Dement Neurocogn Disord. 2025 Oct;24(4):272-285
https://doi.org/10.12779/dnd.2025.24.4.272
pISSN 1738-1495·eISSN 2384-0757

DND Dementia and Neurocognitive Disorder

Original Article

Mesenchymal Stem Cells With Adjuvant Dexamethasone in Patients With Alzheimer's Disease: A Phase IIa Trial

Na Kyung Lee [1,2,*] **Hyemin Jang** [3,4,5,*] **Yejoo Choi,** [2] **Song Hwangbo,** [4,5,6] **Seunghoon Lee,** [7] **Jung Il Lee** [7] **Young Ju Kim,** [5] **Juhee Chin** [5] **Jong Wook Chang** [1,2] **Sang Won Seo** [1,4,5,8,9] **Hyo Jin Son** [2,4,5] **Soo Jin Choi,** [10] **Duk L. Na** [2,4,5,11] **Hee Jin Kim** [1,2,4,5,9]

[1]Department of Health Sciences and Technology, Samsung Advanced Institute for Health Sciences & Technology (SAIHST), Sungkyunkwan University, Seoul, Korea
[2]Cell and Gene Therapy Institute (CGTI), Research Institute for Future Medicine, Samsung Medical Center, Seoul, Korea
[3]Department of Neurology, Seoul National University Hospital, Seoul, Korea
[4]Alzheimer's Disease Convergence Research Center, Samsung Medical Center, Seoul, Korea
[5]Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[6]Department of Neurology, Incheon Sejong Hospital, Incheon, Korea
[7]Department of Neurosurgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[8]Department of Intelligent Precision Healthcare Convergence, Sungkyunkwan University, Suwon, Korea
[9]Department of Digital Health, Samsung Advanced Institute for Health Sciences & Technology (SAIHST), Sungkyunkwan University, Seoul, Korea
[10]Biomedical Research Institute, R&D Center, MEDIPOST Co., Ltd., Seongnam, Korea
[11]Happymind Clinic, Seoul, Korea

Received: Aug 20, 2025
Revised: Sep 29, 2025
Accepted: Oct 1, 2025
Published online: Oct 24, 2025

Correspondence to
Duk L. Na
Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 80 Ilwon-ro, Gangnam-gu, Seoul 06351, Korea.
Email: dukna@naver.com

Hee Jin Kim
Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 80 Ilwon-ro, Gangnam-gu, Seoul 06351, Korea.
Email: evekhj@gmail.com

*Na Kyung Lee and Hyemin Jang contributed equally to this work.

ORCID iDs
Na Kyung Lee
https://orcid.org/0000-0001-6116-2562
Hyemin Jang
https://orcid.org/0000-0003-3152-1274
Jung Il Lee
https://orcid.org/0000-0001-8143-5513

ABSTRACT

Background and Purpose: This phase IIa trial assessed the safety and efficacy of mesenchymal stem cell (MSC) therapy for Alzheimer's disease (AD). An open-label extension (OLE) further explored the adjunctive role of dexamethasone.
Methods: MSCs (n=24) or a saline placebo (n=12) were administered intraventricularly three times at four-week intervals. In the OLE, MSCs and dexamethasone (15 mg, n=5) were administered to patients who received saline in phase IIa. Clinical parameters and cerebrospinal fluid (CSF) markers were evaluated.
Results: MSC therapy exhibited no significant clinical benefits, but was associated with reductions in CSF AD biomarkers (amyloid-beta, phosphorylated-tau, and total-tau) compared to placebo. The MSC group experienced more adverse events (fever, headache, nausea, and vomiting), while co-administration of dexamethasone appeared to attenuate immune-related reactions and limit increases in CSF white blood cell and interleukin-6.
Conclusions: These findings suggest exploratory biological effects of MSCs on AD biomarkers, with dexamethasone potentially mitigating MSC-induced immune responses.

Trial Registration: ClinicalTrials.gov Identifier: NCT02054208, NCT03172117, and NCT04954534

Keywords: Mesenchymal Stem Cell; Dexamethasone; Cerebrospinal Fluid; Inflammation; Cytokine

The inclusion criteria for AD participants were adapted from prior reports.[15] The study's eligible participants were between 50 and 85 years of age, met the National Institute on Aging–Alzheimer's Association (NIA-AA) criteria for probable AD,[33] and had Mini-Mental State Examination (MMSE) scores ranging from 18 to 26. Eligible participants were screened with ^{18}F-florbetaben PET, ^{18}F-fluoro-2-deoxy-D-glucose (FDG) PET, and brain magnetic resonance imaging (MRI). Enrollment was confirmed for participants who met the following criteria: 1) amyloid positivity on ^{18}F-Florbetaben PET and 2) evidence of neurodegeneration, either as structural atrophy on MRI or hypometabolism on FDG PET.

