The use of human umbilical cord mesenchymal stem cells in cerebral sinus venous thrombosis: A case report

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The use of human umbilical cord mesenchymal stem cells in cerebral sinus venous thrombosis: A case report

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ABSTRACT

Background. Cerebral sinus venous thrombosis (CSVT) is considered as uncommon type of stroke and happened in 3-4 cases per million. Despite anticoagulant, some patients still gain minimal or no improvement. Stem cells has been used as alternative treatment in stroke and known to give beneficial effect yet no significant side effects observed. However, the use of stem cells in CSVT had not been studied.

Case Report. In this case, we present a patient with CSVT who had no improvement for thrombosis and clinical condition after anticoagulant and standard treatment.

Conclusions. Stem cells was given to this patient and clinical improvement was observed.

Keywords: Cerebral sinus venous thrombosis, stem cells, stroke, hemorrhage

Abbreviations: Cerebral sinus venous thrombosis (CSVT), Computed Tomography (CT), Intensive Care Unit (ICU), Digital Subtraction Angiography (DSA), anti-double stranded-DNA (anti-DS-DNA), Transcranial Direct Current Stimulation (tDCS), umbilical cord-derived mesenchymal stem cells (UC-MSCs), Repetitive Transcranial Magnetic Stimulation (rTMS), bone marrow mesenchymal stem cells (BM-MSC), subarachnoid

hemorrhage (SAH), bone marrow-mononuclear cells (BM-MNC), human adipose-derived stem cells (hADSC), neural stem cells (NSC)

INTRODUCTION

Cerebral sinus venous thrombosis is a rare neurological disease that is considered as uncommon type of stroke[1,2]. It has varied clinical manifestations thus difficult to differentiate from other neurological diseases. It happened in 12.1 (95% CI, 9.9–14.3) per million person-years[3], with female to male ratio was 3:1 and contributed to 0,5-1% of all stroke[1]. Management of CSVT comprises the used of anticoagulant, thrombolysis, mechanical thrombectomy or drugs that treat symptoms or its clinical manifestation[1,4–7].

Stem cells has been used to treat several neurological diseases, especially in stroke. It has been widely studied in ischemic stroke, but only several studies used it for hemorrhagic stroke. Several studies showed beneficial effect of stem cell with minimal or even no side effect. However, until recently, there is no publication that use stem cells in CSVT cases, which is considered as a type of stroke[8,9]. In this study, we present a case of the use of human mesenchymal stem cells in cerebral sinus venous thrombosis which no improvement observed after given anticoagulant and physiotherapy.

CASE REPORT

A 29-year-old female was admitted to emergency department with decrease level of consciousness. Patient had right-sided headache since 1 month before admitted to hospital that worsened over time. Patient then brought to hospital because she had decrease in consciousness and right-sided weakness. Physical examination showed asymmetrical on nasolabial fold on pain stimuli and right-sided hemiparesis. Computed Tomography scan brain showed intracerebral hemorrhage with elevated intracranial pressure at left frontal lobe. (Figure 1A)

Emergency decompressive craniectomy was performed then patient was admitted to ICU. Tissue histology showed reactive brain parenchyma with sign of bleeding and microthrombus, without sign of malignancy. A repeat of brain CT scan one week after procedure showed improvement of midline shift and brain haemorrhage. (Figure 1B)

Cerebral DSA was performed with result of arterial vasospasm and thrombosis on one third anterior of superior sagittal sinus and probable thrombosis or aplasia from left transverse sinus. (Figure 2) Laboratory examination revealed moderate positive in lupus anticoagulant, and high in anti-DS-DNA (25 IU/mL) (normal value: <10 IU/mL).

After the procedure, medical treatment including anticoagulant therapy and also physiotherapy was given. Patient showed improvement on her consciousness but she could not remember well her condition before procedure and frequently forgetting things after procedure was done, becoming childish and emotionally unstable, also she still cannot stand up and did daily activities because of the weakness on her right extremities. One months after procedure, patient came to our clinic and then planned to be given intraarterial and intravenous stem cell therapy.

We gave human UC-MSCs seven weeks after cerebral hemorrhage and CSVT was diagnosed. Intra-arterial injection of $2x10^6$ UC-MSCs was given through bilateral common carotid artery for anterior circulation and left vertebral artery for posterior circulation. After intraarterial injection of stem cell, we performed diagnostic angiography and found there was no cerebral vascular occlusion. Intra-venous infusion of $26x10^6$ MSCs was also given through peripheral vein. Dizziness was felt during and after procedure for a while, but there is no other symptom felt.

