Long-Term Clinical Efficacy of Human Umbilical Cord Blood Mononuclear Cell Transplantation by Lateral Atlanto-Occipital Space Puncture (Gong’s Puncture) for the Treatment of Multiple System Atrophy

Dianrong Gong1*, Weifei Wang1*, Xiaoling Yuan1, Haiyan Yu1, and Min Zhao1

Abstract

Multiple system atrophy (MSA) is a sporadic, progressive neurodegenerative disease characterized by autonomic nervous dysfunction with parkinsonism or cerebellar ataxia. Mesenchymal stem cell therapy or transplantation of human umbilical cord blood mononuclear cells (hUCB-MCs) may inhibit progression in MSA, but long-term studies are lacking. In addition, injection of stem cells via lateral atlanto-occipital space puncture (LASP, or Gong’s puncture) may efficiently target areas of brain injury and avoid the disadvantages of other methods. This prospective study investigated the long-term clinical efficacy of transplantation of hUCB-MCs via LASP for the treatment of MSA. Seven patients with MSA who received hUCB-MC transplantation via LASP were followed for 3 to 5 years. Neurological function was evaluated before (baseline), at 3, 6, and 12 months, and annually after the first transplantation using the Unified MSA Rating Scale (UMSARS); a lower score indicated improvement. Adverse events were recorded. The best therapeutic effect was observed 3 to 6 months after the first hUCB-MC transplantation. The total UMSARS score at the timepoint of best effect (25.71 ± 11.87) was significantly lower than the score before treatment (42.57 ± 7.96; P = 0.001), but also significantly lower than at the end of follow-up (35.14 ± 18.21; P = 0.038). The UMSARS II score (findings on neurological examination) at the timepoint of best effect was significantly lower than before treatment (P = 0.001). There were no serious adverse events. In conclusion, transplantation of hUCB-MCs via LASP is a safe and effective treatment for MSA.

Keywords
multiple system atrophy, cord blood mononuclear cells, lateral atlanto-occipital space puncture, Gong’s puncture, neurodegenerative disease, parkinsonism

Introduction

Multiple system atrophy (MSA) is a sporadic, progressive neurodegenerative disease characterized by autonomic nervous dysfunction1. There are two clinical phenotypes of MSA: MSA with predominant parkinsonism (MSA-P) and MSA with dominant cerebellar ataxia (MSA-C)2. The worldwide incidence of MSA has increased dramatically in recent years. Rapid disease progression often leads to death within 8 to 9 years after the onset of symptoms3,4. The current treatments for MSA are mostly symptomatic management for autonomic nervous disorders and parkinsonism5. In the past 10 years, the effectiveness of recombinant growth hormone, riluzole, minocycline, lithium, rifampicin, and rasagiline in the treatment of MSA has been evaluated; however, no positive results were observed3,6.
In 2012, a randomized controlled trial showed that treatment with autologous bone marrow mesenchymal stem cells (MSCs) delayed the progression of neurological deficit in patients with MSA-C, suggesting the therapeutic potential of MSCs in MSA treatment. In 2019, Singer et al. reported that intrathecal transplantation of adipose-derived MSCs was a safe, well-tolerated treatment method that significantly suppressed the progression of MSA in a dose-dependent manner. The patients with MSA in both studies were followed for only 1 year, and the long-term efficacy of stem cell therapy for MSA remains unclear.

Human umbilical cord blood mononuclear cells (hUCB-MCs) contain a variety of stem cell populations (eg, hematopoietic stem cells, endothelial stem cells, lymphoblasts, small embryonic stem cells, lymphocytes, and bone marrow cells), as well as neurotrophic factors. The therapeutic effects of hUCB-MCs have been observed in animal models of stroke and spinal cord injury, but the clinical efficacy of hUCB-MCs in MSA has not been investigated.

