
The Role of Adipose Derived Mesenchymal Stem Cells in Enhancement of Peripheral Nerve Injuries Repair

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Abstract: *Background:* About 50% of peripheral nerve injuries leave permanent disability. Trials to enhance nerve repair using stem cells are undergoing. Adipose derived mesenchymal stem cells (ADSCs) are good candidates for cellular-induced regeneration. *Aim of the Work:* The aim of the present work is to evaluate the effect of ADSCs on enhancing repair of peripheral nerve injuries. *Subjects and Methods:* This study was conducted on 18 patients with recent trauma involving nerve injuries at the wrist region. Patients were divided into: Group I: underwent surgical end-to-end closure Group II: underwent surgical end-to-end closure and injection of ADSCs into the nerve sheath and surrounding tissue. Both groups were followed up using clinical assessment using Sensory Recovery Grading and Muscle Strength Grading systems in addition to electrophysiological nerve conduction tests. *Results and Conclusions:* This study collected a range of 1 to 2 x10⁶ ADSCs from an average of 100-150 ml fat. After 1 year, stem cell group showed significantly higher motor and sensory improvement in ulnar nerve injury; while in the median nerve injury, stem cell group showed higher motor recovery with no difference in sensory recovery.

Keywords: Peripheral Nerve, Adipose Stem Cells, Regeneration

1. Introduction

Peripheral nerve injuries result in persistent pain and disability in many patients (1). The peripheral nervous system (PNS) consists of 3 principle cell types: axonal, glial and supporting stromal tissue (2) With an incidence of 300,000 injuries yearly, 50% of which regain full function following treatment, new therapeutic strategies need to be introduced (3).

Following peripheral nerve injury, the neuronal cell body increases in size with dissolving of Nissl bodies and protein synthesis is initiated (4). The distal nerve end undergoes fragmentation after a few days, followed by phagocytosis of debris by local Schwann cells and macrophages(5).

After clearance of myelin debris, Schwann cells produce neurotrophic factors such as nerve growth factor and ciliary neurotrophic factor to promote growth.

Stem cell technology is one of the most promising

approaches for peripheral nerve repair. As Schwann cells are responsible for nerve repair, early studies used autologous Schwann cell transplantation to improve peripheral nerve regeneration.

Mesenchymal stem cells (MSCs) have shown remarkable ability for in-vitro proliferation and maturation into Schwann Cells (6,7). MSCs are found in all body tissues. Traditionally, they were isolated from the bone marrow, however, they were found to be about 2500-fold more in frequency in adipose tissue (8). Experimental studies have shown that ADSCs can differentiate into glial lineage, make them good alternative to Schwann cells in peripheral nerve repair (9,10,11). ADSCs exert their regenerative function through a number of mechanisms: secretion of trophic factors (12), recruitment of endogenous Schwann cells (13), enhancing survival of sensory and motor neurons (14,15),

and possible myelin synthesis (16). These functions, combined with their easy accessibility, rapid expansion and low immunogenicity, make them ideal candidates for peripheral nerve repair (17).

This study would evaluate the role of ADSCs in enhancement of peripheral nerve injury.

2. Subjects & Methods

The study was approved by the local ethical committee and informed consent is signed by every patient after explanation of procedures. The study included 18 patients admitted to Tanta hospital suffering from traumatic nerve injury at the wrist joint.

2.1. Subjects

2.1.1. Inclusion Criteria

Patients with recent trauma (less than 48 hours) of peripheral nerve injuries at the wrist region.

2.1.2. Exclusion Criteria

1. Polytraumatized and multiple levels of injury
2. bone fracture
3. Tendon injury (more than 3)
4. Neuropathy

2.1.3. Patient Groups

Patients were divided into two groups:

Group A: included 10 patients treated by traditional method of repair with end to end anastomosis using magnification loop.

Group B. included 8 patients treated by traditional method plus injection of ADSCs to the nerve sheath and adjacent tissues.

