Effects of Nasal Calcitonin vs. Oral Gabapentin on Pain and Symptoms of Lumbar Spinal Stenosis: A Clinical Trial Study

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ABSTRACT: Lumbar spinal stenosis (LSS) is a chronic and prevalent disease that occurs in 10.8% of the general population, mostly in old age. We designed the first clinical trial study to compare the effects of administering the nasal salmon calcitonin spray and gabapentin in patients with LSS. In this clinical trial, 90 patients with symptoms of neurogenic claudication and magnetic resonance imaging-proven LSS were randomly assigned to nasal salmon calcitonin, gabapentin, or placebo treatments for eight weeks (30 participants in each group). This was followed by a *washout* period of four weeks. After three months of study and after four weeks off the prescription, mean values of Oswestry Disability Index in the calcitonin, gabapentin, and control groups were 23 ± 12.05, 32 ± 16.08, and 38 ± 22.09, respectively ($P \leq 0.05$, calcitonin group vs. gabapentin group, and $P \leq 0.001$, calcitonin group vs. control group with respect to pretreatment scores). Thus, three months after the treatment, although most of the patients in the control group had a satisfactory period of improvement, the improvement in the calcitonin group was more than the other two groups with a significant difference ($P \leq 0.05$ when compared to gabapentin group and $P \leq 0.01$ when compared to placebo group). We revealed that the 200 International Unit (IU) and nasal calcitonin spray daily are more effective compared to 300 mg gabapentin three times per day and the placebo effect for eight weeks of treatment of symptoms of patients with LSS.

KEYWORDS: gabapentin, lumbar spinal stenosis, nasal calcitonin, outcome

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Introduction

Lumbar spinal stenosis (LSS) is a chronic and prevalent disease that occurs in 10.8% of the general population, mostly in old age.[1] LSS is classified according to its etiology.[2] Postacchini[3] classified LSS into primary (congenital), secondary (acquired), and combined forms. Central canal stenosis is mainly produced by hypertrophy of the ligamentum flavum, facet joint, and degenerative spondylolisthesis. Lateral recess stenosis results from compression between the posterior aspect of the vertebral body and disk, and medial aspect of a hypertrophic superior articular facet. Hypertrophy of the facet joint capsule and/or ligamentum flavum, disk protrusion, and vertebral body osteophyte exacerbate the stenosis. The traversing nerve root is compressed in the lateral, and clinically, weakness, numbness, pain, or cramps may develop in one or both legs. These symptoms typically occur when walking or standing beyond a threshold distance and subside when stooping, sitting, or bending forward. These symptoms are appropriately referred to as neurogenic intermittent claudication.[4]

In addition to compression on nerve roots, blood flow is compressed, causing ischemia and periradicular fibrosis. Furthermore, vascular compression increases the metabolic demand of nerve roots and induces neurogenic claudication.[5–7] Magnetic resonance imaging (MRI) is the choice of investigation for the diagnosis of spinal stenosis, wherein the MRI myelography can be described as being beaded in its appearance.[8]

The early organization of LSS requires nonsurgical (conservative) approaches, such as physical therapy exercises, analgesia, and nonsteroidal anti-inflammatory drugs.[8]

Surgery (decompressive laminectomy) is recommended to many patients who are not sufficiently managed with conservative measures alone or who are severely affected.[9] In fact, LSS has become the most common reason for spinal surgery in patients older than 65 years.[6] The advantage of surgical approaches over nonsurgical treatment methods has not been recognized, and the role of various treatment policies remains an active field of investigation.[10] Numerous groups of drugs were used in the management of LSS to reduce pain and increase the ability of patients.

