ORIGINAL REPORT

Safety of Intramedullary Autologous Peripheral Nerve Grafts for Post-Rehabilitated Complete Motor Spinal Cord Injuries: A Phase I Study

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Abstract- Many experimental studies have reported behavioral improvement after transplantation of peripheral nerve tissue into the contused spinal cord, even in large animals. The safety of this treatment in human remains unknown. In this translational phase 1 study, safety of peripheral nerve grafting for chronic spinal cord injuries and possible outcomes are being reported. Twelve complete motor spinal cord injury patients, who had finished their rehabilitation program, were enrolled. There were 4 thoracic and 8 cervical cases. Patients underwent sural nerve preconditioning in the calf, followed 1week later, by intramedullary transplantation of the harvested nerve fascicles. The patients were followed up for potential complications periodically, and final assessment by American Spinal Injury association (ASIA) and Spinal Cord Independence Measure (SCIM) III were reported after 2 years of follow-up. The median duration of the spinal cord injury was 31 months. At two years of follow up, out of 7 cases with ASIA Impairment Scale (AIS) A, 4(57.1%) cases improved to AIS B and 1 (14.3%) case became AIS C. There were 1 patient with transient increased spasm, one case of transient cystitis, 3 patients with transient increased neuropathic pain and 1 case with transient episode of autonomic dysreflexia, all being managed medically. There was no case of donor site infection. The above complications were transient as they responded to temporary medical treatment. It may be deduced that after two years follow-up of patients that the procedure may be safe, however further controlled studies are needed to prove its efficacy.

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Keywords: Spinal Cord Injury; Peripheral Nerve Graft; Safety

Introduction

Spinal cord injuries (SCI) remain amongst the most devastating human ailments worldwide with a heterogeneous epidemiological pattern (1-8), relatively significant disability adjusted life years, and ominous complications, during the time elapsed after injury (9-13). New trials have been undertaken in an effort to diminish the disability adjusted life years of the disease, with an enormous scientific effort to achieve clinically applicable treatments, suitable for conducting SCI clinical trials (14,15). These treatments have been employed, as an adjuvant to rehabilitation programs, to overcome known limitations in achieving plausible clinical outcomes (16-19), and if possible reducing the cost of annual care. Experimental models with Schwann cells, and olfactory ensheathing glia transplantation (20,21) intracellular cAMP modulation as well as stem cell derivatives (22-24), all have been promising (25) for SCI management trials.

Similarly, well-formed neural tissue structures have also been applied for SCI treatment, such as, application of peripheral nerve grafting (PNG) (26,27). Pieces of peripheral nerve have been used to reconnect spinal cord stumps in chronic paraplegic states (28) and shown significant regeneration of myelinated axons (29, 30).

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Preliminary experimental studies on PNG, proven its efficacy in promoting regeneration (31), and, in small mammals it had repairing effects on chronic SCI (32-35), while immune suppression, might not be required (15,36). Clinically, various cell transplantations studies have been conducted previously, and the results reported (25,37,38). Saberi (25) and Wu (39) reported subjects with spinal cord injury receiving intramedullary injection of Schwann cell suspension and a FGF fibrin glue. In the same way, may be samples of this effort the current study we have tried to make a myelotomy and implant the peripheral nerve fascicles into the syrinx, i,e, a solid tissue, not just cell suspension. This may pave the way for the future trials with tissue engineered scaffolds provided safety is established. There are some similarities with our previous study on Schwann cell injection into the spinal cord in their selection criteria; however, the implantation technique is somehow different from that study. Actually the main effort has been tackling larger tissue gaps within the spinal cord, where the axonal sprouting may be a greater problem than small intramedullary cavities which may be easily filled by cell suspension. The problems of preclinical phase including, graft viability, connectivity to the cord, axonal sprouting, alignment, axonal outgrowth, myelination, effectiveness, exacerbation of complications, such as spasticity and neuropathic pain are important issues. A comparison between Schwann cell and peripheral nerve graft reported by Hill (40) has thoroughly surveyed experimentally the two methods, without functional improvement. Meanwhile Hanna (41), mentioned that clinical translation of peripheral nerve grafting for spinal cord injury should be based on evidences coming from large animals, thereafter Cote (26) in a study on spinal cats showed functional and regeneration promotion, after peripheral nerve grafts paving the way toward clinical translation. However one should keep in mind that these studies do not predict safety of the clinical trial; therefore, this study was performed as a phase I safety study. So several recommendations for immediate, further and larger clinical trials (42) and phase 1 studies with the therapeutic interventions in human subjects have been reflected (43) into this study. The aim of this study was to assess the safety of PNG for SCI patients, and report possible outcomes.

