Effects of granulocyte colony–stimulating factor and granulocyte-macrophage colony–stimulating factor on glial scar formation after spinal cord injury in rats

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Object. This study investigated the effects of granulocyte colony–stimulating factor (G-CSF) on glial scar formation after spinal cord injury (SCI) in rats and compared the therapeutic effects between G-CSF and granulocyte-macrophage colony–stimulating factor (GM-CSF) to evaluate G-CSF as a potential substitute for GM-CSF in clinical application.

Methods. Rats were randomly assigned to 1 of 4 groups: a sham-operated group (Group 1), an SCI group without treatment (Group 2), an SCI group treated with G-CSF (Group 3), and an SCI group treated with GM-CSF (Group 4). G-CSF and GM-CSF were administered via intraperitoneal injection immediately after SCI. The effects of G-CSF and GM-CSF on functional recovery, glial scar formation, and axonal regeneration were evaluated and compared.

Results. The rats in Groups 3 and 4 showed better functional recovery and more decreased cavity sizes than those in Group 2 (p < 0.05). Both G-CSF and GM-CSF suppressed intensive expression of glial fibrillary acidic protein around the cavity at 4 weeks and reduced the expression of chondroitin sulfate proteoglycans (p < 0.05). Also, early administration of G-CSF and GM-CSF protected axon fibers from destructive injury and facilitated axonal regeneration. There were no significant differences in comparisons of functional recovery, glial scar formation, and axonal regeneration between G-CSF and GM-CSF.

Conclusions. G-CSF suppressed glial scar formation after SCI in rats, possibly by restricting the expression of glial fibrillary acidic protein and chondroitin sulfate proteoglycans, which might facilitate functional recovery from SCI. GM-CSF and G-CSF had similar effects on glial scar formation and functional recovery after SCI, suggesting that G-CSF can potentially be substituted for GM-CSF in the treatment of SCI.

KEY WORDS • GM-CSF • G-CSF • spinal cord injury • glial scar

This article contains some figures that are displayed in color online but in black-and-white in the print edition.

Abbreviations used in this paper: BBB = Basso, Beattie, and Bresnahan; CSPG = chondroitin sulfate proteoglycan; G-CSF = granulocyte colony–stimulating factor; GFAP = glial fibrillary acidic protein; GM-CSF = granulocyte-macrophage colony–stimulating factor; PBS = phosphate-buffered saline; SCI = spinal cord injury.
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to facilitate antiapoptotic activity and behavioral recovery after spinal cord injury (SCI).10 In addition, GM-CSF prevents apoptotic cell death and adhesion in both hematological and neuronal cells. These findings suggest that GM-CSF can be used for the treatment of CNS injury. Indeed, recent evidence suggests that GM-CSF improves functional recovery and induces axonal regeneration in rats as a result of its inhibitory effects on glial scar formation after SCI,11 and clinical trial results have suggested that GM-CSF plays a role in SCI in humans.22,23

Granulocyte colony-stimulating factor (G-CSF) is a growth factor for hematopoietic progenitor cells that is commonly used to treat neutropenia and to mobilize peripheral blood-derived hematopoietic stem cells for transplantation.25 Its immunoregulatory properties include the ability to expand the monocyte and macrophage subset of cells and aid in antiinflammation.26 It has been reported that G-CSF can enhance tissue regeneration in the brain27 and promote functional recovery after SCI in rodents.17,20 G-CSF also promotes the restoration of damaged spinal cord tissue by mobilizing bone marrow cells into the spinal cord,17 enhances the availability of circulating hematopoietic stem cells in neuronal lesion sites and enhances their ability for neurogenesis and angiogenesis,20 and inhibits apoptosis of neural cells by regulating the expression of apoptosis-related proteins.10 Despite the beneficial effects of G-CSF on functional recovery after SCI, the influence of G-CSF on glial scar formation is not yet known. Also, its clinical application to SCI has not been evaluated well. Thus, we investigated the effects of G-CSF on glial scar formation after SCI in rats and compared the therapeutic effects between G-CSF and GM-CSF to evaluate G-CSF as a potential substitute for GM-CSF.

