ORIGINAL ARTICLE
J Korean Acad Child Adolesc Psychiatry 2024;35(1):82-89
https://doi.org/10.5765/jkacap.230048

eISSN 2233-9183

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Effectiveness and Tolerability of Combination Pharmacotherapy With Stimulant and Non-Stimulant in Children With Attention Deficit Hyperactivity Disorder

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Objectives: This study aimed to investigate the effectiveness and safety of combining psychostimulants and nonstimulants for patients under treatment for attention deficit hyperactivity disorder (ADHD).

Methods: The study included 96 patients aged 6–12 years who were diagnosed with ADHD, among whom 34 received combination pharmacotherapy, 32 received methylphenidate monotherapy, and 30 received atomoxetine monotherapy. Statistical analysis was conducted to compare treatment and adverse effects among groups and to analyze changes before and after combination pharmacotherapy. The difference between combination pharmacotherapy and monotherapy was investigated. Logistic regression analysis was used to identify the predictors of combination pharmacotherapy.

Results: No significant differences were observed between the groups in terms of age or pretreatment scores. The most common adverse effect experienced by 32% of patients in the combination pharmacotherapy group was decreased appetite. Clinical global impression-severity score decreased significantly after combination pharmacotherapy. All three groups showed significant clinical global impression-severity score improvements over time, with no significant differences among them. The predictive factors for combination pharmacotherapy included the Child Behavior Checklist total score internalizing subscale.

Conclusion: Combination pharmacotherapy with methylphenidate and atomoxetine is a relatively effective and safe option for patients with ADHD who do not respond to monotherapy.

Keywords: Attention deficit hyperactivity disorder; Combination; Methylphenidate; Atomoxetine; Child.

Received: July 21, 2023 / **Revised:** September 12, 2023 / **Accepted:** October 3, 2023

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) has highly complex and heterogeneous etiologies, and genetic, neurophysiological, and environmental factors such as perinatal trauma or exposure to toxic substances are known to play a primary role [1,2]. Pharmacotherapy, which involves hyperactivity, impaired concentration, and impulsivity, is the most effective treatment for ADHD. Medications are used to treat ADHD based on the hypothesized etiology of ADHD pertaining to neurochemical abnormalities, in which ADHD symptoms are alleviated by ameliorating dopamine and norepinephrine deficiencies in the brain [3]. Although it varies across the types of drugs and studies, the response rate to pharmacological treatment for ADHD ranges from 50% to 80%, which is a relatively high rate compared to that of other psychiatric disorders [4].

Currently, the most commonly used medications for ADHD are psychostimulants such as methylphenidate and amphetamine and nonstimulants such as atomoxetine, clonidine, and guanfacine [5]. Many studies have found that psychostimulants have a greater effect size than nonstimulants, and major treatment guidelines recommend psychostimulants as the first-line therapy [5-7]. However, there are cases in which patients who do not respond to psychostimulants respond to nonstimulants. In addition, psychostimulants cannot be used in adequate doses owing to adverse effects, such

as the exacerbation of tic symptoms and sleep disorders, despite psychostimulants showing partial efficacy. Furthermore, achieving the desired therapeutic effect solely by using psychostimulants is often difficult in patients who require drugs in the evening time [8].

According to the 2006 Texas children's medication algorithm, methylphenidate or amphetamine is recommended as first-line drug therapy, followed by atomoxetine upon inadequate response [9]. If a patient does not adequately respond to methylphenidate or amphetamine monotherapy, selective combination of psychostimulants with atomoxetine is recommended. Studies have reported the therapeutic efficacy and safety of psychostimulant and nonstimulant combination pharmacotherapy [10-12]. Carlson et al. [11] reported that the co-prescription of these drugs led to a recovery to normal levels in 43% of 24 children with ADHD without an adequate response to atomoxetine or methylphenidate monotherapy, with the rate of adverse effects being similar to that of patients who received monotherapy. Wilens et al. [12] reported that the addition of methylphenidate OROS in 50 patients with an inadequate response to atomoxetine therapy led to approximately 40% improvement on an ADHD assessment scale. However, there remains a large research gap regarding the effectiveness or adverse effects of psychostimulant and nonstimulant combination pharmacotherapies.