2.1.4. Patients were Subjected to

1. Clinical Assessment:

a. History: Patient demographics: age sex occupation, residence and dominant hand.

b. Injury: side, site, mechanism, place, time of injury, previous injuries or disabilities and initial treatment.

c. Medical history: allergies, medications, or substance abuse.

a. Sensory testing: light touch and pin prick tests were done at the tip of the index finger for the median nerve and the tip of little finger for the ulnar nerve.

b. Motor testing: muscle strength was assessed with manual muscle strength testing according to the MRC system. For median nerve injuries the power of the thumb palmar abduction was assessed and for the ulnar nerve injuries, index and little finger abduction and little finger adduction were examined.

B. Nerve Conduction Tests:

Electrophysiological evaluation (motor and sensory nerve conduction tests) were done at 3, 6, 9 and 12 months. Parameters were compared to results of the non-involved side as internal control.

2.2. Methods

2.2.1. Collection of ADSCs

(i). Harvesting

Infiltration of the lower abdomen with normal saline with 1:50,000 epinephrine at a ratio of 1 ml solution per milliliter of aspirated tissue. Adipose tissue is then harvested using a 3-mm diameter blunt tip cannula attached to a 60 ml Luer-lock syringe. The aspirate was collected in sterile conical bottle.

(ii). Isolation of ADSCs

a. Washing with a sterile solution of phosphate buffered saline at equal volume three times to remove dead cells and red cells.

b. Sterile 0.075% Collagenase type I (Sigma-Aldrich) is added to the lipoaspirate for the digestive process, and incubated in a shaking incubator at 37°C for 30 minutes.

c. Sample was centrifuged at 600xg for 10 minutes, supernatant discarded and pellet resuspended in 50 ml of complete medium (DMEM, 10% fetal bovine serum, 1% antibiotic and 1% L-glutamine).

d. Red cell lysis buffer is added to eliminate red cells and sample is filtered through 100um cell strainer.

e. The filtered pellet is resuspended in complete medium.

(iii). Culture

a. Cells were counted, tested for viability using trypan blue exclusion test, and cultured in T75 tissue culture flasks in DMEM-F12 medium enriched with 10% fetal bovine serum, 1% L-glutamine and 1% penicillin-streptomycin and kept at 37°C in 5% CO₂ incubator.

b. Medium was changed every 3-4 days and examined under inverted microscope.

c. At 75-85% confluence, cells were harvested using 2ml 0.1% trypsin-EDTA for 5 minutes at 37°C. After 5 minutes 1 ml fetal bovine serum was added to stop the action of trypsin.

d. The cells were washed, counted and viability tested and prepared for injection.

2.3. Surgical Intervention

Group A: Nerve repair was performed under 3.5x magnifying loupes by end-to-end epineural repair using 8/0 prolene suture materials.

Group B: After 3 weeks from primary repair of the nerve, 2ml of saline containing 2x10⁶ ADSCs at the site of the nerve repair inside the nerve sheath and adjacent tissue.

2.4. Postoperative Care

1. Immobilization of the limb was done and physiotherapy started at the third week.

2. Tracking the regenerating axons using nerve conduction tests and Tinel's sign.

2.5. Follow-up and Assessment of Functional Outcome

Follow up was done using electrophysiology, clinical assessment of sensation using the British Recovery

Grading(18). and motor recovery assessed using Muscle Strength Grading (18).

3. Results

This study was conducted on 18 consecutive patients suffering from traumatic nerve injury at the wrist. Demographic data of the patients is presented in Table (1).

Table (1). Demographic Data of Studied Patients.