After stem cell therapy, the patient underwent neurorestoration programs using tDCS and physiotherapy on day one after stem cells injection. Repetitive Transcranial Magnetic Stimulation (rTMS), physiotherapy, occupational therapy, and virtual reality exercise were performed in 3 weeks after stem cells injection.

Patient was evaluated for her outcome at second weeks and first month after stem cells injection. One day after injection, patient still moved from laying down to sitting position with help. At second weeks after injection, patient was able to sit from laying down, stand from sitting position, standing with good core stability, and walking without assistance but few instabilities still observed. She still need help to do daily activity such as take a bath or dressing. At first month after injection, patient still felt weakness in right side of her body, but significantly improved. She could draw and cut food using her right hand, also taking a bath, and dressing individually. She could read a book and memorize its content. Her cognitive function was evaluated and yield normal result.

DISCUSSION

Patient with CSVT could suffered with neurological deficit, depend on thrombus location. Based on historical examination, this patient had recurrent headache progressed into severe headache with some neurological deficit appeared then, which suggestive to CSVT. Neuroimaging confirmed that there was thrombus located at superior sagittal sinous. Hemorrhage and edema which were the complication of CSVT also observed that

could impair brain tissues around the locus [10]. Cerebral sinus venous thrombosis as in this report could manifest as headache, seizure, hemiparesis, and cognitive impairment.

To date, stem cells were used to treat several neurological cases in studies around the world. Ischaemic and haemorrhagic stroke, epilepsy, cerebral palsy, Parkinson's disease and several other neurological cases were the population being studied in stem cells trials [11–14]. Until recently, there is no publication which used stem cells for CSVT, even though CSVT is known as one type of stroke with similar clinical manifestation. Standard therapy of CSVT recently is using anticoagulant [15]. Stem cells implantation was considered in this patient because after 1 month being given anticoagulant and performing physiotherapy, there was no improvement of thrombosis in superior sagittal sinus, right-sided hemiparesis, decrease in cognitive function because of CSVT and intracranial hemorrhage. Administration of stem cells was performed in order to improve hemiparesis and cognitive decline in patient

Stem cells have been used widely in animal research of intracerebral hemorrhage [8,16]. A meta-analysis showed that stem cells gave significant benefit to intracerebral hemorrhage models, especially when given under 8 hours after onset, but no significant difference if compared between cell types and cell sources [11]. Human UC-MSC, like we used in this study, reported beneficial effects yet no side effect observed. Rats injected intravenously using human UC-MSC were gain significant neurological functional recovery [9]. Other study combined human UC-MSC with hematoma evacuation also on the other study combined human UC-MSC with hyperbaric oxygen and yielded that this combination gave superior results than other single treatment and reduced the loss of neural death [9]. Based on preclinical examination, human UC-MSC was not able to differentiated into target cell, but they acted indirectly through secreted biological substance [9].

In human studies, stem cells for intracerebral hemorrhage were not widely used as in ischemic stroke. The first study using MSC for hemorrhagic stroke was in 2011, even though reported improvement in functional test, they did not differentiate between control and MSC-treated group [17]. Intraventricularly injected autologous BM-MSC $20x10^6$ cells was given with NIHSS improvement [18]. In another study, with placebo-controlled design, 2 deliveries of BM-MSC $2x10^6$ cells were injected intravenously and could improve neuro-restoration and clinical prognosis [19]. A case report which showed allogeneic BM-MSC used in geriatric 80-years old SAH patient, resulted in improvement of ability of speaking and self-care [20]. These studies showed good improvement of using stem cells in

intracerebral hemorrhage [18–20]. There was no significant side effect observed after administration of human stemcells [8].

Motoric function was one that is potentially impaired in CSVT. Stem cells has been known to give effect in this function. Our patient had right hemiparesis with central type of right facial nerve palsy. After stem cells implantation along with neurorehabilitation, her motoric strength was improved after 2 weeks, and significant improvements were observed in 1 month. This finding correlates with studies yielded better motoric function after stem cells therapy. In 3 studies using BM-MNC or/and BM-MSC for intracerebral hemorrhage 1 month after onset showed improvement of NIHSS [21–23] A meta-analysis of stem cells therapy for cerebral palsy showed that stem cells could increase gross motor function significantly [11]. Stem cells benefit of motoric function were also studied preclinically in various rat models [12].