Patients and Methods

Ethical considerations and safety precautions

The trial was conducted in twelve patients having American Spinal Injury Association (ASIA) Impairment Scale (AIS) Grade A and/or Grade B, with approval from the medical ethics committee review board of Tehran University of Medical Sciences (38). Informed consent was obtained from all the patients. All of the clients had been rehabilitated according to standard physical and occupational therapies for their level of injury at least 6 months. They had complete motor SCI, being more than 18 years old (44). The patients underwent new Magnetic Resonance Imaging (MRI) evaluation to check the current status of the spinal cord at injury level. The signal change area dimensions, as a marker of the amount of tissue loss, were measured on midsagital T1-weighted images. Because T2 pulse sequences may overestimate the cavity size and fascicular length may not match defect size. Those being >20 mm rostrocaudally were excluded from the study (Figure 1).

Patients with evidence of untreated canal compromise, cord compression, and spinal angulation deformity >40 degrees were not included. Any evidence of developing and/or expanding syringomyelia over two or more spinal segments excluded the patient from the study. Patients with electrophysiological evidence of muscle fibrosis and moderate-to-severe axonal degeneration on motor nerves, and those without sural sensory responses were also excluded. Almost 32 patients out of 128 cases studied, showed muscle fibrosis especially in the lower limbs mainly due to lower motor neuron involvement due to extensive cord destruction, as well as in those with deep large buttock pressure ulcers. This criterion does not apply to cervical patients who commonly have this phenomenon in one motor segment at the lesion level. The lack of sural response was important because it was an indirect sign of irreversible sural nerve damage, which we used as the donor for the harvest of graft fascicles.

Fortunately this nerve was mostly functional in our patients. The diagnosis was made on the basis of nerve conduction velocity study as well as sensory nerve action potential (SNAP) of sural, superficial peroneal (lower limbs), and median, ulnar, superficial radial nerves (upper limbs). In compound motor action potential (CAMP) study, tibial, deep peroneal, femoral (lower limbs), and median, ulnar, musculocutaneous, axillary nerves were studied. Electeromyographic study was performed on tibialis anterior, peroneous longous, gastrocnemius, vastus medialis, and pelvic muscles if necessary in the lower extremity, and biceps, flexor carpi radialis, first dorsal interosseous muscles, in the upper limbs.

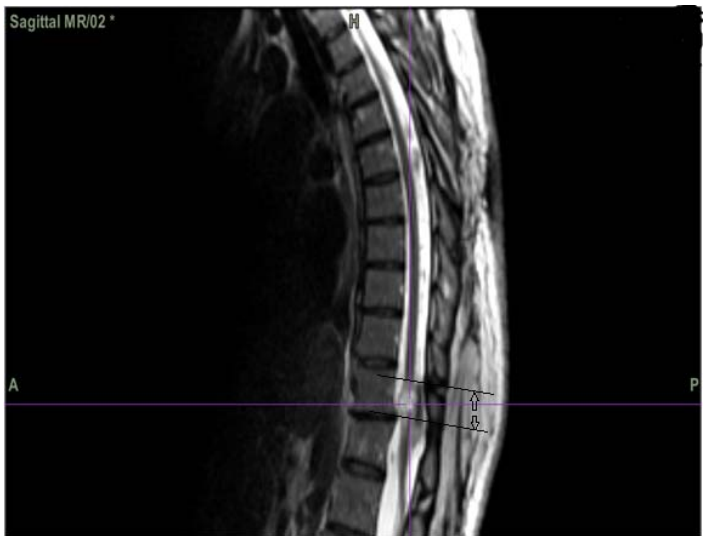

Figure 1. Preoperative T2 weighted MRI of a patient with thoracic spinal cord injury showing the area of signal change (intramedullary cavity). The distance between the arrow tips was assumed as lesion length.