No	Sex	Age	Dominant Hand	Side affected	Nerve affected	Procedure
1	M	20	Right	Right	Median	Conventional
2	M	33	Right	Right	Ulnar	Conventional
3	M	28	Right	Right	Median	Conventional
4	M	37	Right	Left	Ulnar	Conventional + stem cells
5	M	40	Right	Right	Median	Conventional
6	M	35	Right	Left	Ulnar	Conventional +stem cells
7	M	43	Right	Right	Ulnar	Conventional
8	M	19	Right	Right	Median	Conventional +stem cells
9	M	30	Right	Right	Ulnar	Conventional
10	M	18	Right	Right	Median	Conventional
11	F	24	Right	Right	Median	Conventional
12	F	26	Left	Right	Median	Conventional

No	Sex	Age	Dominant Hand	Side affected	Nerve affected	Procedure
13	M	37	Left	Right	Ulnar	Conventional + stem cells
14	M	41	Right	Left	Median	Conventional + stem cells
15	M	45	Left	Right	Median	Conventional + stem cells
16	M	41	Right	Right	Ulnar	Conventional
17	M	33	Right	Left	Median	Conventional + stem cells
18	M	30	Left	left	Median	Conventional + stem cells

3.1. Results of ADSC Separation

The present study was done on 150-250 ml of lipoaspirate from each patient after informed consent then processed as set in methods to yield after culture average of 2×10^6 cells (Table 2). Figure (1) shows morphology of the cultured cells

Table (2). The mean number of stem cells in lipoaspirate.

Passage	Initial number of Cells	Cells in the Confluent layer	Culture days /passage
1st passage	0.20×10^6	0.85×10^6	7 days
2nd passage	0.85×10^6	1.25×10^6	7 days
3rd passage	1.25×10^6	2.00×10^6	6 days

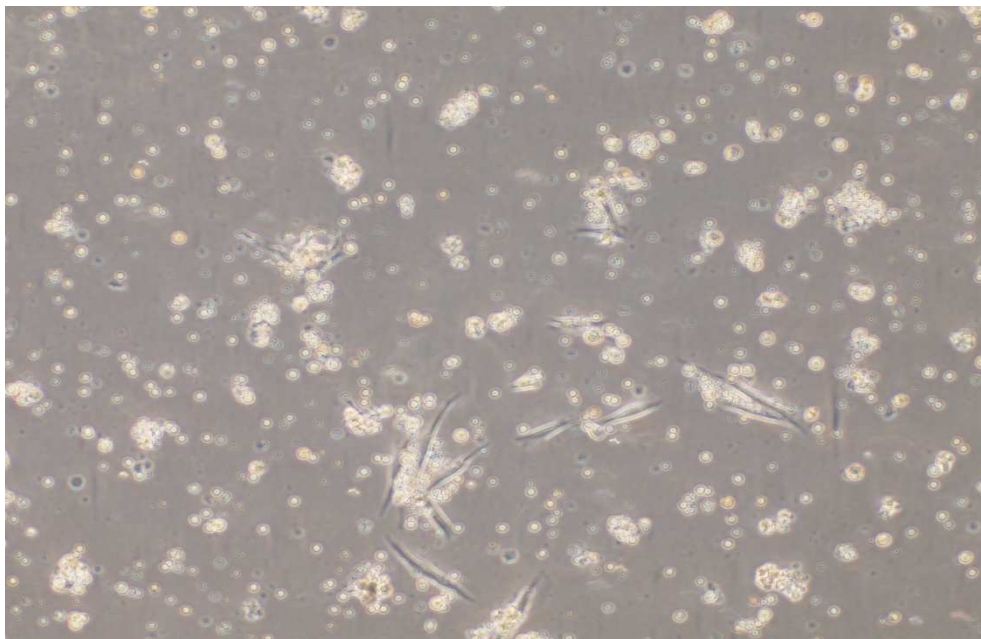


Figure (1). Morphology of ADSCs.

3.2. Clinical Functional Results

3.2.1. Ulnar Nerve

A. Motor assessment(based on Muscle Strength Grading)

- After 3 months :

in Group A. : 3 patients started active movement only with gravity (M2).

1 patient had trace of muscle contaction with no joint movement (M1).

in Group B. : 3 patients reached (M2) in the same period

of time.

