STEM CELL THERAPY: A RAY OF HOPE FOR REVERTING THE AFFECTED BRAIN CELLS

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ABSTRACT

INTRODUCTION: Stem Cells therapy mainly focuses on the use of stem cells, which have the potential, to revert back the affected brain cells into healthy brain cells which provides a ray of hope for the individual that is affected with traumatic brain injury. Traumatic brain injury is sudden damage to the brain brought about by a blast or shock to the head. Traumatic brain injury (TBI) is the main cause of morbidity and mortality in individuals below the age of 45 years in the world. Stem cell therapy uses.

Mainly there are two modes by which stem cells are employed to treat traumatic brain injuries. Exogenous and Endogenous stem cell approaches to treat damage brain. Although the use of stem cell therapy has brought about various ethical concerns which needs to be addressed carefully in order to take full advantage of this mysterious technology being introduced recently.

Stem cell therapy withstands the most effective approach for treating affected brain cells which will further bring plethora of wonders for the human beings if allowed to continue in a progressive way.

CONCLUSION: Stem cell therapy as a new alternative to all previous technologies to treat the damage brain cells have emerged as one of the most effective, long lasting and applicable in true means. All previous therapies that were and are used for the treatment of brain cells have not proven successful due to its low applicability. Stem cell therapy as a technology in its early days also faces various ethical challenges and concerns regarding its use to revert back the affected brain cells.

KEYWORDS: Exogenous stem cells, Endogenous stem cells.

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INTRODUCTION

Traumatic brain injury (TBI) is sudden damage to the brain brought about by a blast or shock to the head. It results in change in the brain function or other evidence of brain pathology brought about by an external force. For example: blows, falls and blast waves.[1]

There are two main types of TBI: Open traumatic brain injury and Closed traumatic brain injury.Open traumatic brain injury is caused when the skull is broken or cracked. This may happen due to foreign object (e.g.: a bullet) when it goes through the skull, enters the brain, and damages specific part of the brain. Symptoms involved in an open TBI vary depending upon the part of the brain being damaged. While Closed traumatic brain injury is caused when an outside force collides with the head, but the skull is not broken or cracked. This may result in, for example: when the head strikes the dashboard in a car accident. In this, damage is typically widespread. Symptoms included in a closed TBI vary depending upon the extent of the damage to the brain.[2]

2. Epidemiology of TBI:

Traumatic brain injury (TBI) is the main cause of morbidity and mortality in individuals below the age of 45 years in the world.Every year, 80,000-90,000 people experience the onset of long-term or lifelong disabilities related with TBI. Males represent 78.8% and females represent 21.2 % of all reported TBI accidents. Around 1.5 to 2 million adults and children are affected by traumatic brain injury (TBI) every year in the US.

The vast majority who are affected by head injury, about 1.1 million will have a mild injury that does not require an admission to the hospital. Another 235,000 people will be hospitalized with a moderate to severe head injury, and approximately 50,000 will be die.

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3. Classification of TBI:

According to severity and mechanism of injury, traumatic brain injuries are classified into three types:

i. Mild: The person is awake, eyes open. Symptoms may include are: confusion, memory loss,bewildered, headache, and brief loss of consciousness.
ii. Moderate: The person is sluggish and dull; eyes open to stimulation. Loss of consciousness lasting for 20 minutes to 6 hours. Some brain swelling or bleeding causing tiredness, but still arousable.
iii. Severe: The person is insensible, eyes do not open, even with stimulation. Loss of consciousness last for more than the 6 hours.This level of injury is fatal and the patient is not likely to come back to the life that they once had.[3]

4. Comparison between Coma and Brain Death

Two of the worst words we can hear in a hospital are comma and brain death. Coma is better than the brain death because no one is going back from brain death while one may recover from a coma. Coma is commonly known as unconsciousness for more than the six hours' duration. During a coma, the individual cannot be awoken, do not respond to any stimuli, and does not play out any active spontaneous movements. while Brain death is a process where the brain action is irreversibly blocked. Brain cannot perform any electrical activity. Due to internal pacemaker, the heart may go on at a slow pace, however, there is no respiration in brain death. Because there are no signals originate from the brain to maintain fundamental functions, only life support machines can keep these functions going. Below are few differences between Coma and Brain death that are discussed.

1. Coma is a reduced level of consciousness due to injury to specific brain part or some metabolic cause. Brain death is due to total brain necrosis.
2. Coma may be reversible, while brain death is irreversible.
3. In coma, there is some brain activity to maintain important function but it is not so in brain death.
4. Brain death is taken as legal death is many countries while coma is not taken as such.