Bladder assessments as determined by urodynamic study were performed to confirm, detrusor hyperreflexia (ruling out areflexia) along with sufficient capacity (>70 ml), without significant vesicouretheral reflux, on sonograms.

Study population

Among 128 cases of SCI with AIS A or B having completed at least 6 months of a standard rehabilitation program, 12 volunteers were qualified according to the above criteria and sequentially scheduled for the study. The adherence to physical as well as occupational therapy protocols, as recommended for the level, and close monitoring for complications in spinal joint clinic was assumed as acceptable program, the same protocols were followed without change in the follow-up period. The exclusions were due to either incomplete rehabilitation programs, or chronic complications and cord lesions larger than 20mm. The assessments included physical examination for any complications, neurological status, and functional changes in terms of ASIA and Spinal Cord Independence Measure (SCIM) III scoring were documented by independent evaluators(44-46). Patients were neurologically examined in terms of sensory, motor, bowel, bladder, and sexual function (47). The patients underwent serial examinations by independent evaluators to detect any neurological changes at 2 weeks post-implantation and regular intervals during 2 year period. Any sign of infection, CSF leakage, pain, and spasm scores were checked. Also, the patients underwent complete neurological examination quarterly.

Procedure

Sural nerve preconditioning was performed on an inpatient basis seven days before the main procedure. The time interval was about 1week, i.e. first the sural nerve was exposed and transected, and buried in the soleus muscle for 1wk, and then the fascicle dissection and implantation procedure took place in the next procedure. At this stage, the proximal 15cm of sural nerve in the upper calf was identified as the main harvest portion for autologous PNG. After induction of local anesthesia, through a 10-cm incision, beginning 4 fingers' breadth below the popliteal skin fold, coursing caudally in the midline on the back of the calf, opening the superficial fascia the sural nerve was exposed and dissected from the homonymous vein. Later, the nerve was distally cut, and the proximal stump was buried between the bellies of subjacent soleous muscle. A week later 10cm of preconditioned sural nerve was resected for preparation. The epineurial sheaths were meticulously removed to obtain the nude nerve fascicles under magnification. They were preserved in autologous serum solution during the procedure (48). Actually autologous serum was obtained and handled by clean method, in positive pressure, filtered atmosphere. There was no further additive or ingredient to the serum. The intramedullary cavity (25) was identified on preoperative MRI, with the patient placed prone after induction of conventional general anesthesia; the level was marked on the skin of the back at midline as

identified by C-arm image intensifier. Through a 7-cm incision and paravertebral muscle dissection and laminectomy, performed at the precise level, a 5-cm durotomy was done under the operating microscope visualization. A midline 10 mm myelotomy was performed meticulously exposing the lesioned cord. The nerve fascicles were cut to the size of the cavity, embedded in the autologous fibrin coagulum as one piece, and were placed in the syrinx. Thereafter the myelotomy was closed with 10-0 sutures. After meticulous hemostasis and watertight dural closure, the wound was closed in an anatomical fashion. The patients received parenteral antibiotics overnight and ambulated in the wheelchair after 48 hours. The previous rehabilitation programs were resumed on follow-up, to prevent any functional decline (49).

Patients were followed for any evidence of systemic and/or local illnesses and complications, at 1 month intervals (50). ASIA sensory and motor assessments formed the basis for the neurological assessments in this trial (51). Sexual function was assessed considering the suggested autonomic ASIA scores. Functional evaluations were performed using SCIM III tool, to assess activities of daily living. Any reports of discomfort, pain, and deterioration as well as general surgical complications were recorded by the evaluator team. Final comparisons were performed after two years with baseline measures and reported (44). The rehabilitation protocol in post-operative period was just resumption of the previous protocols after wound healing.

