http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v14i01.03

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Nebulized Exosome Therapy for Neurological Disorders: A First-in-Field Case Series

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Abstract
This is, to our knowledge, the first-in-field case series describing the use of nebulized exosomes for different neurological disorders. Chronic neurological disorders often present overlapping mechanisms of neuro-inflammation, oxidative stress, and impaired cellular repair, and are frequently resistant to standard therapies, highlighting the need for innovative, regenerative treatment strategies. Nebulized exosome therapy is an emerging approach for treating neurological and neuro-degenerative disorders. Exosomes are nano-sized vesicles that facilitate intercellular communication and carry bioactive molecules, including neurotrophic factors that may aid in recovery from neurological disorders by promoting regeneration of brain cells and tissue. Objective: To evaluate the clinical effects of nebulized Umbilical Cord-Mesenchymal Stem Cells (UC-MSCs) derived exosomes in treatment of neurological disorders.

Methods: *This case series included eight patients, each diagnosed with a single distinct neurological condition: Parkinson's disease / fibromyalgia / post-stroke / chronic dizziness / dementia / Friedreich's ataxia / post-covid / repeated extra-dural haemorrhage. All Patients were treated with nebulized UC-MSCs derived exosomes, number of treatments ranged from 1 to 3 treatments per patient, and the interval between treatments was 4 weeks. Patients' reports were obtained, and subjective clinical assessment and examination were performed for each patient before the treatment, two weeks after each treatment, then six months after the first treatment.*

Results: *Following nebulized exosome therapy, all patients reported and demonstrated clinical improvement in both symptoms and neurological signs, except for the patient with pre-existing dementia.*

Conclusion: *UC-MSCs derived exosomes are emerging as a promising tool in regenerative medicine, and they represent a promising frontier in treatment of neuro-degenerative diseases with a significant potential promising therapeutic effect in different neurological disorders.*

Keywords: *Exosomes, extracellular vesicles, extra-cellular cargo, neuro-inflammatory diseases, intercellular communication, drug delivery, biomarkers, cancer, neuro-degenerative diseases, biogenesis, post-stroke, fibromyalgia, parkinson's disease, dizziness, extra-dural haemorrhage, dementia, Friedreich's ataxia, post-covid, neurological disorders.*

Introduction

To our knowledge, this is the first published case series describing the use of nebulized Umbilical Cord-Mesenchymal Stem Cells (UC-MSCs) derived exosomes for a range of neurological and neuro-inflammatory conditions, including Parkinson's disease, fibromyalgia, stroke, chronic dizziness, dementia, Friedreich's ataxia, post-covid, and extra-dural haemorrhage. No prior clinical studies have documented the use of nebulized exosome therapy in these patient populations.

Exosomes are tiny vesicles, composed of a lipid bilayer membrane that includes phospholipids, cholesterol, and sphingolipids. They typically range from 30 to 150 nanometers in diameter. They are a subtype of extracellular vesicles (cellular secretome "cargo"), that contain various cellular organelles, and bioactive molecules such as proteins, lipids, and RNA including mRNAs, microRNAs, as well as long non-coding RNAs, which can influence the gene expression profiles of recipient cells[9][10].

Exosomes originate from the endosomal compartment of cells. Their biogenesis begins with endocytosis (inward budding of the cell membrane), forming the early endosomes (small vesicles). Then, these early endosomes mature into late endosomes (Multi-Vesicular Bodies "MVBs"). Inside these MVBs, the membrane buds inward to create multiple Intra-Luminal Vesicles (ILVs). Some MVBs fuse with the plasma membrane to release their ILVs into the extracellular space as exosomes. Once outside the cell, exosomes will play a significant role in cellular communication with the nearby cells as well as cells at distant locations[4][7].

Exosomes internalization is a highly versatile process and can occur via endocytosis, direct fusion with the cell membrane, and through specific receptor mediated uptake[6].

UC-MSCs derived exosomes are of particular interest in regenerative medicine and therapeutic interventions. They can be used as biomarkers for the early detection and monitoring of different diseases as their content reflect the molecular state of the parent cells[2][14].