The main approaches of cell therapy for central nervous system diseases include vein infusion, lateral ventricle puncture, lumbar puncture, and stereotactic transplantation. Although intravenous infusion of cells is a simple procedure, the majority of cells that are infused through the vein are trapped and cleared in the lung so that fewer reach the injured site. Furthermore, the number of cells that can enter the brain is very limited because of the blood–brain barrier. Cells injected via lateral ventricle puncture can migrate to the injured brain area and integrate well with host tissues. However, lateral ventricle puncture has certain shortcomings, such as large injury areas and high infection rate. The major disadvantage of lumbar puncture is cell depletion at each nerve root.

The circulation of cerebrospinal fluid in the spinal canal is passive, and it is difficult for cells to enter the ventricular system. There is evidence that microglia and macrophages are active in areas of brain injury, and the local microenvironment of the brain is highly complex. Cells that are implanted in the injured area may be cleared. This impedes cell survival and expansion.

Lateral atlanto-occipital space puncture (LASP, also known as Gong’s puncture since 2018) injects stem cells into the occipital cistern, where they migrate to the target area via endogenous migration. This prevents microglia and macrophages from entering the site of injury and therefore improves cell survival. This prospective study investigated the long-term clinical efficacy of hUCB-MC transplantation via LASP for the treatment of MSA.

**Materials and Methods**

This study was approved by the medical ethics committee of the local hospital (Approval No: 2013165) with informed consent signed by all patients. The procedure for blood collection and isolation of hUCB-MCs was approved by the local ethics committee.

**Patients**

The study population comprised seven patients with MSA who were treated with hUCB-MC transplantation via LASP in the Department of Neurology of our hospital from January 2014 to March 2016. For inclusion, MSA was diagnosed according to the criteria for probable MSA proposed by Gilman et al. in 2008. Furthermore, patients had no serious cerebrovascular or other major digestive, respiratory, or blood diseases; malignant tumors; or unconscious disorders or mental system diseases.

**Preparation of hUCB-MCs**

Fresh cord blood (150 ml) was donated by a healthy woman who underwent cesarean section in our hospital. She had no infections, including hepatitis B, hepatitis C, human immunodeficiency virus, or syphilis. The blood was collected under sterile conditions. The hUCB-MCs were separated from blood samples using a cord blood treatment kit (cat. no. SCR-200I; Ningxia Zhonglianda Biological, China). A 5-ml suspension containing 2–3 × 10^8/ml hUCB-MCs was obtained.

**Transplantation of hUCB-MCs**

All operations were performed in compliance with aseptic principles. The hUCB-MCs were transplanted into patients with MSA via LASP. Each patient was placed supine without a pillow. The highest point of the mastoid was located and the puncture site was 1 cm inferior, and 1 cm posterior, to that point. After local anesthesia, the skin was pierced by a needle.

The direction of LASP was parallel to the imaginary line of the external auditory canal and perpendicular to the longitudinal axis of the cervical vertebra. The needle was inserted along the lower edge of the occipital bone. A sense of breakthrough was experienced two times during the puncture. The puncture was considered successful when cerebrospinal fluid flowed freely after the needle was pulled out. Three milliliters of cerebrospinal fluid were collected. Five milliliters of pre-warmed hUCB-MCs were injected slowly into the cisterna magna. The needle was then removed and the puncture point was pressed with a sterile dressing cover.

The patient was placed supine with a pillow under the head. The pillow was removed 6 to 8 hours after the procedure. Each patient was treated with hUCB-MC transplantation via LASP 2 to 4 times, at intervals of 1 month.

**Follow-up**

Patients were followed for 3 to 5 years. Neurological function was evaluated before the first hUCB-MC transplantation (baseline), at 3, 6, and 12 months, and annually thereafter. Neurological function was scored using the Unified Multiple System Atrophic Rating Scale (UMSARS). The UMSARS
consists of UMSARS I, which quantifies patients’ symptoms and neurological function, and UMSARS II, which quantifies the findings on neurological examination. The timepoint of best effect was considered the follow-up at which patients had the lowest UMSARS total score and the lowest UMSARS II score. Adverse events were also recorded.