Statistical methods

The median and inter-quartile range (IQR) was used to describe the sample. For statistical analysis, the nonparametric Wilcoxon signed-rank test was applied for comparing ASIA scoring, SCIM III scores, before and after treatment. Spearman correlation coefficient was used for calculating intercorrelations between variables; Light touch, Pin Prick, Motor and SCIM changes were also assessed with chronicity of SCI. A P-value <0.05 was considered as statistically significant.

Results

Patient characteristics

Among 12 eligible volunteers, there were 9 men and 3 women. The median age at presentation was 30.5 years (range 19-42 years), and the median duration of SCI after trauma was 31.0 months. The most common cause of SCI was motor vehicle accident (75%), followed by falls (25%). There were 4 (33.3%) patients with thoracic and 8 (66.7%) with cervical injuries. Summary measures for demographics and clinical assessments have been tabulated in Table 1.

Pre-treatment and post-treatment MRIs have been depicted for better comparison in figure 3.

Nine were categorized in AIS A, and the 3 remaining participants had AIS B (Table 1). The rostrocaudal length of the signal change area on T1-weighted MR images was between 7 and 20 mm, with the mean value being 14.4mm.

Table 1. Demographic and clinical features of the patients.

Patient	Sex	Age	Chronicity of SCI (Moths)	Level of SCI	Onset of improvement (Months)	End of improvement (Months)	Before				After			
							LT	PP	M	AIS	LT	PP	M	AIS
1	F	40	6	C4	3	9	12	12	0	A	32	32	10	C
2	M	42	58	C5	1	3	13	13	0	A	15	15	0	A
3	M	29	41	C5	1.5	3.5	22	32	22	A	28	32	22	B
4	F	19	32	C5	2	12	40	40	14	A	44	42	18	B
5	M	32	30	C7	2	6	68	30	28	B	68	30	34	B
6	M	28	48	C7	6	12	78	44	50	B	112	76	50	B
7	M	23	24	C7	2	6	74	50	48	B	74	50	50	B
8	M	23	14	C7	3	8	50	30	36	B	75	31	46	B
9	M	37	6	T4	4	12	41	44	50	A	52	52	50	B
10	M	23	52	T4	3	6	82	82	50	B	82	82	50	B
11	F	39	11	T11	4	9	68	68	50	A	76	76	50	B
12*	M	39	36	T12	1	2	78	78	50	A	78	78	50	A

*The improvement in case (12) was the reversal of neurological decline after surgery

Table 2. ASIA motor and sensory and SCIM III scores* at baseline and after peripheral nerve graft treatment in 12 patients with SCI and their subgroups.

	Preop Median (IQR)	Postop Median (IQR)	Postop-Preop	*P* value
Motor index‡ (upper extremity)	42.0 (16.0-50.0)	48.0 (19.0-50.0)	6.0	0.042
Light touch	59.0 (26.5-77.0)	71.0 (35.0-77.5)	12.0	0.012
Pin prick	42.0 (30.0-63.5)	46.0 (31.3-76.0)	4.0	0.018
SCIM III	29.5 (11.0-40.5)	39.5 (23.5-54.5)	10.0	0.003

*Median values and interquartile ranges are reported. Ranges for score categories are as follows. Motor: minimum 0, maximum 50; light touch: minimum 0, maximum 112; pinprick: minimum 0, maximum 112, SCIM: minimum 0, maximum 100

‡ All patients were paraplegic and lower extremity motor power before and after the intervention was zero

Table 3. Inter-correlation of motor, light touch, pin prick changes and chronicity of SCI.