Written informed consent was obtained from all patients and legally authorized representatives in cases of cognitive impairment. This study was conducted in accordance with the guidelines approved by the Institutional Review Board of Samsung Medical Center. The clinical studies were registered at ClinicalTrials.gov under the approval numbers NCT02054208, NCT03172117, and NCT04954534.

Safety, clinical, and biomarker assessments

Adverse events were assessed at each study visit using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE).[34] Additionally, safety monitoring was conducted at 18, 24, and 36 months, with external oversight provided by C&R Research Inc. To evaluate potential immune responses between MSC-treated participants and placebo recipients, mixed lymphocyte reaction (MLR) testing was conducted at baseline and again 12 weeks following the initial injection. Proliferation of peripheral blood mononuclear cells (PBMCs) was used as an indicator of the alloreactive immune response. In order to assess proliferation, PBMCs were isolated and cultured under three conditions: 1) stimulation with phytohaemagglutinin (PHA) as a positive control, 2) co-culture with unrelated donor PBMCs, and 3) co-culture with the MSCs utilized in the study. Immunological safety was determined if the proliferation rate of the subject's PBMCs co-cultured with the same lot of cells administered was less than or equal to 50% of the highest proliferative response observed with PHA stimulation or co-culture using unrelated donor PBMCs.

The primary clinical endpoint was defined as the change in the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog 11) score over a 24-week period.[35] Secondary outcomes encompassed the Clinical Dementia Rating Scale Sum of Boxes Scores (CDR-SOB),[36] MMSE, the Seoul Instrumental Activities of Daily Living (S-IADL),[37] and the Neuropsychiatric Inventory (NPI).[38] All assessments were conducted at the baseline and subsequently at 4, 8, 12, and 24 weeks following the initial injection. CSF was collected at several time points: immediately prior to and one day following each injection. The time points included baseline, baseline +1 day (after the first injection), 4 weeks and 4 weeks +1 day (after the second injection), 8 weeks and 8 weeks +1 day (after the third injection), as well as 12 weeks and 24 weeks. The analyses encompassed CSF WBC counts; AD biomarkers (Aβ42, to tal tau [t-tau], and phosphorylated tau at threonine 181 [p-tau181]), measured with INNOTEST enzyme-linked immunosorbent assay (ELISA) kits (Fujirebio Europe N.V.)[39]; and MSC-related proteins (decorin, sICAM, GDF-15, progranulin, and galectin-3), assessed by ELISA. Furthermore, florbetaben PET was performed at the baseline and at week 24, with tracer uptake quantified using global standardized uptake value ratios (SUVR).[40] In the OLE study, CSF was collected one day after the first MSC+Dexa injection and seven days after the second and third injections.

Human cytokine array and ELISA

CSF cytokines were analyzed by array and ELISA in six participants: three who participated in both the placebo and MSC+Dexa groups (52-year-old woman, 59-year-old woman, 65-year-old man), and three additional age- and sex-matched participants who received MSC alone (57-year-old woman, 61-year-old woman, 60-year-old man). Among the placebo group, three participants in the MSC+Dexa group were selected for CSF analyses.

The cytokine profiles of the CSF were analyzed using a cytokine array that detected 36 human cytokines (R&D Systems, ary005b). We calculated the relative changes in the levels of cytokine (CCL2, CXCL10, IL-1ra, IL-6, IL-8, IL-18, MIF, and Serpin E1) from baseline.

ELISA was performed using R&D Systems human interleukin-6 IL-6 (DY206), each sample tested in duplicate wells. The ELISA samples were measured three times and averaged.

Statistical analysis

GraphPad Prism software (version 8.0; GraphPad Software Inc., San Diego, CA, USA) was used for statistical analysis. Demographic factors and the prevalence of adverse events following the intervention across the three groups were compared using a Welch's *t*-test (unpaired, two-tailed) or Fisher's exact test with Bonferroni correction.

Efficacy analyses were conducted using two-sample *t*-tests from full analysis set to compare changes in ADAS-Cog 11, CDR-SOB, MMSE, S-IADL, and NPI scores from baseline to each time point between the MSC and placebo groups. Changes in CSF WBC counts, AD biomarkers, and MSC-related markers from baseline to each time point in the MSC and placebo groups were compared using two-sample *t*-tests. Changes in the Florbetaben PET SUVR from baseline to the 24-week mark were investigated within each group using paired t-tests, and subsequently compared between the two groups using two-sample *t*-tests.