**Statistical Analysis**

Data were analyzed using SPSS 20.0 and are shown as mean ± standard deviation. Repeated-measures analysis of variance was applied to compare the UMSARS scores at different timepoints. The Bonferroni test was used to compare the UMSARS scores at each timepoint in pairs. P < 0.05 was considered statistically significant.

## Results

### Clinical Characteristics

Among the seven cases, five were diagnosed as MSA-C and two were categorized as MSA-P (Table 1). There were five men and two women, aged between 53 and 65 years, with a disease course of 18 to 48 months. Five patients were treated with hUCB-MC transplantation, three times. The other 2 patients were treated two and four times, respectively. The follow-up time was 3 to 5 years and the best effect was observed 3 to 6 months after the first transplantation.

### Clinical Efficacy of hUCB-MC Transplantation

For six patients (Pts #1, 2, 3, 4, 6, and 7), both the UMSARS total score and the UMSARS II score were significantly lower at the timepoint of best effect (3–6 months after the first transplant) compared with baseline (before treatment; Table 2). At the end of follow-up, the scores of these patients were also lower than the scores before treatment. The UMSARS score of one patient (Pt #5) did not change significantly after treatment, and the condition of this patient, as indicated by the UMSARS total score and UMSARS II score, had aggravated by the end of follow-up.

The average UMSARS total score and UMSARS II score of all patients with MSA at different timepoints were significantly different (UMSARS total score: mean F = 13.301, P = 0.009; UMSARS II score: mean F = 9.536; P = 0.021; Table 3).

The paired comparison analysis showed that the average UMSARS total score at the timepoint of best effect (25.714 ± 11.870) was significantly lower compared with the score at baseline (42.571 ± 7.955; mean difference = −16.857; P = 0.001). The average UMSARS total score at the end of follow-up (35.142 ± 18.206) was also lower than that before treatment, but not statistically significant. The average UMSARS total score at the end of follow-up (35.142 ± 18.206) was significantly higher than that at the timepoint of best effect (25.714 ± 11.870; mean difference = −9.429; P = 0.038).

The UMSARS II score at the timepoint of best effect was significantly lower than before treatment (mean difference = −6.857, P = 0.001) and had remained low at the end of follow-up (16.428 ± 10.438 cf. 19.142 ± 5.209), but the difference was not statistically significant (mean difference = −2.714, P = 0.797). The UMSARS II score at the end of follow-up was slightly higher than that at the timepoint of

---

**Table 1.** Demographics, Clinical Characteristics, and Follow-up Data of Seven Patients With MSA.

| Gender | Age, y | Course, mo<sup>a</sup> | Subtype | Tx, n | Timepoints | Best effect, mo | FFU, y |
|--------|--------|------------------------|---------|-------|------------|-----------------|--------|
| 1      | M      | 55                     | 24      | MSA-C | 3          | 3               | 3      |
| 2      | F      | 60                     | 30      | MSA-P | 4          | 6               | 5      |
| 3      | M      | 62                     | 36      | MSA-C | 3          | 3               | 4      |
| 4      | M      | 51                     | 36      | MSA-P | 3          | 3               | 4      |
| 5      | F      | 65                     | 48      | MSA-C | 3          | 3               | 3      |
| 6      | M      | 53                     | 18      | MSA-C | 2          | 6               | 5      |
| 7      | M      | 57                     | 24      | MSA-C | 3          | 6               | 5      |

FFU: final follow-up; MSA: multiple system atrophy; MSA-C: final follow-up; MSA-P: final follow-up; Tx: number of treatments.

<sup>a</sup>MSA disease course.