	1	2	3	4	5
1. Chronicity of SCI		- 0.51	-0.36	-0.32	-0.45
2. Motor change			0.14	0.01	0.58*
3. Light touch change				0.80*	0.07
4. Pin prick change					0.01
5. SCIM III change					

*$P<0.05$

Findings based on the ASIA scale

The median of ASIA motor scores improved significantly by 6.0 points from preoperative value to 24 months post-operatively (P=0.042). The ASIA assessment sensory scores showed significant improvement in light touch (12 points, P=0.012) and pinprick (4 points, P=0.018) (Table 2).

After 24 months of treatment, Out of 7 AIS A patients, 4 improved to grade B (57.1%) and one to grade C (14.3%), however, in AIS B patients, no improvement was observed in AIS (Table 1). The onset and end of improvement for each patient has been tabulated in Table 1. Motor improvement had a negative correlation to chronicity with borderline significance (r=-0.51, P=0.093); also sensory changes showed a negative correlation with chronicity of SCI (Table 3).

Sphincteric and sexual findings

Six patients reported new urinary sensations, new fecal sensation was reported by 2 patients, menstrual sensation was observed in 2 patients. Documented new psychogenic erection was not reported in our patients.

Functional assessment

The median SCIM III score of the patients was 29.5 (IQR, 11.0-40.5) and improved to 39.5 (IQR, 23.5-54.5) scores after treatment (P=0.003) (Table 2). Also, significant improvements were observed in some items of SCIM III, such as, bathing (lower body), mobility in bed, mobility indoors, mobility (10-100 meters) and respiration (P<0.05) (Figure 2).

SCIM improvement was significantly positively correlated with motor improvement (r=0.58, P=0.48), but it is not correlated with sensory changes (Table 3). Chronicity of SCI had a considerable negative correlation with SCIM improvement (r=-0.045, P=0.14).

There was no case of permanent neurological worsening or infectious or viral complications. No new increment in syrinx size, neither abnormal tissue nor tumor formation was observed on control MRIs.

Post-operative complications

One of the patients had a transient low-grade fever and 7 had transient nausea, vomiting, and 3 had headaches, one of them associated with hypertension, due to autonomic dysreflexia provoked by surgery. There was a transient neurological decline in 1 patient which resolved after 2 months of rehabilitation.

This patient was a thoracic (T12) AIS A case, after the procedure the Light Touch (78) and Pin Prick (78) scores declined to Light Touch (78) and Pin Prick (76). After two months of follow up, his Light Touch score returned to (78), and Pin Prick score remained unchanged (78); however, no sensory motor promotion was observed in this case, the transient change was attributed to local inflammatory response due to surgical intervention and/or manipulation, none of our cervical patients showed evidence of deterioration.

