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Evaluating the efficacy of N-acetyl-cysteine in combination with naloxone for the treatment of patients with methadone poisoning; a double-blind randomized clinical trial

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ABSTRACT

Introduction: Methadone overdose is a severe and possibly fatal situation. Its routine treatment is naloxone therapy, meanwhile, N-acetylcysteine (NAC) may be effective in its clinical symptom improvement.

Objectives: This study aimed to assess the effectiveness of combining NAC with naloxone in treating patients who have overdosed on methadone.

Patients and Methods: This double-blind clinical trial was conducted on patients with methadone intoxication referred to Kashani Hospital in Shahrekord, Iran, from May to December 2021. Before the study began, written informed consent was obtained from the patients, and they were randomly assigned to two groups of intervention and control, with 32 patients in each group. In the control group, standard treatment with naloxone was administered, whereas in the intervention group, NAC was added to the standard treatment. The outcome measures included hemodynamic parameters, arterial blood gas analysis, and liver functional tests, which were assessed before and after the intervention, were compared between the two groups using statistical tests.

Results: The study results indicated that the mean age of the control and intervention groups was 43.09 and 44.21 years, respectively. Demographic characteristics were similar between the two groups. The comparative analysis of the mean differences in changes in hemodynamic and biochemical parameters between the control and intervention groups revealed that the changes in mean arterial pressure (MAP), respiratory rate (RR), temperature (T), pH, and bicarbonate (HCO_3) were not statistically significant ($P > 0.05$). Conversely, the mean differences in changes of pulse rate (PR), partial pressure of carbon dioxide (PCO_2), partial pressure of oxygen (PO_2), alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP) were found to be statistically significant ($P < 0.05$). This analysis demonstrated significant reductions in PR, PCO_2, and liver function tests (LFTs) including ALT, AST, and ALP in the intervention group compared to the control group. In contrast, the PO_2 showed a positive change, with the intervention group exhibiting a greater increase compared to the control group.

Conclusion: We conclude that NAC has a positive impact on the treatment of methadone intoxication, especially in improving liver function and respiratory parameters.

Trial Registration: The trial protocol was approved by the Iranian Registry of Clinical Trials (IRCT20210222050462N1, https://irct.behdasht.gov.ir/trial/55313; ethical code from Shahrekord University of Medical Sciences; IR.SKUMS.REC.1399.244).

Implication for health policy/practice/research/medical education:
This study highlights the potential benefits of combining N-acetyl-cysteine with standard treatment in the management of methadone poisoning, which can inform clinical practice and improve patient care.

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Clinical Trial

Introduction

The use of opioids for centuries has been an effective option in pain management. When given at proper doses, opioids not only eliminate pain but also help prevent its recurrence in long-term recovery situations (1). Some people benefit from the relieving effect of opioids in chronic pain management (2); however, its abuse is a challenging issue that imposes a substantial burden not just on the individual but also on families and communities; around 10% of the United States population have experienced illicit drug use, with 20 million Americans struggling with it (3). Methadone is a synthetic opioid that can be highly effective in managing withdrawal symptoms and cravings associated with opioid use disorder; however, it can also be dangerous if not used properly or in excessive doses (4). Methadone poisoning is a serious and potentially life-threatening condition that can occur when an individual takes more than the recommended dose of methadone commonly used to treat opioid addiction or when combined with other substances that can enhance its effects and cause consumer deaths (5). In the United States despite the increasing federal resources for reducing opioid-related mortality, found a 71% increase in opium intoxication deaths in the 12 months ending in October 2021 compared to a similar duration in 2016 (6).

Naloxone as a standard treatment for methadone intoxication (7,8) plays an important role in the prevention of mortality caused by opium intoxication through the reverse of respiratory depression (6). This medication is used to reverse opioid overdoses by binding to opioid receptors and blocking the effects of opioids. It is often administered intravenously, intramuscularly, or via nasal spray, and is commonly used in emergencies to counteract the life-threatening effects of opioid poisoning (9). However, some studies showed that, although naloxone administration is the current approach to treat methadone overdose, it may lead to serious problems including respiratory arrest, endotracheal intubation, and mortality (10), and naloxone antidote therapy in acute opioid poisoning does not always clearly demonstrate its sufficient efficacy (11). Overall, the literature indicates that while naloxone is the standard treatment for methadone overdose, its efficacy may be limited, and it can potentially lead to serious adverse effects.