In the Republic of Korea (ROK), the National Health Insurance Service (NHIS) began using two ADHD drugs with different mechanisms on December 1, 2019 [13]. In the ROK, amphetamines are prohibited, and methylphenidate, atomoxetine, and clonidine are the only approved drugs for use as first-line drug therapies for ADHD. Therefore, treating patients is difficult if these first-line monotherapies fail owing to any reason, such as inadequate efficacy or adverse reactions [14]. However, many clinicians still do not fully utilize a combination of psychostimulants and nonstimulants to treat ADHD because of limited research and clinical experience regarding combination pharmacotherapy for ADHD.

Therefore, we hypothesized that methylphenidate and atomoxetine combination pharmacotherapy would be safe and significantly effective in children with ADHD who do not have adequate responses to drug monotherapy. In addition, we investigated the predictors of being indicated for combination pharmacotherapy in children with ADHD. Ultimately, we aimed to provide information that would help establish combination pharmacotherapy as a viable treatment option for ADHD.

METHODS

Participants

We retrospectively reviewed and analyzed the medical records of patients diagnosed with ADHD by a pediatric psychiatrist at Keimyung University Dongsan Hospital per Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) between December 2019 and February 2023.

Children aged 6–12 years who were prescribed psychostimulant methylphenidate and/or nonstimulant atomoxetine at least twice were enrolled. The monotherapy group comprised children who had never received drug therapy for ADHD and had undergone either methylphenidate or atomoxetine monotherapy, whereas the combination pharmacotherapy group comprised children who received both methylphenidate and atomoxetine at least twice. Patients with intellectual disability, autism spectrum disorder, epilepsy, severe medical conditions, or severe psychiatric disorders requiring hospitalization were excluded from the study. For patients who failed to attain adequate therapeutic effects with one drug or were not eligible for dose escalation owing to adverse effects, combination pharmacotherapy was prescribed if they wished for aggressive treatment; for other patients, monotherapy was continued.

Basic patient information, including age, sex, body weight, comorbidities, and type and dose of the drug (mg/kg), was obtained from their medical records.

Assessment tools

In this study, the severity of ADHD symptoms was assessed using the Korean version of the Swanson, Nolan, and Pelham rating scale version four (SNAP-IV), while attention was assessed using the comprehensive attention test (CAT) [15,16]. Anxiety was assessed using the Korean version of the State-Trait Anxiety Inventory for Children (STAI-C), and emotional, behavioral, and social adaptation problems were assessed using the Korean version Child Behavior Checklist (K-CBCL) [17,18]. The degree of improvement after treatment was assessed by a psychiatrist using the clinical global impression-severity (CGI-S) [19].

Statistical analysis

Data were analyzed using IBM SPSS (version 25.0; IBM Corp., Armonk, NY, USA). First, the demographic and clinical data for each group were analyzed using one-way analysis of variance (ANOVA) or Kruskal–Wallis and chi-square tests, depending on the normality of the data. To determine the therapeutic effects in the combination pharmacotherapy group, the CGI-S scores after the first drug therapy and after

adding the combination pharmacotherapy were analyzed using a paired sample t-test or Wilcoxon signed-rank test, depending on the normality of the data. The degree of change in the CGI-S scores after using drugs in the combination pharmacotherapy and methylphenidate or atomoxetine monotherapy groups was analyzed using repeated measures ANOVA. Finally, the predictors of indications for combination pharmacotherapy were analyzed using logistic regression analysis with sex, age, ADHD presentation, comorbidities, and Full-scale intelligence quotient (FSIQ), SNAP-IV, CAT, STAI-C, and K-CBCL scores at baseline. Statistical significance was set at $p<0.05$.

Ethics statement

In this study, we conducted a retrospective analysis of medical records and personally identifiable information was not collected or recorded. This study was approved by the Institutional Review Board of Keimyung University Dongsan Hospital (IRB No. DSMC 2023-01-131).

RESULTS

Demographic and clinical data

A total of 96 participants were enrolled, of whom 71 (74%) were male. Thirty-four patients were in the combination pharmacotherapy group, and 32 and 30 were in the methylphenidate and atomoxetine monotherapy groups, respectively. A total of 79 patients underwent combination pharmacotherapy at our hospital during the study period. After excluding ineligible patients, 34 were enrolled in the study. A total of 132 patients underwent methylphenidate monotherapy, with 32 selected for the study based on the sample size of the combination pharmacotherapy and atomoxetine monotherapy groups. Of the 44 patients who underwent atomoxetine monotherapy, 30 were enrolled in the study after excluding ineligible patients. The most common reasons for atomoxetine monotherapy were tic disorder and Tourette syndrome (23 cases).