Calcitonin is a polypeptide hormone synthesized in the thyroid gland. It controls calcium, recovers mineralization in

skeleton, and decreases metabolism. Additionally, some studies discovered that calcitonin releases β-endorphins and can be used as an analgesic agent.[11,12] Earlier studies have shown that administration of calcitonin is effective in the treatment of LSS.[13] An intranasal formulation of salmon calcitonin is now available and is frequently accepted for the treatment of various skeletal disorders.[6] The useful effects of calcitonin have been observed within four to six weeks.[11,13–15] Although the mechanism of action of calcitonin is unknown, some studies report that it acts nonspecifically by increasing the level of endogenous opioids (β-endorphins).[16,17] Alternatively, others have suggested that calcitonin may improve the symptoms of LSS by enhancing circulation to ischemic cauda equina.[13] Flushing or nausea, the two main side effects, is observed in less than 5% of patients treated with calcitonin.[11,13,14]

Gabapentin is an anticonvulsant agent, although some authors assert it as an analgesic agent. Gabapentin is an effective drug for pain relief in patients with radicular pain due to LSS.[18] Moreover, other studies specified that gabapentin decreases pain intensity and analgesic consumption in combination with other agents or when used alone.[19,20] The reviewed articles propose that gabapentin and calcitonin have analgesic effects and decrease the metabolism and demand of nerves; on the other hand, intranasal salmon calcitonin is now accessible and is universally administered for the treatment of patients with skeletal disorders. Moreover, to the best of our knowledge, there is no article comparing the effects of gabapentin and calcitonin in LSS. Hence, in this study, we compared the effects of nasal calcitonin and oral gabapentin in patients with symptomatic LSS.

Materials and Methods

We designed the first clinical trial study to compare the effects of administering the nasal salmon calcitonin spray and that of gabapentin in patients with LSS in the period of 2013–2015. In this study, among 133 patients, 90 female patients, aged ≥45 years, with symptoms of neurogenic claudication and MRI-proven LSS were recruited. We tried to study a more homogeneous patient population; thus, the symptoms of participants included paresthesia, back and leg pain, neurogenic claudication, areflexia, and spinal canal diameter ≤13 mm in MRI. The exclusion criteria were as follows: patient disagreement, vascular claudication, symptomatic pathology in knee or hip, previous LSS surgery, pregnancy, renal failure, malignancy, and other neurological diseases including diabetic neuropathy. All patients had leg pain, in one or both legs, which was intensified by prolonged standing or walking and relieved by resting or leaning forward. Our research complied with the principles of the Declaration of Helsinki. The study was approved by the local institutional ethics committee (Code:IR.MAZUMS.REC.91-232) and the trial was given ethical approval by the Iranian Registry of Clinical Trials (IRCT No 2014091519185N1). Moreover, the study protocol was explained to all patients and informed written consents were obtained. Finally, 90 patients were enrolled and randomized in gabapentin (n = 30), salmon calcitonin (n = 30), and placebo (n = 30) groups. We used sequential numbers for randomization; in this case, the first number was given to the first patient who received 200 IU nasal calcitonin spray daily for eight weeks (calcitonin group, n = 30). Sequentially, the next number was given to the next patient who received 300 mg gabapentin three times per day (gabapentin group, n = 30) for eight weeks. The next number was given to the next patient who received a placebo drug for eight weeks. This schedule was repeated for all patients. All patients received a similar nonsteroidal anti-inflammatory drug during nights.

This was followed by a washout period of four weeks. The questionnaire was completed by the three groups at the end of eight weeks of treatments and finally at 12 weeks after the beginning of the study. Both participants and study staff (site investigators and trial coordinating center staff) were masked to treatment allocation (Fig. 1).

Following this, we performed neurological examination, peripheral pulse evaluation, and hip and knee movement range test. This was followed by the Oswestry Disability Index (ODI) and patient satisfaction index (PSI), which were completed by all patients.

Assessment of outcome. We logged ODI scores at follow-up examinations two and three months after the study and directed the PSI (a modified subitem of the NASS outcome questionnaire) to evaluate patient satisfaction with the posttreatment result.[21]

Statistical analysis. Data were analyzed using SPSS version 18. Categorical data are presented as numbers (%), and continuous data are presented as mean ± SD. We used the chi-square or Fisher's exact test to compare categorical variables and the Student's t-test to compare continuous variables. $\alpha < 0.05$ was considered significant.