The human cytokine array and ELISA results were analyzed for statistical differences between the MSC and MSC+Dexa groups using a Welch's *t*-test (unpaired, two-tailed). A *p*-value of ≤ 0.05 indicated statistical significance.

RESULTS

Trial participants and baseline characteristics

In the phase IIa study, 12 participants were randomly assigned to receive the placebo, while 24 were randomly assigned to receive MSCs (**Fig. 1** and **Table 1**). All participants completed three repeated injections of placebo or MSCs, except for one (a 74-year-old male), who refused to receive a third injection due to nausea after the second injection.

In the OLE study, four participants completed three repeated injections of MSC+Dexa, while one (a 65-year-old female) discontinued because of fever and headache after the first injection.

Changes in clinical outcome and AD biomarkers

In the phase IIa trial, MSC did not show clinical benefit. There were no significant differences in ADAS-Cog 11, CDR-SOB, MMSE, S-IADL, or NPI scores between the MSC and placebo groups (**Supplementary Table 1**).

Table 1. Characteristics of participants and adverse events following intracerebroventricular injection

Variables	Phase IIa study		Open-label extension study	*p*-value (Placebo vs. MSC)	*p*-value (Placebo vs. MSC+Dexa)	*p*-value (MSC vs. MSC+Dexa)
	Placebo (n=12)	MSC (n=24)	MSC+Dexa (n=5)			
Age*	61.8±5.1	65.5±6.8	62.0±6.5	0.068	0.941	0.313
Sex, female†	6 (50.0)	18 (75.0)	4 (80.0)	0.471	>0.999	>0.999
Education*	11.3±6.0	13.0±4.3	8.8±6.5	0.381	0.491	0.226
Amyloid PET positivity	12 (100.0) [12]	24 (100.0) [24]	5 (100.0) [5]	N/A	N/A	N/A
Adverse events†						
Nervous system related						
Fever (>37.5°C)	0 [0]	21 (87.5) [47]	1 (20) [1]	<0.001	0.882	0.020
Chills	1 (8.3) [12]	10 (41.7) [27]	0 [0]	0.177	>0.999	0.401
Headache	3 (25.0) [4]	22 (91.7) [63]	3 (60) [5]	<0.001	0.840	0.380
Nausea	4 (33.3) [10]	21 (87.5) [54]	2 (40) [4]	0.005	>0.999	0.137
Vomiting	2 (16.7) [6]	20 (83.3) [47]	0 [0]	0.001	>0.999	0.003
Dizziness	2 (16.7) [4]	4 (16.7) [7]	0 [0]	>0.999	>0.999	>0.999
Hypoesthesia	4 (33.3) [7]	3 (12.5) [7]	0 [0]	0.571	0.782	>0.999
Paraesthesia	0 [0]	0 [0]	1 (20) [1]	>0.999	0.882	0.517
Delusion	0 [0]	0 [0]	0 [0]	N/A	N/A	N/A
Administration site conditions						
Ommaya site pain	0 [0]	0 [0]	0 [0]	N/A	N/A	N/A

Values are expressed as mean ± standard deviation or number of subjects (%) [number of events].
MSC: mesenchymal stem cell, Dexa: dexamethasone, PET: positron emission tomography, N/A: not applicable.
*Age and Education: Welch's *t*-test (unpaired, two-tailed).
†Sex and adverse events: Fisher's test (Bonferroni correction).

The florbetaben PET SUVR changes from baseline to 24 weeks showed a slight increase (0.05±0.10) in the placebo group and a slight decrease (−0.01±0.09) in the MSC group. However. these differences did not reach statistical significance between the two groups (p=0.055).

For CSF AD biomarkers,[41] Aβ42 and p-tau levels from baseline to baseline+1d, 4 week+1d, and 8 week+1d were significantly decreased in the MSC group compared to the placebo group (all $p \leq 0.05$). Changes in t-tau levels from baseline to baseline+1d and 4 weeks+1d also showed a significant decrease in the MSC group (all $p \leq 0.05$) (**Fig. 2**). For MSC-related markers in CSF, MSC group showed notable increases in Decorin (at baseline+1d), sICAM-1 (at all visits except at 24 weeks), GDF-15 (at all visits except for 12 and 24 weeks), Progranulin (at all visits), and Galectin-3 (at baseline+1d, 4 weeks+1d, and 8 weeks+1d), compared to the placebo group (all $p \leq 0.05$) (**Supplementary Fig. 1**).

