Original Article

The Efficacy of N-Acetylcysteine in the Treatment of Methamphetamine Dependence: A Double-blind Controlled, Crossover Study

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Abstract

Objective: Preclinical studies and early pilot clinical investigations have suggested that N-acetylcysteine (NAC) may be useful in treatment of methamphetamine (METH) dependence. The present study evaluated whether NAC would suppress craving to the METH.

Methods: In a double-blind, controlled crossover clinical trial, 32 METH-dependent volunteers were chosen to receive either NAC (1200 mg/day) or placebo, randomly. They were intervened in two four-week sessions. During first session they received either 1200 mg/day of NAC (group A) or placebo (group B). After three days of washout period, next session started with the crossover intervention of the previous regimen. During these eight weeks, all participants received standardized, and Matrix Model of treatment. Craving was assessed using the Cocaine Craving Questionnaire-Brief (CCQ-Brief). The data were analyzed using SPSS version 20.0 (SPSS Inc. Chicago, Illinois, USA).

Results: In 23 subjects who completed the study, the mean score of CCQ-Brief reduced in four consecutive weeks with NAC treatment. The mean (SD) scores of carving in group A and B were 3.38 (1.16) and 5.96 (1.03), at the end of first session; and 4.57 (1.88) and 3.2 (0.86), at the end of the second session, respectively. Our findings indicate that the main effect was significant for NAC ($P < 0.001$). Across placebo and NAC conditions, only mild side effects were noted, and the number of subjects who reported side effects did not differ.

Conclusion: The NAC showed good efficacy in suppressing METH craving, and may be a useful pharmacological treatment for METH dependency.

Keywords: Craving, dependency, methamphetamine, N-acetylcysteine, pharmacotherapy

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Introduction

Methamphetamine (METH) is a psycho-stimulant drug, and its dependence causes many public health problems, and criminal justice cases. According to estimation of the United Nations, globally there were about 14 – 53 million annual users, aged 15 – 64 years old.[1] The METH dependence can be a devastating disorder, with adverse effects across the lifespan, in the community and at home.[2] A substantial body of evidences indicates that METH abuse can lead to persistent and serious psychiatric, cognitive and neurological dysfunction. It can affect the development and well-being of children who have been exposed to this substance in the uterus.[3,4]

However, current standard treatment of METH dependence is the Matrix Model, which combines cognitive, behavioral, and psychological approaches.[5,6] We did not find any appropriate pharmacological regimen with accepted efficacy for the treatment of METH dependency, which may improves compliance and reduces the relapse.[7–9] Results of previous studies about the use of sertraline, mirtazapine, bupropion, modafinil, ondansetron, dextroamphetamine, risperidone, aripiprazole, naltrexone, baclofen and gabapentin did not show consistent efficacy of these drugs.[9–11]

An important characteristic of substance dependency is difficulties to prevent from its relapse. Craving and drug-seeking behaviors are important manifestations of dependency, because they predispose the relapse, and perpetuate the addiction. Therefore, reducing them is a major step of the treatment. Chronic and severe METH abuse is associated with deep alterations in brain circuits, which results in severe craving for the substance. Thus, the use of an effective pharmacotherapy that could reduce craving is an important goal of treatment of addiction.[12]

There is some evidence which shows the role of glutamatergic abnormalities in the substance craving.[13,14] The amino acid N-acetylcysteine (NAC) stimulates inhibitory metabotropic glutamate receptors and thereby reduces the release of glutamate from the synapsis. Restoring extracellular glutamate concentration in the nucleus accumbens, blocks the reinstitution of compulsive behaviors.[15,16] These characteristics have made the NAC a potential promise for the addiction treatment.

Treatment strategies for METH use disorders have been based on strategies in the studies showed the effectiveness of NAC in the cocaine use disorders, because these two substances share many features.[15,17–20] According to DSM-IV TR, the criteria for

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intoxication and withdrawal of cocaine and METH are similar. In fact, these two substances have nearly similar mechanism of action and produce similar intoxication signs and symptoms as well as similar withdrawal signs and symptoms including craving.[8,17,18] In previous studies, NAC has shown promise in reducing cocaine use,[15,19,20] but a double-blind, placebo-controlled study of NAC plus Naltrexone, showed no differences between METH and placebo on outcomes.[10]

Few studies have been reported concerning the treatment of METH dependency. There are also some cues, which show the effectiveness of NAC in cocaine dependent patients. Therefore, the aim of this study is to evaluate the efficacy of NAC in suppression of craving for METH in dependent patients.

