ORIGINAL ARTICLE

Spiritual Effect of Intervention on Oxytocin and its Receptor (OXTR) in Women Patients with Breast Cancer

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ABSTRACT

Background: The immune system plays an effective role in improving the quality of life of many patients with malignant diseases such as cancer. Oxytocin has recently been recognized to play an important role in promoting the immunity. Oxytocin is effective in homeostasis through various ways, including spiritual intervention.

Aim: To evaluate the effectiveness of spiritual intervention on oxytocin level and its receptor (OXTR) in improving the function of immune system in women with breast cancer.

Methods: This study was a quasi-experimental study a performed from October to December 2018. Fifteen patients were selected by targeted sampling, and then randomly assigned to the following groups. The first group had 12 sessions of spiritual intervention, the second group had 12 sessions of non-psychological training that focused on physical care related to their illness, and third group did not receive any intervention as control group.

Results: The results showed that oxytocin and its receptor were 100 times higher in the patients with breast cancer compared to healthy controls. The changes in the three groups at the follow-up stage were not significant compared to the pre-test and post-test, indicating no effect of spiritual intervention and group training compared to the control group. In addition, OXTR levels did not show any difference between the groups.

Conclusion: Despite numerous studies on the effect of psychological interventions such as spiritual intervention and oxytocin on the immune system, it is suggested to evaluate the effectiveness of spiritual intervention in patients with breast cancer in pathways other than oxytocin and OXTR.

Keywords: Spiritual Intervention, Oxytocin, Oxytocin Receptor, Immune System, Breast Cancer

INTRODUCTION

Breast cancer is a multifactorial fatal disease and one of the most common types of cancer among women. Despite many advances in early diagnosis and appropriate treatment, the underlying causes of cancer-related death remain among women unclear¹. In 2008, breast cancer comprised 23% (13.8 million) of all new cases and 14% (458,400 cases) of worldwide cancer deaths, accounting for about half the incidence and 60% of related deaths. The disease usually occurs in developing countries.² The prevalence of the disease among Iranian women is also increasing and with increasing the life expectancy and an aging population in Iran, it is expected to increase in the coming years.³ Treatment of cancer has adverse effects on the immune system; therefore, exposure to psychological stressors initiates physiological changes in the patient's body.⁴ Therefore, the most important factor against cancer is the ability of the immune system and the strengthening the immune system's ability to identify and eradicate cancer cells.⁵ Repeated exposure to a variety of stresses has adverse psychological and physiological effects that decrease the immune system's function and cause the patient to effectively deal with the disease. In cancer

patients with high stressors, the number of killer cells (Natural killer cells or CD8⁺ T cells) decreases and their effect reduces; thus the function of the immune system is impaired.⁶ Immune activities are regulated by various components such as genetic variations, cytokines, hormones, excitement, nutrition, metabolism, sleep, age, neural activity, and pathogens of which the interaction of neuroendocrine and the immune system is crucial.7 In this regard, the oxytocin-secreting system (OSS) of the hypothalamus is known to be a key factor in the regulation of the immune system. Herein, the regulatory role of the immune system in the neuroendocrine network belongs to the hypothalamic-neurohypophysical system (HNS).8 Blocking the signaling of oxytocin receptors can inhibit T cell differentiation and increase the expression of inflammatory cytokines;9In addition, oxytocin has been shown to contribute to increased hematopoietic cell production and survival of CD8 cells.¹⁰ Therefore, oxytocin as a key regulator of the immune system can directly regulate the immune system by activating OXTR and the sympathetic system.¹¹ OXTRs are expressed on immune organs, tissues, cells, and bone marrow stem cells, 12,13 General cancer health can be achieved by modifying the perception and behavior patterns and treatment of patients'

