Stem Cell Therapy in Patients with Cerebral Palsy

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History

- **1953**: Leroy Stevens concluded stem cells are pluripotent
- **1968**: Robert A. Good performs first successful bone marrow transplant
- **1981**: Martin Evans and Gail Martin isolate first pluripotent stem cells (from mice embryos)
- **1998**: James Thomson and Jeffrey Jones created batch of pluripotent stem cells derived from early embryos -- *showed potential for transplantation medicine*

> Dates for human trials vary, but the first clinical trial we can find in pediatric patients with CP was published in 2010
The Theory of Stem Cell Transplantation in Kids with CP

Common Problem: **Hypoxic Ischemic Insult** (supply of blood to brain is limited)

Lack of BF decreases and destroys nerve function:

- Death of oligodendrocytes → decline of myelin → degradation/death of neurons → motor impairments

The Theory...

- Inject stem cells to...
  - Eliminate damaged cells
  - Replace damaged with new healthy cells
  - Stimulate repair of damaged cells
  - Improve overall function
Treatment Process

Uses different types of stem cells:

❖ **Mesenchymal cells** located in umbilical cord and bone marrow
  ➢ Provide nutrition and structural support to region of injury in brain

❖ **Neural precursor cells** located in inside the brain and spinal cord
  ➢ Can migrate and replace damaged cells
  ➢ Highly invasive to extract cells from a patient

❖ **Pluripotent cells** located in embryonic stem cells
  ➢ Can differentiate into many or all cell types in the body
  ➢ Ethical situation

❖ **Induced PSCs** created from skin cells
  ➢ Think this is the BEST OPTION for treatment = Why?
    ■ Autogenic
    ■ Eliminate tissue rejection and donor lists

Injection of cells:

❖ **Lumbar puncture**
❖ **IV infusion**
❖ **Intracerebral**

**Risks:**
- Graft vs. host diseases
- Infection
- Damage to organs and blood vessels
Continuing Education/Workshops

❖ Performed by physicians, but there are resources to learn more about the current research:

➢ International Society for Stem Cell Research (ISSCR)
  ■ San Francisco, CA; June 2016

➢ Changing the Face of Modern Medicine: Stem Cells & Gene Therapy
  ■ Florence, Italy; October 2016

❖ Most relevant for PTs: Physical Therapy and the Future of Regenerative Medicine

➢ E-learning course thru APTA (LMS-426)
➢ not exclusive to use for CP, but it is covered as a potential population
➢ 0.2 CEUs, $75 member, $120 non-member
Indications

❖ **current treatment** or **potential benefit** for patients with:

➢ certain types of cancer (esp. leukemia)
➢ aplastic anemia
➢ Parkinson’s Disease
➢ Type I Diabetes Mellitus
➢ Retinal Disorders
➢ SCI, TBI
➢ CP

Stem cell transplantation is being explored as a therapeutic option for many diseases/conditions and while the research indicates promising potential there is much to be done to prove the safety, [consistent] efficacy, and ideal protocol before it is adopted for clinical use.
Contraindications

❖ No consistently identified contraindications

❖ One resource mentioned
  ➢ chronic and acute infectious processes
  ➢ severe concomitant diseases

❖ The research is still developing, so it will be important to watch for new contraindications
Stem cells therapy in cerebral palsy: A systematic review (Kulak-Bejda A. et al. 2016)

Purpose: To present the best available stem cell therapies for children with CP.

Studies included:

❖ **1 RCT (Ib):** Methods:
  ➢ N = 96, 10m-10yr
  ➢ Intervention: Allogenic umbilical cord blood
  ➢ Control: placebo

❖ **6 Open label non-randomized control trials (III):** Methods:
  ➢ N = 17-94, 1-32yr, hemi/di/quadriplegic spastic CP, GMFCS I-V
  ➢ Intervention: Autologous cord blood (3), neural progenitor, neural stem cell-like, bone marrow mesenchymal stromal, or M2 macrophages
  ➢ Method: Intravenous (3), lateral ventricle (1), subarachnoid (1), intradural (1)
  ➢ Control: none (3), rehab (2), or placebo (1)
Follow-up duration: 3 months to 5 years

Outcome measures used:

- GMFM (activity)
- FMFM (activity)
- GMPM (activity)
- GMFCS (activity)
- CT/DTI/MRI (BS&F)
- PDMS-FM (activity)
- Modified Ashworth (BS&F)
- Geselle Questionnaire (BS&F)
- PEDI (activity, participation)
- QUEST (BS&F, activity)
- Bayley II (BS&F, activity)
- Denver (activity)
Stem cells therapy in cerebral palsy: A systematic review (Kulak-Bejda A. et al. 2016)

Summary of Results:

**Efficacy** - Promising
- Improved strength, increased motor development, decreased spasticity
- Gross and fine motor improvement (PDSM)
- Improved mean GMFCS levels
- NO difference in language or cognition

**Safety** - Inconclusive
- Some reported no adverse events
- Some did not report on safety at all
- Report of one death, one focal hemorrhage, fever, pneumonia, irritability
- Temporary nausea, hemoglobinuria, hives with intravenous injection

More evidence needed.
Umbilical Cord Blood Therapy Potentiated with Erythropoietin for Children with Cerebral Palsy: A Double-blind, Randomized, Placebo-Controlled Trial (Min K. et al. 2013)

Purpose
Is allogenic UCB + EPO followed by on-going rehab an effective treatment for kids with CP?