Methods

Study design and participants

This study is a randomized, double-blind, controlled crossover clinical trial with an active medication condition (NAC) and a matching placebo, which was carried out in 2013. It has been registered on the Iranian Registry of Clinical Trials with identifier Number IRCT201205317841N2. The study followed the Declaration of Helsinki on Biomedical Research Involving Human Subjects and was approved by the Ethics Committee from the Isfahan University of Medical Sciences. All participants provided written informed consent.

Subjects were chosen for treatment-seeking METH dependent patients who referred to the psychiatric emergency service and psychiatric clinic of Noor Hospital (Isfahan, Iran). All subjects met the following inclusion criteria: 1) 18 – 65 years of age; 2) current diagnosis of methamphetamine dependency according to the Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision criteria (DSM-IV TR); 3) willing and able to comply with study procedures; and 4) willing and able to provide written informed consent. Subjects also met none of the following exclusion criteria: 1) any serious medical condition that may interfere with safe study participation; 2) current lactation, pregnancy or inadequate contraception; 3) current serious suicidal intention or plan; 4) previous treatment with NAC; 5) abnormal liver function tests at screening; 6) any physical conditions linked to adverse events related to NAC (e.g. history of asthma or seizure activity);[15] 7) dependency on any substance other than methamphetamine, and nicotine; and 8) concurrent psychiatric disorders (e.g., bipolar disorder or schizophrenia) which needs using mood stabilizers, antidepressants or antipsychotics.

A total of 54 individuals were screened by psychiatrist. At the screening visit, after providing demographic data, subjects received electrocardiography (EKG), urine toxicology screen, liver function tests (i.e., aspartate transaminase (AST) and alanine transaminase (ALT)), urine pregnancy test, and a physical examination to ensure that the results did not preclude the use of NAC. Psychiatric diagnoses were obtained using the Structured Clinical Interview for DSM-IV (SCID).[21]

Finally 32 subjects met all inclusion and no exclusion criteria. Eligible subjects were allocated into two groups with simple randomization by a third party physician using tables of random numbers, and received either of NAC (A) or placebo (B). Nine patients dropped out of the study process because of non-compliance (Figure 1).

