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Original Article

Effects of intra-articular versus peri-articular dextrose prolotherapy in knee osteoarthritis: A clinical trial study

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ABSTRACT

Objectives: This study aims to compare the effectiveness of two different approaches of novel dextrose prolotherapy (DPT) including intra-articular and peri-articular techniques in participants with knee osteoarthritis (KOA) without effusion.

Patients and methods: Between August 2018 and November 2018, a total of 51 participants with KOA without effusion were randomly assigned to two groups as the intra-articular prolotherapy group (Group A, n=27) and peri-articular prolotherapy group (Group B, n=24). Treatment was administered two times with two-week interval. The Visual Analog Scale (VAS), Western Ontario and McMaster Universities Arthritis Index (WOMAC), and Oxford Knee Scale (OKS) questionnaires were filled at baseline, four and eight weeks after the first injection.

Results: At four and eight weeks, the mean VAS, OKS, and WOMAC scores improved from baseline in both groups ($p<0.001$). The mean WOMAC and OKS scores showed no significant difference between the two methods. The mean VAS score showed superiority of the intra-articular method ($p <0.05$).

Conclusion: Both peri-articular and intra-articular DPT were effective in patients with KOA. There was no superiority in terms of functional improvement between the two groups. However, intra-articular prolotherapy was more effective in decreasing pain in such patients.

Keywords: Intra-articular injection; knee; osteoarthritis; prolotherapy.

Knee osteoarthritis (KOA) is a destructive and disabling disease that influences up to 6% of population more than 30 years old resulting in pain, joint stiffness, and decreased function.[1] It affects most adults with age 65 or more with a prevalence of 33.6% (12.4 million) in the United States by the year 2008.[2] The origins of the pain are clearly unknown. However, it is believed that intra- and peri-articular structures are the sources of the pain.[2-4] There are several treatment options for KOA, ranging from pain killers to injection and surgery.[1,2] One of the injection-based therapies for KOA is prolotherapy. It involves the injection of irritants like hypertonic dextrose for treatment of chronic musculoskeletal pain through the probable mechanism of proliferation of fibroblasts, collagen synthesis, and tissue healing.[5,6] The definite mechanism of action for DPT is unclear. However, several multimodal mechanisms were suggested such as initiating a local inflammatory cascade inducing the growth factor and collagen deposition resulting in a connective tissue repair, strengthening of the structures and reducing pain.[7,8] Wilson et al.[9] also showed a multifactorial mechanism for DPT in this way that it dehydrates cells at the site of injection inducing cell rupture by producing an osmotic gradient which initiates an acute inflammatory cascade, followed by tissue healing.

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Several human studies have revealed the positive effects of dextrose prolotherapy (DPT) for different musculoskeletal disorders such as rotator cuff related shoulder pain and hallux rigidus.[6,10] There are positive results for this method in KOA, as well.[5] Topol et al.[11] showed the chondrogenic effects of intra-articular DPT in severe KOA. Some other studies showed that prolotherapy improves the pain, stiffness, physical function and flexion range of motion of the affected knee.[12-14] Pain of prolotherapy, as an its complication, is self-limited and usually subsides by painkillers such as acetaminophen. If the pain does not respond to acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are indicated.[15] There are two general approaches to prolotherapy which are widely used, and physicians usually combine the aspects of both techniques. The first technique was called Hackett method. In this method, dextrose is the preferred irritant, with a frequency of treatment lasting months with sessions every 6 to 12 weeks. The West Coast method predominantly utilizes a combination of phenol, dextrose, and glycerin or sodium morrhuate with weekly sessions. In general, the injection of a small volume of an irritant solution on painful structures in several sessions every 2 to 12 weeks is the mainstay of this method.[7] There are multimodal approaches for prolotherapy injection in KOA and there are some concerns regarding the complications of the intra-articular injections such as septic arthritis that may cause to refuse the injection by the patients,[16] as well as there are not enough studies to compare the efficacy and safety of peri-articular and intra-articular approaches for DPT in such patients. In the present study, we, therefore, aimed to compare the effectiveness of these two methods on decreasing pain and improving functions in patients with KOA without effusion.