5. Stem Cells

Stem cells have the capacity to induce neuroprotection, inflammatory suppression and neural repair, allowing reconstruction of totally damaged tissues or preventing partially damaged cells from evolving to cell death.[4]

5.1. Use of stem cells in treatment of TBI:

Mainly there are two modes by which stem cells are employed to treat traumatic brain injuries.

1. Exogenous stem cell Therapy.
2. Endogenous stem cell Therapy.

5.1.1. Exogenous Stem Cells:

In exogenous mode of treatment mainly cells used are as follow:

5.1.1.1 Embryonic stem cells:

These cells have potential to develop into any kind of cell. Their beneficial characteristic is production of huge number of cells on culture.[5] This property is utilized to produce neuron according to nature of injury i-e depending on injury location that which part of brain or neuron is damaged. Successful clinical trials have been conducted on animal models, however knowledge at broader level is required to make them suitable for humans.[6]

5.1.1.2 Neural stem cells:

These cells have extensive ability to renew themselves and differentiate into multiple kinds of cells that are neurons, dendritic cells, ganglion etc. Their outstanding feature is the survival for longer duration and this property is applied for neural recovery in case any brain trauma occurs. The effectiveness of this kind of treatment can be increased by using human neural stem cells and transplanting them which provided long term neural recovery in an experimental trial on rat models[7]. The work done by Phillips et al, 2001 provided the evidence if neural stem cells are treated with a virus that has growth promoting factors for neurons then it resulted in better brain function i-e better learning power and movement. These cells are mainly transplanted into animals. However, they have limited applications in case of largescale use. But successful trials have been conducted which have shown their potential for neurological recovery largely.

5.1.1.3 Induced pluripotent stem cells:

These cells are of significant importance in therapy of stem cells. Various transcription factors are involved to differentiate the somatic cells into embryonic stem cells which can be taken from patients and are programmed in a way that they are converted into induced pluripotent stem cells.[8]

The usefulness of these stem cells lie in the prevention of rejection by immune system as they are derived from the cells of patients. However, using viral vectors for introducing transcription factors may cause tumor when transplantation is carried out. So such kinds of hurdles need to be overcome to increase efficiency of these cells.[9]

5.1.1.4 Mesenchymal stem cells:

These cells have potential to differentiate into different kinds of cells. Their route of administration can be intravenous or direct injection at the site of brain tumor that is formed after injury (Lam etal., 2013). They are involved in secreting growth factors, gene and protein interactions and immune strengthening effects. They have many advantages over other cells because of ease of isolation, least immune rejection, rapid expansion and their ability to reach injured area and surrounding inflamed area (Ucceli etal.,2006).They secrete multiple growth as well as neurotrophic factors that aid in self repairing mechanisms of tissues.

5.1.1.5 Adipose derived stem cells:

These cells represent promising application in treating brain injuries resulting in improved motor functions (Arbodela etal.,2011).In various investigation studies, the adipose derived stem cells were differentiated into Schwann cells that resulted in significant recovery after brain injury. These cells can effectively reduce the condition of gliosis whenever brain injury occurs (Yang etal.,2011).

5.1.2. Endogenous Stem Cell Therapy

Endogenous stimulation has many advantages as it is less invasive, and avoids ethical concerns and issues happening within embryonic cells and having no rejection issues.

There are two different regions in adults for endogenous synthesis of neurons;

- Sub ventricular Zone (SVZ) in lateral ventricle.
- Sub granular Zone (SGZ) in hippocampus.[9]

Therapeutics have been designed to stimulate neurogenesis towards the injured areas of brain. Endogenous stimulation can be done by release of certain growth factors such as EGF, FGF-2, bFGF, aFGF, BDNF, NGF, NT-3, VEGF, GDNF, IGF-1 and SDF-1 alpha.[10]

These growth factors can be injected intraventricular, or intraparenchymal. Some authors report that growth factor not only improve proliferation, but also promote increased migration and gliogenesis of Neural Precursor Cells (NPCs).