**Table 2.** UMSARS Scores of Seven MSA Patients at Baseline, Best Score, and Final Follow-up and After hUCB-MC Transplantation.

|       | UMSARS total | UMSARS II |
|-------|--------------|-----------|
|       | Baseline     | Best      | FFU   | Baseline     | Best      | FFU   |
| 1     | 39           | 22         | 25    | 17           | 10         | 12    |
| 2     | 45           | 26         | 40    | 19           | 11         | 14    |
| 3     | 34           | 15         | 18    | 15           | 6          | 7     |
| 4     | 49           | 30         | 36    | 24           | 17         | 21    |
| 5     | 55           | 50         | 73    | 28           | 26         | 38    |
| 6     | 33           | 17         | 26    | 13           | 6          | 10    |
| 7     | 43           | 20         | 28    | 18           | 10         | 13    |

FFU: final follow-up; hUCB-MC: human umbilical cord blood mononuclear cell; MSA: multiple system atrophy; UMSARS: Unified Multiple System Atrophic Rating Scale.
best effect (16.428 ± 10.438 cf. 12.285 ± 7.087), but the difference was not statistically significant (mean difference = 4.143, \( P = 0.070 \); Table 3).

**Adverse Events**

One patient (Pt #2) had a fever on the second day after treatment, with a maximum body temperature of 38.0°C. After antipyretic treatment, the body temperature returned to normal. Another patient (Pt #6) experienced pain and discomfort at the puncture site. The symptoms disappeared on the third day after transplantation without special treatment. There were no other adverse events or complications during follow-up.

**Discussion**

The current study found that the neurological function of patients with MSA improved after hUCB-MC transplantation, with the best effect observed at 3 to 6 months after the first treatment, and no patient experienced any severe adverse event related to transplantation. These findings suggest that hUCB-MC transplantation via LASP is a safe and effective treatment method for MSA.

In this study, hUCB-MC transplantation via LASP appeared to improve MSA symptoms and delayed disease progression at the 3- to 5-year follow-up, as reflected by changes in the UMSARS and UMSARS II scores. Gong et al.\(^{14}\) in 2018 optimized the puncture position and route of LASP based on cervical 1–2 lateral puncture and cerebellomedullary cistern puncture (Gong’s puncture), which effectively prevented injuries in the vertebral artery and medulla oblongata. Since then, more than 1,000 operations with Gong’s puncture have been performed, with high effectiveness and safety. Stem cells that are transplanted into the cisterna magna by lateral ventricle puncture can reach the target area via endogenous migration, which prevents these cells from directly entering the inflammatory environment of the injury site, thereby improving cell survival\(^{21}\). Gong’s puncture also prevents cell loss in the lung via intravenous infusion or at the nerve root via lumbar puncture. The cisterna magna connects with the fourth ventricle. Therefore, theoretically, LASP is as effective as lateral ventricle puncture, but with less injury or complications.

Mononuclear cells can be readily separated from human umbilical cord blood and used for allogeneic transplantation with low immunogenicity\(^ {22}\). There is evidence that hUCB-MCs are neuroprotective, and this highlights their potential for the treatment of neurodegenerative diseases\(^ {23}\). In animal models of stroke and spinal cord injury, hUCB-MCs can migrate to the damaged brain area and replace damaged neurons, thereby improving the local brain microenvironment, reducing inflammation, and promoting regeneration of blood vessels and nerves\(^ {10,11}\). Karlupia et al.\(^ {24}\) found that hUCB-MC therapy is more effective than cord MSC therapy in improving the neurological function of rodents with ischemic stroke.

In the present study, hUCB-MC transplantation via LASP showed good therapeutic effects for patients with MSA. A significant improvement in the neurological function was observed at 3 to 6 months after the first transplantation, as evidenced by significantly lower total UMSARS and UMSARS II scores compared with before treatment. Both scores tended to increase from the timepoint of best effect to the end of follow-up. The average annual increase in UMSARS score of patients with MSA is 17.2\(^ {25}\), which is much higher than the experience of our patients (−1.6). This suggests the long-term efficacy of hUCB-MC transplantation via LASP.

