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OXYTOCIN IMPLICATION FOR SCHIZOPHRENIA FUTURE TREATMENT

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ABSTRACT

Introduction: Schizophrenia is a mental disorder, manifested as positive symptoms, negative symptoms, and cognitive dysfunction. Antipsychotic medication is given to treat schizophrenia; however, recently, antipsychotic medication is less effective in improving negative symptoms and cognitive deficits. Several neurotransmitters and neuropeptides are believed to be involved in the mechanism of schizophrenia, one of which is oxytocin.
Methods: The author uses the literature review method with international journals limited to the period from 2014 to 2024 that discuss oxytocin as a treatment in schizophrenia patients.
Results: Several results of studies showed that schizophrenia therapy using oxytocin improved negative symptoms and cognitive function in schizophrenia patients. These studies are based on previous research, which showed lower concentrations of oxytocin in schizophrenia patients.
Discuss: Oxytocin acts as a human behavior regulator, and the oxytocinergic system is involved in the emergence of schizophrenia symptoms. Oxytocin administration through intranasal is chosen to deliver oxytocin because it reaches the central nervous system more easily. Oxytocin administration can improve oxytocin concentration in cerebrospinal fluid. Increasing oxytocin levels is significant in improving negative symptoms and cognitive function in schizophrenia patients.
Conclusion: Oxytocin administration intranasally can increase oxytocin concentration to improve negative symptoms and cognitive function in schizophrenia patients.

Keywords: schizophrenia, oxytocin, antipsychotic.

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INTRODUCTION

The word schizophrenia originates from 2 words: schizo, meaning cracked or broken, and phrenia, meaning mind or soul. Therefore, people who suffer from schizophrenia are someone who have a broken mind or broken soul (splitting of personality).[1] Schizophrenia is a clinical syndrome marked by several severe psychopathologies, including cognitive aspects, emotion, perception, behaviour, and thought disorder as the main symptoms.[2]

The prevalence of schizophrenia in the United States is 1%. The incidence rate in men is like that in women. The onset of the disease in men is earlier (15-25 years old) than in women (25-35 years old). 90% schizophrenia patients who are undergoing therapy are in the age range of 15-55 years old.[2] Based on the results of Basic Health Research in 2007, 2013, and 2018, showed shows that mental disorders in Indonesia, with a diagnosis of schizophrenia, have a fluctuating prevalence of mental disorders. In 2007, the prevalence of mental disorders in Indonesia was 4.1 per 1,000; in 2013, it decreased to 1.7 per 1,000, and in the 2013-2018 period, it increased 4-fold over the last 5 years to 7 per 1,000.[1.] Schizophrenia has multifactorial causes. The pathophysiology of schizophrenia is not yet precisely known and is very variable, similar to its etiology. Several hypotheses have been proposed, including genetic factors, neurotransmitter disturbances, and disruption of both functional and morphological aspects of the brain. Children with parents who suffer from schizophrenia have a 5% risk of developing a similar condition.[3]

According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), Schizophrenia is

characterized by a combination of negative symptoms, cognitive dysfunction, and positive symptoms.[4] Negative symptoms divide into two dimensions of psychopathology, which are amotivation (anhedonia, avolition, asociality) and decrease of expression (alogia and blunted affect). Negative symptoms are present in at least 50% of schizophrenia patients, represent a significant burden, as these symptoms are associated with poor social functioning and role performance, reduced quality of life, and low recovery rates.[5] Positive symptoms include deviation of perception, such as auditory hallucination and visual hallucination, delusions, such as false or fixed beliefs, and disorganized behavior or speech. Seven specific cognitive deficit domains are working memory, attention/alertness, visual and verbal learning and memory, information processing speed, reasoning and problem-solving, and social cognition.[6] It is important to understand and recognize negative symptoms and cognitive dysfunction, as these two often precede the emergence of positive symptoms.[4]

Treatment of schizophrenia patients may use pharmacotherapy and non-pharmacotherapy. Pharmacotherapy uses medication aimed at patient control, preventing harm to the patient, and reducing symptoms of psychosis. One of the pharmacotherapies for schizophrenia patients is antipsychotics.[1]

In the dopamine hypothesis, it was found that there is central dopamine hyperactivity. Increased dopamine activity in the limbic system is associated with positive symptoms. The serotonin hypothesis showed that excessive serotonin could generate both negative and positive symptoms.[3]

Antipsychotic medication generally works through its antagonist dopamine receptor postsynaptic effect, and it has two categories of generation. The first generation of antipsychotics, or typical antipsychotics, is an antagonist of dopamine receptors, which could decrease positive symptoms. Meanwhile second generation of antipsychotics, or atypical antipsychotics is an antagonists of serotonin-dopamine receptors and could decrease both positive and negative symptoms; they also have milder extrapyramidal side effects than the first generation of antipsychotics.[2,4]