- After 6 months :

in Group A. : 1 patient can make movement against gravity but with no resistance

in Group B.: All the 3 progressing patients are in (M3)

- After 12 months:

In Group A.: 1 patient can do some independent movement (M4)

In Group B.: 1 patent in M4 and 2 patients with normal

strength

B. Sensory assessment (based on Sensory Recovery Grading)

- After 3 months:

patients in Group A and Group B. reached to (S1) with deep cutaneous pain sensibility of the little and lateral half of the ring finger

- After 6 months:

patients in both groups reached (S2) with return of superficial cutaneous pain and tactile sensibility

- After 9 months :

2 out of four in Group A had disappearance of any previous reaction (S3) compared to 2 out of 3 in Group B

- After 12 months :

2 out of 4 in Group A had some recovery of two-point discrimination ≥ 15 mm compared to 2 out of 3 in Group B.(S3+)

3.2.2. Median Nerve

A)Motor assessment :

- After 3 months: all patients reached M2

- After 6 months:3 out of 6 patients of Group A (60%)

reach M3

4 out of 5 patients of Group B (80%) reach M3

- after 9 months : 1 patient in Group B. reached M5

- After 12 months : 40% of Group B reached M5

B)sensory assessment:

- After 3 months : both groups reached S1

- After 6 months: both groups reached S2

- After 9 months: 4 of 6 patients of Group A reached S3

Compared to 4 of 5 in Group B

- After 12 months :3 out of 6 patients of Group A reached S3+ compared to 3 out of 5 in Group B

Electrophysiological functional outcome :

It's performed to determine if functional re-innervation occurred through the nerve repair and evaluate the role ADSCs after injection in the nerve sheath

3.2.3. Ulnar Nerve

A) Motor nerve conduction:

Along the period of 3,6,9,12 months motor nerve conduction showed significant difference in the distal motor latency and amplitude ($P < 0.05$).

Table (3). Motor nerve conduction of the ulnar nerve in both groups.

Ulnar nerve (7 patients)	3 months		6 months		9 months		12 MONTHS	
	Gp.A	GpB	GpA	GpB	GpA	GpB	GpA	GpB
(MEAN)								
DML(ms)	7.3	6.8	6.625	5.83	5.35	4.48	4.375	3.77
Amplit.(mv)	0.225	0.5	0.775	1.3	1.275	2.42	2.47	3.84
p.value(DML)	0.043		0.042		0.045		0.063	
p.value(amplit)	0.043		0.036		0.036		0.052	

B)sensory nerve conduction: along the period of 3,6,9,12 months insignificant differences in the distal sensory latency

amplitude and conduction velocity ($P \geq 0.05$)

Table (4). Sensory nerve conduction of the ulnar nerve in both groups.

Ulnar nerve (7 patients)	3 months		6 months		9 months		12 MONTHS	
	Gp.A	GpB	GpA	GpB	GpA	GpB	GpA	GpB
(MEAN)								
DML(ms)	7.4	6.43	5.95	5.86	5.38	4.47	4.72	3.96
Amplit.(mv)	1.97	1.9	4.05	3.77	7.22	7.13	9.42	11.9
Velocity(ms)	16	17.3	27	31.3	34.5	39	41	45
p.value(DML)	0.235		0.335		0.442		0.529	
p.value(amplit)	0.152		0.425		0.438		0.542	
p.value(velocity)	0.235		0.425		0.357		0.410	

3.2.4. Median Nerve

As in ulnar nerve motor and sensory nerve conduction

results of sensory nerve conduction of the ulnar nerve.

Table (5). Motor nerve conduction of the Median nerve.

Median nerve (11 patients)	3 months		6 months		9 months		12 MONTHS	
	Gp.A	GpB	GpA	GpB	GpA	GpB	GpA	GpB
(MEAN)								
DML(ms)	7.5	7.7	6.8	6.2	6.1	5.3	4.7	4.2
Amplit.(mv)	0.1	0.5	2.6	3.41	3.3	4.5	4.4	5.2
p.value(DML)	0.053		0.042		0.066		0.051	
p.value(amplit)	0.052		0.053		0.063		0.047	

Table (6). Sensory nerve conductions of the median nerves.