Previous studies showed that stem cells can live in the brain and spinal cord for 3 months in animal models, including primate models\(^ {26,27}\). This may explain why the timepoint of best effect after hUCB-MC transplantation in the present study was 3 to 6 months. The stable, long-term effects of transplantation of hUCB-MCs via LASP may be the result of activating endogenous neural stem cells, improving the brain microenvironment, regulating the immune system, and promoting secretion of various neurotrophic factors\(^ {28}\).

In the present study, the neurological function of one MSA patient did not significantly improve after treatment and had even aggravated by the end of follow-up. This may be due to a long disease course (4 years) and severe symptoms (high UMSARS score) before treatment. Hence, early treatment for MSA is highly recommended.

In this study, we did not include a placebo surgery group because previous evidence confirmed that a placebo effect on neurological function could last up to 1 year after treatment\(^ {29}\). To eliminate any influence of LASP on efficacy, we followed the patients for 3 to 5 years, and both the total UMSARS and UMSARS II scores were applied to evaluate

### Table 3. Average UMSARS Total Score and UMSARS II Score of Seven Patients With MSA at Baseline and After hUCB-MC Transplantation.

|                  | Baseline | Best effect | FFU   | F value | P value |
|------------------|----------|-------------|-------|---------|---------|
| UMSARS           | 42.57 ± 7.96 | 25.71 ± 11.87 | 35.14 ± 18.21 | 13.301  | 0.009   |
| UMSARS II        | 19.14 ± 5.21 | 12.29 ± 7.09  | 16.43 ± 10.44  | 9.536   | 0.021   |

FFU: final follow-up; UMSARS: Unified Multiple System Atrophic Rating Scale.

\(^{a}\) \( P < 0.05 \) compared with the scores before treatment.

\(^{b}\) \( P < 0.05 \) compared with the scores at the timepoint of best effect.
neurological function. Nevertheless, this study was limited in that only seven patients with MSA were recruited and they were from the same hospital, which may impede the generalization of the current findings. In addition, only one assessment tool was used to evaluate neurological function. Future investigations with other evaluation methods are needed. Finally, it is worth noting that the effects of cell therapy on central nervous diseases have been investigated mostly in uncontrolled and nonrandomized clinical studies, and could not be shown definitively in placebo-controlled, randomized trials. Therefore, multicenter, double-blind, placebo-controlled, randomized clinical trials need to be performed to confirm the findings of the present study.

In conclusion, this study showed that the neurological function of patients with MSA improved after hUCB-MC transplantation, and no severe adverse events related to transplantation were observed. These findings suggest that hUCB-MC transplantation via LASP is a safe and effective treatment method for MSA.

Acknowledgments
We thank the Mayora Group for funding support for Dr Dianrong Gong, Chief Physician of Neurology, Liaocheng People’s Hospital, and her team to conduct research on the treatment of multiple system atrophy (MSA) using umbilical cord blood stem cell (UCBSC) transplantation through lateral puncture of the occipital space. We also thank all the authors for providing us with additional data upon our request.

Author Contributions
D.G. provided the concept and study design. M.Z. finished data collection. X.Y. and H.Y. finished data analysis. W.W. was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Ethical Approval
This study was approved by the medical ethics committee of the Liaocheng People’s Hospital (Approval No: 2013165).

Statement of Human and Animal Rights
All procedures in this study were conducted in accordance with the ethics committee of the Liaocheng People’s Hospital (Approval No: 2013165) approved protocols. The procedure for blood collection and isolation of hUCB-MCs was approved by the local ethics committee. This article does not contain any studies with animal subjects.

Statement of Informed Consent
All the participants were informed of the right to withdraw from the study at any time, and all participants provided written informed consent. Issues of privacy and confidentiality were strictly maintained.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article:
Funded by the Mayora Group.

