What's new in SCI?

Dr Wunna Aung
Consultant in spinal cord injury Rehabilitation

Treatment Strategies For SCI

- 1- Neuro-protection
  - Minimising secondary injury
  - Reducing inhibitory environment
- 2- Neuro-regeneration
  - Cellular (tissue) replacement
  - Reconnection (surgical)
  - Creating permissive environment
- 3-Additional strategies
  - Physical treatment

Minimising secondary injury

- Human trials
  - Methylprednisolone(NASCIS I, II & III)
  - Naloxone (NASCIS II)
  - Lazaroid (Tirilazard)(NASCIS III)

  - Thyrotrophin Releasing Hormone
    - Act as neuroprotective partial opiod antagonist
    - Prospective randomised trial (n=20)with placebo arm–complete injury > no benefit, incomplete injury > significant improvement in outcome measure
  - Nimodipine
    - Prospective placebo controlled Randomised trial in France(n=106)– no statistical differences in outcome at 1 year
  - Gacyclidine
    - Glutamate receptor antagonist
    - Prospective placebo controlled Randomised trial (n=272)– no statistical differences in outcome at 1 year.

Minimising secondary injury

- Human trials
  - **Minocycline**
    - anti-inflammatory and antiapoptotic effects(reduced neuronal and oligodendroglial apoptosis)and reduced microglial activation.
    - Results of phase II placebo controlled Randomised trial (n=27/25)(2012)- overall six points greater motor recovery with minocycline than placebo
  - **Glibenclamide**
    - Acting via inhibition of the recently characterized Sur1-Trpm4 channel.
    - acts on microvessels to reduce oedema formation and secondary haemorrhage, it inhibits necrotic cell death, it exerts potent anti-inflammatory effects and it promotes neurogenesis-all via inhibition of Sur1. Two clinical trials, one in TBI and one in stroke, currently are underway.
  - **Hypothermia**
    - cooling (32-33 c) reduce inflammatory response, apoptosis and improve neurological recovery
    - Case control study of systemic hypothermia(n=35)- 43% improved at least one ISNCSCI grade at follow up 10.07 (±1.03) months(2012)

Minimising secondary injury

- **Preclinical studies**
  - **Methothrexate**
    - attenuates early neutrophil infiltration and the associated lipid peroxidation , does not induce neurotoxicity in the uninjured spinal cord in rats
  - **RhoA inhibiting NSAIDs(ibuprofen & indomethacin)**
    - suppress intracellular RhoA signal -Reduce generation of amyloid-beta42 peptide -improve significant axonal growth and increase axonal myelination along the white matter tracts-functional recovery following axonal injury in the CNS.
  - **ATB-346**
    - a novel H2S-releasing derivative of naproxen
    - Study in mice-a reduction of proinflammatory cytokines; an improvement in apoptosis level and nitros active stress state was clearly decreased .
  - **Calpain inhibitors(calcium activated cysteine protease)**
    - improved functional outcomes with post-injury administration of calpain inhibitors in rats.
  - **chondroitinase ABC**
    - increased the expression of the anti-inflammatory cytokine IL-10,accompanied by a reduction in the proinflammatory cytokine IL-12B in injured spinal tissue
  - **Cyclosporine**
    - inhibit the mito permeability transition phenomenon by binding to cyclophilin D protein. Although it works in rats with brain injury , not with sci.

Minimising secondary injury

- **Curcumin-**
  - promotes the spinal cord repair via inhibition of glial scar formation and inflammation by decreased the expression of IL-1beta and NO.
- **Interleukin-33**
  - decreasing tissue loss, demyelination and astrogliosis in the contused mouse spinal cord
  - reduce the expression of pro-inflammatory tumor necrosis factor-alpha and promoted the activation of anti-inflammatory arginase-1 positive M2 microglia/macrophages, which chronically persisted in the injured spinal cord for up to at least 42. days after the treatment, reduced T-cell infiltration into the spinal cord
- **Melatonin**
  - antioxidative, antiapoptotic, neuroprotective, and anti-inflammatory properties. suppresses the expression of NF-$\kappa\beta$ regulated adhesion molecules, and reduces the production of proinflammatory cytokines.
  - -administration of melatonin 10 mg/kg body weight significantly diminished iNOS expression and NO

- **Riluzole**
  - blocking voltage-sensitive sodium channels and antagonism of presynaptic calcium-dependent glutamate release. decreased the amount of necrosis in the gray and white matter, the combination with MP resulted in decreased spinal cord cavitation