Methods

Rat SCI Model and Administration of GM-CSF and G-CSF

Animal experiments were performed in an authorized animal care facility at Inha University School of Medicine and approved by the institution’s Committee for the Care and Use of Laboratory Animals. A total of 66 male Sprague-Dawley rats (Sang Jung Co.), each weighing 280–300 g, were randomly assigned to 1 of 4 groups: Group 1 (n = 12) was a sham-operated group that underwent a sham operation without SCI; Group 2 (n = 18, control group) was an SCI group treated with phosphate-buffered saline (PBS); Group 3 (n = 18) was an SCI group treated with G-CSF; and Group 4 (n = 18) was an SCI group treated with GM-CSF.

Each animal was anesthetized by intraperitoneal injection with ketamine (2 mg), and a laminectomy from T-8 to T-10 was performed. An SCI was made by applying a vascular clip (Biomer Vessel Clip, Aesculap) at the T-9 level of the spinal cord for 15 minutes (occlusion pressure 0.2–0.25 N). The sham group underwent the same operation, but the vascular clip was not applied. The clip model for rat SCI has been shown to be reproducible and clinically relevant.21,22

Following the method above for the SCI model, we confirmed that the animals showed equivalent injury, determined by locomotor and histologic testing in the preliminary study (data not shown).

G-CSF (Dong-A Pharmaceutical Co.) and GM-CSF (Hanson Biotech) were administered to the rats as described previously.23 An amount of 20 μg in 1 ml of G-CSF (Group 3) or GM-CSF (Group 4) was intraperitoneally injected once immediately after SCI. Group 2 was injected intraperitoneally with PBS after SCI. From our preliminary experiments for appropriate injection timings, we found that the efficacy of GM-CSF injection immediately after the injury, which was determined by locomotor recovery, cavity size, and GFAP expression, was the best among the other methods (not statistically significant), such as one-time injection immediately after the injury, one-time injection 3 hours after the injury, daily injection for 3 days after the injury, and daily injection for 5 days after the injury.

Behavior Analysis: Locomotor Recovery of the Rats With SCI

The therapeutic activities of G-CSF and GM-CSF on SCI were examined with the open-field walking test of the Basso, Beattie, and Bresnahan (BBB) scale analysis. Locomotor recovery was assessed 3 days, 1 week, 2 weeks, 3 weeks, and 4 weeks after the injury; the total number of samples decreased over time, because rats were sacrificed for analysis or died unexpectedly (Table 1). Two researchers who assessed the functional recovery of the rats were blinded to treatment.

H & E Staining and Measurement of Cavity Size

The histological and immunohistological examinations were performed by blinded evaluators. All the experimental rats were sacrificed using urethane anesthesia and were perfusion fixed transcardially with 4% paraformaldehyde in PBS at 3 days, 1 week, or 4 weeks after SCI. A 2-cm length of spinal cord tissue was removed from around the injury epicenter and embedded in paraffin wax. Longitudinal sections (4 μm thick) from the dorsal to the ventral region were prepared. The sections were deparaffinized and hydrated by sequential incubations in xylene and ethanol. After being washed in distilled water for 5 minutes, the sections were stained sequentially with hematoxylin for 2 minutes and eosin for 15 seconds. The sections were then dehydrated and mounted.

Among the H & E–stained serial sections obtained 3 days, 1 week, and 4 weeks after SCI, a central section was chosen for measurement of the cavity size. The stained images were used to outline the cavity in Adobe Photoshop (version 8.0), and the pixels inside the cavity were counted automatically. The outline of the cavity was defined as marginal white matter adjacent to the lesion area. Average values were obtained by counting pixels inside the outlines for each group and were used for comparative analysis between groups.

Immunohistochemical Analysis

The spinal cord sections were prepared as described above and incubated independently with mouse monoclonal antibodies against GFAP (1:1000; Chemicon, Inc.),
neurocan (1:1000; Chemicon, Inc.), NG2 (1:1000; Upstate), phosphacan (1:1000; Chemicon, Inc.), and neurofilament (M&H) (1:200; Chemicon, Inc.) overnight at 4°C. The sections were then incubated with horse anti–mouse antibody conjugated with Texas Red (1:500; Aviva Systems Biology) for GFAP, phosphacan, and neurofilament and with fluorescein isothiocyanate (FITC, 1:200; CoreSciences) for neurocan for 1 hour at room temperature. Peroxidase-labeled horse anti–mouse antibody was used as a secondary antibody for NG2, and the results were visualized with 3,3′-diaminobenzidine (brown). The fluorescence images were examined under a laser scanning confocal microscope (MRC 1024; Bio-Rad). Immunohistochemical staining and acquisition of images were performed at the same time for different groups under the same experimental procedure. The fluorescence intensity of each image was measured from the peripheral region of the lesion epicenter with ImageJ (version 1.36, National Institutes of Health).