Results

The mean age of patients was 52.03 ± 8.66 years, 50.59 ± 6.83 years, and 51 ± 6.33 years in calcitonin, gabapentin, and placebo groups, respectively, and the difference was not significant. Three patients in the gabapentin group and one patient in the calcitonin group withdrew from the study as they had no tolerance to the medication. A total of 21 (70%) patients in the gabapentin group, 19 (63%) patients in the calcitonin group, and 20 (66%) patients in the control group had paresthesia prior to trial entry, and the difference was not significant (P = 0.39). Twelve weeks after treatment, paresthesia persisted in 15 (50%), 11 (36.6%), and 14 (46.6%) patients in the gabapentin, calcitonin, and placebo groups, respectively. The observed difference was not statistically significant (P = 0.18). Moreover, 20, 22, and 19 patients in the gabapentin, calcitonin, and control groups, respectively, had claudication prior to trial entry (P = 0. 59). Furthermore, 12 weeks after treatment, 15 (50%), 6 (20%), and 18 (60%) patients in

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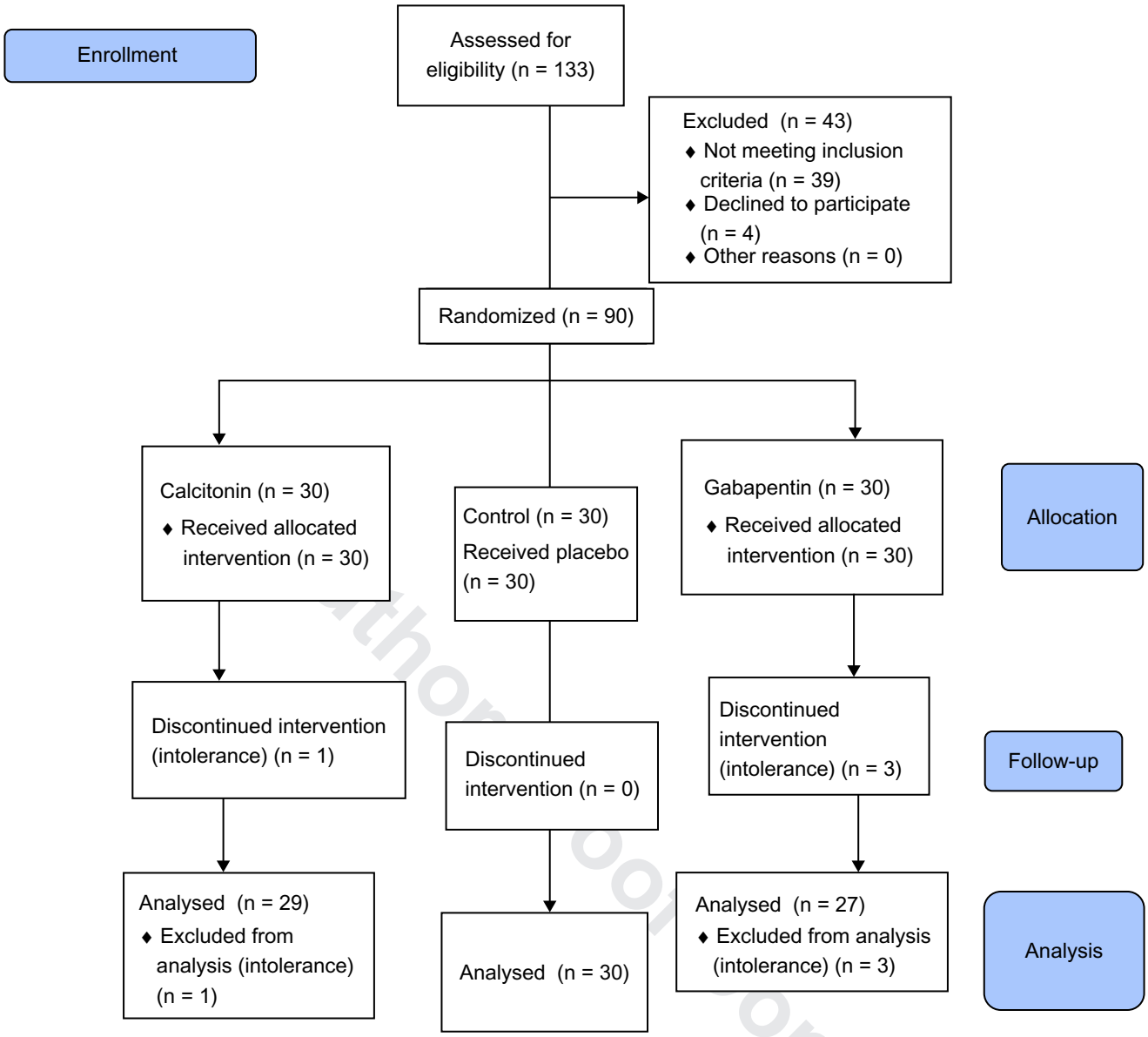