Unlike motoric function, cognitive function rarely observed and still gave conflicting results among studies, whether stem cells could be beneficial or nothing improved [24]. Intravenous administration of hADSC in intracerebral hemorrhage mouse model gave improvement of cognitive function [25]. Traumatic brain injury rat model transplanted with NSC gave improvement in cognitive function after being observed for at least 2 months [12]. Other study observing progressive neuronal loss in hippocampus rat models yielded interesting results [24]. Improvement was observed significantly 3 months after transplantation, but only for memory function which was related to hippocampus [24]. Other function such as object recognition which involved cortical region did not affected [24]. Our patient at first had difficulty to memorize, but after stem cells implantation, she could memorize what she had read, and cognitive test resulted in good outcome.

CONCLUSION

The use of stem cells for CSVT has never been performed or published in research, but several publication had used stem cells for intracerebral haemorrhage, also others used it for evaluating motoric or cognitive function and yielded good outcome. Patient in this case had been given hUC-MSC intraarterial and intravenously, continued with neurorestoration therapy, and we found good outcome at second week of evaluation. The improvement continue for the next month. Further clinical research is highly needed for the use of stem cells in CSVT, with or without intracerebral haemorrhage complications.

Patient consent

Patient in this case was already infomed and given consent.

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Conflict of interest

There was no personal or financial relationship that would lead to bias the content of this case report

Author's contributions

Conceptualization, M.K., Y.R. and F.I.W.; methodology, M.K., Y.R. and F.I.W.; validation, M.K., and Y.R.; formal analysis, M.K., and Y.R.; investigation, M.K., Y.R. and F.I.W.; resources, M.K., Y.R. and F.I.W.; data curation, M.K., Y.R. and F.I.W.; writing—original draft preparation, F.I.W.; writing—review and editing, M.K., Y.R. and F.I.W.; visualization, F.I.W.; supervision, M.K., and Y.R.; project administration, F.I.W.; funding acquisition, M.K. All authors have read and agreed to the published version of the manuscript.

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REFERENCES

1. Palanisamy M, Vijayakumar R. Erratum: Cerebral Venous Thrombosis: A Comprehensive Review (European Neurology DOI: 10.1159/000509802). Eur Neurol. 2020;83(5):554.
2. Idiculla P, et al. Cerebral venous thrombosis: A comprehensive review. Eur Neurol. 2020;83(4):369–79.
3. Zhou L, Yu A, Ngo L, Hill M, Field T. Incidence of cerebral venous thrombosis: A population based study, systematic review, and meta-analysis. Stroke. 2022;54:169–77.
4. Saposnik G, et al. Diagnosis and management of cerebral venous thrombosis: A scientific statement from the American Heart Association. Stroke. 2024;55:e77–90.
5. Behrouzi R, Punter M. Diagnosis and management of cerebral venous thrombosis. Clin Med. 2018;18(1):75–9.
6. Ulivi L, Squitieri M, Cohen H, et al. Cerebral venous thrombosis: a practical guide. Pract Neurol. 2020;20:356–67.
7. Palanisamy P, et al. Endovascular management of cerebral venous thrombosis: a tertiary-centre experience. Pol J Radiol. 2023;88:e349–55.
8. Gong YH, Hao SL, Wang BC. Mesenchymal Stem Cells Transplantation in Intracerebral Hemorrhage: Application and Challenges. Front Cell Neurosci. 2021;15(March):1–13.
9. Zhou J feng, Xiong Y, Kang X, Pan Z, Zhu Q, Goldbrunner R, et al. Application of stem cells and exosomes in the treatment of intracerebral hemorrhage: an update. Stem Cell Res Ther [Internet]. 2022;13(1):1–21. Available from: https://doi.org/10.1186/s13287-022-02965-2
10. Alvis-Miranda H, Castellar-Leones S, Alcala-Cerra G, Moscote-Salazar R. Cerebral sinus venous thrombosis. J Neurosci Rural Pr. 2013;4(4):427–38.
11. Eggenberger S, Boucard C, Schoeberlein A, Guzman R, Limacher A, Surbek D, et al. Stem cell treatment and cerebral palsy: Systemic review and metaanalysis. World J Stem Cells. 2019;11(10):891–903.
12. Zhou Y, Shao A, Xu W, Wu H, Deng Y. Advance of Stem Cell Treatment for Traumatic Brain Injury. Front Cell Neurosci. 2019;13(August).
13. Aligholi H, Safahani M, Asadi-Pooya AA. Stem cell therapy in patients with epilepsy: A systematic review. Clin Neurol Neurosurg [Internet]. 2021;200(November 2020):106416. Available from: https://doi.org/10.1016/j.clineuro.2020.106416
14. Kim JT, Youn DH, Kim BJ, Rhim JK, Jeon JP. Recent Stem Cell Research on

Hemorrhagic Stroke: An Update. J Korean Neurosurg Soc. 2022;65(2):161–72.