N-acetylcysteine (NAC) is a compound with various therapeutic applications that benefit in treating multiple substance use disorders, including addiction. A meta-analysis found that NAC significantly reduced craving symptoms and withdrawal syndrome in individuals with substance use disorders (12). Additionally, NAC has been shown to attenuate neurotoxic damage in individuals using methamphetamine (13); therefore, it may be effective in alleviating cognitive and psychiatric symptoms associated with methadone use.

NAC is known for its antioxidant properties and potential in chelating heavy metals like lead (14), it has also demonstrated efficacy in managing methamphetamine dependence by reducing craving and addiction severity (13). On the other hand, naloxone interventions have been highlighted as crucial in addressing opioid overdose rates, especially among methadone-treated individuals, emphasizing the importance of enhancing naloxone carry rates through targeted (15). Therefore, combining NAC with naloxone could potentially offer a multifaceted approach by addressing oxidative stress, reducing craving, and improving harm-reduction behaviors in patients with methadone poisoning, warranting further research to explore its full therapeutic potential.

Objectives

The objective of this study is to evaluate the efficacy of NAC in combination with naloxone for the treatment of patients with methadone poisoning in a double-blind randomized clinical trial. The study aims to determine if the addition of NAC to the standard treatment of naloxone can improve clinical outcomes in patients with methadone poisoning.

Patients and Methods

Study design and participants

This double-blind, randomized clinical trial was conducted on patients with methadone poisoning at Kashani Hospital in Shahrekord, Iran from May to December 2021. Patients with methadone poisoning referred to Kashani Hospital during the study period were eligible for inclusion. The participants were divided into two groups; the intervention group received standard treatment (naloxone) plus NAC, while the other group received the naloxone alone. Various parameters were monitored and compared between the two groups to evaluate the efficacy of NAC in the treatment of methadone poisoning.

Inclusion and exclusion criteria

Inclusion criteria included a confirmed diagnosis of methadone poisoning, age ≥ 18 years, and ability to provide written informed consent. Exclusion criteria included not being willing to continue the study, a history of severe allergic reactions to the treatment medications, severe liver or kidney disease, or other significant medical conditions that could impact the study's outcome.

Sample size

The sample size was determined based on the expected rate of successful treatment in the control group and the desired power to detect a significant difference between the control and intervention groups. A total of 64 patients were enrolled in the study, with 32 patients assigned to each group.

Randomization

Patients were randomly assigned to either the control or intervention group using a computer-generated

randomization schedule. The allocation was concealed from the researchers and patients until the end of the study.

Blinding

Both the researchers (or the caregivers who take care of patients) and patients were blinded to the treatment assignment. The researchers or the caregivers who take care of patients were unaware of the treatment group assignments, and the patients were not informed of the specific medications they were receiving.

Data collection

Prior to the initiation of any intervention, written informed consent was obtained and signed by all participating patients. The demographic characteristics were collected. Subsequently, hemodynamic parameters were meticulously monitored and recorded, including vital signs such as blood pressure, heart rate, temperature, and respiratory rate (RR). Additionally, blood samples were collected for subsequent analysis, and arterial blood gas (ABG) analysis and liver function tests (LFTs) were performed to establish baseline values for these critical parameters.