Figure 1. Flow diagram.

Table 1. Characteristics of patients at baseline and four and eight weeks after treatment.

		CALCITONIN	GABAPENTIN	CONTROL
Age		52.03 ± 8.66	50.59 ± 6.83	51 ± 6.33
Paresthesia	start	19 (63%)	21 (70%)	20 (66%)
	12 weeks	11 (36.6%)	15 (50%)	14 (46.6%)
Claudication	start	22 (73%)	20 (66.6%)	19 (63.3%)
	12 weeks	6 (20%)*	15 (50%)	18 (60%)

Note: *$P < 0.01$ compared with two other groups.

the gabapentin, calcitonin, and control groups, respectively, had claudication. This difference was statistically significant for the calcitonin group compared to the other two groups ($P \leq 0.01$; Table 1).

The mean ODI was an important parameter for functional assessment in our study. ODI in the calcitonin, gabapentin, and control groups before treatment were 40.35 ± 16.56, 38.46 ± 16.56, and 39 ± 17.11, respectively. While after prescription, in eight weeks, the mean values of ODI in the calcitonin, gabapentin, and control groups were 31 ± 17.04, 30.42 ± 16.07, and 36 ± 14.09, respectively. Although ODI in the control group was not improved, there was not any significant relationship ($P = 0.91$; Table 2).

After three months of study and four weeks after the end of the prescription, the mean values of ODI in the calcitonin, gabapentin, and control groups were 23 ± 12.05, 32 ± 16.08, and 38 ± 22.09, respectively ($P \leq 0.05$, calcitonin group vs. gabapentin group, and $P \leq 0.001$, calcitonin group vs. control group with respect to pretreatment scores).

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Table 2. ODI at baseline and four and eight weeks after treatment.

	BEFORE TREATMENT	8 WEEKS AFTER TREATMENT	12 WEEKS AFTER TREATMENT
Calcitonin	40.35 ± 16.56	31 ± 17.04	23 ± 12.05*
Gabapentin	38.46 ± 16.56	30.42 ± 16.07	32 ± 16.08
Control	39 ± 17.11	36 ± 14.09	38 ± 22.09

Note: *$P < 0.05$ compared to gabapentin group and $P < 0.01$ compared to control group.

Thus, three months after the treatment, although most of the patients in the control group had a satisfactory period of improvement, improvement in the calcitonin group was significantly more than that in the other two groups ($P \leq 0.05$ compared to the gabapentin group and $P \leq 0.01$ compared to the placebo group; Table 2).

In the present randomized study, PSI was 93.3% during the three-month follow-up period in the calcitonin group compared with 77.2% and 74.3% in the gabapentin and control groups, respectively ($P < 0.01$; Table 3).

Discussion

LSS is the narrowing of the central spinal canal, the neural foramen, or lateral recess. The first case of spinal stenosis was reported in 1802, which gradually and sympathetically developed over the next 150 years.[22,23] Hypertrophy of the ligamentum flavum, or zygapophyseal joint, and vertebral body osteophytes are the most common abnormalities leading to encroachment.[24] The infringement induces leg and low back pain or neurogenic claudication, which is worsened by walking and relieved after a few minutes of sitting or flexion of the lumbar spine.[25,26] Both surgery and medication are applied for treatment of patients with LSS, although little is known about the efficacy of surgical and nonsurgical management of LSS.[27] However, most clinicians consider conservative management, such as physiotherapy and medication, as a suitable initial treatment for managing LSS.