Important growth factors which are mostly used for neurogenesis are: -

I. CBP/p300- phosphorylated Smad complex: Conjugated with NSCs, they can determine differentiation. If associated with Signal Transducers and Activators of Transcription (STAT) phosphorylated 3, the NSCs differentiate into cells with astroglia cells. Alternatively, if attached with proneural basic Helix Loop-Helix (bHLH) factor, such as neurogenin 1 and 2, cells differentiate into a neuronal lineage. SOX2 gene also plays an important role in neural differentiation.[11]

II. RE1-Silencing Transcription Factor (REST): Control most of the gene regulations. Act as suppressor of neuron differentiation in non-neuronal and its regulation stimulates the genes involved in differentiation of neurons.[12]

III. Brain-Derived Neurotrophic Factor (BDNF): Comparison of BDNF of healthy versus damaged brain shows that BDNF is important for survival of progenitor cells in adults .[13]

IV. Polysialic Acid (PSA): Their presence in damaged brain cell help them to reproduce o rebuild by providing the desired condition for differentiation.Polysialic Acid (PSA)regulates cell interactions and is harnessed to stimulate tissue repair by:

- Replacement of cells and
- Rebuilding of neural connections.[14]

6. Comparison Between Exogenous and Endogenous Stem Cell Therapy

In exogenous stem cell therapy, transplantation of embryonic stem cells (ESCs) and induced-pluripotent stem cells (iPSCs) into damaged area of brain lead to maturation and differentiation of neurons. Endogenous therapy is restricted to SVZ and SGZ of brain and is continuously producing neurons, and then migrated to damaged area of brain and replace them.[15]

7. Controversial trial to reanimate dead brain

Our brains are poor at regenerating cells that are dead through injury or any disease while therapies using neural stem cells opens the way to replace lost cells. Advancement in field of stem cell technology and its use in treating traumatic brain injuries gives scientist a ray of hope to recur dead brain, which is being criticized for cheating the death but Is brain death sufficient to declare a person dead and when bodies are biologically alive as a result of life support? This puts to new debate of declaring a person dead and if brain death and death are same.[16] At the same time, Is there a wisdom to treat the person with stem cells to regenerate the dead part rather than removing the life aid and letting the person to die. This makes us think that isscience far ahead to make it possible? The challenge is accepted by a US company BioQuark along with Revita Life Sciences firm in India to resuscitate brain dead patients. The project named ReAnima faced an immense criticism but CEO of Bioquark,Pastor replies that same response was observed against Organ transplantation and now that just seems like a dumb story and we are much ahead now. Pastor is impressed by the regenerative capabilities of various species like amphibians and planarians who have ability to regenerate their brain even after it's completely lost.

Dr. Himanshu Bansal, investigator of the project and conjointly owner of the Anupam Hospital, where initial clinical test is going to be conducted, is extremely hooked into theproject.The project has been given ethical permission by Institutional Revenue Board to use 20 brain dead patients able to breathe on ventilator.[17] The clinical trial would involve injecting stem cells that differentiate into neurons. Then injecting with peptide called BQ-A, which is taken from ooplaasm. Moreover, these peptides have ability to target the dead neurons.Following this steps involves the median nerve stimulation and transcranial laser therapy after 15 days. Cox a Pediatric surgeon who has done research on mesenchymal stem cells is not much hopeful about this trial and says though some brain cells as that of sub ventricular zone are able to grow on culture even after a person is declared brain dead but that does not mean that stem cells can make new neurons and make successful connections,as neurons require continuous blood flow which is lost in brain dead people .Despite all the efforts to diminish Pastor's courage he is optimistic to run the project and says that the only thing is to put right people and right minds to this project.

8. Ethical Concerns

There are many ethical issues raised when a project like ReAnima is under its way. The disparagers of this project complains that there is a lack of consent of participants in this trial which is ethically not acceptable.Though this trial is dependent on consent from family of participant who is brain dead but still there are many reservations.[18] Moreover, some people think that such a claim gives nothing more than a false hope to families and friends.Another ethical issue raised in this debate is whether the person will regain his true mental state or we will be introduced with someone who has lost his memory completely.The critics argue that it raises serious ethical questions when it comes to reverting the dead brain of a person and what if the person returns to an extremely dangerous mental state,worse than it was before. The debate on ethical issues persist and many consider it as a sciencefiction that has no practical approach.

CONCLUSION

Stem cell therapy as a new alternative to all previous technologies to treat the damage brain cells have emerged as one of the most effective, long lasting and applicable in true means. All previous therapies that were and are used for the treatment of brain cells have not proven successful due to its low applicability. Stem cell therapy as a technology in its early days also faces various ethical challenges and concerns regarding its use to revert back the affected brain cells. These ethical issues need serious consideration to bear in mind so that the therapy can be used not only for the patients of brain cells but also various other stem cell therapies curing skin burns, bone formation etc. Stem cell therapy is a way forward to treat and cure all those patients as these cells have the potential to be converted into any kind of cells. Hopefully, this stem cell therapy and technology would provide a ray of hope for all the patients and would provide good health to them.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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