UC-MSCs derived exosomes can modulate immune responses and gene expression, they can reduce inflammation and promote tissue regeneration, they can influence cell proliferation, migration, and differentiation[12][13].

UC-MSCs derived exosomes can protect dopamine-producing neurons in the substantia nigra[1][12][14].

UC-MSCs derived exosomes reduce oxidative stress and neuro-inflammation of the brain, they contain anti-apoptotic proteins and growth factors such as Brain-Derived Neurotrophic Factor (BDNF), and Vascular Endothelial Growth Factor (VEGF), they enhance neurogenesis, angiogenesis, neuronal survival, synaptic plasticity, and glial cell activation[12][8][13][5][11]. They are being explored for their potential in treating conditions like Parkinson's and Alzheimer's diseases[1][14].

Cribriform plate is a porous structure in the skull that separates the nasal cavity from the brain. This could offer a route for communication with the central nervous system (CNS). The small size of the UC-MSCs derived exosomes makes them capable of passing through small openings like those in the cribriform plate. The lipid bilayer membrane allows them to fuse with cell membrane, leveraging the normal neuronal connections of olfactory nerve and trigeminal branches to be transported to the CNS, helping in the treatment of Alzheimer's or Parkinson's[1][3].

Methods

This case series included eight patients, each one of them is diagnosed with a distinct chronic clinical neurological condition:

1) Parkinson's disease with muscle rigidity, gorilla gait, and decreased facial expressions.
2) Fibromyalgia with blurred vision, sleep disturbance, cognitive difficulties (foggy brain), headache, pain all over the body, fatigue, loss of energy, irritable bowel syndrome and depression.
3) Post-stroke with residual motor weakness and dysarthria.
4) Chronic dizziness and unbalance.

5) Dementia with memory loss, disorientation, poor judgment, impaired reasoning and problem solving.
6) Friedreich's ataxia with slurred speech, difficulty swallowing, muscle weakness of both lower limbs, motor dysfunction, and poor balance.
7) Post-covid neurological disorders causing back and bilateral lower limb muscular weakness resulting in gait impairment.
8) Repeated extra-dural haemorrhage causing motor weakness, dysarthria, unbalance, cognitive, functional and coordination impairments.

Each one of the eight patients was asked to sign a consent explaining this novel approach, then patients' reports were obtained, and subjective clinical assessment and examination were done for each patient before the treatment. Patients were treated with UC-MSCs derived exosomes, using a nebulizer machine (nebulizer converts liquid medication into aerosolized particles). In this case series, piston compressor nebulizer "pure" was used. For each patient, one vial of 4.92×10^{10} lyophilized exosomes was used per treatment (lyophilized exosomes are exosomes that have been freeze-dried using lyophilization, which is a process that removes water under low pressure and temperature. Lyophilization preserves and stabilizes biological materials of exosomes allowing long-term storage at room temperature, and makes transportation easier). Each vial was reconstituted and diluted in 5mL of sterile saline. A large-bore needle (18G) was used to withdraw the exosomes from the vial, and transfer them in the medication cup of the nebulizer. An additional 5mL of sterile saline was added to the nebulizer cup for more dilution of the exosomes. The cup was wrapped in aluminum foil as the UC-MSCs derived exosomes used for the treatments were sensitive to light. Each patient was asked to inhale the reconstituted exosomes via the nebulizer, being instructed to perform a slow inhalation through the nose, and a slow expiration from the mouth. Treatment was done over a period of one hour as the patient was given brief resting periods during the treatment to ensure comfort and tolerability. Each one of the patients with Parkinson's disease and post-stroke received only one treatment. Each one of the patients with fibromyalgia, dementia, and chronic dizziness received two treatments, with an interval of four weeks between them. Each one of the patients with Friedreich's ataxia, post-covid, and repeated extra-dural haemorrhage received three treatments, with an interval of four weeks between them. Patients' reports were obtained, and subjective clinical assessment and examination were done for each patient two weeks after each treatment, and six months after the initial treatment.

