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Original Article

Pregnant Patients with Sudden Sensorineural Hearing Loss: Treatments and Efficacy

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BACKGROUND: The aim of this study was to study the safety and effectiveness of oral and tympanic hormone injection in the treatment of sudden sensorineural hearing loss during pregnancy.

METHODS: Data were collected via prospective method. A total of 102 pregnant women with sensorineural hearing loss as experimental group and another 102 patients of sensorineural hearing loss without pregnancy as control group were simultaneously included in the study. Pure tone audiometry test was examined at pre- and posttreatment in 1 week, 2 weeks, and 12 weeks. The experimental group received oral and tympanic hormones, while the control group was treated with the Clinical Practice Guideline: Sudden Hearing Loss (2019) of USA. Recovery rate and hearing gain were assessed by the Clinical Practice Guidelines.

RESULTS: After treatment, the effects of the experimental group and the control group were compared at the 1st, 2nd, and 12th week after treatment. It was found that at the 12th week after treatment, the curative effect of the experimental group was significantly different from that of the control group, and the difference was statistically significant.

CONCLUSION: The pregnant women with sensorineural hearing loss were more serious than nonpregnant women, and the treatment efficacies were worse than control group. For pregnancy patients with sudden deafness, oral steroids and tympanic cavity injection is an effective, safe first-line treatment option.s.

KEYWORDS: Dexamethasone, pregnant, sudden sensorineural hearing loss

INTRODUCTION

Sudden sensorineural hearing loss (SSNHL) is defined as sensorineural in nature with 3 consecutive frequencies more than 30 dB in less than 72 hours in unilateral or bilateral ears whose pathogenesis has not been elucidated clearly for a long time. Hypothesis such as viral infection, vascular occlusion, perforation of the labyrinthine membranes, immune-mediated mechanisms, and abnormal stress response in the cochlea have been proposed to explain the pathogenesis of SSNHL.[1] The estimated incidence of this sickness is about 5-20 cases per 100 000 annually. Actually, the exact incidence is underestimated, because many patients who recover self-healing (such as low-frequency SSNHL) or carelessness are unlikely to receive medical therapy.[2]

The incidence of pregnancy with SSNHL is lower when compared to ordinary people, but severe hearing loss, vertigo, and tinnitus often occur.[3] Previous studies have shown that similar to gestational hypertension, pregnancy-related hearing loss may be a new disease due to changes in sex hormone levels, hypercoagulable state, and stress state during pregnancy.[4]

Although there have been many studies on treatment options for SSNHL, such as anticoagulants, vasodilators, plasma, diuretics, proposed dilators, hyperbaric oxygen, etc. There are significant differences in treatment guidelines between the United States and China; however, systemic and topical steroids are the preferred treatment options. Steroids have been employed in the management of SSNHL and administered as a single option or combined with other drugs. The first use of intratympanic therapy in SSHL was reported in 1996, and the intratympanic therapy (inject dexamethasone or methylprednisolone) has been used as a salvage treatment to all patients who failed the first systemic treatment.

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Table 1. General Information of Patients in the Experimental Group and the Control Group

	Number	Age	Initial Treatment Time	Combined Diseases	Concurrent Symptoms	Gestation		Oral Corticosteroids	Intratympanic Corticosteroids
						< 28 weeks	> 28 weeks		
Experimental group	102	20-43 (28.71 ± 5.54)	1-24 (6.81 ± 7.36)	14	18	74	28	80	22
Control group	102	19-64 (27.41 ± 4.24)	1-22 (4.65 ± 4.07)	18	25	–	–	–	–
t/Z		1.873	0.020	0.593	1.444	–	–	–	–
P		.063	.475	.441	.23	–	–	–	–

The statistical comparison between the experimental group and the control group was carried out using the *t*-test or the Mann–Whitney *U* test. The general information of the patients in the experimental group was compared with the control group ($P > .05$), and the difference was not statistically significant.