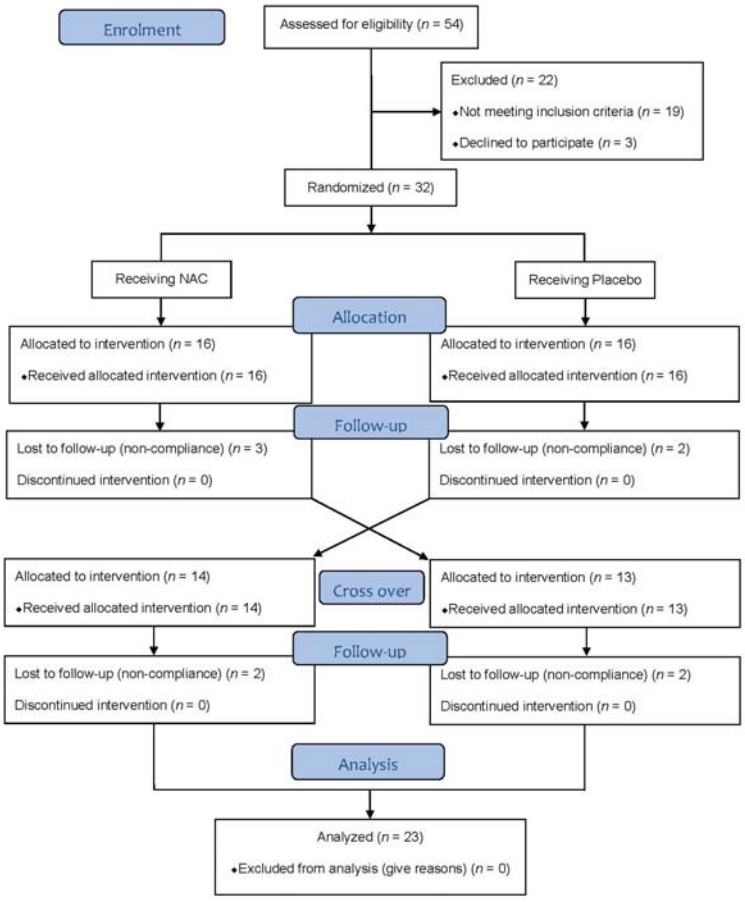

Figure 1. Study design flowchart

Procedures and variables assessment

The study performed in two four-week sessions. At the first session the group A received 600 mg/day of NAC effervescent tablets (Avicenna, Iran), and after one week the dosage was raised to 1200 mg/day; and the group B received the placebo in the same form and packages as NAC. After this four weeks (i.e. first session), each group has had three days of washout period, and did not receive any drug during this period.[15] Then, the second session started and each group received the crossover intervention of the first session, i.e. the group A received placebo and the group B received NAC. Through these eight weeks, all participants received standardized, Matrix Model of treatment in the form of 60-min, one times-a-week group sessions.[5]

The dosing of NAC was based on safety and efficacy data derived from human studies of cocaine dependence.[15] At each visit, participants received 1-week supply of medication in blister packages and instructed in how to self-use the medication at home. To monitor the adherence, they were required to bring the drug packets to the clinic at the next visit for pill counts.

METH craving was assessed using the Cocaine Craving Questionnaire-Brief (CCQ-Brief). The criteria for intoxication and withdrawal of cocaine and METH are similar according to DSM-IV TR. In fact, these two substances have nearly similar mechanism of action and produce similar intoxication signs and symptoms as well as similar withdrawal signs and symptoms, including craving.[8,17,18] The CCQ-Brief consists of 10 out of the 45 items from the CCQ-Now, with a strong internal reliability (α = 0.92), that is loaded heavily on the general craving factor of the scale. Items are measured on a seven-point visual analogue scale with "strongly disagree" at one pole and "strongly agree" at the other. The total score (obtained by averaging all items) is used as a measure of global craving.[22] The translation and back-translation methods were used to make the Persian translation of CCQ-Brief valid. CCQ-Brief was translated into Persian by two psychiatrists and then two other bilingual psychiatrists translated the same text into the first language. Translated texts were evaluated by the translation team for the final decision.[23] In translation of this questionnaire which was used for patients, we used the word METH (crystal) instead of cocaine.

The following measures were completed at each weekly visit: 1) frequency of methamphetamine use (days per week); 2) urine toxicology for METH; 3) medication side effects; and 4) CCQ-Brief score.

Blinding

Randomization was done by a third party physician using tables of random numbers. CCQ-Brief score was assessed by a psychologist who was not informed about grouping of the subjects.

Statistical analysis

The data were analyzed by Chi-Square Test, Fisher's Exact Test, Independent T-test and Mann-Whitney Test for demographic and clinical differences between two groups. Fisher's Exact Test was used for analysis of side effect differences between two groups. The main effect of the drug, carry over effect, and periodic effect, were assessed by Repeated Measure of ANOVA. Before analyzing for the main effect, we checked for a period and carryover effects. First, we run ANOVA, repeated measure analysis to find out for each of these two effects. In this trial, there was no carryover effect, but the period effect was statistically significant. Hence, we run "ANOVA repeated measure" analysis to find out the main effect because of the existence of a significant period effect (adjusting the main effect). If there had been any carryover effect, we must analyze just the first stage of data and ignore the data in the second stage.

The data were analyzed using Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Chicago, Illinois, USA). P-value < 0.05 was considered statistically significant.

Results

Baseline Profile

Twenty-three patients completed the study. These subjects all had the normal range of EKG, liver function tests (i.e., AST and ALT) and physical examination at the beginning. The mean (SD) age was 29.21 (4.93) years, ranging from 22 to 40 years old. The mean (SD) years of dependency was 4.1 (2.2), ranging from 1 to 8 years. There were 19 (82.6%) male and 4 (17.4%) female.

Comparison of the baseline profile of subjects, including age, sex, marital status, occupation, educational level and family history of substance dependency revealed no statistically significant differences between two groups (Table 1).

The mean (SD) years of dependency was 4.36 (2.09) in group A and 3.90 (2.33) in group B. Mann-Whitney Test, showed that the difference was not significant (P = 0.515).