Results

Each treatment was followed by subjective improvement observed by the patient, that started by the second or third day post-treatment. Two weeks after each treatment, all patients reported and showed measurable symptomatic improvements, and functional recovery:

1) Parkinson's patient showed enhanced motor coordination, improved facial expressions, and reduced rigidity.
2) Fibromyalgia patient reported a reduction of both pain and headache intensity, improvement in cognitive and mental clarity, enhancement in mood and emotional stability, decrease of mental clouding (brain fog), and restoration of visual sharpness. The patient also reported general improvement in quality of life with restored energy and better sleep quality.
3) Post-stroke patient exhibited better upper and lower limb strength, and speech clarity.
4) Chronic dizziness patient experienced reduced vertigo episodes and better balance.
5) Dementia patient did not show significant improvement.
6) Friedreich's ataxia patient reported an improvement in speech and communication. Talking became clearer and the words were better understood.
7) Post-covid patient showed improvement in the muscle performance of both lower limbs,

which made the gait better, easier, and with more stability.

8) Repeated extra-dural haemorrhage patient reported notable multi-domain improvements. Enhancements were observed in motor function, with increased balance and limb coordination. Improvements were noticed and reported in the thinking process and speech clarity particularly in articulation and fluency with better cognitive responsiveness including attention and word retrieval. The patient started going back to work after the second treatment.

No adverse effects were observed in any patient. Patients continued to show persistent improvements for six months after the initial treatment.

Discussion

This case series explores the clinical effects and safety of nebulized UC-MSCs derived exosomes in eight patients with varied chronic neurological disorders, including Parkinson's disease, fibromyalgia, post-stroke, chronic dizziness, dementia, Friedreich's ataxia, post-covid, and repeated extra-dural haemorrhage. Despite the diversity of diagnoses, all patients had persistent, treatment-resistant symptoms and limited therapeutic options. Following 1 to 3 treatments of inhaled nebulized exosome therapy, each patient demonstrated symptomatic improvement in at least one functional domain. These included enhancements in facial expressions, motor coordination, speech clarity, cognitive responsiveness, balance, energy levels, as well as reduction in rigidity, pain, dizziness, brain fog, and blurred vision. Improvements were often reported within 48 to 72 hours of treatment, and benefits persisted for several months.

The positive clinical responses observed across different conditions may be attributed to the broad bioactivity of UC-MSC derived exosomes. Nebulized delivery offers a non-invasive route that may enhance CNS targeting through the olfactory, trigeminal and respiratory pathways, delivering regenerative signals, and making exosomes particularly promising in treating CNS disorders. No adverse effects were observed in any patient, supporting the safety and tolerability of nebulized exosome therapy in this small cohort. The non-invasive administration method avoids complications associated with injections, it enhances the bioavailability of exosomes improving the therapeutic efficacy. Also being a non-invasive method makes it a highly attractive and a patient-friendly option for CNS-targeted therapies, and the rapid onset of perceived benefit further underscores the feasibility of this delivery method.

However, this case series has notable limitations. The sample size is small, and the outcomes are only based on patient reports, and subjective clinical assessment and examination.

Future research should involve controlled clinical trials, objective outcome measures, and mechanistic studies to establish efficacy, ideal dosing, schedules, and long-term safety.

Conclusion

Although many promising results have been reported, the exact mechanisms by which exosomes mediate their effects remain incompletely understood. UC-MSCs derived exosomes are emerging as a promising tool in regenerative medicine, and they represent a promising frontier in treatment of neuro-degenerative diseases. Nebulized exosome therapy appears to be a safe and well-tolerated intervention, with multi-system benefits in patients suffering from chronic treatment-resistant neurological and systemic disorders. This novel approach offers an efficient treatment via administration through the intranasal cavity, as UC-MSCs derived exosomes do have the potential to cross the cribriform plate and go directly to the CNS. While the results are promising, additional research is needed to expand upon these preliminary results to evaluate the long-term outcomes, and to focus on establishing dosing guidelines and defining the ideal therapeutic exosome manufacturing and characterization to be standardized, to ensure consistent content, purity, and functional activity for effective and safe treatments.

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