The management of pregnant patients with SSNHL has proven to be greatly challenging due to the limited clinical experience and complications (gestational hypertension, gestational diabetes, and hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). According to theUS Food and Drug Administration (FDA), class A and B medicines could be used in pregnant patients of SSHL. Some studies indicated that tympanic injection of glucocorticoids or combine with Dextran 40 can achieve good therapeutic effects on pregnancy with SSNHL.[5,6]

Glucocorticoids are the first-line medicines for the treatment of SSNHL and are classified as class B drugs by the FDA. The purpose of our study was to verify the efficacy and safety of methylprednisolone injection into the tympanic cavity and oral prednisone in the treatment of pregnant patients with SSNHL and to compare the efficacy with that of ordinary sudden deafness.

MATERIAL AND METHODS

This prospective study included 102 pregnant women and 102 women with SSNHL from 2015 to 2020 of 2 hospitals. All of patients were unilateral enrolled and those who were pregnant were compared with those who were not pregnant. Patients with low-frequency sudden deafness less than 30 days from onset to consultation were excluded from the study due to the self-healing.The time from onset to consultation was less than 30 daysAll patients met certain audiometric criteria (2019 Clinical Practice Guideline, USA): (a) Sensorineural in nature(b) Occurs within 72 hours(c) Meets some audiometric criteria: the most commonly used audiometric criterion for SSNHL is a decrease in hearing of 30 dB affecting at least 3 consecutive frequencies. Before treatment, all patients had been examined by aural surgeon, imaging, and audiology-related examinations in order to exclude middle, inner ear, and central disease, such as sensorineural hearing loss caused by heredity, drugs, and Meniere's disease. Laboratory tests include female hormones, antinuclear antibody spectrum, Torch virus, neutrophil cytoplasmic antibodies, complete humoral immunity, lupus anticoagulant and cardiac coagulation antibodies, syphilis, HIV, etc. The age and the time of the first treatment after the onset of disease the combined diseases and concurrent symptoms in the experimental group and the control group were included as the main factors for controlling bias in the 2 groups. The combined diseases includes diabetes, hypertension, impaired glucose tolerance during pregnancy, and pregnancy-induced hypertension. Concurrent symptoms includes tinnitus and vertigo. The main factors of controlling bias is from the experimental group and the control group: the age and the time of the first treatment after the onset of disease, the combined diseases and concurrent symptoms.

This study was approved by Ethics Committee of of Suining Central Hospital (Approval No: LLSLH20220128). All patients had signed the informed consent.

Case Information

This study included 102 patients with SSNHL during pregnancy. The minimum age of the experimental group was 20 years, and the maximum age was 43 years; the average age was 28.71 ± 5.52 years. The earliest gestational week was 12, the latest was 36 weeks, and the average of gestational week was 24.37 ± 5.95. The initial treatment time was 1 day at the earliest and 24 days at the latest, and the average treatment time was 6.81 ± 7.36 days. The minimum age of the control group was 19 years and the maximum was 64 years, with an average of 38.12 ± 11.31 years. The initial treatment time was 1 day at the earliest and 22 days at the latest, and the average of treatment time was 4.65 ± 4.07 days. The experimental group had 74 cases before 28 weeks of gestation and 28 cases over 28 weeks. The initial treatment time was less than 14 days in 80 cases and more than 14 days in 22 cases. The difference of age, initial treatment time, combined diseases, and concurrent symptoms between the 2 groups were not statistically significant ($P > .05$) (Table 1).

Treatment

In the experimental group, drug treatment strictly followed FDA standards, and class A and B drugs were selected. The treatment of the control group followed the Clinical Practice Guideline of Sudden Hearing Loss (2019 USA and 2015 China). The experimental group received systemic corticosteroid intervention and tympanic steroids within 2 weeks. Additionally, intratympanic steroid treatment of salvage was recommended for more than 2 weeks after the onset of SSHNL. The total course of treatment was 2 weeks. There were

MAIN POINTS

- Pregnant women with sudden sensorineural hearing loss have a more severe degree of hearing loss than non pregnant group.
- The degree of hearing improvement in pregnant women with sudden sensorineural hearing loss group is worse than the non pregnant group.
- Oral and tympanic injection of steroid hormones is an effective, safe, and first-line treatment options for patients with sudden deafness during pregnancy.

