Psychiatry Research 269 (2018) 271–277

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Sodium nitroprusside treatment for psychotic symptoms and cognitive deficits of schizophrenia: A randomized, double-blind, placebo-controlled trial

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ARTICLE INFO

Keywords:
Sodium nitroprusside
Schizophrenia
Psychotic symptoms
Cognitive function
Clinical trial

ABSTRACT

Schizophrenia presents with a broad range of negative, positive, and cognitive symptoms, and comprehensive treatment is still a challenge. Sodium nitroprusside (SNP) has been reported to rapidly reduce psychotic symptoms and improve cognitive functions in patients with schizophrenia, providing a new possible direction for treatment. In this study, we tested whether SNP can improve psychotic symptoms and cognitive function in schizophrenia patients with longer disease history. This was a randomized, double-blind, placebo-controlled trial conducted between May 2016 and April 2017. Forty-two schizophrenia patients aged 18–45 years were recruited from Henan Province Mental Hospital. Baseline psychiatric symptoms were measured using the Positive and Negative Syndrome Scale (PANSS), and baseline cognitive functions were measured using the Wechsler Adult Intelligence Scale. Patients received two SNP or placebo infusions (0.5 μg/kg per min for 4 h) at a one-week interval. We reassessed psychiatric symptoms and cognitive functions using the same tests shortly after the first and second infusions and 4 weeks after the second infusion. We did not find any significant effect of SNP over placebo on psychotic symptoms or cognitive functions, although SNP was relatively well tolerated with a good safety profile.

1. Introduction

The cardinal characteristics of schizophrenia are positive, negative, and cognitive symptoms (Carbon and Correll, 2014). Although both first and second generation antipsychotics are effective in treating acute symptoms, approximately 70% of patients do not achieve symptom remission within 3 years (Novick et al., 2009). Further, despite decades of research into the cognitive deficits of schizophrenia, there are no satisfactory pharmacological agents capable of restoring cognitive function (Weickert et al., 2015). Cognitive deficits are core characteristics of schizophrenia (Aquila and Citrome, 2015), and their severity strongly influences functional outcome (Bhagyavathi et al., 2015), so treatment is a priority. Recent studies have shown that Sodium nitroprusside (SNP) can improve cognitive functions in patients with schizophrenia, providing a new possible direction for treatment.

SNP has been in clinical use since 1929 for severe hypertension (Johnson et al., 1929). Its main mechanism of action is through the release of nitric oxide (NO), leading to vasodilation. The interest in SNP as a potential antipsychotic agent first arose from studies in animals. In animal studies, Kandratavicius et al. (2015) found that SNP improved long-term ketamine-induced memory deficits in rats (Kandratavicius et al., 2015) and Trevlopoulou et al. (2016) reported that SNP attenuated cognitive deficits and psychosis-like behaviors (social withdrawal and anxiolytic-like behaviors) induced by ketamine in rats (Trevlopoulou et al., 2016). In human trial, Maia-de-Oliveira et al. (2015b) found that SNP improved cognitive deficits in patients with schizophrenia.

The mechanisms of SNP may improve cognitive function remains unclear. Numerous studies published in recent years have implicated glutamatergic system dysfunction in the pathogenesis of schizophrenia, especially hypoactivity of the NMDAR (Deakin et al., 1989; Mohn et al., 1999), and more recent clinical evidence suggests dysregulation of the glutamate–NO–cyclic guanosine monophosphate (cGMP) network in schizophrenia (Miuller and Schwarz, 2007). After infusion, SNP is

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https://doi.org/10.1016/j.psychres.2018.08.079
Received 1 December 2017; Received in revised form 7 July 2018; Accepted 19 August 2018
Available online 21 August 2018
0165-1781/

converted to NO, bypassing brain NMDA receptors to directly elevate tissue NO levels. These findings have led to the hypothesis that the effects of SNP may be mediated via the NMDAR or downstream signaling pathways (Stone et al., 2016). There is also evidence that SNP acts directly on NMDA receptors, which could compensate for the NMDAR hypoactivity in schizophrenia (Oliveira et al., 2008; Dhami et al., 2013).

In rodents and schizophrenia patients, SNP also appears effective against schizophrenia-like symptoms. Bujas and colleagues observed that SNP completely abolished the behavioral effects and c-fos expression induced by phencyclidine (Bujas-Bobanovic et al., 2000), a blocker of *N*-methyl-D-aspartate (NMDA) glutamate receptors (NMDARs) frequently used to induce schizophrenic-like behaviors in rodents. Maia-de-Oliveira et al. (2015a) reported that a single-dose of SNP also prevented psychosis-like behavior induced by the NMDAR antagonist ketamine in rats and that this effect lasted at least one week. In an early human trial, Hallak et al. (2013) reported that a 4-h infusion of 0.5 μg/kg SNP per min led to a significant reduction in psychotic symptoms (Hallak et al., 2013). Moreover, Maia-de-Oliveira et al. (2014) found that SNP improved symptoms in patients with clozapine-refractory schizophrenia (Maia-de-Oliveira et al., 2014). Thus, SNP may possess broad therapeutic efficacy against schizophrenia symptoms. But there is also different result reported. In Stone's study they failed to found SNP has any effect on psychotic symptoms in patients with schizophrenia (Stone et al., 2016).