ORCID iD
Dianrong Gong https://orcid.org/0000-0002-0458-0597

References
1. Jellinger KA. Multiple system atrophy: an oligodendrogial-neuronal synucleinopathy 1. J Alzheimers Dis. 2018;62(3): 1141–79.
2. Ortiz JF, Bette S, Tambo W, Tao F, Cozar JC, Isaacson S. Multiple system atrophy—cerebellar type: clinical picture and treatment of an often-overlooked disorder. Cureus. 2020;12(9): e10741.
3. Krismer F, Wenning GK. Multiple system atrophy: insights into a rare and debilitating movement disorder. Nat Rev Neurol. 2017;13(4): 232–43.
4. Coon EA, Sletten DM, Suarez MD, Mandrekar JN, Ahlskog JE, Bower JH, Matsumoto YJ, Silber MH, Benaroch EE, Fealey RD, Sandroni P, et al. Clinical features and autonomic testing predict survival in multiple system atrophy. Brain. 2015; 138(Pt 12): 3623–31.
5. Burns MR, McFarland NR. Current management and emerging therapies in multiple system atrophy. Neurotherapeutics. 2020; 17(4): 1582–602.
6. Povse W, Seppi K, Fitzter-Attas CJ, Wenning GK, Gilman S, Low PA, Giladi N, Barone P, Sampaio C, Eyal E, Rascol O, et al. Efficacy of rasagiline in patients with the parkinsonian variant of multiple system atrophy: a randomised, placebo-controlled trial. Lancet Neurol. 2015;14(2): 145–52.
7. Lee PH, Lee JE, Kim HS, Song SK, Lee HS, Nam HS, Cheong JW, Jeong Y, Park HJ, Kim DJ, Nam CM, et al. A randomized trial of mesenchymal stem cells in multiple system atrophy. Ann Neurol. 2012;72(1): 32–40.
8. Singer W, Dietz AB, Zeller AD, Gehrking TL, Schmelzer JD, Schmeichel AM, Gehrking JA, Suarez MD, Sletten DM, Minota Pacheco KV, Coon EA, et al. Intrathecal administration of autologous mesenchymal stem cells in multiple system atrophy. Neurology. 2019;93(1): e77–87.
9. Pimentel-Coelho PM, Rosado-de-Castro PH, da Fonseca LM, Mendez-Otero R. Umbilical cord blood mononuclear cell transplantation for neonatal hypoxic-ischemic encephalopathy. Pediatr Res. 2012;71(4 Pt 2): 464–73.
10. Newcomb JD, Ajmo CT Jr, Sanberg CD, Sanberg PR, Pennypacker KR, Willing AE. Timing of cord blood treatment after experimental stroke determines therapeutic efficacy. Cell Transplant. 2006;15(3): 213–23.
11. Saporta S, Kim JJ, Willing AE, Fu ES, Davis CD, Sanberg PR. Human umbilical cord blood stem cells infusion in spinal cord injury: engraftment and beneficial influence on behavior. J Hematother Stem Cell Res. 2003;12(3): 271–78.
12. Yu D, Silva GA. Stem cell sources and therapeutic approaches for central nervous system and neural retinal disorders. Neurosurg Focus. 2008;24(3–4): E11.
13. Amer MH, Rose FRAJ, Shakesheff KM, Modo M, White LJ. Translational considerations in injectable cell-based therapeutics for neurological applications: concepts, progress and challenges. NPJ Regen Med. 2017;2:23.
14. Gong D, Yu H, Yuan X. A new method of subarachnoid puncture for clinical diagnosis and treatment: lateral atlanto-occipital space puncture. J Neurosurg. 2018;129(1): 146–52.
15. Baek W, Kim YS, Koh SH, Lim SW, Kim HY, Yi HJ, Kim H. Stem cell transplantation into the intraventricular space via an Ommaya reservoir in a patient with amyotrophic lateral sclerosis. J Neurosurg Sci. 2012;56(3): 261–63.