**ED-1 Macrophage Staining**

The deparaffinized sections were prepared and incubated with mouse monoclonal antibody (ED-1) detecting activated microglia/macrophage (MCA-341GA; Serotec) overnight at 4°C. The sections were then incubated with biotinylated horse anti–mouse immunoglobulin G (H + L) (1:200; Vector Laboratories, Inc.) for 1 hour at room temperature. Immunoreactivity was visualized with 3,3′-diaminobenzidine (brown) and counterstained with hematoxylin. The stained sections were rinsed with tap water, immersed in PBS for 5 minutes, mounted on slides, dehydrated with a gradient of ethanol, cleared, and coverslipped.

**Statistical Analysis**

Quantitative data are presented as means ± the standard deviation. Statistical analysis was performed with SPSS version 18.0 (SPSS, Chicago, IL). The nonparametric Kruskal-Wallis test was used to compare differences between the groups. A p value < 0.05 was considered statistically significant.

**Results**

**Locomotor Recovery of the Rats With SCI**

After the operation, 6 rats died unexpectedly (1 in Group 1, 2 in Group 3, and 3 in Group 4). The BBB scores for the 4 groups at each time point are shown in Fig. 1. All the rats were completely paraplegic after the operation except for those in the sham group (Group 1). The rats in Groups 3 and 4 had significantly higher BBB scores from 2 weeks to 4 weeks than the rats in Group 2 (p < 0.05), indicating that G-CSF and GM-CSF had positive effects on their functional recovery after SCI. Four weeks after the injury, the average BBB scores in Groups 2, 3, and 4 were 6.5, 11.9, and 10.3, respectively. There was no significant difference in functional recovery between Groups 3 and 4.

**G-CSF and GM-CSF Reduced Cavity Sizes**

Each injured spinal cord was histologically examined 3 days, 1 week, and 4 weeks after the injury. These spinal cords showed destructive changes 3 days after SCI and clear cavitation with glial scar formation 1 week after SCI (Fig. 2A). Four weeks after SCI, the cavities were larger and the marginal white matter adjacent to the lesions was severely damaged, which probably caused loss of connectivity between the caudal and rostral spinal cord tissues in the rats in Group 2. Four weeks after SCI, the average cavity size measured by counting pixels was 51.6 ± 10³ in Group 2, 34.3 ± 10³ in Group 3, and 26.1 ± 10³ in Group 4. The cavity sizes were significantly reduced in the rats in Groups 3 and 4 compared with those in Group 2 (Fig. 2B; 33.5% reduction in Group 3 and 49.5% reduction in Group 4, p < 0.05), and the marginal white matter seemed to be more intact in the rats in Groups 3 and 4, suggesting that early administration of G-CSF or GM-CSF protects spinal cord tissues from progressive degenerative changes and enhances structural integrity by reducing lesion volume.

**G-CSF and GM-CSF Repressed GFAP Expression**

The expression of GFAP was examined by immunohistochemical analysis 3 days, 1 week, and 4 weeks after SCI. In Group 2 rats, the expression of GFAP increased gradually from 3 days to 4 weeks, and strong expression of GFAP was observed in the areas surrounding the lesions at 4 weeks (Fig. 3A). Administration of G-CSF or GM-CSF did not prevent an early increase in GFAP expression 3 days after SCI. However, 1 week after injury, GFAP expression was lower in Groups 3 and 4 compared with those in Group 2. Four weeks after SCI, the strong expression of GFAP observed in the areas surrounding the lesions at 4 weeks in Group 2 was not observed in Group 3 or 4. Quantitative analysis with ImageJ confirmed that G-CSF and GM-CSF suppressed increases in GFAP expression.