Six patients in the combination pharmacotherapy group had anxiety disorders, three had depressive disorders, one had somatization disorders, and one had oppositional defiant disorders. There were four patients with anxiety and two with depression in the methylphenidate monotherapy group. In the atomoxetine monotherapy group, one patient had anxiety and one had eating disorder. Many patients receiving atomoxetine monotherapy had tic and Tourette syndrome; therefore, patients with tic and Tourette syndrome were excluded from the study. Drug dose was 0.90±0.44 mg/kg for methylphenidate and 0.90±0.34 mg/kg for atomoxetine in the combination pharmacotherapy group. The mean doses in the methylphenidate and atomoxetine monotherapy groups were 0.87±0.24 and 0.99±0.31 mg/kg, respectively. The mean time until maximal improvement of CGI-S score was 8.28±5.75 weeks in the combination pharmacotherapy group, 6.74±4.62 weeks in the methylphenidate monotherapy group, and 8.93±6.59 weeks in the atomoxetine monotherapy group, with no significant differences among the three groups. Baseline SNAP-IV, FSIQ, and STAI-C scores were also not significantly different among the three groups. However, the baseline K-CBCL score was higher in the combination pharmacotherapy group than that in the other monotherapy groups (67.62±8.99, 64.85±7.60, 63.52±11.41), and the prevalence of comorbidities was also higher in the combination pharmacotherapy group (32%, 19%, 7%). The most common reason for combination pharmacotherapy was inadequate therapeutic effects (15 cases; 44.1%), followed by short duration of effect (10 cases; 29.5%) and inability to increase the drug dose due to adverse effects (9 cases; 26.5%) (Table 1).

Adverse effect after adding other class medication in combination pharmacotherapy group

We investigated the adverse effects of adding another class of medication to combination pharmacotherapy. After adding atomoxetine to methylphenidate, nine of the 32 patients developed adverse reactions. Six patients had a reduced appetite, and there was one case each of nausea/vomiting, irritability, and weight gain. Two patients had methylphenidate added to their atomoxetine regimen, and one patient each experienced reduced appetite and nausea/vomiting (Table 2). Of the 34 patients in the combination pharmacotherapy group, only two experienced serious adverse effects that required discontinuation of the drug therapy.

Comparison of treatment effects using CGI-S

We compared CGI-S scores before and after treatment to investigate the therapeutic effects of combination pharmacotherapy. The mean baseline CGI-S score was 5.18±0.76, and the mean CGI-S score after the first-line drug therapy was 4.32±0.81. The mean CGI-S score after the combination pharmacotherapy was 2.32±0.81. There was a significant reduction in the CGI-S score after combination pharmacotherapy ($p<0.001$) (Fig. 1).

In terms of the degree of change in the CGI-S score from baseline to the time of maximum therapeutic effect, all three groups showed a significant reduction in the CGI-S score ($p<0.001$); however, the degree of change in the score did not significantly differ among the three groups ($p=0.142$). In other words, there were no significant differences in CGI-S scores among the three groups after the final treatment (Table 3).