Subjects
96 children with all GMFCS levels of Spastic CP (age: 10 mo to 10 yrs)

Methods
Subjects were divided into 3 random groups
1. Group 1 = received UCB potentiated with rhEPO and rehab (“pUCB group”)
2. Group 2 = received rhEPO, placebo UCB and rehab (“EPO group”)
3. Group 3 = received rehab only with placebo UCB and placebo rhEPO (“control group”)

*Stem cells delivered through intravenous injection
Umbilical Cord Blood Therapy Potentiated with Erythropoietin for Children with Cerebral Palsy: A Double-blind, Randomized, Placebo-Controlled Trial (Min K. et al. 2013)

Assessment tools were documented at 0, 1, 3 and 6 months: Relation to ICF Model

❖ GMPM → activity limitations
❖ GMFM → activity limitations
❖ Bayley II → activity limitations
❖ PEDI → activity limitations and participation restrictions
❖ WeeFim → activity limitations and some participation restrictions
❖ MMT → BS&F
❖ Quality of UE Skills Test → BS&F and activity limitations
Umbilical Cord Blood Therapy Potentiated with Erythropoietin for Children with Cerebral Palsy: A Double-blind, Randomized, Placebo-Controlled Trial (Min K. et al. 2013)

**Effective: Probably YES**

Allogenic UCB potentiated with EPO followed by rehab proved to have the most significant changes in:

- Motor function at 3 mo
- Cognitive function 1 mo

**Safe: Maybe Not**

10 Adverse Events:

- 9 patients were hospitalized (more frequent from pUCB group)
  - Due to pneumonia, irritability and elevated Hgb levels
- 1 death at 14 weeks post-treatment
  - 25 mo old female in pUCB group
  - Determined not to be related to treatment

Purpose
To evaluate safety of autologous bone-marrow derived CD133 positive cell intrathecal injection

Subjects
12 patients, 4-12 years old with definitive diagnosis of CP
10/12- Spastic CP, 1 Ataxic, 1 Athetoid

Methods
After screening and baseline tests, 12 subjects underwent BM aspiration from iliac crest

Prepared cells were injected into subarachnoid space at L3-L4 level within 24 hrs of BM puncture

*NO control group

Exclusion criteria:
*Risk of hip subluxation/dislocation
*Significant scoliosis (>90 degrees curvature)
*History of selective dorsal rhizotomy
*Change in spasticity medicine within past 6 months
*Receiving Baclofen intrathecally
*Existence of metallic or electrical implants
*Severe cognitive disorders
Intrathecal Injection of CD133-positive enriched bone marrow progenitor cells in children with cerebral palsy: feasibility and safety (Zali et al, 2015)

Clinical assessment: Relation to ICF Model

- GMFM-66 (activity)
- GMFCS (activity)
- Berg Balance Scale (BS/F and activity)
- Modified Ashworth Scale (BS/F) *was used to measure spasticity
- FIM & FAM (activity and some participation)
- MRI & EEG (BS/F)
Intrathecal Injection of CD133-positive enriched bone marrow progenitor cells in children with cerebral palsy: feasibility and safety (Zali et al, 2015)

Is CD133 positive enriched bone marrow progenitor stem cell transplantation safe?

- **No serious AE** that necessitated hospitalization or medications were reported during 6 month follow-up

- **No new** abnormal MRI findings after 6 months

- **Symptoms at 1 week**
  - 5 patients - HA, nausea, vomiting
  - 11 patients - Back pain that resolved with rest

- **At 6 months**
  - 1 patient - seizure
    - 19-year-old male
    - History of controlled seizures
    - Had stopped anticonvulsants 3 years before
    - Imaging and EEG did not show any new abnormal findings
Intrathecal Injection of CD133-positive enriched bone marrow progenitor cells in children with cerebral palsy: feasibility and safety (Zali et al, 2015)

Is CD133 positive enriched bone marrow progenitor stem cell transplantation effective?

<table>
<thead>
<tr>
<th>Functional measure</th>
<th>At baseline</th>
<th>At 6 month</th>
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</thead>
<tbody>
<tr>
<td>GMFM-66</td>
<td>13.6±10.6</td>
<td>19.7±14.0</td>
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<tr>
<td>GMFCS</td>
<td>4.8±0.6</td>
<td>4.3±1.0</td>
</tr>
<tr>
<td>FIM+FAM (motor portion)</td>
<td>58.5±10.1</td>
<td>91.4±22.5</td>
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<tr>
<td>MAS</td>
<td>3.3±1.4</td>
<td>2.5±1.3</td>
</tr>
<tr>
<td>BBS</td>
<td>0.2±0.4</td>
<td>2.4±4.4</td>
</tr>
<tr>
<td>FIM+FAM (cognitive portion)</td>
<td>30.7±13.9</td>
<td>53.1±14.6</td>
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</tbody>
</table>
The procedure is **safe and effective** for motor and cognitive functioning however the therapeutic mechanism is unclear.

- Necessary to compare transplanted patients to a control group.
- Small sample size.
Conclusions

Research indicates Safe and Effective, but more high level clinical trials are needed before we can confidently employ stem cell therapy as a treatment of choice for children with CP.

CP is highly variable, and the efficacy of this treatment may depend on GMFCS level, age, etc.

Stay up to date on current research so that you can have a knowledgeable discussion with parents.
References

http://www.neurodevnet.ca/sites/default/files/neurodevnet/download/stem%20cell%20newsletter_eng.pdf
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