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**TABLE 1: Number of rats used in the study**

<table>
<thead>
<tr>
<th>Group</th>
<th>Total No.</th>
<th>Sacrificed for Staining at 3 Days</th>
<th>Sacrificed for Staining at 1 Wk</th>
<th>Sacrificed for Staining at 4 Wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>sham (Group 1, n = 12)</td>
<td>11*</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>SCI &amp; PBS (Group 2, n = 18)</td>
<td>18</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>SCI &amp; G-CSF (Group 3, n = 18)</td>
<td>16*</td>
<td>6</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>SCI &amp; GM-CSF (Group 4, n = 18)</td>
<td>15*</td>
<td>6</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>total no. (n = 66)</td>
<td>60*</td>
<td>22</td>
<td>20</td>
<td>18</td>
</tr>
</tbody>
</table>

* Missing number is due to death.
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after SCI (p < 0.05) 1 and 4 weeks after injury (Fig. 3B). There was no significant difference in GFAP expression between Groups 3 and 4.

G-CSF and GM-CSF Repressed CSPG Expression

The expression of CSPGs, such as neurocan, NG2, and phosphacan, was examined by immunohistochemical analysis 3 days, 1 week, and 4 weeks after SCI. In Group 2, the expression of neurocan clearly increased at 3 days and then decreased slightly but was still high at 1 and 4 weeks (Fig. 4A). Quantitative analysis with ImageJ showed that Groups 3 and 4 suppressed the expression of neurocan at each time point (Fig. 4B, p < 0.05, compared with Group 2), suggesting that G-CSF and GM-CSF suppress the expression of neurocan after SCI.

The expression of NG2 was approximately 10-fold higher in Group 2 than in Group 1 at 3 days, 6.5-fold higher at 1 week, and 2.2-fold higher at 4 weeks (Fig. 5). In Groups 3 and 4, the administration of G-CSF or GM-CSF suppressed approximately 30% of NG2 expression at 3 days and 1 week (p < 0.05, compared with Group 2).

In Group 2, the expression of phosphacan increased by 1.9-fold at 3 days, 3.3-fold at 1 week, and 3.6-fold at 4 weeks over that in Group 1 (Fig. 6). Immunohistochemical staining revealed that G-CSF and GM-CSF reduced the expression of phosphacan, but quantitative analysis did not reveal a statistically significant difference from Group 2. The exception was at 1 week, when phosphacan expression was significantly lower in Group 4 than in Group 2 or 3 (p < 0.05). G-CSF did not suppress phosphacan expression at any time point. There was no significant difference in CSPGs expression between Groups 3 and 4.

Effect of G-CSF and GM-CSF on the Integrity of Axon Fibers

Four weeks after SCI, Group 2 showed severe disarrangement of axon fibers in the marginal white matter (data not shown). In Groups 3 and 4, the axon fibers were relatively well arranged and preserved much intact (p < 0.05, compared with Group 2), suggesting that early administration of G-CSF or GM-CSF protects axon fibers from destructive injury and facilitates axonal regeneration. There was no significant difference in the integrity of the axon fibers between Groups 3 and 4.
Effect of G-CSF and GM-CSF on Macrophage Activation After Injury

Previous studies found that the number of activated microglia/macrophages is highest 3 days after SCI and decreases gradually to approximately 50% of this level at 4 weeks.11 Thus, we studied the effects of G-CSF and GM-CSF on microglia/macrophage activation 3 days after SCI by using immunohistochemistry for ED-1, a marker of activated microglia/macrophages. There was no expression of ED-1–positive cells in the sham group (Group 1). However, ED-1–positive cells were found in the other 3 groups (data not shown). Three days after injury, the rats in Groups 3 and 4 had 1.5 times as many...

Fig. 3. Spinal cord tissues were immunostained for GFAP 3 days, 1 week, and 4 weeks after the injury. Values relative to those of the sham group (Group 1) are depicted in the histogram. A: In Group 2 rats, the expression of GFAP increased gradually from Day 3 to Week 4. At 4 weeks, stronger expression of GFAP was observed in the areas surrounding the lesions (L). G-CSF and GM-CSF suppressed an increase in GFAP expression at 1 and 4 weeks. Original magnification ×200. B: Quantitative analysis with ImageJ confirmed that G-CSF and GM-CSF suppressed the increase in GFAP expression 1 and 4 weeks after injury (asterisks indicate p < 0.05). However, there was no significant difference between Groups 3 and 4.