Schizophrenia patient often experience anxiety in conjunction with their psychotic symptoms; therefore, the usage of antipsychotics is often combined with antianxiety. Psychoeducation is also useful to treat patients as one of the non-pharmacological therapies.[1]

There are only 70% patients with antipsychotic medication who reached remission. [2] Schizophrenia patients frequently have difficulty running social function, considering evidence that antipsychotics were not effective in improving social function.[7] This condition occurs because the currently available antipsychotic medications are effective in alleviating positive symptoms, yet it less effective in alleviating negative symptoms and cognitive deficits in schizophrenia patients. Negative symptoms are symptoms that are most predictive of a poor prognosis in schizophrenia patients [4] Consequently, it is important to have a better therapeutic approach; thus, it would be a potential therapy for schizophrenia patients, especially to treat the negative symptoms domain and cognitive deficit domain.

Neuropeptide hormones have become the main focus of their relationship with mental and physiological systems. The most studied of all these peptides is oxytocin. Oxytocin works as a hormone in the peripheral circulation and as a neurotransmitter in the central nervous system.[8]

Oxytocin is a peptide hormone. This hormone is synthesized in the paraventricular nucleus and supraoptic of magnocellular neurons within the hypothalamus. Oxytocin could affect the body through the oxytocin receptor, which is connected with the G protein. This hormone is secreted from the posterior pituitary during labour, breastfeeding, and stressful conditions.[8]

Oxytocin receptor is found in several central nervous system, such as the prefrontal cortex, accumbens nucleus, lateral septum, hippocampus, amygdala, terminalis striae, medial preoptic area, cerebellum, Meynert basal nucleus, olfactory nucleus, vertical area of Broca, diagonal band, septal nucleus, hypothalamus, pallidus globus, and ventral pallidus.[8,9] Hypothalamus- pituitary-adrenal system (HPA), acetylcholine, GABA, glutamate, opioid, cannabinoid, catecholamine, indolamine, and steroid have a relationship with oxytocinergic system [8]

A certain study confirmed that oxytocin affected some aspects such as social behavior, attachment, empathy, psychological resilience, responses to acute and chronic stress, responses to fear, emotional and behavioral processing, eating behavior, immunological and anti-inflammatory effects, and wound healing. Some studies showed oxytocin in schizophrenia patients had a lower concentration than healthy people as a control, and had a reverse correlation with negative symptoms.[8]

In healthy people, one dose of oxytocin administration intranasally provides a direct route to the brain via cerebrospinal fluid to improve social cognition, including recognition of emotions, theory of mind, social perception, empathy, and accurate levels of affection. Besides intranasal, intravenous administration of oxytocin could also influence human behavior significantly.[9]

Several studies of functional Magnetic Resonance Imaging (fMRI) demonstrated oxytocin has significant effects on modulating social brain function. Brain social refers to a system that regulates social cognitive, social behavior, affective regulation, including the medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), inferior frontal gyrus, superior temporal sulcus, temporoparietal junction, anterior and posterior cingulate cortex (ACC/PCC), precuneus, amygdala, and anterior insula. Activation in this area and also in the dorsolateral prefrontal cortex (DLPFC) has been proven to be positively correlated with endogenous peripheral oxytocin levels during social perception tasks. DLPFC is known to be involved in cognitive control and working memory.[9]

Oxytocin administration in healthy people is most consistent in modulated amygdala activity. Intranasal oxytocin evidently improved amygdala functional connectivity with another social brain area, including OFC, ACC, and precuneus.[9] Studies that examined endogenous oxytocin levels in schizophrenia patients reported various results, and several results suggest that endogenous oxytocin levels in schizophrenia patients are lower than in healthy populations. Dysregulation of oxytocin has been proven to be associated with several symptom domains of schizophrenia, especially in negative symptoms and cognitive deficits. Negative correlation between oxytocin level and negative symptoms has been reported in many studies. Higher concentration of peripheral oxytocin levels tends to be associated with increased social awareness and better recognition of emotions, as well as the ability to process information and faster working memory.[10]

METHOD

The author uses the literature review method with international journals limited to the period from 2014 to 2024. The literature used discusses schizophrenia, oxytocin, and antipsychotics.