Table 2. Detailed Treatment Measures for Each Group

		Experimental Group		Control Group			
		Systemic Corticosteroids	Intratympanic Corticosteroids	Systemic Corticosteroids	Intratympanic Corticosteroids	Vasodilators/Vasoactive Substances	Hyperbaric Oxygen Therapy
1	Timing of treatment	Immediate, ideally within first 14 days.	1. Immediate 2. Salvage (rescue) after initial treatment fails or after 2 weeks of symptom onset	Immediate, ideally within 6 weeks	1. Immediate 2. Salvage (rescue) after initial treatment fails or after 2 weeks of symptom onset	Immediate, ideally within 6 weeks	Immediate
2	Dose	Prednisone, 1 mg/kg/day (usual maximal dose is 50 mg/day)	Methylprednisolone 40 mg/mL or 30 mg/mL	Prednisone, 1 mg/kg/day (usual maximal dose is 60 mg/day)	Methylprednisolone 40 mg/mL or 30 mg/mL	Extract of *Ginkgo biloba* leaves injection 35mg/day, Batroxobin 10BU at first day, then 5BU once every other day	Once a day
3	Duration/ frequency	Full dose for 5 days	Inject 0.4-0.8 mL into middle ear space up to 4 injections over a 2-week period	Full dose for 7-14 days, then taper over a similar time period	Inject 0.4-0.8 mL into middle ear space up to 4 injections over a 2-week period	Intravenous drip within 2 weeks	10-14 days

80 pregnant patients who received oral corticosteroids. Only 22 pregnant patients had received the treatment of systemic corticosteroids and intratympanic corticosteroids. The treatment details of the 2 groups are shown in Table 2.

Examination Items

All patients were examined by pure tone audiometry before treatment and 1, 2, 4, and 12 weeks after treatment. The distortion product optoacoustic emission and auditory brainstem response were applied to detect the cochlea and posterior lesions. If the patient experiences vertigo, brain magnetic resonance imaging, vestibular evoked myogenic potential, video head pulse test, and Fitzgerald–Hallpike test must be performed to exclude hearing loss and vertigo attacks caused by central diseases.

Statistical Analysis

All statistical analyses were performed using SPSS software version 22.0 (IBM SPSS Corp.; Armonk, NY, USA).Generalized estimated model (GEM) was used to evaluate the consistency between the experimental group and the control group after different treatments. The experimental group was divided into groups according to gestational week and initial treatment time, and repeated measures analysis of variance was used for comparison of the 2 groups. $P < .05$ was considered statistically significant. At the same time, the effectiveness of the experimental group was compared with the control group.

RESULTS

All infants and young children had normal scores at birth.

The GEM was used to evaluate the consistency of the experimental group and control group with different regimens. The box plot of 2 groups are shown in Figures 1 and 2.

The results of the GEM had showed that although the basic situation and treatment plan of the experimental group and the control group were different, the efficacy tended to be consistent, but the final difference of the 2 groups was not statistically significant ($\chi^2 = 2.314$, $P = .128$). The results are shown in Table 3.

PTA, pure tone average.

The experimental group treatment program developed in this study was consistent with the Clinical Practice Guideline: Sudden Hearing Loss of American Academy of Otolaryngology Head and Neck Surgeons (updated 2019).[7]

The effective rate of total deafness in the experimental group was 33.33% (18/54). The effective rate of total deafness in the control group was 75% (36/48). Compared with the effective rate of the 2 groups, the difference was statistically significant. The effective rate of pregnancy-induced flat deafness in the experimental group was 22.92% (11/48), and the effective rate of flat deafness in the control group was 55.56% (30/54). Compared with the effective rate of the 2 groups, the difference was statistically significant ($P < .05$). The total effective rate of treatment of deafness in the experimental group was 28.43% (29/102). The total effective rate of the control group was 64.71% (66/102). Compared with the total effective rate of the 2 groups, the difference was statistically significant ($P < .01$).

We believed that patients with concurrent deafness during pregnancy have a worse treatment efficacy than patients without pregnancy. Table 4 shows the statistical data.