PATIENTS AND METHODS

Study design and study population

This single-center, double-blind, parallel-group randomized clinical study was conducted at Shiraz Medical School, Shiraz University of Medical Sciences, Department of Physical Medicine and Rehabilitation between August 2018 and November 2018. Patients with KOA were included and the effects of intra-articular versus peri-articular DPT were compared. Eligible patients had KOA without knee joint effusion and aged between 40 and 70 years of both sexes complaining of knee pain, crepitation and joint stiffness continued for at least three months before the study enrollment.

Patients with ages between 40 and 70 years with diagnosis of KOA based on clinical criteria of the American College of Rheumatology (ACR)[17] and negative ballottement test in physical examination and Grade 2 and 3 KOA based on the Kellgren-Lawrence Grading Scale[18] that their clinical symptoms and signs continued for at list three months before this study were included. Exclusion criteria were as follows: having severe genu valgum or genu varum, active infection involving the knee or skin like cellulitis, development of effusion during study, having history of intra- or peri-articular injection during the three last months, history of rheumatic or inflammatory disease involving the knee joints, prior total knee arthroplasty, poorly controlled diabetes mellitus with HbA1c more than 7.5%, body mass index (BMI) more than 40 kg/m^2, history of knee trauma or fracture during the three last months, history of acute lumbosacral radiculopathy or peripheral neuropathy in both lower limbs, history of cancer, bleeding disorders, and pregnancy.

Randomization and blinding

In this study, a total of 60 participants were allocated to two parallel groups including intra-articular prolotherapy (Group A) and peri-articular prolotherapy (Group B) using blocked randomization assignment method and random block size of six. For blinding, the patients were not aware of the allocated group. Considering two points of injection in peri-articular group in contrast to the only one point of injection in intra-articular group, the injector was recommended to insert the needle subcutaneously at the other point around the involved knee without injecting solution in the intra-articular group in order to improve patient's blinding. In addition, the researchers who followed the patients by questionnaires, as well as statisticians, were blinded to the group allocation.

Of a total of 60 participants who were assessed for eligibility and included in the study, nine did not complete the study due to poor compliance and personal etiologies (n=3 in Group A and n=6 in Group B). Finally, a total of 27 cases (12 males, 15 females; mean age: 55.7±5.2 years; range, 40 to 70 years) participated in Group A and other 24 cases (9 males, 15 females; mean age: 54.7±4.5 years; range, 40 to 70 years) participated in Group B (Figure 1).