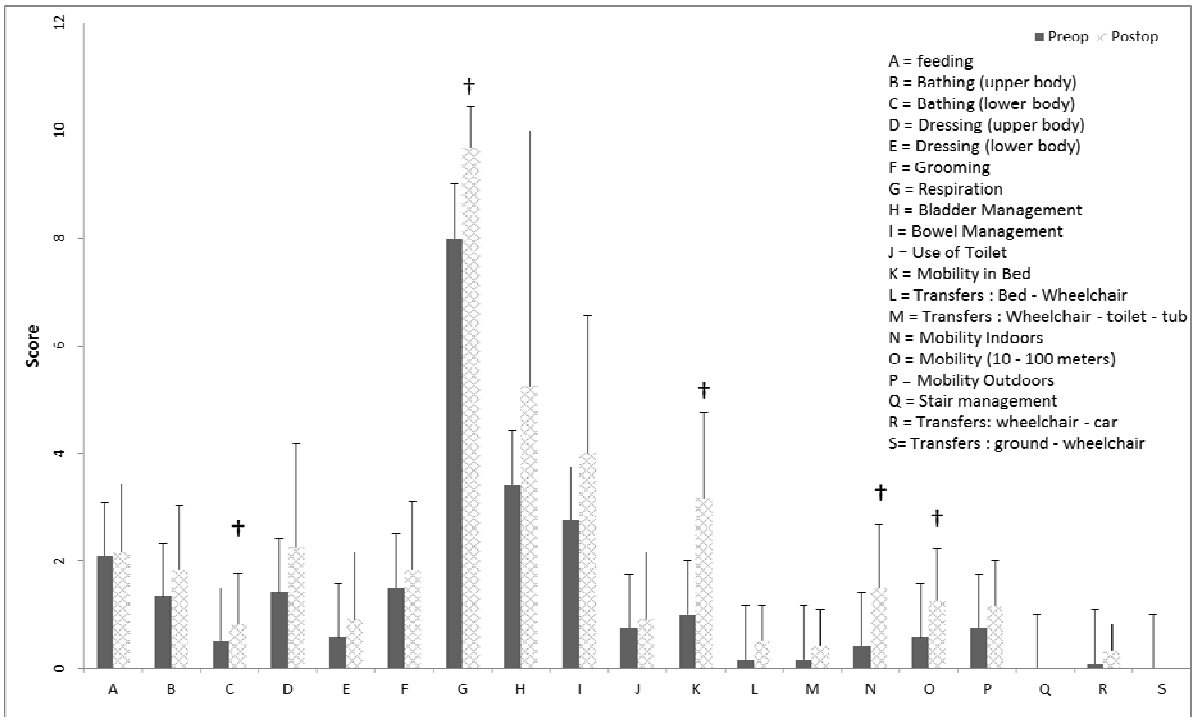

Figure 2. Spinal cord independence measure (SCIM) III scores, before and after peripheral nerve graft. Cross symbol (†) shows significant improvement in some items of SCIM, such as, bathing (lower body), mobility in bed, mobility indoors, mobility (10-100 meters), and respiration.

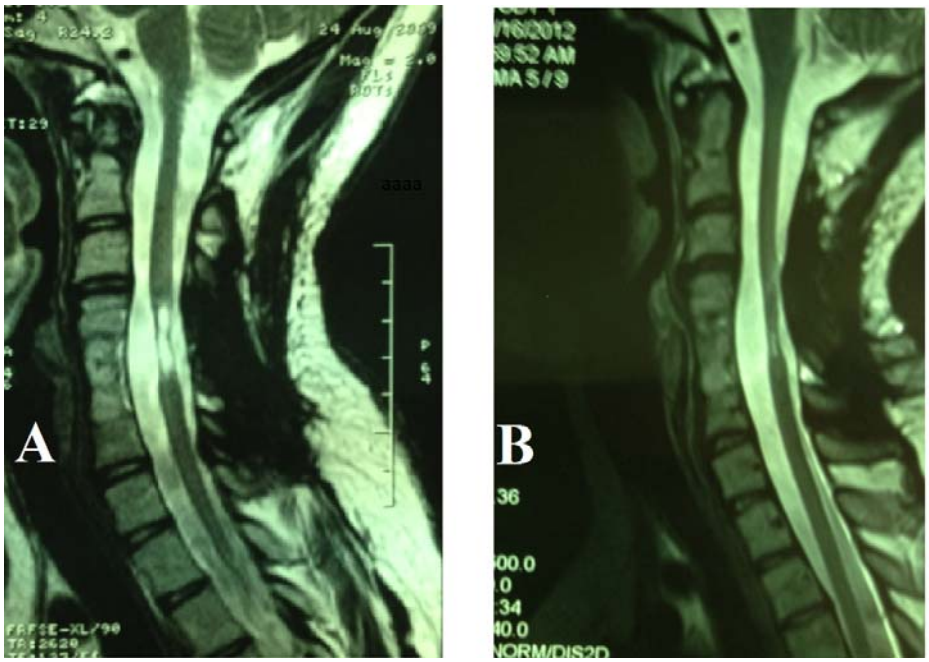

Figure 3. A: pre-operative T2 weighted MRI of a patient with cervical spinal cord injury. B: Post-operative T2 weighted MRI of the same patient obtained 2 years after transplantation, showing the high signal area of myelomalacia replaced by isointense signal (peripheral nerve graft).