The pure tone average (PTA) of the flat-type group in the experimental group and the control group was 66.14 ± 16.41 and 44.38 ± 13.78 at 1 week, 63.31 ± 17.34 and 38.92 ± 14.89 at 2 week, and 61.33 ± 17.67 and 36.05 ± 15.71 at 12 weeks, respectively. By comparison, the difference was statistically significant ($Z1$ week $= 5.974$, $P < .01$; $Z2$ weeks $= 6.118$, $P < .01$; $Z12$ weeks $= 6.191$, $P < .01$). The PTA of the total deaf type in the experimental group and the total deaf type in the control group was 85.98 ± 11.51 and 80.45 ± 24.13 at 1 week, 81.06 ± 13.14 and 75.07 ± 25.88 at 2 weeks, and 77.55 ± 14.44 and 71.11 ± 28.43 at 12 weeks. The difference was statistically significant ($t1$ week $= 1.521$, $P < .01$; $t2$ weeks $= 1.488$, $P < .01$; $t12$ weeks $= 1.454$, $P < .01$). The total PTA of the experimental group and the control group was 76.64 ± 17.61 and 63.47 ± 26.85 at 1 week, 72.70 ± 17.60 and 58.15 ± 27.87 at 2 weeks, and 69.92 ± 17.91 and 54.71 ± 29.01 at

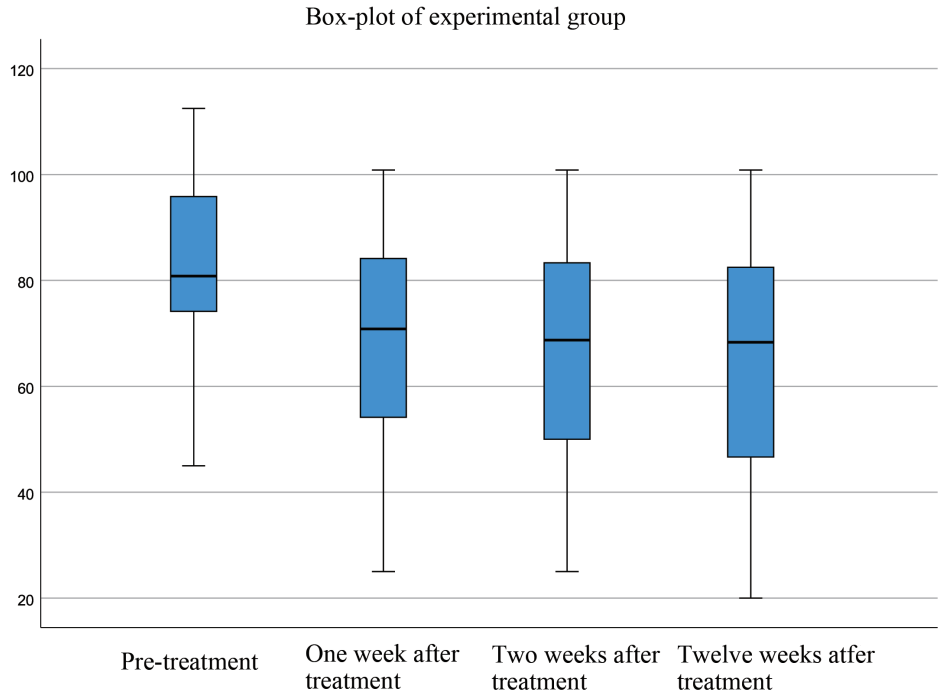

Figure 1. Box plot of the experimental group.

12 weeks after treatment. By comparison, the difference was statistically significant ($t1$ week = 3.702, $P < .01$; $t2$ weeks = 4.102, $P < .01$; $t12$ weeks = 3.826, $P < .01$). Table 5 shows the statistical data.

DISCUSSION

This study found that the total efficiency was 28.43% in the experimental group and 64.71% in the control group. Although the treatment regimen is different between the experimental and the control groups, the efficacy tends to be consistent, and there is no statistically significant difference in efficacy between the 2 groups. The treatment plan for the experimental group developed in this study is consistent with the efficacy achieved by the international guidelines of SSNHL in the diagnosis and treatment. The box-plot shows that there are no outliers in the data, and each group of data is approximately normally distributed with equal variance. The study found that the treatment effect from the onset to the treatment within 2 weeks was significantly better than that after 2 weeks. It means that the initial treatment time was significantly correlated with the average hearing