Reducing inhibitory environment and creating permissive environment

- Inhibitory environment
  - Physical barrier- gliosis
    - chondroitinase
  - Biochemical barrier-
    - Nogo protein
    - Myelin Associated Glycoprotein
    - Oligodendrocyte myelin glycoprotein
      - Above 3 protein activate Rho enzyme culminating in cytoskeletal disassembly and axonal growth cone collapse.
    - NO
    - Free radicals
    - Arachidonic acid derivatives

Reducing inhibitory environment and creating permissive environment

- Human trials
  - Anti-Nogo Ab
    - Nogo gene-related protein(NI35, NI250) inhibit axonal regeneration.
    - Anti-Nogo Ab restore corticospinal axonal regeneration and locomotion in rats and primates.
    - Phase 1 trial (first-in-human trial) of intrathecally administered Ab has completed→In comparison to continuous i.t. infusion, repeated i.t. bolus injection appears to improve treatment safety and is supported by pharmacokinetic data demonstrating relevant CSF exposure(2011).

Reducing inhibitory environment and creating permissive environment

- Rho antagonist
  - Cethrin (recombinant C3 transferase) – undergone phase I/IIa trial.
  - drug was well tolerated , potential to improve neurological recovery in a functionally meaningful manner .
    - Participants in all Cethrin dose groups improved an average of 16.4 +/- 17.3 points from baseline in total motor score (TMS) and 12.2 +/- 10.5 points in upper extremity motor score (UEMS) during the year after injury; compared to 9.6-13.2 point TMS recovery and 8.8 +/- 9.6 point UEMS recovery seen in historical individuals. In addition, 31% of Cethrin-treated cervical participants converted two or more AIS grades in the year after injury, and 44% converted two or more motor levels. These trends also compare favorably with historical data: only 17% of historical individuals convert two or more AIS grades in the year following injury, and 24%-33% convert two or more motor levels. BioAxone is presently planning a placebo-controlled, randomized Phase IIb trial to further examine Cethrin in acute cervical spinal cord injury.2014. open label trial.

Replacement of cells after neuronal cell death

- **Foetal(neural cells) tissue transplantation**
  - differentiation into neurons and glia -to form functional neuronal relays across injured spinal cord .
  - ethical concerns. Multiple donor sources in very short period of time for collection.
  - One study in Russia- FNCs therapy reduced mortality rate from 7.2 % to 2.2 % and disability rate from 48.8 % to 17 % compared to conventional treated control.
- **Stem cell transplantation**
  - 3 steps- purification, grown in cells cultures and transplanted back in to sc.
  - Use autologous BM stem cell – no issue with tissue rejection
  - Single centre study in Turkey- Treatment of chronic spinal cord injured patients(all ASIA A) with autologous bone marrow-derived hematopoietic stem cell transplantation:

    1-year follow-up showed- 7 become ASIA C and 2 become ASIA B.

Replacement of cells after neuronal cell death

- **Schwann cell transplantation**
  - SC provide neurotrophin, ECM and cell adhesion properties that favours axonal regreneration. SC are good for genetic manipulation ie can be utilised to carry gene . Unwanted effect- promote gliosis
  - Initial clinical reports from studies in Iran and China are suggestive of clinical safety.
- **Olfactory Ensheathing Cells transplantation**
  - neurosensory cells of olfactory epithelium, have growth promoting properties for neurons and able to migrate extensively in CNS.
  - OEC- Olfactory mucosa and Olfactory bulb origin.
  - Phase I /IIa clinical trials- safe and feasible , 2 patients improved ASIA A to B/C and one patient remained A but level lowered at 1 year(Tabakow P et al 2013), no difference in ASIA in 6 pt(Mackay-Sim et al 2008)

Reconnect and recover normal function in neural pathways

- setting up bridge at the point of injury to allow damaged axon regenerate over the gap
  - **predegenerative nerve graft** eg siatic nerve- increased cell proliferation in the graft, trophic factors/ growth promoting substance, a large number of Schwann cells . Faster regenreation.
  - **Biomaterial conduit**- using (1) cell free biocompatible materials(degradable polylactide fibres coated with Schwann cells) (2) synthetic polymers (hydrogel implants).

Physical Therapy

- Low-level LASER therapy
- Functional electrical stimulation (FES).
  - applied externally
  - Implanted
- Oscillating field stimulator
- Spinal central pattern generator
  - Pharmacological stimulation of spinal CPG- 5HT receptor agonist, alfa agonist
  - Physiatric stimulation of spinal CPG- gradual verticalisation- body-weight-supported treadmill training.

Conclusion

- Single therapeutic intervention is unlikely to facilitate complete functional recovery.
- The best potential strategy is combination of treatments.

Thank you.