psychological stress following cancer.¹⁴ During the psychological disruptions caused by cancer, individuals are unable to meet their basic needs for love, hope, goals, and communication with others, which in this situation can benefit from religion and spiritual resources for psychosocial-spiritual adjustment.¹⁵ Spirituality as an aspect of the individual includes a semantic component, a faith-based component, and an element of existential opposition.¹⁶ Improvement in spiritual health can reduce stress and depression, improve quality of life, improve psychological status, and reduce emotional stress in patients and can be used as an effective adaptive approach.¹⁷ Spirituality gives patients the opportunity to gain a sense of control over the psychological trauma of cancer and to evaluate negative events in a different way and to create a stronger sense of control.¹⁸ Numerous studies expressing the effectiveness of spiritual intervention in improving physiological function in patients with breast cancer have shown that the feeling of satisfaction with spiritual outcomes has a potent effect by immune messenger neuropeptides, which the results of these effects include the prevention of disease, enhancing disease tolerance, and the faster recovery of the disease.¹⁹ Women who rated spiritual expression more importantly had more circulating white blood cells and greater total lymphocytes.²⁰ Although the tumor response rate was significantly higher in patients with high levels of faith than in other patients, the mean number of lymphocytes after chemotherapy was significantly higher in patients with spiritual faith, and they survived 3 years more.²¹ However, given the importance of the effectiveness of spiritual interventions to improve immune function in the group of women with breast cancer, and few studies in this area, this study aimed to evaluate the effectiveness of spiritual intervention on oxytocin and OXTR level in improving the function of the immune system in women with breast cancer.

MATERIAL AND METHOD

This study was a quasi-experimental study a performed from October to December 2018. The study population consisted of all women with breast cancer referred to Shohada-e-Tajrish Hospital, Shahid Beheshti University of Medical Sciences Cancer Research Center, Azar Clinic, and Khatam Al Anbia Hospital. Patients completed and signed written informed consent form at clinical stages 1 and 2 of breast cancer, ranging from 25 to 65 years with minimal literacy. Study and patients were assigned on the basis of national/international breast cancer protocols and approved according to local law and regulations, by the Institutional Review Boards of each participating referral hospital.

The first treatment for patients was surgery first, then chemotherapy and radiation therapy if necessary (were not neo adjuvant). By the end of their radiotherapy and chemotherapy, it had been at least six months and a maximum of one year. Exclusion criteria were LABC (advanced and metastatic cancer), Neo adjuvant (those who had undergone chemotherapy and then surgery), significant clinical disorder, psychiatric drug use for the past three months, participation in other therapies or their current membership, their reluctance to donate blood, and to discontinue any cooperation. The sample size was determined based on Cohen's table ¹⁸ with effect size of 0.5 and the power of 0.8 for each group, which was at least 11 considering subjects' and the dropout was considered.¹⁵The sample size was first calculated as targeted and then randomly assigned to the experiment group and two control groupsin which the participants were measured three times. The first measurement of oxytocin and OXTR in blood serum is called pre-test, the second measurement is post-test and the third measurement is followed-up. The level of serum cytokines was measured in these three phases.

After random sampling and assignment to groups, the experiment group was the patients with breast cancer who underwent 12 sessions of spiritual intervention. The first control group consisted of the patients with breast cancer who completed 12 sessions of training (except psychological content), the second control group included the patients with breast cancer who did not receive any intervention or training. Educational and spiritual intervention sessions were held once a week for 90 minutes. Serum oxytocin and OXTR levels were measured in all three groups before, after and three months after the last session. To evaluate serum oxytocin and OXTR, 5 ml of venous blood was taken from the patients and their serum was separated and stored at -20°C until the day of the test. Serum levels of cytokines were measured and quantified by Enzyme-linked Immunosorbent Assay (ELISA) (IBL company, Germany) with minimum detection limit of pa/ml.

Spiritual intervention: In spiritual intervention, the therapist invites the patient to explore spiritual issues and issues in order to improve and restore health along with other therapies such as medication, and emphasizes spiritual issues by means of mental approaches. Spiritual intervention means considering cultural-religious beliefs and the intrinsic relationship with a divine power, beyond the boundaries of religious beliefs in different religions that guide patients toward God's divine power.²² Training stress management strategies with spiritual resources and attention to the meaning and quality of life are useful in helping patients' personal independence and awareness in improving their treatment process.²³Therefore, we can use patients' spiritual beliefs and traditional ethnic values as a spiritual and supportive resource to improve the spiritual health of patients with cancer.²⁴Spiritual intervention in the present study was based on a twelve-session spiritual intervention package standardized by Vaziri et al. at ShahidBeheshti University Cancer Research Center.²⁵The contents of the package are listed in Table 1.