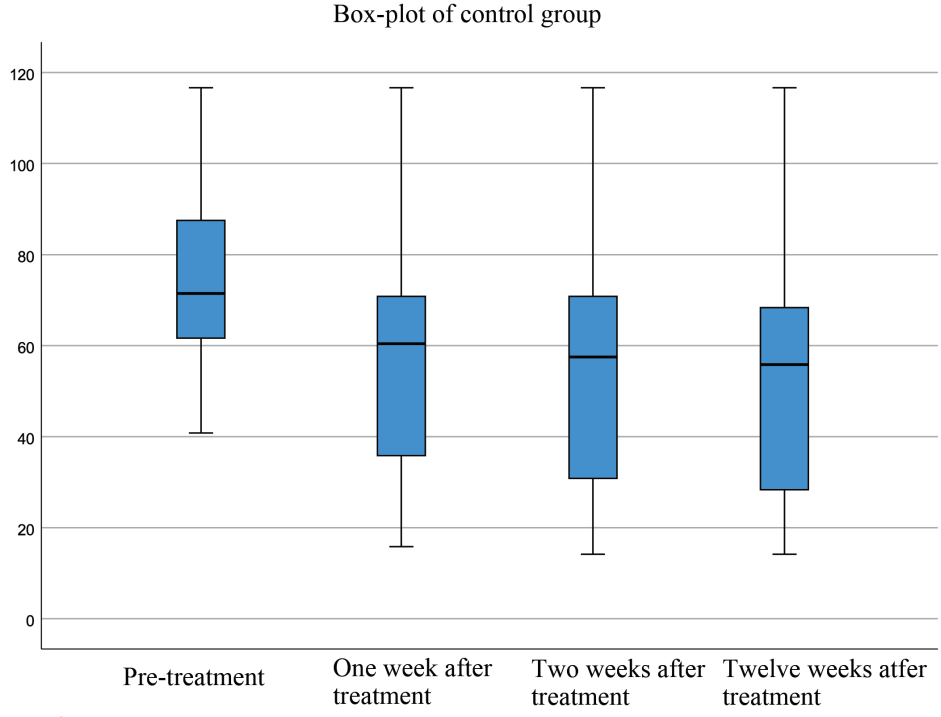

Figure 2. Box plot of the control group.

Table 3. The Results of the 2 Groups of Generalized Estimated Model

	Experimental Group	Control Group
Number (n)	102	102
Mean of age (years)	28.71 ± 5.54	27.41 ± 4.24
Valid number (%)	29 (28.43%)	66 (64.71%)
Initial treatment time (days)	6.81 ± 7.36	4.65 ± 4.07
PTA of pre-treatment (dB)	84.45 ± 14.83	80.29 ± 21.13
PTA of 1 week after treatment (dB)	76.64 ± 17.61	63.47 ± 26.85
PTA of 2 weeks after treatment (dB)	72.70 ± 17.60	58.15 ± 27.87
PTA of 12 weeks after treatment (dB)	69.92 ± 17.91	54.71 ± 29.01
χ^2	2.314	
P	.128	

threshold improvement, and there was no significant correlation between pregnancy period and treatment efficacy.

According to the guidelines of SSNHL in diagnosis and treatment from China in 2015 and the United States in 2019, glucocorticoids are usually used as the first choice for initial and salvage treatment in patients with sudden deafness within 2-6 weeks after symptoms appear. It was based on a meta-analysis and an observational study.[8,9] These steroids include methylprednisolone, prednisolone, solumedrol, and dexamethasone, which can be administered via oral, intravenous, and intratympanic injection or postauricular injection. In this study, methylprednisolone was administered by tympanic injection, while prednisone was administered orally.

The guideline on prescribing drugs in pregnancy and breastfeeding from British Society for Rheumatology and British Health Professionals in Rheumatology have showed the evidence about prednisone that it is safe to be taken orally by pregnant patients.[10] The evidence had also showed that the glucocorticoids do not contain fluoride and can be used at all stages of pregnancy. There was a meta-analysis which showed that the relationship between maternal corticosteroid used during the first trimester of pregnancy and risk of orofacial clefts was small.[11] But the prednisone's drug specification clearly states that the glucocorticoid animal experiment was teratogenic, and these studies have shown that glucocorticoids may induce fetal orofacial clefts.[12] However, in our study, after half a year of follow-up, no malformations and developmental abnormalities were found in the infants.