Median nerve (11 patients)	3 months		6 months		9 months		12 MONTHS	
	Gp.A	GpB	GpA	GpB	GpA	GpB	GpA	GpB
(MEAN)								
DML(ms)	6.4	6.3	5.7	5.1	4.8	4.5	2.7	2.5
Amplit.(mv)	5.2	5.3	8.72	9.25	16.1	17.4	28.4	30
Velocity(ms)	15.5	17.2	24	25.5	31.8	32.8	41	42.32
p.value(DML)	0.325		0.226		0.352		0.541	
p.value(amplit)	0.049		0.635		0.886		0.514	
p.value(velocity)	0.294		0.103		0.533		0.541	

4. Discussion

Spontaneous peripheral repair is unsatisfactory despite microsurgical intervention. Various technologies are used to augment the regenerative capacity of peripheral nerves (19). One of the most promising approaches is the use of cellular therapy as a potentiator repair. As Schwann cells play an important role in peripheral nerve regeneration, attempts to transplant Schwann cells have been exploited (20). However, this procedure is hampered by the invasive method of obtaining autologous Schwann cells.

Mesenchymal stem cells have been proven to transdifferentiate into Schwann-like cells (21, 22)

Mode of action of MSC in neuroregeneration is diverse: promote endogenous neuronal growth, reduce apoptosis and down-regulate the inflammatory process through secreted factors. MSCs can also mediate modification of microenvironment enhancing endogenous neural regeneration. MSCs moreover induce survival and regeneration of neurons through secretion of trophic factors (23).

MSCs have been reported to be isolated from different sources. Since first described by Friedenstein et al from the bone marrow, they have been isolated from adipose tissue, peripheral blood, lungs and heart(24). Adipose-derived mesenchymal stem cells (ADSCs) express phenotypic and gene expression profiles similar to bone marrow derived MSCs (25). Moreover, they can be easily harvested with high frequency from subcutaneous fat, and show higher proliferative potential than bone marrow-derived MSCs (26, 27).

Gimble et al (2007) summarized the characteristics of ideal cells for regenerative application in the following criteria: can be harvested in abundant quantities using a minimally invasive procedure, can be differentiate into the required cell lineage in a reproducible method, and can be safely and effectively transplanted(28).

Adipose tissue stem cells can fulfill all these criteria. Adipose tissue can be collected in large amounts with minimal complications. ADSCs can be isolated from the collected lipoaspirate in relatively simple procedure, with no effect on cell viability.

ADSCs share the same biological characteristics of bone marrow derived MSCs with the superadded advantage of abundance and high proliferation(29).

In this study, we evaluated the role of ADSCs in enhancing peripheral nerve injury repair. Processing aspirated fat from 100-150 cc fat produced ADSCs ranging from 1×10^6 to 3×10^6 which agrees with the results by other workers who reported that processing 300ml of lipoaspirate can yield from 1×10^7 -to 6×10^8 ADSCs with $>90\%$ viability (30).

In this study, the clinical and electrophysiological studies showed motor improvement in the stem cell group more than the conventional surgery group.

Stem cell group showed superior motor recovery in ulnar nerve after one year than the conventional group, with no difference in sensory recovery. In Median nerve injury, 40% of the stem cell group reached normal strength compared to none in the traditional group, while 60% showed sensory recovery compared to 50% in traditional group These results agree with those of Kingham et al (31), Dezawa et al and Keihoff et al (32).

No complications were noticed after injection of ADSCs in nerve sheath. The procedure of liposuction and stem cell injection was well tolerated.

5. Conclusion

This pilot study proves the safety, and efficacy of using ADSCs to improve nerve repair in peripheral nerve injury. Thus stem cell therapy can be used safely as an adjuvant to surgical correction of peripheral nerve injuries. Further controlled trials should be performed using dose escalation to reach optimum therapeutic settings.

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