Intervention

Patients were randomly assigned to the two groups of intervention and control. Both groups received standard treatment consisting of supportive care, including activated charcoal administration, fluid resuscitation, close monitoring of vital signs, and administration of naloxone according to the standard protocol. Naloxone, an opioid antagonist, was administered intravenously (IV) to patients with methadone poisoning in this study, the dosage and frequency were adjusted based on the patient's addiction status; in non-addicted patients, naloxone was administered at a dose of 0.4 mg, repeated once every 5 minutes until the patient's oxygen saturation (SpO_2) reached above 93%, while in addicted patients, a lower dose of 0.05 mg was used, repeated once every 5 minutes until the target oxygen saturation was achieved, to avoid precipitating acute opioid withdrawal symptoms that can occur with rapid opioid antagonist administration, and the lower initial dose and slower titration aimed to gradually reverse the opioid effects while minimizing the risk of withdrawal symptoms. The maintenance dose of naloxone was initiated at a rate of 2/3 of the wake-up dose, which was defined as the dose that restored the patient's consciousness or alleviated respiratory depression. This maintenance infusion was administered for 24 hours, after which a naloxone taper was commenced. During the taper phase, the naloxone dose was reduced by half every 6 hours until it reached zero, ensuring a gradual and controlled reversal of the opioid effects while minimizing the risk of precipitated withdrawal symptoms (16). In the intervention group in addition to the standard protocol, the administration of NAC was conducted as same as the used protocol in the acetaminophen intoxication. The 21-hour IV protocol of NAC involves a three-stage administration regimen. The loading dose of 150 mg/kg is administered in 200 mL of 5% dextrose in water (D5W) for 60 minutes. This is followed by a continuous infusion of 50 mg/kg in 500 mL of D5W over the next 4 hours, which translates to a rate of 12.5 mg/kg/h. The final stage involves a continuous infusion of 100 mg/kg in 1000 mL of D5W over the remaining 16 hours, resulting in a rate of 6.25 mg/kg/h (17,18).

Outcome measurement

Following the completion of the intervention, the patient was monitored for an additional 24 hours without receiving any further naloxone or NAC administration. During this period, the patient's symptoms were closely monitored, and once they had remained symptom-free for the full 24 hours, the outcome parameters including hemodynamic parameters, ABG analysis, and liver LFTs test which was measured at baseline were remeasured to determine the efficacy of the treatment protocol in achieving a successful reversal of the methadone poisoning.

Statistical analysis

The outcome measure was analyzed using the Statistical Package for the Social Sciences (SPSS) version 27 (IBM Corp., USA). The chi-square and Fisher's exact tests were used to compare the qualitative data between the control and intervention groups. Quantitative data were analyzed using the Wilcoxon rank-sum or paired t-test and Mann-Whitney U or independent *t* test, depending on the data distribution. To assess the data normality, the Kolmogorov-Smirnov test was conducted, and to evaluate the homogeneity of variance, the Levene test was employed. All statistical tests were two-tailed, and a *P* value of 0.05 or less was considered statistically significant.

Results

At the inception of the study, 101 patients were enrolled and evaluated for eligibility; 36 of them failed to meet the inclusion criteria and were excluded. The 65 remaining patients who met the inclusion criteria were randomly assigned into two groups: a control group (n = 32) and an intervention group (n = 33). All patients in both groups received the allocated intervention, except for one patient in the intervention group who did not receive the intervention due to an adverse reaction to NAC. All patients who received the intervention completed the study protocol and were included in the final analysis (Figure 1).

Results demonstrated that the mean age was 43.09 ± 17.18 years in the control group and 44.21 ± 15.15 years in the intervention group. The independent t-test indicated that this difference in mean age between the two groups was not statistically significant. Most patients