Interventions

Participation in this study was voluntarily. The

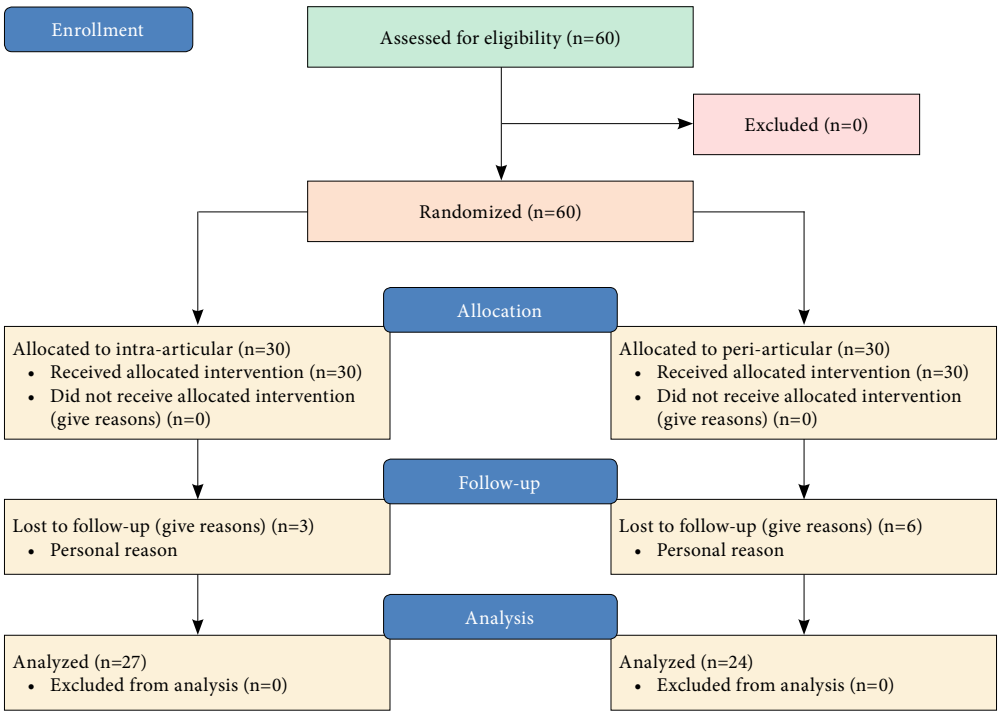

Figure 1. CONSORT flowchart.

patients were assured that they could leave the study anytime they were not willing to continue study and this would not affect their treatment. At the beginning of the study, demographic characteristics of participants were recorded including: age, sex, height and weight. Before injections, the Visual Analog Scale (VAS), Western Ontario and McMaster Universities Arthritis Index (WOMAC) and Oxford Knee Scale (OKS) questionnaires were filled by the participants. Then, injections were performed for both groups. The injection repeated two weeks later based on the allocated group technique. In Group A (intra-articular group), participants laid on bed with placing a pillow under the involved knee resulting in its flexion to 30 degrees and, then, the practitioner prepared the knee under sterile condition and marked the inferolateral side of the knee joint. Next, 5 mL dextrose 25% by a 23-gauge (G) syringe was injected at that site. Preparation of dextrose 25% included 2.5 mL lidocaine 2% plus 2.5 mL dextrose 50%. The final concentration of the solution was derived from the previous studies.[6,10] The injector also inserted the needle subcutaneously at the other point around the involved knee without injecting any solution in this group in order to improve patient's blinding. For Group B (peri-articular group), participants were placed in a supine position with the 30-degree knee flexion. The knee was examined and tender points were marked around the knee up to two points to puncture the skin. Then, 5 mL of dextrose 25% were injected under sterile condition by using a 25-G syringe around knee joint maximum in two points (lateral or medial) with almost 2.5 mL of solution injection for each point in different directions and subcutaneously using skin sliding. These points were the most painful points, except for pes anserine bursitis. Preparation of dextrose 25% included 2.5 mL lidocaine 2% plus 2.5 mL dextrose 50%. For both groups, the second injection was performed two weeks after the first one. The prespecified protocols were achieved from a study by Farpour and Fereydooni[16] Both groups were asked to hold ice pack for 5 min on the puncture sites for first two days, have relative knee rest for 72 h, and continue doing quadriceps isometric contraction exercises as before injections.[19] The participants in both groups were asked to avoid consumption of anti-inflammatory medicine or other treatments for KOA. Then, they were asked to return two and six weeks after the second injection (four and eight weeks after the first injection, respectively). On these visits, VAS, WOMAC, and OKS questionnaires were filled by the participants. In addition, we included one knee in participants with bilateral KOA which met the inclusion and exclusion criteria and, if

both of knees were the same, we chose the right-side knee for this study.

Study outcomes

Demographic characteristics of the participants were recorded and radiological grading of the KOA was noted. The VAS questionnaire with 0-10 scales was used to assess the severity of pain, in which 0 indicates without pain and 10 indicates the worst possible pain. The WOMAC was used to assess the patient's function, pain, and stiffness. The questionnaire includes three domains, pain (five items), stiffness (two items) and physical function (17 items). The validity and reliability of the Persian format of this questionnaire were confirmed before.[20] The OKS was also used to assess patient's function consisting of 12 questions with 0-5 ordinal scale. The Persian version of this questionnaire was also valid and reliable.[21] For interpreting both WOMAC and OKS, each answer had five ordinal scales: none=0, mild=1, moderate=2, severe=3, extreme=4.The patients were followed by a second colleague who was not aware of the group allocation at baseline, four and eight weeks after the first injections. The patients were also asked to report any adverse reaction and side effect.

Statistical analysis

Based on the previous study by Farpour and Fereydooni[16] and considering type one error of 5% (α=5 %), power of 80% (effect size: 0.8) and β=0.2, the sample size was calculated as minimum 25 in each group.