RESULT

Several results of research strengthen evidence that oxytocin administration helps relieve negative symptoms. Cross cross-sectional study done by Guzel et al, which was assessed with Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression (CGI) scale, dan General Assessment of Functioning (GAF) scale for symptom assessment, and performed serum analysis to find out the correlation between oxytocin levels. This research showed a positive correlation between oxytocin level and the GAF scale. This result showed that the schizophrenia patient had a low concentration level of oxytocin. Therefore, researchers conclude that oxytocin and the decreasing severity of schizophrenia were related. Those also could improve patients' general function.[11]

In 2021, Sabe et al conducted a meta-analysis study regarding the dose response of oxytocin administration in schizophrenia patients. The result was that higher doses of oxytocin are more effective in improving negative and positive symptoms, especially through intranasal administration to obtain better clinical evidence.[5]

A clinical randomized examination done by Feifel et al reported that intranasal administration of 40 IU oxytocin twice a day for three weeks significantly decreased subscale negative score in PANSS and increased verbal memories, which were assessed with the California Verbal Learning Test (CVLT) in schizophrenia patients [12]

Lee et al proved that hospitalized schizophrenia patients who were administered 20 IU intranasal oxytocin twice a day for three weeks could alleviate negative symptoms, assessed by the Scale for the Assessment of Negative Symptoms (SANS).[12] Administration of 24 IU intranasal oxytocin twice daily throughout twelve weeks was conducted to 68 subjects who were diagnosed with schizophrenia and schizotypal disorder, discovered negative symptoms improved significantly, and there was an increase in social function in a better direction.[13]

Randomized controlled trial of 24 IU and 40 IU doses of intranasal oxytocin for six weeks showed improvement of schizophrenia patients.[12] Gibson et al in 2014 conducted a double randomized controlled trial. This trial aimed to evaluate intranasal oxytocin effect twice a day for six weeks to social cognitive includes emotion recognition, theory of mind, empathy and social perception in schizophrenia patients as assessed by the PANSS score, *The Emotion Recognition-40, Theory of Mind Picture Stories Task, The Eyes Test, The Interpersonal Reactivity Index, The Trustworthiness Task, The Ambiguous Intentions Hostility Questionnaire-Abbreviated Version, role play*. The results were analyzed using an independent T test showed improvement in fear recognition [$t(7) = 2,37$, $p = 0,05$], perspective taking [$t(4) = 3,26$, $p = 0,03$], and reduction of negative symptoms [$t(7) = -5,00$, $p = 0,002$] in the group who received oxytocin.[7]

In addition to administering intranasal oxytocin twice a day for three weeks, Pedersen et al conducted research for a week. The result showed oxytocin administration was able to significantly reduce the PANSS negative subscale score ($p < 0.08$). This treatment also improved cognitive deficit through the Task Brune. Modabbernia et al conducted a trial of intranasal oxytocin for eight weeks twice daily, and it indicated that the total score of PANSS, positive domain score, and negative domain score gained improvement, even after oxytocin administration in the fourth week.[6]

Short-term oxytocin treatment within the second to eighth week twice daily has been examined in schizophrenia patients by a randomized controlled study design with a placebo. During the first trial (after three weeks of observation), there was a significant improvement in all schizophrenia psychopathology, such as global function, negative symptoms, and verbal memory.[9]

Research conducted through fMRI evaluation showed that intranasal oxytocin reduced and normalized hyperactivation of the amygdala, mPFC, and ACC. In 2014, Dodhia et al found that oxytocin could normalize resting-state functional connectivity between the left and right amygdala and the rostral ACC/mPFC, which is usually hypoconnected in social anxiety disorder patients [9]

A study conducted with 240 subjects, 160 subjects were schizophrenia patients who had received antipsychotic treatment, meanwhile 80 subjects were healthy controls. The PANSS scale is used to evaluate psychotic symptoms. This study measured oxytocin plasma concentration based on a positive correlation between central oxytocin and peripheral oxytocin concentration. Pearson correlation coefficients were calculated to explore correlations between psychopathology and other continuous variables, including plasma oxytocin levels. Plasma oxytocin levels were inversely related to the PANSS total score ($r = -0.688$, $p < 0.001$), with the conclusion that schizophrenia patients had lower oxytocin levels, which is consistent with our hypothesis and supports the idea that dysfunction of the oxytocinergic system is related to schizophrenia.[14]

Bargiota et al in 2023 conducted a randomized clinical trial with subjects in the condition of prodromal psychosis and new psychosis categorical, which were approved by criteria for Ultra High Risk psychosis. The interventions used were 40 IU intranasal oxytocin or placebo, 24 IU or placebo and social cognitive therapy, and oxytocin-induced changes in various domains were the results observed in this study. The outcome was oxytocin administration related to decreased severity of psychotic symptoms at the beginning of the psychosis phase. Another study showed that a group of patients with oxytocin 24 IU combined with social cognitive therapy produced significantly fewer symptoms of psychosis.[13]

