Ochsner Health System
Neurosciences Symposium

Biologic Therapies for Peripheral Nerve Pathology

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Disclosure

I have nothing to disclose
Objectives

- Biochemical basis for the use of biologic therapies
- Current research in platelet rich plasma
- Current research in stem cell therapies
- Future outlook
Biologic Invasion

Results by year

PRP

Results by year

Mesenchymal stem cells
Nerve Regrowth

- Axonal regeneration
- Re-myelination
- Restoration of synaptic connections
- Recover physiologic functions/skeletal muscle

Figure 1: Changes occurring in a peripheral nerve following compression injuries adopted and modified from Ref[1].
Platelet-Rich Plasma (PRP)

- PRP is an autologous concentrate of platelets made from whole blood.
- Platelet concentration: Not defined.
- WBCs/RBCs present/absent or concentration: Not defined.
Platelet-Rich Plasma (PRP)

Contents of platelets: **Alpha granule:** contains 30 bioactive proteins, including PDGF, TGF-beta, IGF, VEGF, EGF, platelet factor 4, IL-1, platelet derived endothelial growth factor, epithelial cell growth factor, osteocalcin, osteonectin, fibrinogen, vitronectin, fibronectin, thrombospondin.

**Delta granule:** ADP (pro-coagulant), ATP, ionized calcium, histamine, serotonin, epinephrine.

**Lambda granule:** Lysosomal enzymes.
Platelet-Rich Plasma (PRP)

- Platelets are vehicle for **growth factor delivery**
- IGF-1 required for axon myelination
- Trigger mitosis and induce angiogenesis
- VEGF can stimulate axonal outgrowth and enhance Schwann cell proliferation
- Provides matrix for migration of tissue forming cells.
- Chemotactic for fibroblasts, mesenchymal cells, monocytes, and neutrophils.
- Decreases infections
Zheng et al, 2013

- Cultured rat Schwann cells with varying concentrations of PRP (40%, 20%, 10%, 5% and 2.5%)
- PRP significantly stimulated SC proliferation and migration compared to untreated controls in a dose-dependent manner
- Suppression seen with high PRP concentrations (40%)
- The expression and secretion of nerve growth factor and glial cell line-derived neurotrophic factor were significantly increased
Emel et al, 2011

- Compared the effects of IGF-I and PRP on Sciatic Function Index (SFI), sensory function (SF), axon count, and myelin thickness/axon diameter ratio (G-ratio) in a rat model of crush-injured sciatic nerves.
Emel et al, 2011
Emel et al, 2011
Küçük et al, 2014

- Effects of PRP on a sciatic nerve injury model in rats (N=12/24 sciatic nerves)
- Angle of climb was 63.6 degrees in the PRP group, 38.33 in the control group
- In the PRP group, CMAP amplitudes of the gastrocnemius and interdigital muscles were 14.01mV and 0.85mV, respectively. In the control group, CMAP amplitudes were 5.78mV and 0.24mV, respectively
- The average number of total axons in the control group was 879.3 and 1,969.50 in the PRP group
- All differences were statistically significant
Malahias et al, 2015, Pilot study

- Effects of a single injection of PRP on the clinical symptoms of carpal tunnel syndrome
- N=14 (excluded pts with prior corticosteroid injections, prior surgery, etc)
- Injected 1-2cc of PRP under U/S guidance
- No complications
- Mean VAS reduced ~50% at 1 month post-injection
- Q-DASH score ~70% reduced at 3 months
- U/S cross sectional area of the median nerve was normalized or reduced in 10/14
- 3 underwent open CTR
Kuffler et al 2014

- Refreshed both the central and distal nerve stumps of nerves causing neuropathic pain, inserting the nerve stumps into a collagen tube, and filling the tube with autologous PRP
- Induced the resected axons to regenerate across long gaps
- Some injuries 3.5 years later
- 94% of the patients, including one with excruciating neuropathic pain, had elimination of pain
Peripheral motor nerve injury treated with PRP

- Group 1 (N=3): No intervention, spontaneous recovery
- Group 2 (N=5): Saline injections
- Group 3 (N=6): PRP with scaffold

- Week 8, 70% of PRP group were CMAP-positive; no response in the other groups
- Histomorphometric analysis at 12 weeks: axonal density of groups 1 and 2 were significantly inferior to the control and the PRP group. No significant differences between the control and PRP groups
- Morphometry of the target muscles indicated that the PRP group had the lowest percentage volume reduction at 12 weeks
Sánchez et al, 2014

- Application of PRP for the treatment of peroneal nerve palsy with drop foot secondary to multi-ligament knee injury
- 28 y/o M with severe axonotmesis; 11 months post-injury
- Serial ultrasound intraneural infiltraions of PRP
- Complete but partial useful recovery obtained at 21 months post-injection EMG with complete reinnervation of the peroneus longus and improved reinnervation of the tibialis anterior
Mesenchymal Stem Cells

- Easily expanded, multipotent stromal cells found in most tissue that can differentiate into a variety of cell types
- Can home in on injured tissue
- Non-immunogenic, paracrine function (secretome)
- Schwann cell collection causes new damage to nerve segments and prolonged doubling time reduce the practicality
- MSCs are capable of cross oligolineage boundaries between mesodermal to ectodermal lineages to form a comparable Schwann cell
Mesenchymal Stem Cells

- Harvest sites: bone marrow, adipose, umbilical cord, dental pulp
- Source may differ in their differentiation propensity and secretory profiles
- Effects of MSCs on nerve injury models: Modulation of the inflammatory environment on the site; Modulation of the Wallerian degeneration stage; Increased thickness of the myelin sheaths; Accelerated fiber regeneration and in increased numbers; Improved fiber organization; Enhanced vascularization of the regenerating site; and Reduction of fibrotic scaring.
Mesenchymal Stem Cells

- May use conduits: Polyglycolic Acid (PGA), Poly-carprolactone (PCL), Collagen, Polyvinyl alcohol
Zarbakhshsh et al, 2016

- Effects of bone marrow and umbilical cord stromal cell transplantation in regenerating rat peripheral nerves
- 10 mm segment of the left sciatic nerve in rats was removed and replaced with a silicone tube
- Bone marrow stromal cells (BMSCs) and human umbilical cord stromal cells (HUCSCs) were respectively obtained from rat and human
- Cells cultured and placed into the silicone tube
Zarbakhshsh et al, 2016
Zarbakhshsh et al, 2016
Ke et al, 2015

- Effect of transplanting BMSCs that produce netrin-1 in a rat model of sciatic nerve crush injury

- Netrins are a family of secreted proteins that direct the migration of neuronal cells and axon growth cones during neural development, are angiogenic, and induce proliferation of Schwann cells

Fig. 3 Bar graphs demonstrated the motor nerve conduction velocity (MNCV) in 4 weeks after transplantation. *P<0.05.
Unanswered Questions

- Optimal PRP concentrations/preparations
- Best source of harvesting stem cells
- Use of differentiated vs undifferentiated cells
- Optimal number of injections
- Unknown side effects
- Combination products
References

References


THANK YOU