16. Khasawneh AH, Garling RJ, Harris CA. Cerebrospinal fluid circulation: what do we know and how do we know it. Brain Circ. 2018;4(1): 14–18.
17. Veizovic T, Beech JS, Stroemer RP, Watson WP, Hodges H. Resolution of stroke deficits following contralateral grafts of conditionally immortal neuroepithelial stem cells. Stroke. 2001;32(4): 1012–19.
18. Huang L, Fu C, Xiong F, He C, Wei Q. Stem cell therapy for spinal cord injury. Cell Transplant. 2021;30:1–16.
19. Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, Wood NW, Colosimo C, Dürr A, Fowler CJ, Kaufmann H, et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology. 2008;71(9): 670–76.
20. Wenning GK, Tison F, Seppi K, Sampaio C, Diem A, Yekhlef F, Ghoryayeb I, Ory F, Galitzky M, Scaravilli T, Bozi M, et al. Development and validation of the Unified Multiple System Atrophy Rating Scale (UMSARS). Mov Disord. 2004;19(12): 1391–1402.
21. He S, Luan Z, Qu S, Qiu X, Xin D, Jia W, Shen Y, Yu Z, Xu T. Ultrasound guided neural stem cell transplantation through the lateral ventricle for treatment of cerebral palsy in children. Neural Regen Res. 2012;7(32): 2529–35.
22. Kim JY, Jeon HB, Yang YS, Oh W, Chang JW. Application of human umbilical cord blood-derived mesenchymal stem cells in disease models. World J Stem Cells. 2010;2(2): 34–38.
23. Boltze J, Reich DM, Hau S, Reymann KG, Strassburger M, Lobsien D, Wagner DC, Kamprad M, Stahl T. Assessment of neuroprotective effects of human umbilical cord blood mononuclear cell subpopulations in vitro and in vivo. Cell Transplant. 2012;21(4): 723–37.
24. Karlupia N, Manley NC, Prasad K, Schäfer R, Steinberg G. Intracerebral transplantation of human umbilical cord blood mononuclear cells is more efficacious and safer compared with umbilical cord mesenchymal stromal cells in a rodent stroke model. Stem Cell Res Ther. 2014;5(2): 45.
25. Geser F, Wenning GK, Seppi K, Stampf Kountchev M, Scherfler C, Sawires M, Frick C, Ndayisaba JP, Ulmer H, Pellecchia MT, Barone P, et al. Progression of multiple system atrophy (MSA): a prospective natural history study by the European MSA Study Group (EMSA SG). Mov Disord. 2006;21(2): 179–86.
26. Isakova IA, Baker K, Dufour J, Gaupp D, Phinney DG. Preclinical evaluation of adult stem cell engraftment and toxicity in the CNS of rhesus macaques. Mol Ther. 2006;13(6): 1173–84.
27. Deng YB, Liu XG, Liu ZG, Liu XL, Liu Y, Zhou GQ. Implantation of BM mesenchymal stem cells into injured spinal cord elicits de novo neurogenesis and functional recovery: evidence from a study in rhesus monkeys. Cytotherapy. 2006;8(3): 210–14.
28. Pan K, Deng L, Chen P, Peng Q, Pan J, Wu Y, Wang Y. Safety and feasibility of repeated intrathecal allogeneic bone marrow-derived mesenchymal stromal cells in patients with neurological diseases. Stem Cells Int. 2019;2019:8421281.
29. McRae C, Cherin E, Yamazaki TG, Diem G, Vo AH, Russell D, Ellgring JH, Fahn S, Greene P, Dillon S, Winfield H, et al. Effects of perceived treatment on quality of life and medical outcomes in a double-blind placebo surgery trial. Arch Gen Psychiatry. 2004;61(4): 412–20.
30. Huang H, Chen Lin Mao G, Sharma H. Clinical neurorestorative cell therapies: developmental process, current state, and future prospective. J Neurorestoratology. 2020;8(2): 61–82.