Statistics analysis: Data were analyzed by SPSS software version 21. The normality was assessed by Kolmogorov-Smirnov test. Data were analyzed by ANOVA test. In the present study, p <0.05 was considered statistically significant.

RESULTS

The first notable finding of this study was that oxytocin serum levels were approximately 100 times higher in patients with breast cancer than in healthy controls. Thus, the rate of oxytocin secretion in the experiment and training groups was significantly higher than healthy individuals without. On the other hand, the results obtained from the comparison of the data shown in Figure 1 show that the level of oxytocin serum level in the pre-test and post-test group did not differ but in the follow-up phase was higher than the pre-test (p < .05) post-test (p < 0.01). It was shown that the oxytocin level was not different in the pre-test and post-test phase of the training group, but this value was higher in the follow-up phase than the pre-test (p < 0.05)

and post-test (p <0.05). In addition, oxytocin level was not different in the group without spiritual intervention and training in pre-test and post-test, but its value was significant in follow-up (p <0.05). Also, the level of oxytocin receptor (OXTR) had no effect on oxytocin function due to the lack of related changes to decrease or increase it in later stages in all groups (Fig 2). Therefore, it seems that spiritual intervention of other non-oxytocin and its receptor pathways (such as dopamine and serotonin) can affect the healing of cancer patients.

| Target | Acquaintance of members with each other, knowledge of the reasons for the formation of the challenge group (awareness of the implicit and personal meaning of spirituality and its definition in terms of each member, examination of the ballef in superior and eacred power in |
|------------------|--|
| | the members, and recall of perceptions and beliefs of therapists about spirituality) |
| Second session | Introspection |
| Target | Introspection |
| | 1.Overview of the first session; 2. Individual / medical examination of the group; 3. Meeting preparation; 4. Group status; 5. Introducing |
| | the subject of the second session; 8. Presenting homework and reminding the day and time of the next meeting |
| Third session | The sources of fear and anxiety and our resources in front of them |
| Target | Finding sources of fear and anxiety and resolving it |
| | 1.Meeting preparation; 2. Group status review; 3. Third session review; 4. Reflection on assignments; 5. Introducing a third session |
| | (sources of fear and anxiety and coping with them); 6. Reflection on assignments; Practice recognizing fear, anxiety, and relaxation. 8. |
| Fourth Soccion | Providing nomework and reminding the day and time of the next meeting. |
| Target | Infinity and inferitable |
| Taiget | Understanding our endressness and innernance |
| | and reminding the day and time of the next meeting |
| Fifth meeting | Inheritance on the seal circuit and Inheritance on the hate circuit |
| Target | Understanding the results of malice and affection |
| U U | 1. Meeting preparation; 2. Prayer at the beginning; 3. Group status review; 4. Review of the fourth session; 5. Reflection on |
| | assignments6;. Introducing the fourth session (inheritance on the seal circuit and inheritance on the Keane circuit); 7. Sealing and |
| | abstinence from the Kane; 8. Summing up the session; Meeting |
| Sixth Session | Understanding meditation and calculation |
| Target | Understanding meditation and calculation |
| | 1. Meeting preparation; 2. Prayer at the beginning; 3. Group status review; 4. Review of the fifth session; 5. Meditation; 6. Introducing the single service of the fifth session; 5. Meditation; 6. Introducing the single service of the fifth session; 5. Meditation; 6. Introducing the single service of the fifth session; 5. Meditation; 6. Introducing the single service of the fifth session; 5. Meditation; 6. Introducing the single service of the fifth session; 5. Meditation; 6. Introducing the single service of the single service of the servi |
| | sixti session (mediation and calculation), weeting session 9. Fresenting homework, Kenning the Day and Hour of the Next Meeting and Provide for the Ead of the Mexima |
| Seventh session | And traying for the Little of the Meeting. |
| Target | Perform mediation and mediation |
| J | 1. Preparing a meeting; Initial prayer; 2. Studying group status; 3. Reviewing the sixth session; 4. Reflecting on assignments; 5. |
| | Introducing the seventh session (meditation and calculation); 6. Meditation and calculation practice; Session 8; Homework Presentation; |
| | Form Distribution; Reminder of Next Session Date and End of Prayer Meeting |
| Eighth session | Understanding forgiveness and resolving anger |
| larget | increasing forgiveness and resolving anger toward oneself and others and the world, acceptance, patience, perseverance, responsible |
| | action, and personal and social benefit. 1 Session Preparation: Praver at the beginning: 2 Studying Group Status: Reviewing Seventh Session: 3. Reflecting on Tasks: 4 |
| | Introducing Seventh Session (Forgiveness and Resolution of Anger): Meeting Summary: 7. Homework Presentation; Form Distribution; |
| | Day and Hour Reminder of the Next Meeting and Prayer End of the Meeting. |
| Ninth session | Forgiveness and resentment of anger |
| Target | Increasing forgiveness and resolving anger toward oneself and others and the world, acceptance, patience, perseverance, responsible |
| | action, and personal and social benefit; 1. Meeting preparation; 2. Group status review; 3. Eighth session review; 4. Assignment; 5. |
| | introducing the ninith session (anger forgiveness and resolving); b. Anger forgiveness and resolving practice; Homework assignment; |
| Tenth meeting | Terminder to use day and time of the field session and player for the end of the session |
| Target | Increased self-control in maintaining awareness, hope and expectation; acceptance, patience, persistence, tolerance; responsible action; |
| J | and personal and social benefit |
| | 1. Session preparation; Prayer at the beginning; 2. Group status review; 3. Ninth session review; 4. Meditation; 5. Introducing the ninth |
| | session: Computation and Meditation and Stability. 6. Computation and Meditation Practice (Self-care)7 5. Meeting Summary; 8. |
| | Homework Presentation; Remembrance Day and Hours of the Next Meeting and Prayer End of the Meeting |
| Eleventh session | Computation and Meditation and Stability |
| larget | Self-care in maintaining awareness, hope and expectation; acceptance, patience, resilience, tolerance; responsible action; and personal |
| | and social benefit. 1. Mosting Propagation: Proves at the beginning: Studying Crown Status: Perviousing Teath Section: Pollecting on Teaks: Introducing |
| | Eleventh Session Calculation and Mediating and Stability (Self-Estimation): Homework Presentation: Remembrance Day and Hours of |
| | Next Meeting and End of Prayer |
| Twelfth session | Together, the Sustainability Stabilization Sessions and the Announcement of Course Completion |
| Target | Self-care in maintaining awareness, hope and expectation; acceptance, patience, persistence, tolerance; responsible action; and |
| | personal and social benefit. |