Statistical analysis was performed using the SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA). Continuous data were expressed in mean ± standard deviation (SD) or median (min-max), while categorical data were expressed in number and frequency. To analyze inter-group comparisons, repeated measure analysis of variance (ANOVA), and standard t-test were used. Paired t-test was used for intra-group comparison. A *p* value of <0.05 was considered statistically significant.

RESULTS

The baseline characteristics of participants, including age, sex, and the grade of radiology are presented in Table 1. There was no significant difference between two groups in terms of demographic characteristics (p=0.78 for age, p=0.67 for sex, and p=0.74 for radiological grading).

The mean VAS, OKS, and WOMAC scores of the participants at baseline, four and eight weeks after the first injection are shown in Table 2. There was no significant difference between the groups at baseline for the scores obtained from each questionnaire (p=0.364 for WOMAC, p=0.067 for OKS, and p=0.251 for VAS). The mean baseline WOMAC scores were 60.97±13.74 in the intra-articular group and 65.88±17.43 in the peri-articular group. After DPT, the scores improved through the fourth and eighth weeks (42.00±11.47, 31.60±11.30 in the intra-articular group and 43.92±13.37, 35.29±10.78 in the peri-articular group after four and eight weeks, respectively). The decrease in the mean WOMAC scores was significant within each group (p<0.001), but it was not statistically significant between two groups (p>0.05). Changes in OKS scores also occurred in both groups throughout the study. The participants underwent intra-articular prolotherapy with a mean OKS score of 34.00±3.33, 23.41±5.37, and 20.22±5.87 at baseline, four and eight weeks, respectively. In the other group which underwent peri-articular injection of 25% dextrose water (PASI-D25W), the mean OKS score was 32.25±4.05

TABLE 1
Baseline characteristics of participants in both intra-articular (group A) and peri-articular (group B)

	Group A			Group B			
Variables	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			55.7±5.2			54.7±4.5	0.67
Sex							0.78
Male	12	44.4		9	37.5		
Female	15	55.6		15	62.5		
Radiologic grade knee osteoarthritis							0.74
Grade 2	22	81.5		18	75		
Grade 3	5	18.5		6	25		

SD: Standard deviation.

TABLE 2
Comparison of WOMAC, OKS and VAS scores between Intra-articular (group A) and Peri-articular (group B) prolotherapy groups in knee osteoarthritis

	Group A	Group B	Within groups	Between groups
Scale	Mean±SD	Mean±SD	*p*	*p*
WOMAC				
Baseline	60.97±13.74	65.88±17.43	-	0.364
4th week	42.00±11.47	43.92±13.37	<0.001	0.449
8th week	31.60±11.30	35.29±10.78	<0.001	0.179
OKS				
Baseline	34.00±3.33	32.25±4.05	-	0.067
4th week	23.41±5.37	28.59±5.16	<0.001	0.947
8th week	20.22±5.87	21.00±5.55	<0.001	0.668
VAS				
Baseline	7.52±1.01	7.92±1.06	-	0.251
4th week	5.00±1.52	5.79±1.010	<0.01	0.032
8th week	3.89±1.67	4.71±1.16	<0.001	0.040

WOMAC: Western Ontario and McMaster Universities arthritis index; OKS: Oxford Knee scale; VAS: Visual Analog Scale, SD: Standard deviation.

at baseline and 23.59±5.16 and 21.00±5.55 at four and eight weeks, respectively. The changes for OKS score were significant within each group (p<0.001), but they were not significant between both groups (p>0.05). The VAS scores decreased in both groups throughout the study. Accordingly, the mean VAS scores in the intra-articular group were 7.52±1.01, 5.00±1.52, and 3.89±1.67 at baseline, four and eight weeks, respectively. The mean VAS scores in the peri-articular group were 7.92±1.06, 5.79±1.10, and 4.71±1.16 at baseline, four weeks and eight weeks, respectively. There was a significant improvement in the VAS scores within each group (p<0.001), as well as between two groups with more improvement in the intra-articular group (p=0.032 at four weeks and p=0.040 at eight weeks after injections). The trend of changes in WOMAC, OKS, and VAS scores is illustrated in Figures 2, 3, and 4, respectively.