Calcitonin advances mineralization in bones and has been used as a therapeutic adjunct in the treatment of osteoporosis and Paget's disease. The detection of its analgesic properties has led to its adjunctive use in diseases related to bone pain. The mechanism of the analgesic effect of calcitonin is not clear. However, some studies have reported that calcitonin treatment decreases the pain experienced by LSS patients throughout movement.[15,28,29] The strong central analgesic effect of calcitonin on hypothalamic receptors increases in the volume of circulating endogenous opioids, and the inhibition of prostaglandin E2 synthesis and its antidepressant actions may depend on this outcome.[30]

Khan and Kaptan, in an experiment in Tokyo, investigated the efficacy of gabapentin monotherapy against both acute and chronic radicular pain, which are caused by lumbar disk hernia or LSS. They revealed that gabapentin decreased pain and improved walking distance in patients with LSS.[31] In agreement with these results, another systemic review by Ammendolia et al detected that prostaglandins, gabapentin, and vitamin B1 were effective agents in pain relief and improved walking distance.[32] Harmoniously, in a review by Tran et al, the evidence derived from randomized controlled trials pertains to the nonsurgical treatment of LSS. They revealed that parenteral calcitonin decreases pain in patients with LSS.[33] However, their study indicated that intranasal calcitonin was not effective in these patients. Moreover, they signified that calcitonin injections did not improve LSS symptoms more than paracetamol or placebo.[33] In line with these findings, Peng et al.[34], in a review, investigated the effects of calcitonin on LSS. They indicated that in patients with LSS, calcitonin was not more effective than the placebo. Again, another systematic review by Coronado-Zarco et al.[35] analyzed the level of evidence in the effectiveness of calcitonin on the treatment of neurogenic claudication in patients with LSS. They suggested that calcitonin administration in the treatment of neurogenic claudication has no benefit in patients with LSS. In line with these findings, Eskola et al detected only a little improvement in walking distance after eight weeks of treatment with calcitonin.[11] Furthermore, Tafazal et al.[12] compared the outcome of salmon calcitonin nasal spray with that of a placebo nasal spray in patients with MRI-confirmed

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Table 3. Patient satisfaction following decompression of LSS.

FU PERIOD	GROUP (%)		
	CALCITONIN	GABAPENTIN	CONTROL
2-month			
PSI (overall satisfaction w/op)	82.2	78.3	77.2
Satisfaction w/pain reduction	83.8	78.4	71.3
Satisfaction w/improved performance	84.1	74.3	63.6
3-month			
PSI (overall satisfaction w/op)	93.3	77.2*	74.3*
Satisfaction w/pain reduction	94	79.3	79.4
Satisfaction w/improved performance	91.6	78.4**	74.3**

Notes: **$P < 0.01$ compared with calcitonin. ***$P < 0.01$ compared with calcitonin. *$P < 0.05$ compared with calcitonin. **$P < 0.05$ compared with calcitonin.

LSS. They did not reveal any efficacy for intranasal calcitonin in patients disabled due to LSS.

In contrast, Burnaz et al evaluated the clinical effects of calcitonin in patients with LSS in an experiment conducted in Turkey. They revealed that calcitonin significantly increased walking distance and decreased claudication and pain.[10] The reasons for such discrepancies are not clear, but it may depend on different methods, patient selection, and different measurements in these trials.

Younis and Radhwany investigated the effect of miacalcic nasal spray in the management of spinal stenosis. A total of 39 patients with spinal stenosis were divided into two groups, both treated conservatively, but one of them used calcitonin nasal spray in the treatment plan. The study revealed that 84% of patients treated with calcitonin nasal spray had good pain relief, while the response for claudication distance was approximately the same for both patient groups. No patient developed any side effect. The study concluded that calcitonin nasal spray is effective in alleviating symptoms of patients with spinal stenosis.[8]

The present study is the first clinical trial study to compare the effectiveness of both gabapentin and nasal calcitonin in conservative treatment of spinal canal stenosis.