 Table 1: Protocol of spiritual intervention, the twelve-session spiritual intervention package

 First session
 Understanding and grounding the re-experience of spirituality



Fig 1: The level of oxytocin serum level in the pre-test, post-test, and follow-up spiritual phases in comparison to healthy controls. The level of oxytocin serum level in the pre-test and post-test group did not differ but in the follow-up phase was higher than the pre-test (p < .05) post-test (p < 0.01).

Fig. 2: The level of oxytocin receptor (OXTR) level in the pre-test, post-test, and follow-up spiritual phases in comparison to healthy controls. The level of oxytocin receptor (OXTR) had no effect on oxytocin function due to the lack of related changes to decrease or increase it in later stages in all groups.



DISCUSSION

The purpose of this study was to investigate the effectiveness of spiritual intervention on oxytocin hormone secretion and its receptor (OXTR) in patients with breast cancer. Our hypothesis for the start of this study was that oxytocin and OXTR play a significant role in inhibiting cell growth and proliferation. Various studies have also shown

that oxytocin as a drug with anti-inflammatory and antioxidant properties²⁶ is able to improve oxidative damage.²⁷However, the significant efficacy of oxytocin is meaningless without the presence of OXTR.²⁸Therefore, in a previous study, the preventive role of oxytocin and its receptor in the development of breast cancer was investigated. It was much higher and about 7.8 times higher.¹³The result of the present study, on the one hand,