Based on these findings, our aims were to (1) assess the safety of SNP, (2) determine if SNP can significantly improve psychotic symptoms, and (3) investigate the benefits of SNP on cognitive impairments in schizophrenia patients.

2. Methods

2.1. Participants

Participants were recruited from inpatients of Henan Province Mental Hospital, a tertiary class-A hospital with 1200 beds. The sample size was chosen based on a recent study of SNP in patients with schizophrenia (Hallak et al., 2013). The data were collected between May 2016 and April 2017. We recruited 50 patients. All patients and their families were given complete information on the study procedures and policies, including the freedom to withdraw at any time without consequences, and all provided written informed consent. Inclusion criteria were a Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) diagnosis of schizophrenia, age 18–45 years, Han ethnicity, competent and willing to give informed consent, able to complete the required evaluations, females willing to have a pregnancy test before treatment, acute psychotic episode PANSS score $\geq$70, and currently taking antipsychotics. The exclusion criteria were DSM-IV diagnosis of alcohol/substance abuse within the past month or alcohol/substance dependence within the past 6 months, recent use of street drugs (confirmed by a urine toxicology test), history of seizures/head trauma with loss of consciousness resulting in cognitive sequelae/rehabilitation, pregnant/breastfeeding, any relevant medical illness (including untreated hypothyroidism, hyponatremia, ischemic heart disease, hypotension, impaired cerebral circulation, renal impairment, vitamin B12 deficiency, or Leber's optic atrophy), prior history of intolerance to SNP, any change in psychotropic medication in the previous 6 weeks, or history of any major medical illness.

2.2. Study procedure

This was a randomized double-blind, placebo-controlled clinical trial (ChiCTR-OIC-No.: ChiCTR-OIC -16008216). Ethical approval was obtained from the Henan Province Mental Hospital Ethics Committee and was conducted in accordance with the Declaration of Helsinki and other applicable regulatory requirements. At the screening visit, participants underwent psychiatric evaluation using the Positive and Negative Syndrome Scale (PANSS). Current antipsychotic medication, as well as drug, alcohol, and smoking histories were obtained, and a physical examination was performed to establish the patients' eligibility for the trial. Routine blood, biochemical, and urinalysis results, height and weight, blood pressure, heart rate, and ECG were obtained. Participants then underwent cognitive assessment using the Wechsler Adult Intelligence Scale, including digit symbol, digit span, and verbal fluency tests.

Participants were randomized 1:1 to SNP or placebo arms using a random number table. SNP was infused at 0.5 μg/kg/min for 4 hours two times at a one-week interval. The placebo was a 5% glucose solution that was infused over the same length of time. Experimental infusion standards and conditions were identical for both groups, and both patients and front-line study staff were blind to the assigned intervention. An unblinded clinical research nurse diluted the SNP with isotonic glucose solution to achieve the required dose, but this nurse did not undertake any other task in the study. The prepared solution or placebo was wrapped in opaque packages to protect the SNP from ultraviolet light and ensure blinding of the study team.

A fully trained anesthetist and a cardiologist were present during each infusion to ensure safety. A micropump was used to ensure drip speed, and multifunctional monitoring of heart rate, respiration, and blood oxygen saturation was conducted during infusion. Blood pressure was measured every 5 min until the end of infusion. Emergency medicine and nursing support were available on site at all times. PANSS and cognitive assessments were repeated after completing the first and second infusions. After the infusion was complete, the monitoring equipment disconnected, and venous access removed, we asked participants how they felt during the infusion. We encouraged participants to ask questions related to the study procedures if they experienced any unexpected bodily or psychological sensations. Four weeks after the second infusion, participants were re-evaluated using the PANSS and Wechsler Adult Intelligence Scale.

2.3. Statistical methods

Clinical, demographic, and behavioral data were analyzed using SPSS statistical software, version17.0 (SPSS Inc). The χ^2 test was used to compare categorical variables and the independent 2-tailed *t* test to compare continuous variables between groups. PANSS total score and subscores were compared by two-way analysis of variance for repeated-measures (RM-ANOVA), with treatment (SNP or placebo) and time (baseline, after first infusion, after second infusion, 4 weeks after second infusion) as factors. If the RM-ANOVA was significant, an independent 2-tailed *t* test or a paired 2-tailed *t* test was conducted.

3. Results

3.1. Patient characteristics

Fifty participants agreed to participate in our study and were assessed for eligibility. Of these, eight discontinued participation prior to randomization due to difficulties keeping research appointments (n = 5), psychotic exacerbation (n = 2), or because family members requested that the participant be treated with Modified Electroconvulsive Therapy (MECT) (n = 1). The remaining 42 individuals were randomized to receive either SNP or placebo and all completed the study procedures (Fig. 1). Baseline clinical and demographic details were well matched between placebo and SNP groups (Table 1), with no significant differences in age, sex ratio, years of education, length of illness, smoking status, number of hospitalizations, marital status, and native place between groups. Unlike the Hallak's study (Hallak et al., 2013), there were no antipsychotic drug restrictions in this study, and all patients received any antipsychotic drug according to need. We didn't design a single application of the drug for