이후 체성감각유발전위 검사, 운동신경유발전위 검사 상의 변화와 환자들의 운동 또는 감각점수의 변화와의 연관성을 찾아볼 수 없었다. 운동 또는 감각점수의 호전과 더불어

체성감각유발전위 검사 상의 변화를 보인 환자도 있었지만, 운동 또는 감각점수의 호전은 있었지만 체성감각유발전위 검사, 운동신경유발전위 검사 상의 변화가 전혀 관찰되지 않았던 환자들도 있었다.

따라서 환자의 신경학적 회복을 평가하는 방법으로 사용되기에는 한계가 있을 것이다.

핵심되는 말 : 줄기세포 이식술, 체성감각유발전위 검사, 운동신경유발전위 검사