In this trial, we compared the effect of gabapentin and calcitonin in 90 female patients with LSS with a mean age of 52 years and revealed the effects of two agents compared with placebo effect on LSS symptoms.

After eight weeks of treatment, mean values of ODI in the calcitonin, gabapentin, and control groups were 31 ± 17.04, 30.42 ± 16.07, and 36 ± 14.09, respectively. Although the ODI in the control group was not improved, there was not any significant relationship between the three groups ($P = 0.91$; Table 2).

Moreover, after three months of study and four weeks after the end of the prescription, the mean values of ODI in the calcitonin, gabapentin, and control groups were 23 ± 12.05, 32 ± 16.08, and 38 ± 22.09, respectively ($P \leq 0.05$, calcitonin group vs. gabapentin group, and $P \leq 0.001$, calcitonin group vs. control group with respect to pretreatment scores).

Interpretation of the results showed that prior to discontinuation of drugs, although the performance of the control group patients had less improvement, no significant differences in the influence of drugs were observed in the three groups. A month after discontinuation of treatment, antianalgesic and metabolic effects of calcitonin appeared to be persistent, and the disability scores in the calcitonin group improved significantly compared to the other two groups, especially the control group.

In the present randomized study, PSI was 93.3% during the three-month follow-up period in the calcitonin group; these results are significantly superior to the gabapentin and control groups. If analysis of long-term follow-up data confirms these results, nasal calcitonin may prove advantageous for patients with lumbar stenosis, reducing the need for additional surgery.

In our experience, three patients in the gabapentin group and one patient in the calcitonin group had no tolerance to the medication and hence withdrew from the study. However, during this study, we did not detect any adverse effects related to calcitonin or gabapentin in the rest of the patients. Previous trials revealed some problems in patients under gabapentin, such as dizziness or sleepiness. Also, they reported that some of the patients experienced sickness or rashes with calcitonin.[32]

Although several studies on the beneficial effect of the use of calcitonin (special intranasal salmon) did not express distress, with this prospective case–control study on the effects of calcitonin on disability, we not only verified the antianalgesic reports of Younis et al and Burnaz et al regarding calcitonin use in spinal stenosis patients but also showed the persistent effect of it in improving the disability of these patients.[11,12,35]

Gabapentin can greatly reduce pain, but it is not effective in reducing the disability of spinal stenosis patients in the long term.

In our study, a follow-up period was three months for all patients. Symptoms and scores continued to be stable during that period. Yet, long-term follow-up data are mandatory and will be collected; the sample size was relatively small and the duration of follow-up was short (12 weeks), limiting the ability to generalize the results of our survey. Further controlled investigations are recommended with longer follow-up periods and larger series to validate the findings reported here. Moreover, during recent years, spine surgery and divers' class of medications such as steroids, opioids, and analgesics were used for treatment of patients with LSS. However, little is known about the efficacy of surgical and nonsurgical managements. Some comparative studies are required to compare surgical and nonsurgical managements.

Conclusion

We revealed that administration of 200 IU of nasal calcitonin spray daily is more effective compared to 300 mg gabapentin three times per day and a placebo effect for eight weeks of treatment of symptoms of patients with LSS. Double-blind placebo-controlled studies should be conducted and long-term effects of calcitonin should be evaluated. Calcitonin treatment for LSS must be considered before surgical treatment, particularly in the elderly, in whom LSS is more common and higher surgical risk is involved.

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Abbreviations

ODI: Oswestry Disability Index
LSS: lumbar spinal stenosis

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Author Contributions

Conceived and designed the experiments: KH. Analyzed the data: LA. Wrote the first draft of the manuscript: KH. Contributed to the writing of the manuscript: KH, LA. Agree with manuscript results and conclusions: KH, LA, AI. Jointly developed the structure and arguments for the paper: KH, LA. Made critical revisions and approved final version: KH, LA, AI. All authors reviewed and approved of the final manuscript.

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