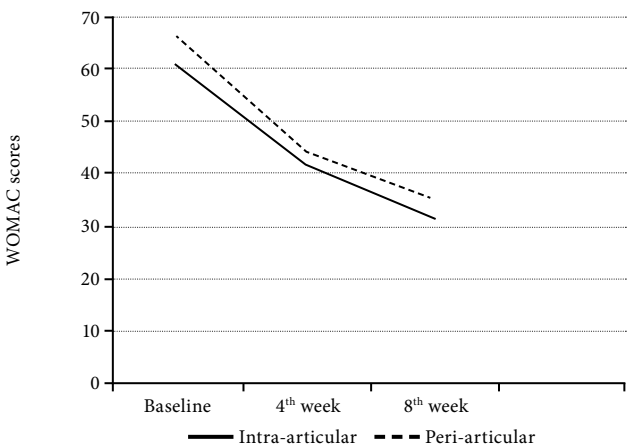

Figure 2. Trend of change in Western Ontario and McMaster Universities arthritis index (WOMAC) scores in both intra-articular and peri-articular prolotherapy groups in patients with knee osteoarthritis.

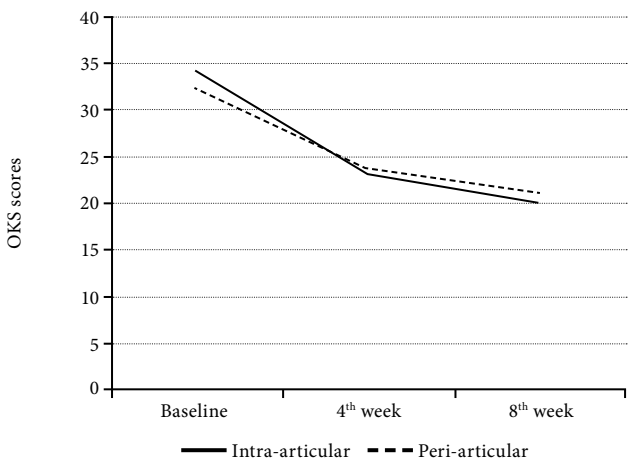

Figure 3. Trend of change in Oxford Knee scale (OKS) scores in both intra-articular and peri- articular prolotherapy groups in patients with knee osteoarthritis.

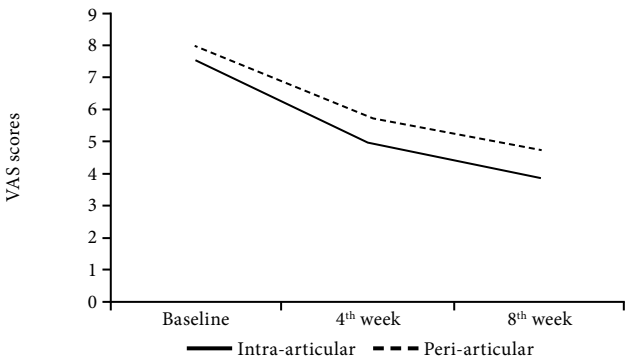

Figure 4. Trend of change in Visual Analog Scale (VAS) scores in both intra-articular and peri- articular prolotherapy groups in patients with knee osteoarthritis.