Table 1. Demographic data and clinical characteristics

Characteristics	Combination pharmacotherapy group (n=34)	Stimulant monotherapy group (n=32)	Non-stimulant monotherapy group (n=30)	Total (n=96)	p
Sex					0.600
Male	25 (74)	22 (69)	24 (80)	71 (74)	
Female	9 (26)	10 (31)	6 (20)	25 (26)	
Age (yr)	7.79±1.91	8.16±1.85	8.30±1.78	8.07±1.85	0.410
Comorbidity	11 (32)	6 (19)	2 (7)	19 (20)	0.036*
Presentation					0.410
Combined	27 (79)	24 (75)	18 (60)	69 (72)	
Inattentive	7 (21)	8 (25)	12 (40)	27 (28)	
Drug dose (mg/kg)					
Stimulant	0.90±0.44	0.87±0.24	-	0.88±0.35	0.483
Non-stimulant	0.90±0.34	-	0.99±0.31	0.94±0.33	0.254
SNAP-IV total	25.21±10.19	24.19±9.19	19.97±11.19	23.23±10.34	0.054
Inattention	13.68±5.58	13.78±4.89	11.03±5.42	12.88±5.40	0.060
Hyperactivity	11.53±5.58	10.41±5.58	8.93±6.58	10.34±6.14	0.148
FSIQ	91.39±15.77	91.14±12.51	93.85±14.00	92.06±14.10	0.614
TAIC	32.29±8.29	33.13±8.44	31.22±6.18	32.26±7.72	0.691
SAIC	34.59±8.69	32.97±7.39	31.44±5.47	33.07±7.40	0.547
K-CBCL total	67.62±8.99	64.85±7.60	63.52±11.41	65.48± 9.38	0.026*
Internalization	60.48±12.20	61.96±8.73	58.78±9.29	60.49±10.24	0.467
Externalization	67.76±8.87	63.56±9.73	61.65±13.02	64.54±10.69	0.027*
CGI-S baseline	4.32±0.81	4.63±0.71	4.67±0.84	4.53±0.79	0.164
CGI-S endpoint	2.32±0.81	2.25±0.80	2.30±0.70	2.29±0.77	0.786
Time to maximum improvement in CGI-S (weeks)	8.28±5.75	6.74±4.62	8.93±6.59	7.96±5.69	0.521

Values are presented as mean±standard deviation or number (%). *p<0.05. CGI-S, clinical global impression severity; FSIQ, Full-scale intelligence quotient; K-CBCL, Korean version Child Behavior Checklist; SAIC, state anxiety inventory for children; SNAP-IV, Korean version of the Swanson, Nolan, and Pelham rating scale version four; TAIC, trait anxiety inventory for children

The predictive factors of combination pharmacotherapy in patients with ADHD

We conducted logistic regression analysis to identify the predictors of indications for combination pharmacotherapy for ADHD. The visual CAT (p=0.006), total K-CBCL (p=0.023), and internalization K-CBCL (p=0.031) scores were significant predictors (Table 4).

DISCUSSION

The responses to ADHD medications were generally high. However, owing to the limited availability of diverse medications, limited therapeutic options are available if first- or second-line drugs are ineffective or lead to adverse effects [20]. In fact, many studies have reported suboptimal adherence among individuals with ADHD, primarily due to subpar efficacy of the drugs and adverse effects; the remission rate is low owing to the difficulty of continuing pharmacotherapy despite a high treatment response [21]. From a clinical standpoint, the availability of a range of treatment options indicates that remission can be achieved in a higher number of patients, and understanding the efficacy and safety of diverse treatment options is crucial for patient treatment in clinical practice [22].

In this study, we first compared the characteristics of patients who underwent psychostimulant or nonstimulant monotherapy for ADHD with those who underwent combination therapy using both drugs. Although the patient groups were largely similar in their characteristics, patients who underwent combination pharmacotherapy had higher baseline K-CBCL scores than those who underwent monotherapy. This may imply that among ADHD patients, those who actually experience difficulties in problem behaviors and social adaptation may find it challenging to be treated with only one drug. Furthermore, patients who underwent combination pharmacotherapy had more comorbidities than those who underwent monotherapy, which is consistent with previous findings that treatment is more challenging and that mono-

therapy is often ineffective in patients with ADHD and other psychiatric comorbidities [23,24]. Patients with more comorbidities display more behavioral and emotional problems and treating these patients with psychostimulant or nonstimulant monotherapy may be difficult.

Table 2. Adverse effect after adding other class medication in combination pharmacotherapy group

Variable	Combination pharmacotherapy group	
	Add atomoxetine (n=32)	Add methylphenidate (n=2)
Adverse effect		
Loss of appetite	6 (18.6)	1 (50)
Sleep disturbance	0	0
excessive tiredness	0	0
Nausea/vomiting	1 (3.1)	1 (50)
Irritability	1 (3.1)	0
Stomachache	0	0
Weight gain	1 (3.1)	0
Hand tremor	0	0
Total	9	2

Values are presented as number or number (%).