15. Warnock L, Huang D. Heparin. In: StatPearls. StatPearls Publishing; 2024.
16. Li C, Qin H, Zeng L, et al. Efficacy of stem cell therapy in animal models of intracerebral hemorrhage: an updated meta-analysis. Stem Cell Res Ther. 2022;13.
17. Bhasin A, et al. Autologous mesenchymal stem cells in chronic stroke. Cerebrovasc Dis Extra. 2011;1:93–104.
18. Al Fauzi A, Suroto N, Bajamal A, Mh M. Intraventricular transplantation of autologous bone marrow mesenchymal stem cells via Ommaya reservoir in persistent vegetative state patients after haemorrhagic stroke: report of two cases & review of the literature. J Stem Cells Regen. 2016;12:100–3.
19. Tsang K, Ng C, Zhu X, Wong G, Lu G, Ahuja A, et al. Phase I/II randomized controlled trial of autologous bone marrow-derived mesenchymal stem cell therapy for chronic stroke. World J Stem Cells. 2017;9:133–43.
20. Brunet M, Chen S, Khandelwal P, Hare J, Starke R, Peterson E, et al. Intravenous stem cell therapy for high-grade aneurysmal subarachnoid hemorrhage: case report and literature review. World Neurosurg. 2019;128:573–5.
21. Li Z, Zhang Z, Guo C, Geng F, Qiang F, Wang L. Autologous bone marrow mononuclear cell implantation for intracerebral hemorrhage-a prospective clinical observation. Clin Neurol Neurosurg. 2013;115(1):72–6.
22. Zhu J, Xiao Y, Li Z, Han F, Xiao T, Zhang Z, et al. Efficacy of surgery combined with autologous bone marrow stromal cell transplantation for treatment of intracerebral hemorrhage. Stem Cells Int. 2015;
23. Chang Z, Mao G, Sun L, Ao Q, Gu Y, Liu Y. Cell therapy for cerebral hemorrhage: five year follow-up report. Exp Ther Med. 2016;12(6):3535–40.
24. Yamasaki TR, Blurton-Jones M, Morrissette DA, Kitazawa M, Oddo S, LaFerla FM. Neural stem cells improve memory in an inducible mouse model of neuronal loss. J Neurosci. 2007;27(44):11925–33.
25. Kuramoto Y, Takagi T, Tatebayashi K, Beppu M, Doe N, Fuijta M, et al. Intravenous administration of human adipose-derived stem cells ameliorates motor and cognitive function for intracerebral hemorrhage mouse mode. Brain Res. 2019;

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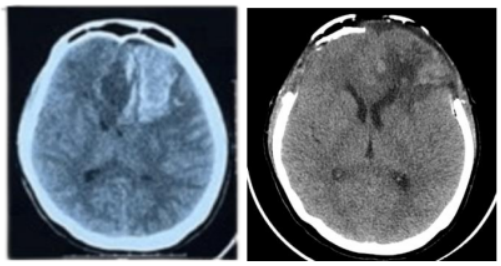
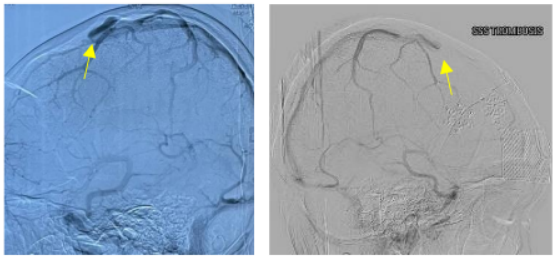
FIGURES



A B

Figure 1. (**A**) Non-contrast CT Brain at admission; (**B**) Non-contrast CT Brain after craniotomy



A B

Figure 2. (**A**) First DSA, attempted after craniotomy; (**B**) Second DSA, attempted during intraarterial stem cells injection

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