and the presentation of numerous scientific evidences on the prophylactic role of oxytocin in preventing inflammation and growth on the other hand, led us to investigate its efficacy based on spiritual intervention in patients with breast cancer; but this time, due to ethical issues, oxytocin and OXTR in the tissue were unavailable and tested in the blood serum. Spiritual intervention has previously been chosen as a progressive therapy model that is more closely related to individuals' mental concepts. Oxytocin as an effective hormone in various psychological and physical dimensions was also measured using different models of psychological interventions. Therefore, we aimed to investigate the effectiveness of spiritual intervention on oxytocin and OXTR in a new study in breast cancer patients. Previous studies have shown that increased levels of oxytocin can act as an active ingredient against the infectious process by reducing pro inflammatory response and oxidative stress²⁹ and thus can reduce immune complications and have protective effects by restoring homeostasis.³⁰In addition, it can respond to immune and infectious threats by managing adaptive responses and be active in potential risk aversion.³¹The oxytocin secretion system, along with the hypothalamuspituitary-adrenal (HPA) axis, plays an important role in regulating the immune system, normal development of the immune system and physiological responses to adverse effects and can coordinate the activities of other organs with immune responses.¹¹ Oxytocin plays an important role in the monitoring and evaluation of disease by balancing the pathway of cancer and can be a potential diagnostic and therapeutic target in various malignancies.³² Thus, by rapidly detecting and killing malignant cells, it can inhibit the growth of some tumors, thereby playing prominent inhibitory effects on breast cancer. Breast cancer by inhibiting amino peptidase with regulated insulin (an oxytocinase) releases the pituitary oxytocin and reduces the hypothalamic oxytocin catabolism.33After cancer development, the activity of oxytocinase is significantly increased in human breast cancer tissue³⁴, resulting in a decrease in oxytocin levels in breast tissue. Since oxytocin can inhibit the growth of breast cancer cells,³⁵ its reduction in breast tissue can partly provide breast tumorigenesis, while increasing its release as a compensatory function can prevent the proliferation of tumor cells in breast cancer. However, unlike the remarkable immune function of oxytocin in relation to the immune system, oxytocin can also facilitate tumorigenesis in some tissues and has an opposite effect on the inhibition of cell growth.³⁶ The regulatory and essential role of oxytocin in the secretion of other malignancy-inhibiting hormones in the body has also been demonstrated.³⁷Numerous effects of oxytocin on various body systems and organs and physiological processes related to the immune response and homeostasis functions have been demonstrated.³⁸ Since oxytocin possesses endogenous anti-inflammatory capacity by balancing inflammatory and non-inflammatory factors and by using Treg cells, it can be used to determine the disease incidence and function models with the aim of immune responses.³⁹Meanwhile, providing effective psychological and social interventions activate the antibiotic effects of oxytocin by utilizing its anti-inflammatory capacity.40Inadequate release of oxytocin is associated

with many social and emotional disorders such as autism spectrum disorders,⁴¹ anxiety and depression, which are likely to be determined by the HPA axis and many other factors⁴²such that neuron activity inhibits oxytocin and impairs basic immune function.43 In HIV-infected women, at low oxytocin levels, there is an inverse relationship between the experiences of stress and CD4⁺ T cell counts, whereas there is a significant relationship between stress levels and CD4⁺ T cell counts at high levels of oxytocin.⁴⁴ Therefore, oxytocin with anti-anxiety effects can improve the health status of this group by affecting some safety parameters. These findings suggest that oxytocin modulates immune functions by revising and correcting abnormal behaviors; for example, it avoids hyperactivity, thymus anxiety, and adrenal hypertrophy during stress⁴⁵ consequently, it can emerge as one of the key structures of the brain that controls immune responses. In this regard, oxytocin has great therapeutic potential for many infectious and non-infectious inflammatory diseases and is relatively safe despite remarkable biological functions.⁴⁶ Not withstanding all that has been described for the efficacy of oxytocin, it is worth noting that the different effects of oxytocin (proliferative, apoptotic, and neutral effects) on breast cancer tumor cells depend on the physiological conditions and duration of treatment⁴⁷.