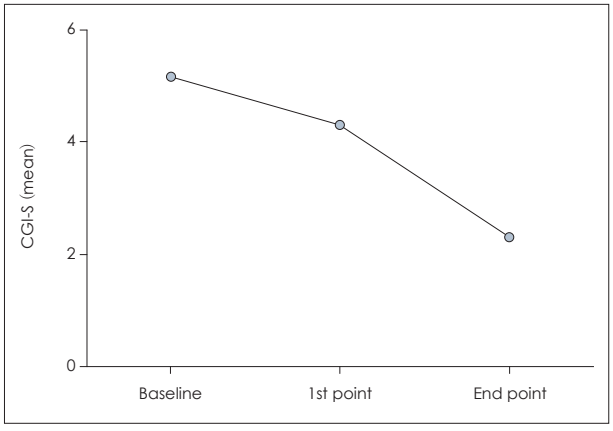

Fig. 1. CGI-S change in combination pharmacotherapy group. Baseline: Medicationfree state. 1st point: After monotherapy but before combination pharmacotherapy. End point: After combination pharmacotherapy. Baseline to 1st point: 60.56±81.09 weeks. 1st point to end point: 8.28±5.75 weeks. CGI-S, clinical global impression-severity.

Next, we investigated the adverse reactions to combination pharmacotherapy. Eleven of the 34 patients developed new adverse effects after adding another class of drugs to their existing regimen, and the most common symptoms were gastrointestinal symptoms such as reduced appetite and nausea/vomiting. These results are in line with previous reports that gastrointestinal symptoms are the most common side effects of methylphenidate and atomoxetine [8,25]. Furthermore, these studies reported that most patients developed mild adverse effects early after initiating pharmacotherapy, except for two patients; all patients in our study showed gradual improvement of symptoms without severe gastrointestinal reactions that warranted discontinuation of treatment even with adequate doses of combination pharmacotherapy.

In this study, the most common reason for transitioning to combination pharmacotherapy was inadequate therapeutic effect achieved with monotherapy. Bahn and Seo [10] reported that inadequate therapeutic efficacy was the most common reason for attempting combination pharmacotherapy. Here, initiating combination therapy in patients who did not achieve adequate therapeutic effects with monotherapy led to a significant reduction of the CGI-S score, and 23 out of 34 patients (67.65%) achieved a CGI-S score of 2 or lower, a criterion for remission used in many studies [26]. Compared to the 50%–80% response rate and 30%–60% remission rate after first-line therapy in patients with ADHD in general, these rates suggest that combination therapy is a good treatment option for patients who are unresponsive to initial treatment [4,27]. However, many previous studies that reported remission rates only analyzed patients who underwent treatment for a relatively short period, in contrast to our retrospective analysis of a study population consisting of patients who underwent treatment during several hospital visits. Hence, the actual treatment response and remission rates of combination therapy may be lower than the previously reported rates.

Finally, we performed a logistic regression analysis to discern the predictors of indications for combination pharmacotherapy following the failure of monotherapy for ADHD. In general, the ADHD patient population is largely hetero-

Table 3. Comparison of treatment effects using CGI-S

	Combination pharmacotherapy group	Stimulant monotherapy group	Non-stimulant monotherapy group	RM ANOVA
Before combination pharmacotherapy (combination group) or baseline (monotherapy group) CGI-S	4.32±0.81	4.63±0.71	4.67±0.84	p=0.142
After combination pharmacotherapy (combination group) or after monotherapy (monotherapy group) CGI-S	2.32±0.81	2.25±0.80	2.30±0.70	

Values are presented as mean±standard deviation. CGI-S, clinical global impression severity; RM ANOVA, repeated-measures analysis of variance

Table 4. The predictive factors of combination pharmacotherapy in ADHD patients

Variable	B	Wals	OR	p	95% CI
Sex	0.614	0.435	1.849	0.509	0.298–11.473
Age	-0.200	0.477	0.819	0.490	0.465–1.443
Presentation	-1.570	1.627	0.208	0.202	0.019–2.322
Comorbidity	-0.057	0.003	0.945	0.955	0.131–6.795
SNAP-IV inattention	-0.103	0.998	0.902	0.318	0.737–1.104
SNAP-IV hyperactivity	-0.050	0.213	0.952	0.644	0.771–1.174
CAT visual	1.176	7.511	5.816	0.006*	1.651–20.482
CAT auditory	0.295	0.234	1.344	0.628	0.406–4.441
CAT inhibition control	-1.138	2.706	0.320	0.100	0.083–1.124
CAT selective interference control	1.890	3.629	6.621	0.057	0.947–46.285
FSIQ	0.030	0.919	1.030	0.338	0.969–1.096
TAIC	-0.020	0.102	0.980	0.749	0.864–1.111
SAIC	0.063	1.019	1.065	0.313	0.942–1.205
K-CBCL total score	0.141	5.190	1.152	0.023*	1.020–1.300
K-CBCL internalizing score	-0.130	4.638	0.878	0.031*	0.780–0.988
K-CBCL externalizing score	-0.080	0.990	0.923	0.320	0.790–1.080