Extract of Ginkgo biloba leaves Injection: Many studies had shown that patients with SSNHL have been treated with Ginkgo biloba extract. The results of these studies also suggested that the extract of *Ginkgo biloba* leaves injection was safe and effective in the treatment of SSNHL.[13-15] But none of these studies had mentioned that the extract of *Ginkgo biloba* leaves injection can be offered to pregnant women. The pharmacological action of the extract *Ginkgo biloba leaves* stimulates the release of catecholamines and inhibits degradation. It stimulates the formation of arterial vasodilatation by stimulating the production of prostacyclin and endothelium and maintains the tension of arteries and veins. At the same time, it has the efficacy of reducing the viscosity of whole blood, improving the plasticity of red blood cells and white blood cells, and improving blood circulation.The safety of Ginkgo biloba extract in pregnant women with SSNHL remains controversial.

Dextran-40: The pharmacological action of dextran-40 is mainly to attach to the surface of red blood cells and platelets, depolymerize the accumulated red blood cells and platelets, and reduce blood viscosity, thereby improving microcirculation. Two retrospective studies we have retrieved mention that dextran-40 was safe and effective.

Table 4. Statistics of the Effective Cases of Patients in the Each Type of Group

	Total Deaf Type		Flat Type		All Groups	
	Valid Number	Total Number	Valid Number	Total Number	Valid Number	Total Number
Experimental group	18	54	11	48	29	102
Control group	30	54	36	48	66	102
P	0.020		0.000		0.000	
χ^2	5.4		26.053		26.97	

Chi-square test was used to compare the total response rate between experimental and control groups, $P < .05$ was statistically significant.

Table 5. Statistics of Pure Tone Average of Each Type of Group

	Flat Type				Total Deaf Type				All Groups			
	Pre-treatment	1 week	2 weeks	12 weeks	Pre-treatment	1 week	2 weeks	12 weeks	Pre-treatment	1 week	2 weeks	12 weeks
Experimental group	71.23 ± 8.67	66.14 ± 16.41	63.31 ± 17.34	61.33 ± 17.67	96.07 ± 7.56	85.98 ± 11.51	81.06 ± 13.14	77.55 ± 14.44	84.45 ± 14.83	76.64 ± 17.61	72.70 ± 17.60	69.92 ± 17.91
Control group	61.31 ± 10.62	44.38 ± 13.78	38.92 ± 14.89	36.05 ± 15.71	97.17 ± 11.62	80.45 ± 24.13	75.07 ± 25.88	71.11 ± 28.43	80.29 ± 21.13	63.47 ± 26.85	58.15 ± 27.87	54.71 ± 29.01
t/Z	4.518	5.974	6.188	6.191	-0.519	1.521	1.488	1.454	1.625	3.702	4.102	3.826
P	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000

The Mann–Whitney *U* test or Student's *t* test was used to compare the treatment efficiency of each type of deafness in the experimental and control groups, with $P < .05$ in the 3 stages. The differences were all statistically significant.

However, there was no stratified analysis of dextran-40 and glucocorticoids, and so we do not know the therapeutic efficacy of dextran-40. So, it need further researches to indicate the dextran-40 efficacy and adverse reactions.[16,17] Additionally, according to the results released by the FDA, there were 366 reports of clinical adverse events of dextran from 1969 to 2004, of which 90 cases (24.6%) were anaphylaxis/anaphylactoid events.[18]

We believe that the reason for poor efficacy of pregnant women with SSNHL is the insecurity of the medication, and the changes in hemorheology and hormone levels.

In conclusion, compared to the non pregnant group, pregnant women with SSNHL have a more severe degree of hearing loss, and face greater challenges in treatment. Additionally, our study reveals that oral and tympanic injection of steroid hormones is an effective and safe treatment method in pregnant group.

Ethics Committee Approval: This study was approved by Ethics Committee of of Suining Central Hospital (Approval No: LLSLH20220128).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.Y.; Design – S.Y., W.Z.; Supervision – W.Z.; Resources – S.Y., W.Z.; Materials – C.L., C.Z., S.Y.; Data Collection and/or Processing – C.L., C.Z., S.Y.; Analysis and/or Interpretation – C.L.; Literature Search – S.Y., C.Z.; Writing – S.Y., W.Z.; Critical Review – W.Z.

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