Fig. 4. Spinal cord tissue specimens immunostained for chondroitin sulfate proteoglycan 3 days, 1 week, and 4 weeks after injury. Values relative to those of the sham group (Group 1) are depicted in the histogram. A and B: The expression of neurocan increased at 3 days and then decreased slightly but was still high at 1 and 4 weeks in Group 2. Quantitative analysis with ImageJ showed that G-CSF and GM-CSF suppressed the expression of neurocan at each time point (asterisks indicate p < 0.05). There was no significant difference between Groups 3 and 4. Original magnification ×200.
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Discussion

Because the influence of G-CSF on glial scar formation is poorly understood, we examined whether the suppressive effects of G-CSF on glial scar formation could result in good functional recovery and axonal regeneration after SCI, and these effects of G-CSF on SCI were compared with GM-CSF to evaluate G-CSF as a potential substitute for GM-CSF. We found that both G-CSF and GM-CSF had positive effects on functional recovery and axonal regeneration and had suppressive effects on glial scar formation. Previous studies found that GM-CSF plays a beneficial role after SCI in animals and in humans. In rats, GM-CSF improves functional recovery and axonal regeneration as a result of its inhibitory effects on glial scar formation after SCI. Consistent with those of previous studies, our results suggest that GM-CSF reduces glial scar formation through the suppression of GFAP and CSPG expression. Also, both G-CSF and GM-CSF had similar effects on functional recovery, cavity

Fig. 5. Spinal cord tissue specimens immunostained for chondroitin sulfate proteoglycan 3 days, 1 week, and 4 weeks after injury. Values relative to those of the sham group (Group 1) are depicted in the histogram. A and B: The expression of NG2 increased significantly at 3 days and then rapidly decreased at 1 and 4 weeks. Administration of G-CSF and GM-CSF resulted in a 30% reduction in the expression of NG2 relative to that in Group 2 at 3 days and 1 week after the injury (asterisks indicate p < 0.05). There was no significant difference between Groups 3 and 4. Original magnification ×100.

Fig. 6. Spinal cord tissue specimens immunostained for chondroitin sulfate proteoglycan 3 days, 1 week, and 4 weeks after injury. Values relative to those of the sham group (Group 1) are depicted in the histogram. A and B: The suppressive effects of G-CSF and GM-CSF on the expression of phosphacan were quite different from their effects on the expression of neurocan and NG2. The expression of phosphacan was significantly lower at 1 week in the rats in Group 4 than in those in Groups 3 (double dagger indicates p < 0.05) and 2 (dagger indicates p < 0.05). Original magnification ×200.
size reduction, inhibition of GFAP and CSPG expression, maintenance of the integrity of axon fibers, and activation of macrophages after SCI.

Previous studies showed that G-CSF has beneficial effects on functional recovery after SCI. G-CSF can promote neurogenesis and angiogenesis and inhibit apoptosis of neural cells by regulating the expression of apoptosis-related proteins. Thus, G-CSF may be an appropriate substitute for GM-CSF in treating SCI; it has similar effects on CNS injuries, but unlike many other materials, it has already been approved as a safe drug with neuroprotective effects via any injection route. With regards to glial scar formation, G-CSF suppressed the expression of CSPGs and GFAP. Because G-CSF suppresses GFAP expression after SCI, it might also suppress astrocyte activation within glial scars after SCI, resulting in the down-regulation of CSPG expression and other inhibitory molecules for axonal regeneration. This mechanism might explain the better BBB scores and axonal regeneration in Groups 3 than in Group 2. Previous studies showed that the suppression of GFAP and CSPG expression improves functional recovery by reducing glial scar formation and providing a favorable environment for axonal regeneration. In addition, a reduction in cavity size is often involved in functional recovery after CNS injury. It is possible that the reduced glial scar formation in Groups 3 and 4 resulted in better maintenance of the integrity of the axon fibers 4 weeks after SCI.