DISCUSSION

Knee osteoarthritis is one of the most common debilitating diseases, particularly in the elderly population. Among a variety of treatment approaches, DPT is a novel approach in the management of many musculoskeletal disorders with the possible known mechanism of regeneration and tissue healing.[16,22] There are some evidences showing the improvement of radiological grades and ultra-sonographic findings after prolotherapy in patients with tendon, ligaments or meniscal damages.[23] In addition, a study by Johnson et al.[24] revealed that DPT could directly induce the chondrocyte proliferation in patients with KOA when intra-articular approach was used. In the present study, we concluded that DPT with both peri-articular and intra-articular approaches seemed to be effective for decreasing pain and improving the function in participants with KOA at least for eight weeks after the injection with no superiority to each other in terms of improving function using WOMAC and OKS questionnaires. However, more pain reduction was achieved from intra-articular prolotherapy approach by consideration of VAS scale. Farpour and Fereydooni[16] showed that there was no significant difference between two groups in terms of pain reduction and functional improvement in such patients using the same questionnaires. The results of the aforementioned study are consistent with our study results, particularly in terms of functional improvement using WOMAC and OKS questionnaires which could be due to the same sample size and injection methods. Having no significant difference between two groups in terms of functional status in such patients resulted from the fact that both the aforementioned study and our study confirmed that peri-articular DPT could be an alternative technique for intra-articular method with the same efficacy in terms of functional improvement. However, we showed more pain reduction using VAS scale in the intra-articular group in contrast to the aforementioned study that might be due to some differences between solution components, the volume of the injected solution, the number of injected points or the study group selection in this way that we excluded cases of KOA with joint effusion. In another study, Sit et al.[14] reported that intra-articular DPT could decrease pain, improve function and quality of life in KOA compared to blinded normal saline injections. These results are consistent with our findings. However, the aforementioned authors compared the effects of intra-articular DPT with placebo injection. Moreover, larger sample size, longer follow-ups, as well as the supra patellar approach for intra-articular injection were some other differences of the aforementioned study with our study. In addition, Rezasoltani et al.[25] reported that peri-articular prolotherapy created more decreasing pain in contrast to intra-articular group using VAS scale in patients with KOA. The difference between this study and our study can be explained by the fact that their injection points corresponded to nerve exits and, therefore, they were lining up more with the concept of peri-neural injection treatment instead of peri-articular subcutaneous tender points performed in our study.

The difference between peri-articular subcutaneous prolotherapy and mesotherapy for the pain management is that mesotherapy is defined as an intradermal or subcutaneous analgesic injections mostly NSAIDs to increase the local concentration of them at the target site, as well as reducing their systemic side effects.[26] However, prolotherapy is a type of regenerative injection therapy using an irritant solution such as dextrose to induce inflammatory cascade and the release of cytokines with multifactorial mechanisms of actions resulting in proliferation of fibroblasts, collagen synthesis, and healing while injecting around or within the injured tissues.[5,6,16] In addition, more effectiveness of intra-articular DPT revealed in our study may be due to the chondrogenic effects of this approach in patients with KOA according to some previous researches.[11,24]

Nonetheless, there are some limitations to this study. First, the sample size is relatively small. Although we selected 60 patients with KOA without effusion (n=30 in each group), nine participants left and did

not continue injection mainly due to poor follow-ups, as they had to come from far away cities during the study. In addition, we included patients aged between 40 and 70 years which was a wide range of age. It might be better to narrow the age range of participants. Also, despite no significant difference between two groups in terms of grade severity of KOA as well as all included patients had Grade 2 or 3 of severity, it would be better to analyze the results for pain and function according to the radiological grade severity. We planned two injection sessions, but a similar study with more sessions showed different results; thus, more injection sessions would be preferable. Furthermore, the follow-up period in our study was too short; therefore, some other studies with longer follow ups in the future is recommended. Moreover, it would be better to analyze each part of the WOMAC questionnaire including patient's function, pain and stiffness separately to achieve more definite results about the efficacy of our interventions on each part. Finally, we followed patients by subjective assessments using mentioned questionnaires without evaluating the radiological changes after the injections. The lack of a placebo or controlled group is another limitation to our study as well. Therefore, further studies with more participants, injection sessions, longer follow up periods with having controlled group and objective assessment methods are recommended.

In conclusion, both peri-articular and intra-articular DPT showed the same efficacy at least for a short period of time in patients with KOA. There was no superiority in terms of functional improvement between two groups. However, intra-articular prolotherapy was more effective in decreasing pain in such patients. Based on these findings, we suggest intra-articular DPT, as an alternative technique for pain reduction and functional improvement in patients with KOA.

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Ethics Committee Approval: The study protocol was approved by the Shiraz University of Medical Sciences (SUMS) Ethics Committee (date: 22.05.2018, no: IR.SUMS.MED.REC.1397.088). The Iranian Registry of Clinical Trial (IRCT) approved this retrospectively registered study at 2018-07-18 with reference number "IRCT20171111037396N1". The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: All authors had equal contributions in all aspects of this research.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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