*$p<0.05$. ADHD, attention deficit hyperactivity disorder; B, unstandardized coefficients; CAT, comprehensive attention test; CI, Confidence interval; FSIQ, Full-scale intelligence quotient; K-CBCL, Korean version Child Behavior Checklist; OR, odds ratio; SAIC, state anxiety inventory for children; SNAP-IV, Korean version of the Swanson, Nolan, and Pelham rating scale version four; TAIC, trait anxiety inventory for children

geneous despite having similar symptom groups; therefore, patients diagnosed with ADHD vary in their emotional and behavioral characteristics [28]. In this study, a high K-CBCL score, which translates to more prominent emotional and behavioral problems, was identified as a predictor of combination pharmacotherapy. Previous reports that children with ADHD and other psychiatric symptoms are more difficult to treat than those with ADHD symptoms alone support our findings [29]. Furthermore, children with such emotional and behavioral characteristics often display several uncertain physical symptoms and are thus sensitive to adverse effects, making it difficult to differentiate between adverse effects and their existing physical symptoms. Therefore, monotherapy is often inadequate for treating children [30]. Our results indicate that the visual CAT score is another predictor of combination pharmacotherapy. Although this suggests that patients with poor visual attention are not adequately treated with first-line monotherapy, additional research is needed to compare the visual score with other CAT scores.

This study has several limitations. First, this was a retrospective study, and there were differences in certain characteristics among the study groups, with inadequate data on the therapeutic efficacy and adverse effects of combination pharmacotherapy for ADHD. For instance, there is much information about patients' baseline data; however, CGI and information on patients' medical records are the only data available to determine therapeutic outcomes and adverse effects after combination pharmacotherapy. Hence, future studies should establish more systematic plans and utilize additional instruments to compare outcomes. Second, we analyzed a relatively small sample size from a single facility. Future studies should analyze a larger population with diverse characteristics from more facilities. Third, in contrast to prospective studies, we set the treatment period as the time until the maximum improvement of symptoms was observed, without setting a particular assessment duration or time point. This was done to observe whether adequate symptom improvement was achieved when pharmacotherapy was continued for a certain period. However, we could not determine the level of improvement after a particular period or at a certain time point because we set the study period as the time until maximum improvement was achieved. Furthermore, we could not determine whether the improvement in symptoms was solely due to the effects of the drugs or was influenced by other factors, calling for additional studies. Finally, as we analyzed the outcomes of combination pharmacotherapy determined by a single clinician based on clinical judgment, more clinical data and evidence need to be accumulated to conduct studies according to an established combination pharmacotherapy protocol.

CONCLUSION

In pediatric research, prospective and systematic randomized controlled trials are challenging due to medical ethics.

Therefore, there are limited drug research data, and many studies rely on retrospective analyses. This study is significant in shedding light on the safety and efficacy of combination pharmacotherapy for ADHD amid the limited research data on this alternative treatment approach for patients who do not respond to monotherapy. Moreover, with more research data accumulated based on our findings, we aim to attain a higher treatment success rate for patients with ADHD that is not well controlled with drug monotherapy by attempting this new treatment approach involving combination pharmacotherapy, with careful consideration of adverse effects.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Hojun Lee, Na Yeong Kong. Data curation: all authors. Formal analysis: Hyung Nam Park, Hee-Cheol Kim, Yang Tae Kim, Sung-Won Jung. Methodology: Hee-Cheol Kim, Hojun Lee. Supervision: Hee-Cheol Kim, Sung-Won Jung, Hojun Lee. Writing—original draft: Hyung Nam Park, Sung-Won Jung, Hojun Lee. Writing—review & editing: Na Yeong Kong, Sung-Won Jung, Hojun Lee.

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Funding Statement

None

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