Adverse events

In the phase IIa trial, subjects in the MSC group exhibited a considerably elevated incidence of fever ($p<0.001$), headache ($p<0.001$), nausea ($p=0.005$), and vomiting ($p=0.001$) in comparison to those administered a placebo. In contrast, the OLE study demonstrated that the addition of dexamethasone resulted in a reduced incidence of fever ($p=0.020$) and vomiting ($p=0.003$) in the MSC+Dexa group compared to the MSC group. The overall rate of adverse events did not differ significantly between the MSC+Dexa and placebo groups (**Table 1**). CSF cultures obtained after fever episodes were negative for bacterial growth. The elevated body temperature and increased CSF WBC counts resolved without the administration of antimicrobial agents. MLR testing demonstrated that all participants remained immunologically stable.

In the phase IIa trial, serious adverse drug reactions (SADR) occurred in one participant (a 65-year-old female) in the MSC treatment group, who required additional admission

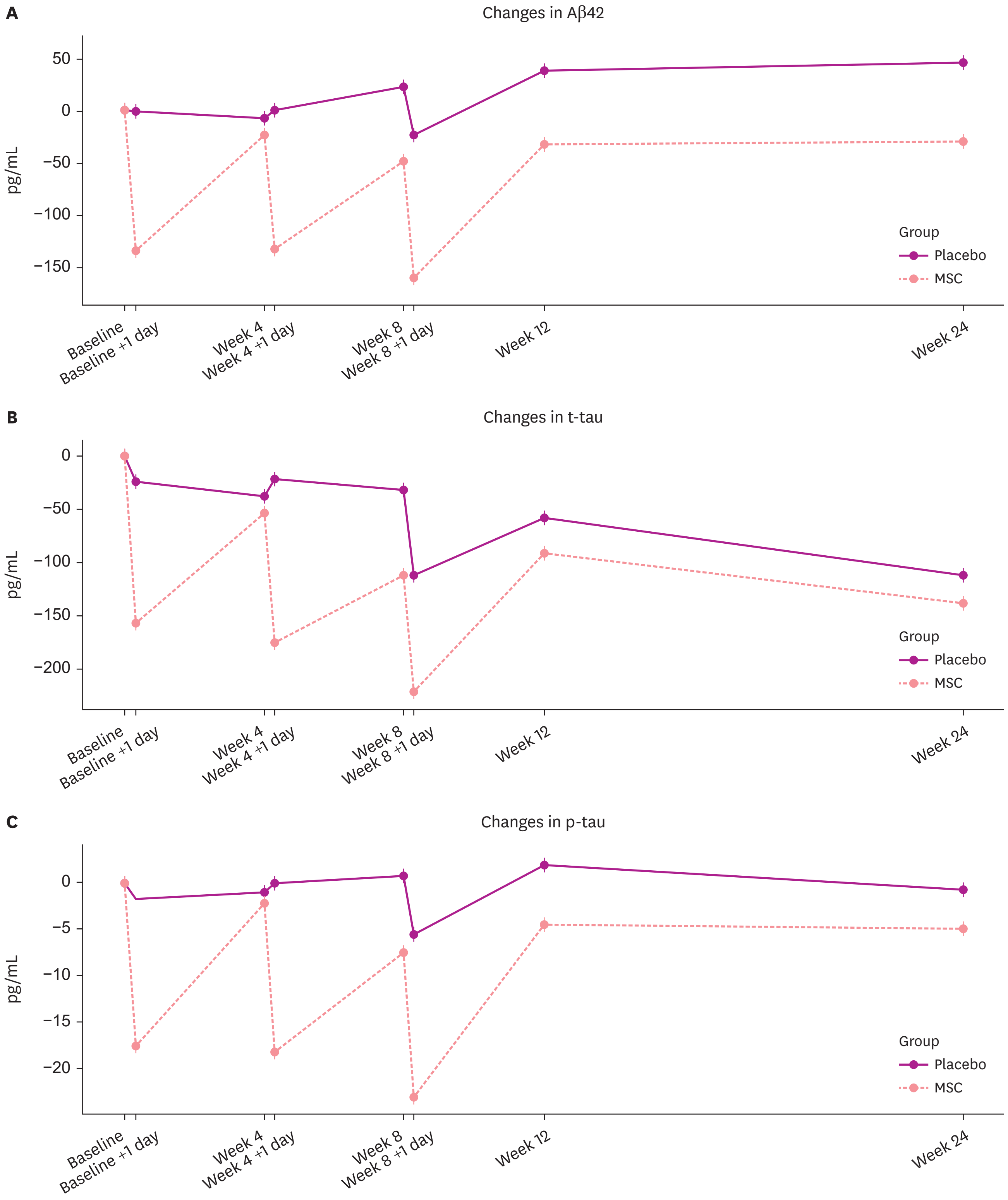

Fig. 2. Changes in cerebrospinal fluid levels of Alzheimer's disease biomarkers following MSC (n=24) or saline (placebo; n=12) injection into the lateral ventricle. Levels of (A) Aβ42 (B) t-tau, and (C) p-tau. The cerebrospinal fluid was analyzed immediately before and one day after each injection at baseline (baseline, baseline +1 day after first injection), 4 weeks (4 week, 4 week+1 day after second injection), and 8 weeks (8 week, 8 week+1 day after third injection) as well as at 12 weeks and 24 weeks. Data for one participant from the MSC group is missing from the post-third injection time points.
MSC: mesenchymal stem cell, Aβ42: amyloid beta 42, t-tau: total tau, p-tau: phosphorylated tau.