According to CCQ-Brief the mean (SD) of carving score was 6.4 (0.47) in group A and 5.95 (0.65) in group B before intervention (week 0), and there was not any significant difference between two groups (P = 0.072).

There were nine subjects who dropped out of the study process because of non-compliance. Comparing these subjects with those who completed the study (23 subjects) in baseline profiles, showed no statistically significant differences between two groups (Table 2). The mean (SD) years of dependency was 4.1 (2.22) in compliant group and 3.66 (1.58) in the non-compliant group. Mann-Whitney Test showed that the difference was not significant (P = 0.535). According to CCQ-Brief the mean (SD) of carving score was 6.06 (0.76) in compliant group and 5.88 (0.69) in non-compliant group before intervention (week 0), and there was not any significant difference between these two groups (P = 0.540).

Outcomes

The mean (SD) scores of carving in group A and B were 3.38 (1.16) and 5.96 (1.03), at the end of the first intervention period; and were 4.57 (1.88) and 3.2 (0.86), at the end of the second intervention period, respectively. The mean score of craving for both groups in different consecutive weeks are shown in Table 3. We first run ANOVA, repeated measure analysis to find out about any of the period and carryover effects. In this trial, there was no carryover effect (P = 0.237) but period effect was statistically significant (P = 0.029). Hence, we run "ANOVA repeated measure" analysis to find out any main effect because of existence of a period effect (adjusting the main effect). The analysis shows that the scores were reduced during the consecutive weeks with NAC, while this was not true for the placebo, so the main effect was significant for NAC (P < 0.001).

Tolerability and side effects

Although non-significant, the reported side effects were nausea,

Table 1. Demographics and clinical characteristics of subjects (n = 23)

Characteristics	Group A (start with NAC) N = 11	Group B (start with placebo) N = 12	P
Age, Mean (SD) year	29.9 (4.7)	28.5 (5.1)	0.532
Sex			1.000
Male	9 (81.8)	10 (83.3)	
Female	2 (18.2)	2 (16.7)	
Marital Status			0.089
Single	9 (81.8)	5 (41.7)	
Married	2 (18.2)	7 (58.3)	
Family History of Substance Dependency			0.214
Positive	5 (45.5)	9 (75)	
Negative	6 (54.5)	3 (25)	
Occupation			1.000
Yes	3 (27.3)	3 (25)	
No	8 (72.7)	9 (75)	
Educational Level			0.371
Under Educate (high school diploma)	9 (81.8)	7 (58.3)	
Educated (academic education)	2 (18.2)	5 (41.7)	
All variables are Number (%) unless otherwise indicated; P: P-value is extracted from Independent Samples Test and Fisher's Exact Test			

Table 2. Demographics and clinical characteristics of compliant and non-compliant subjects (n = 32)

Characteristics	Compliant N = 23	Non-compliant N = 9	P
Age, Mean (SD) year	29.21 (4.9)	26.55 (4.6)	0.174
Sex			1.000
Male	19 (82.6)	7 (77.8)	
Female	4 (17.4)	2 (22.2)	
Marital Status			1.000
Single	14 (60.9)	5 (55.6)	
Married	9 (39.1)	4 (44.4)	
Family History of Substance Dependency			0.453
Positive	14 (60.9)	4 (44.4)	
Negative	9 (39.1)	5 (55.6)	
Occupation			0.407
Yes	6 (26)	4 (44.4)	
No	17 (74)	5 (55.6)	
Educational Level			1.000
Under Educate (high school diploma)	16 (69.6)	6 (66.7)	
Educated (academic education)	7 (30.4)	3 (33.3)	
All variables are Number (%) unless otherwise indicated; P: P-value is extracted from Independent Samples Test and Fisher's Exact Test			

Table 3. Cross-over effect on mean score of craving

Groups	First intervention period					WP	Second intervention period				ME	CE	PE
	Week 0	Week 1	Week 2	Week 3	Week 4		Week 5	Week 6	Week 7	Week 8	P	P	P
A	6.4 (0.4)	5.5 (0.6)	4.9 (1.0)	4.6 (0.6)	3.3 (1.1)		3.7 (1.3)	4.2 (1.3)	4.3 (1.6)	4.5 (1.8)	< 0.001	0.237	0.029
B	5.9 (0.6)	5.5 (0.8)	5.3 (1.1)	5.2 (1.0)	5.9 (1.0)		5.1 (0.7)	4.3 (1.1)	3.7 (0.8)	3.2 (0.8)			
WP: washing period (3 days); ME: main effect; CE: carry-over effect; PE: period effect; P: P-value is extracted from repeated measure of analysis variance test; A: start with NAC; B: start with placebo													