There were no patients with superficial wound and/or deep infections or CSF leakage. Follow-up MR imaging studies at 2 years did not reveal any mass or deformity related to the procedure (Figure 3). There

were 1 patient with transient increased spasticity (one score increment in modified Ashworth scale), one case of transient cystitis, 3 patients with transient increased neuropathic pain and 1 case with transient episode of autonomic dysreflexia, all being managed medically. Transient increased spasms and pain lasted for a 4 weeks period, during this period the patients received Gabapentin 300 mg and/or Baclofen 10 mg three times a day orally, tapered after 6 weeks. There was no case of donor site infection.

Discussion

In an effort to promote neurological improvement after SCI, many interventions have been made to curb secondary loss of tissue, cellular bridges to span cavities, in addition to modifying factors for cell growth, inflammatory response, scarring, neutralizing inhibitory factors, and rehabilitation to maximize the overall effect (49). Most neurodegenerative treatments may have safety risks (52); therefore, evidence-based medicine criteria and ethical standards (53), should form the basis for their recommendation (54). New interventions require efficacy evaluation using proper outcome measures (17, 55). We used ASIA motor sensory scores as the main outcome measure as well as clinical standards for safety assessments such as, self report for pain and modified Ashworth scale for spasticity, and SCIM III for functional outcomes, and neuroimaging (MRI) to assess any mass or deformity formation (35). Application of transplantation strategies for the repair of sustained SCI remains the long sought after "Holy Grail", however regenerative approaches have been reported to be more successful, when applied in the subacute phase of injury, because in the chronic phase a strategy to overcome the effects of glial scar, may be required (56). All the patients in our study were in the chronic stage. Also scarring may occur at the PN spinal cord interface.

Anatomically, supralesional peripheral nerve grafts, performed after 2 to 3 weeks have been associated with neural regeneration in experimental models (57) and also, some axons within the peripheral nervous system bridges have been shown to originate from neurons in the brain stem and spinal cord (58). Many studies on the subacute and chronic SCI, treated by PNG with and without additional trophic factors, and/or scaffolds, are in favor of behavioral improvement (59-64). Fibrin/fibronectin gel has supported good axonal ingrowths in SCI cavities (65), and regarding the safety of autologous serum reported before, in this study we applied it as a scaffold to encompass and support the nerve fascicles. It may have neurodegenerative effect as well as keeping the fascicles together in the gap, however the net contribution of each possible effect to various outcomes needs to be clarified in separate studies.

Many studies have found that neurological outcomes may be better in patients with shorter disease duration; this finding may be due to prominence of glial scar problem in older lesions (66-69). Conduction of studies early in the course of SCI may be suggested for future studies. Noteworthy to mention again scarring can also occur at PN/ spinal cord interface at the site of transplantation.

To enhance the neuroregenerative effect of PNG several experimental strategies have been suggested Biochemically, matrix -metalloproteinase 2 (70), macrophage derived polyamines(71), glial cell line-derived neurotrophic factor (72), neurotrophin-3 (73), gonadal steroids (74), and N-acetyl cysteine (75), fibroblast growth factor (76-81), anti-inflammatory drugs, and fibrin glue, have all been shown to have this effect. Still all of these modalities require established safety evaluations before consideration for clinical application.

Experimentally preconditioning has been studied elsewhere. Pre-degenerated axons of cut nerves are infiltrated to a greater extent with regenerating axons (82). Also mechanically stressed peripheral nerve grafts (83,84), have been used before. Preconditioning was performed for our patients 1 week before PNG assuming it as a safe procedure for clinical trial. Actually at first for both procedures, (ie preconditioning and harvest-implant) informed consent was obtained, however to eliminate cumulative risk, if there was a problem in the preconditioning stage of the sural nerve, the next step would not have taken place (85) however this never happened in our series.