for markedly elevated CSF WBC counts (>1,000/uL) one day after the second injection. The participant exhibited no atypical MRI findings, and the CSF WBC count diminished to 12/μL within two days without further therapeutic intervention. The patient subsequently received the third injection. Subsequent Gram staining of the CSF showed negative results. No SADR was observed in the placebo group. In the OLE study, SADR occurred in one participant (a 65-year-old female) who required additional admission for fever. CSF WBC in CSF was elevated over two weeks. CSF Gram staining revealed gram-positive cocci. The patient received intravenous antibiotics for two weeks and discontinued participation in the study.

Dexamethasone mitigated increment of CSF WBC counts in CSF induced by MSCs

In comparison with the baseline, CSF WBC counts measured one day after injection were significantly elevated in the MSC group ($p<0.001$). However, no significant changes were observed in either the placebo or MSC+Dexa groups (**Fig. 3**). Concurrently, the MSC+Dexa group exhibited a marked decrease in CSF WBC counts relative to the MSC group ($p=0.015$). Differential cell analysis indicated a predominance of neutrophils at post–day 1 in both MSC-treated cohorts: The MSC group exhibited a neutrophil percentage of 73.2%±11.6%, a lymphocyte percentage of 9.1%±7.1%, and an eosinophil percentage of 0%. The MSC+Dexa group demonstrated a neutrophil percentage of 60.8%±37.4%, a lymphocyte percentage of 14.2%±12.8%, and an eosinophil percentage of 0%.

Dexamethasone mitigates the elevated immune related cytokine levels following MSC injection

Human cytokine arrays were performed for three participants in each group. Eight (CCL2, CXCL10, IL-1ra, IL-6, IL-8, IL-18, MIF, and SerpinE1) of the thirty-six cytokines tested were detected in the CSF one day after MSC or MSC+Dexa injection, with no change detected after saline injection (**Supplementary Fig. 2**). The relative changes in cytokines at day 1 compared

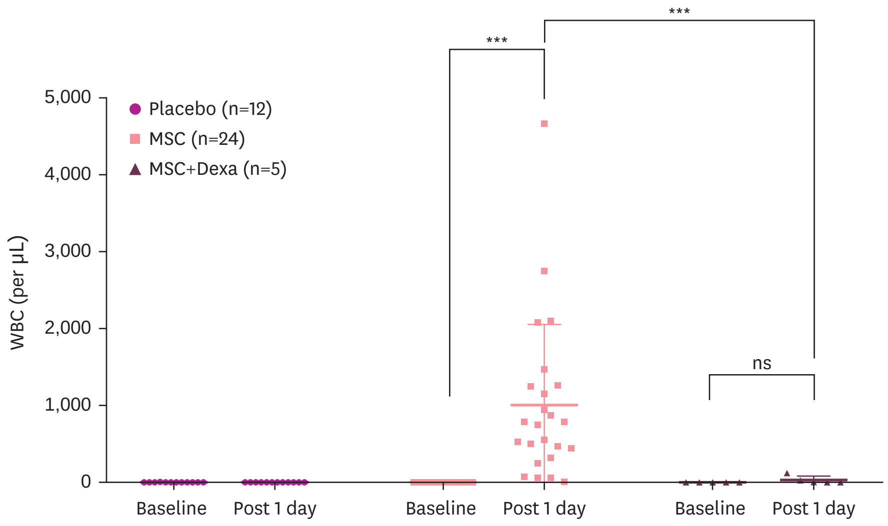

Fig. 3. CSF WBC count at baseline and 1-day after injection of saline, MSCs, or MSCs + Dexa.
CSF WBC: cerebrospinal fluid white blood cell, MSC: mesenchymal stem cell, Dexa: dexamethasone.
Statistical significance was defined as ns (not significant), $^{***}p<0.001$ (post 1-day MSC vs. post 1-day MSC+Dexa, $p=0.015$).