Table 4. Frequency of elicited side effects of treatment

Side effects	NAC (*N* = 23)	Placebo (*N* = 23)
Nausea	1 (4.3)	0 (0)
Abdominal cramp	1 (4.3)	1 (4.3)
Blunting	2 (8.7)	0 (0)
Diarrhea	1 (4.3)	2 (8.7)
Constipation	3 (13)	3 (13)
Mild headache	1 (4.3)	0 (0)
Dry mouth	1 (4.3)	0 (0)
All variables are presented as number (%)		

abdominal cramp, blunting, diarrhea, constipation, mild headache and dry mouth; patients reported no other adverse experiences (Table 4). The overall rate of side effects was not different between two groups significantly (P = 0.353). None of the patients left the study because of side effects.

Discussion

This controlled crossover study compared the NAC and the placebo efficacy in reducing the craving for METH and their side effects, in METH dependent patients. We used drug treatment in conjunct with the Matrix model of treatment. The results showed that NAC was effective in reducing the METH craving in studying subjects. NAC was safe and well tolerated by treatment-seeking METH-dependent subjects. No unexpected side effects were reported and in general, side effects appeared to be mild and self-limited, and often occurred during the beginning of treatment.

Our results validate the clinical insight that has developed over the years of conducting clinical trials in the treatment of addiction with NAC. In previous studies with cocaine, the results is consistent with our findings. Different studies with various doses of NAC (1200, 2400, 3600 mg/day) showed that this drug causes significant reduction in craving, self-reported use and the amount of time which patients spent on cocaine using.[15,19,24,25]

On the other hand, in a recent study, LaRowe, et al. concluded that the NAC did not reduce cocaine use in dependent individuals who actively using, but there is some evidence that it prevents from returning to cocaine use in patients who had achieved abstinence from cocaine.[20] We did not find enough studies which have evaluated the NAC efficacy in reducing METH craving, to compare our findings with it. But in a double-blind study, Grant, et al. failed to demonstrate greater efficacy for NAC plus naltrexone compared with placebo.[10] This is inconsistent with our results, but the present study had a crossover method. This Method is more powerful and also we used NAC in conjunct with the Matrix model of treatment which may potentiate the effect of drug. In fact, it is possible that pharmacotherapy may have greater benefit, when is used in conjunction with psychotherapy.[6,10]

Most of other studies used NAC up to 2400 mg/day for METH or cocaine, but in our study the maximum dose was 1200 mg/day. This may show that lower doses of drug can also be effective. Therefore, using of lower doses is recommended because of lower costs and more compliance of patients.

In our study, after withdrawal of NAC with crossover to placebo through four consecutive weeks, the craving score increased from 3.7 (1.3) to 4.5 (1.8). This may indicates that NAC has a limited enduring effect for relapse prevention. However, in rat studies, Reichel, et al. and Zhou, et al. found that after two weeks of NAC treatment, reduction in cocaine craving lasts about 15 and 40 days long, respectively.[26,27] This matter should be considered for future experiments of NAC on dependent humans, because our knowledge about the development of anti-relapse effect is poor.

The NAC was safe and tolerable in this study. This finding is in agreement with LaRowe, et al. study on safety and tolerability of NAC which concluded that the number of subjects that reported side effects in the NAC group was not different from the number of subjects that reported side effects in the placebo group.[15] Although we used lower doses of NAC (1200 mg/day), which may cause lower side effects, but other studies which used different doses of NAC, also did not find any significant differences between the number of subjects who showed side-effects with different dosages (i.e. 1200, 2400 and 3600 mg/day).[24]

This study had some limitations. The first limitation was the few representation of female patients in the sample. This is because of the fewer proportions of females in our studied community, i.e. METH users in our country. The second limitation was our evaluation of the compliance of patients to the NAC regimen through patient reports and pill counts. This may be better evaluated and managed in future studies.

In summary, this study showed that NAC was an effective and safe choice for reduction of the METH craving in dependents, in an outpatient setting. It may be a promising new treatment for treating of METH dependence.

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