It should be noted that the extent and time course of CSPG expression differed between CSPG molecules. Tang et al. reported the time courses of changes for neurocan, NG2, and phosphacan; NG2 peaked around 7 days postinjury, neurocan peaked between 7 and 14 days postinjury, and phosphacan remained elevated substantially later after injury, even 35 days postinjury. Understanding the extent and time course of CSPG content changes is important for predicting the challenges facing regenerating axons. In this study, the time course of CSPG changes was slightly different from those of previous studies, although the overall patterns are similar. In Group 2, neurocan and NG2 had their peak expression at an early stage (3 days and 1 week after injury), whereas phosphacan had its peak expression at a late stage (4 weeks after injury). Both G-CSF and GM-CSF showed suppression of neurocan and NG2 expression at an early stage. This might have reduced glial scar formation, allowing G-CSF and GM-CSF to promote axonal regeneration and functional recovery at a later stage. Compared with neurocan and NG2, phosphacan showed an initial decrease in expression at the lesion sites and then a marked increase in expression in long-term glial scars. Thus, the role of phosphacan after SCI might differ according to the time course of its expression. Additional experiments are needed to explain the differences in the suppression of phosphacan expression between G-CSF and GM-CSF. Rolls et al. suggested that CSPGs exert a beneficial effect on CNS recovery after injury by inducing insulin-like growth factor 1 and matrix metalloproteinase expression and by attenuating tumor necrosis factor–α levels. They concluded that CSPGs can play a beneficial role in CNS recovery but only by careful regulation of their presence: blocking CSPG production immediately after SCI decreases spontaneous recovery, whereas the restriction of CSPG biosynthesis in the acute phase improves recovery. Our results suggest that both G-CSF and GM-CSF had beneficial effects on axonal regeneration and functional recovery by restricting the expression of some CSPGs.

The activation of microglia and macrophages might be a mechanism by which G-CSF improves functional recovery and axonal regeneration. CNS injury is usually accompanied by the activation of microglia and macrophages. These cells are thought to provoke and exacerbate neuronal degeneration and inflammation after injury, but they can also play a beneficial role in neuronal repair by scavenging invading microorganisms and myelin debris and by releasing neurotrophic and neuroprotective molecules. The ability of GM-CSF to activate macrophages and facilitate neural repair during Wallerian degeneration in the peripheral nervous system has been reported. In this study, G-CSF and GM-CSF increased the activation of macrophages, suggesting that both G-CSF and GM-CSF promote functional recovery and protect neural tissues after SCI.

In this study, functional recovery was examined with the open-field walking test of BBB scale analysis. The locomotor function of SCI rats treated with PBS tended to recover 1–4 weeks after the injury. In rats in the treated groups (Groups 3 and 4), compared with those treated with PBS, locomotor function recovered significantly 2 weeks after the injury (Fig. 1). To achieve more precise functional assessments, we should have performed sensory testing or bladder assessments, although most of the previous studies used only locomotor analysis to assess functional recovery. We examined only locomotor function because it is very difficult to obtain quantified results with sensory testing and bladder assessments. It was a limitation that we assessed functional recovery by locomotor analysis only.

From our results, it can be expected that G-CSF might show similar beneficial effects on SCI in humans. For clinical applications of G-CSF, however, the injection method should be considered carefully, especially when and how. Intraperitoneal injection of G-CSF immediately after injury is not applicable in clinical cases. Thus, well-organized and protocol-based research should be performed to study the clinical applications of G-CSF in humans.

Conclusions

Granulocyte colony–stimulating factor suppresses glial scar formation after SCI in rats, perhaps by restricting the expression of GFAP and CSPGs, which might facilitate functional recovery from SCI. GM-CSF and G-CSF had similar effects on glial scar formation and functional recovery after SCI, suggesting that G-CSF can potentially be substituted for GM-CSF in treating SCI.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Choi, Chung, Park. Acquisition of data: Chung, MH Kim, Yoon. Analysis and interpretation of data: Chung, MH Kim, Yoon. Drafting the article: Chung. Critically revising the article: Choi, KH Kim. Reviewed submitted
version of manuscript: all authors. Statistical analysis: Choi, MH Kim, KH Kim. Administrative/technical/material support: Choi, KH Kim, Park. Study supervision: Park.

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