Transient low-grade fever, transient nausea, and vomiting could be attributed to general anesthesia. Headaches in 2 cases were attributed to intraoperative cerebrospinal fluid drainage, and one possibly due to preoperative autonomic dysreflexia. There was a transient neurological decline in one patient, which resolved after 2 months of rehabilitation, this could be due to effect of surgical manipulation, and/or local reaction to the transplanted tissue. To minimize tissue manipulation the myelotomy was centered at the very point of the spinal cord lesion (abnormally looking tissue) in the midline. There were no patients with superficial wound and/or deep infections or CSF

leakage. Follow-up MR imaging studies at 2 years did not reveal any mass or deformity related to the procedure (Figure 3). There was 1 patient with transient increased spasticity (1 score increment in modified Ashworth Scale), 3 patients with mild transient neuropathic pain and 1 case with transient episode of autonomic dysreflexia, all successfully managed medically. These effects may be explained on the basis of temporary local inflammatory response. The transient cystitis, in one case was due to Foley catheterization with negative culture results. For safety precaution, any side effect (like infection), making the implantation of predegenerated fascicles into the spinal cord a threat for the patient, was an indication to stop proceeding to the next step, although this never happened in our cases.

High quality standards may even further diminish these untoward effects, and make the procedure even safer. The suggestions include: minimizing the surgical trauma by possibly using minimally invasive methods, strict aseptic technique during urinary catheterization, prophylaxis of cystitis if indicated, early resumption of clean intermittent catheterization instead of permanent Foley catheterization, prevention of nausea and vomiting in the postoperative course by changing anesthesia plan and administration of preventive medications in the induction phase of anesthesia, and precautions to prevent episodes of autonomic dysrefelexia.

Studies show that even a relatively small number of regenerated supra-spinal axons can promote a significant measure of functional improvement (86,87), the significant SCIM III score changes in our patients (15) may be explained on this basis. However changes in SCIM III scores are not always the result of a demonstrated change in neurological activity, in fact it may be due to neural adaptation or plasticity of the spinal cord (44), therefore the functional improvements in terms of SCIM III scores should be interpreted in the same way. Although rehabilitation in chronic spinal cord injury may improve SCIM scores, however the neurological status rarely changes after 24 months and most SCI cases may be assumed neurologically stable after this period.

Clinically, many trials of cell and tissue transplantation into the injured spinal cord found them to be safe and feasible (88-93). Our study was technically similar to the latter method, because formed tissue was applied for transplantation. In a single case report; from another center, a chronic paraplegic patient in whom nerve graft and growth factor were used simultaneously had shown significant motor recovery (94).

The enrolled populations in this study are more or less heterogeneous, compared to Schwann cell study (25), as well as sample size, however further studies with controlled design may be mandatory to compare the effects of nerve fascicle and cell suspensions in terms of neurological recovery. Fortunately, the complications do not seem to be so major in any of the studies.

Most of AIS B patients in this series had either cervicothoracic or thoracic lesions with no motor score changes, while most AIS A patients had cervical lesions that showed a change to AIS B and even C after treatment. The author has previously (25) shows that motor recovery below the neurological level is more commonly detected in cervical lesions, than the thoracic lesions, possibly because, intercostal motor recovery does not change motor ASIA scores in thoracic patients. The same scenario was observed in this study. Minimally invasive cell delivery approaches, are preferable to avoid further scar formation, and damage to the spinal cord, as was the inability to repeat the treatment (55), however our technique was not minimally invasive. The role of spinal cord untethering and syrinx drainage should also be mentioned as a potential explanation for neurological changes, from AIS A to B/C. The contribution of rehabilitation should also be considered, although determination of the net effect may require a controlled study.

On the other hand, in this study the patients and investigators were not blinded, and there may be a confounding placebo effect, necessitating conduct of future trials with controlled blinded groups. Also we can not predict fiber alignment, cell permeation into the injury niches, and SC migration after PNG. Therefore sophisticated paraclinical evaluations, such as tractography, and nanotechnology for cell tracing may be promising to achieve these goals. In conclusion, autologous peripheral nerve grafting for motor complete SCI may be safe. It seems that further controlled studies are needed to show the efficacy of PNG in individuals with SCI.

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