DISCUSS

Relationship between Oxytocin and Schizophrenia

The etiology of schizophrenia is heterogeneous, as no single gene causes its pathophysiology. Consequently, a few neurotransmitter and neuropeptide systems are believed to be involved in the mechanism of schizophrenia symptoms. Besides of dopamine hypothesis, the glutamate hypothesis is that N-methyl-D-aspartate (NMDA) contributes to negative symptoms and cognitive dysfunction related to schizophrenia. Researchers who learned about the cholinergic system and gamma aminobutyric acid (GABA) found that this neurotransmitter system might also play a role in psychotic and cognitive deficits found in schizophrenia patients. Neuropeptides are released simultaneously with neurotransmitters; therefore, neuropeptides are believed to be related to schizophrenia pathophysiology. One of those neuropeptides is oxytocin.[4]

The role of oxytocin has been discussed in many physiological and psychological studies. Oxytocin could improve prosocial behavior by strengthening empathy, social memory, and emotional perception. Besides, oxytocin also acted as a regulator of anxious feelings related to its nature as an anxiolytic and an anxiogenic. Consequently, oxytocin is considered a human behavior regulator, and the oxytocinergic system is involved in schizophrenia symptoms.[15]

A single dose of 40 IU intranasal oxytocin increased functional connectivity in the rest state between the amygdala and left middle temporal gyrus, superior temporal gyrus, and angular gyrus, which contributed towards negative symptoms of schizophrenia.[12] Furthermore, the caudate and left supplementary motor area, precentral gyrus, and triangular inferior frontal gyrus are also related to greater cognitive insight and lower negative symptoms.[16]

Usage of Oxytocin in Schizophrenic Patients as a Future Treatment

The rapid metabolism of oxytocin within peripheral circulation raised challenges to its usage as therapy.[16] Previous studies revealed oxytocin injection reduced symptoms of psychosis and anhedonia in schizophrenia patients. Oxytocin administration through intravenous had poor ability to penetrate blood blood-brain barrier; meanwhile, it had a short half-life within plasma, approximately only about 3-20 minutes, therefore intranasal route of oxytocin administration was chosen in subsequent studies.[9]

Currently, there is an option for intranasal administration of oxytocin because it is easier than injection administration. There was proof that oxytocin administration through intranasal administration increased oxytocin concentration within cerebrospinal fluid in humans or animal models.[4]

Oxytocin therapy through intranasal or nose spray was chosen to deliver oxytocin so it is easier to reach the central nervous system. Oxytocin studies in humans through intranasal administration at a dose of 20-40 IU, where this dose follows empirical evidence from research that has been carried out previously.[16] Intranasal oxytocin administration was chosen because of its higher ability to cross blood blood-brain barrier better. At the same time, olfactory and trigeminal transportation in the nasal area contributed to oxytocin administration. The fact that intranasal administration is noninvasive and well tolerated, and also does not have any side effects similar to the placebo, led to the widespread usage of intranasal oxytocin in practice. One study showed exogenous oxytocin administration could increase endogenous oxytocin production [8] Research conducted on non-human primates has proven that intranasal administration of oxytocin increased oxytocin levels in cerebrospinal fluid. Administration of oxytocin was observed from 15-120 minutes after administration. In a study conducted on humans, a dose of 24 IU of oxytocin was given to eleven research subjects. The result was increased oxytocin levels in the cerebrospinal fluid at the 75th minute. The protocol in the oxytocin study is carried out for response assessment 30 minutes after administration of oxytocin, because in healthy individuals, there are significant behavioral and physiological responses from oxytocin induction [16]

Bargiota et al found that a single dose of intranasal oxytocin could increase social function due to its significant cerebral perfusion in the hippocampus and dentate gyrus. Oxytocin can also decrease the response of the inferior frontal gyrus during the emotional empathy period. Moreover, during the inferential social empathy process, basic social and emotional ability modulate neural response in the left inferior frontal gyrus; therefore, overall, this study provided ideas for new treatment options towards prodromal psychosis due to targeting multiple neural regions in the brain.[13] Dose-respons meta-analysis evidenced that higher doses could be more effective in both positive and negative symptoms. Nonetheless, to get a clinical effect, more frequent administration of intranasal oxytocin might be necessary.[5]

CONCLUSION

Schizophrenia is a mental disorder that has multifactorial causes. Its pathophysiology is not known for certain yet; however, a number of hypotheses have been mentioned that dysregulation of neurotransmitters and neuropeptides is related to its process. Recently, therapy for schizophrenia has been using antipsychotics, which have a better effect in improving positive symptoms. Nonetheless, antipsychotic medication has less effect on negative symptoms and cognitive deficits in schizophrenia patients. Several previous studies stated that levels of the neuropeptide oxytocin were lower in schizophrenia patients. Therefore, research conducted studies aimed to determine the effect of oxytocin administration in schizophrenia patients. The results showed oxytocin administration, particularly through the intranasal route, increased oxytocin levels and significantly improved negative symptoms and cognitive deficits in schizophrenia patients.

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