Although some functions of oxytocin were described, oxytocin would not be effective per se. Whether oxytocin stimulates or inhibits cell growth depends on the intrinsic and complex properties of OXTR signaling cascades, OXTR signaling pathways, as well as the cellular and molecular composition of individual organs.48 Oxytocin receptor (OXTR), which classically understood in terms of reproductive tissues and brain function, has also been identified in endothelial cells, smooth muscle cells, and monocytes.⁴⁹ Indeed, OXTRs are expressed in the thymus and blocking OXTRs differentiates T cells in the thymus.¹⁰ Increasing doses of oxytocin in continuous contact with its receptor, OXTR, can lead to desensitization, thereby protecting cells that are highly prone to agonist stimulation over the long term.⁵⁰ In this regard, the presence of OXTR in breast and tissue cancer cells via Real-time polymerase chain reaction (RT-PCR) and immunohistochemistry (IHC) tests has been reported.⁴⁸ In addition to the brain, immune organs can also modulate the activity of adjacent T cells by production regulating oxytocin and managing immunological functions through OXTR and regulate both negative and positive T cell selections.⁵¹ As therapeutic aspects of oxytocin expression have been demonstrated, the widespread presence of OXTR is also significant for the immune system and for the relief of numerous diseases in this domain. An animal study has shown that induction of the OXTR antagonist elicits depressive-like behavioral responses.⁴³ OXTR expression in cancer cells in different types of cancer is one of the therapeutic targets for OXTR antagonists in the treatment. One study showed that there was a relationship between oxytocin and its receptor and liver carcinoma cells, which affected patients' survival.⁵²The impact of the presence of OXTR on breast tissue has also been suggested by numerous studies.13 The biological effect of oxytocin on neoplastic pathology has been determined. In this regard, oxytocin acts as a growth factor by activating specific receptors such as OXTR. The anti

proliferative effect of oxytocin on neoplastic or epithelial cells (mammals and endometrium) has been shown, indicating remarkable OXTR function.²⁸A study by Cassoni et al. showed that the oxytocin/OXTR system could play a significant role in controlling prostate neoplastic pathology.⁵³ In addition, the psychological effects of this receptor cannot be overlooked. The relationship between the oxytocin receptor (OXTR) and psychological resources has been reported such that those who inherit "A" allele have lower levels of optimism, mastery, and self-esteem in comparison those who are G/G homozygote. OXTR has also been associated with depressive symptoms, suggesting that the effects of OXTR on depressive symptoms may be largely due to the effect of OXTR on psychiatric mediators.54The effectiveness of different psychological interventions over time has also been shown to affect physiological changes, especially hormonal changes. A study of rational psychological therapy for oxytocin in the treatment of post-traumatic stress disorder showed that oxytocin is a combination of the medicinal effects that lead to a "sense of security", it is a prerequisite for successful treatment of Post-Traumatic Stress Disorder (PTSD). Therefore, oxytocin may be a potential candidate for treatment of patients to PTSD via potential decrease in fear response (reducing amygdale activation, inhibiting fear response, and enhancing extinction learning) and enhancing social interaction (activating brain regions associated with social reward for participation in therapeutic alliance)⁵⁵. The effectiveness of yoga has also been shown on oxytocin levels. Accordingly, schizophrenic patients treated with yoga were able to obtain an improvement in endogenous plasma oxytocin levels.⁵⁶ In addition, a personalized-based study of patients with depression showed that, contrary to previous reports about the anti-anxiety properties of oxytocin, this hormone can increase anxiety during treatment sessions and decrease nonverbal behaviors that disrupt social communication. When previous findings were repeated, it was shown that oxytocin improved social cognition in the depressed group of patients. These results inform researchers that in some populations and clinical contexts, OT has heterogeneous mental complications that may include acute anxiety.57,58 This study was initiated with the considerable care and effort of a team of specialists, including psychologists and geneticists. Selection and placement of patients with breast cancer into three groups, with all the difficulties associated with collecting partition and grouping them over a six-month period, are reliable points. Given the specific changes of oxytocin in breast cancer patients, no study has evaluated the spiritual intervention to measure oxytocin and this supports the innovation of the study. But the limitations of the study may be the difficulty in sampling and the effort to keep the specimens in study for the three stages of blood sampling, the lack of simultaneous study in patients' tissues as the most important limitation.

CONCLUSION

Considering the widespread expression of OXTR and the wide-ranging effects of oxytocin on the immune system, in alleviating significant diseases and injuries and specific function of oxytocin due to its secretion rate in different

therapeutic models on the one hand, and the effectiveness of psychological interventions on physiological dimensions on the other hand, it is suggested that future studies should be conducted with more precise variables that can provide a more conclusive result. May be one of the best of these studies is to evaluate the effectiveness of psychological interventions on oxytocin levels and to achieve an acceptable dose to prevent cancer growth in the cell line.

Ethical conduct of research: The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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Conflicts of interest:: No potential conflicts of interest were disclosed.

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