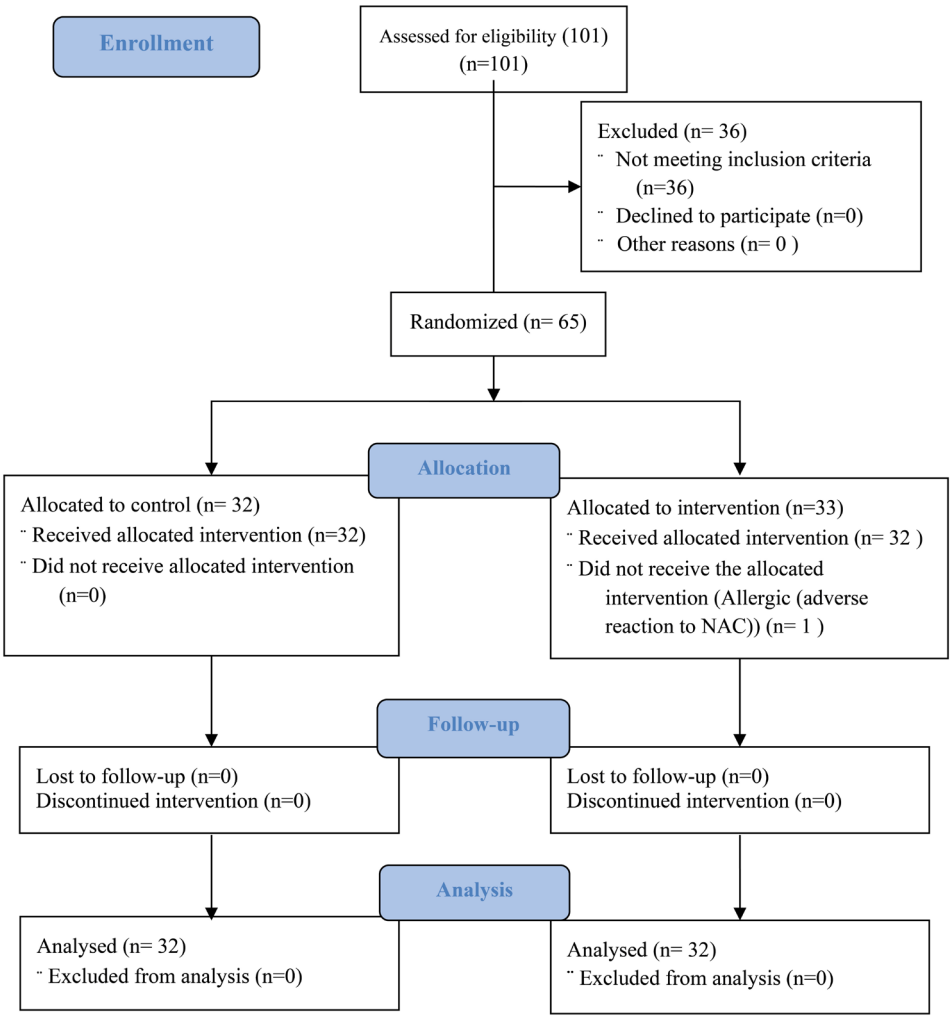

Figure 1. CONSORT flow diagram of the study.

(n = 61) did not have hypertension (HTN), with 50.8% in the control group and 49.2% in the intervention group. The chi-square test indicated that the difference in HTN prevalence between the groups was not significant. Also, the majority of patients (n = 59) do not have diabetes, with 49.2% in the control group and 50.8% in the intervention group; this difference in diabetes prevalence between the groups was not statistically significant. Regarding height and weight, the difference in their mean between the two groups of control and intervention was not statistically significant (Table 1).

The comparative analysis of clinical characteristics between the control and intervention groups at admission and after the intervention completion time revealed that, at the admission time, the mean differences in mean arterial pressure (MAP), RR, temperature (T), pH, partial pressure of carbon dioxide (PCO_2), partial pressure of oxygen (PO_2), bicarbonate (HCO3), alanine transaminase (ALT), and alkaline phosphatase (ALP) between the two groups were not statistically significant. In contrast, the mean difference in pulse rate (PR) and aspartate transaminase (AST) was found to be statistically significant. Following the completion of the intervention, a comparative analysis of clinical characteristics between the control and intervention groups revealed that the mean differences in MAP, RR, T, pH, and HCO3 between the two groups remained non-significant. In contrast, the mean differences in AST and PR persisted as statistically significant. Furthermore, the PCO2, PO2, ALT, and ALP exhibited a significant change from non-significant at admission to significant after the intervention completion time (Table 2).

A comparative analysis of clinical data within the control and intervention groups at admission and post-intervention completion revealed distinct patterns. In the control group, the mean differences in MAP, PR, PO2, HCO3, and AST was not statistically significant. Conversely, the mean differences in RR, pH, PCO2, ALT, and ALP were substantial. In contrast, within the intervention group, the mean differences in RR, PR, pH, PCO2, PO2, HCO3, AST, ALT, and ALP were statistically significant before and after the intervention. Notably, MAP and T did not exhibit significant differences (Table 3).

The comparison analysis of mean changes in clinical

Table 1. Demographic characteristics of included patients and comparison between control and intervention groups

Variable	Sub-variable	Group				*P* value
		Control		Intervention		
		No.	%	No.	%	
Gender	Male (n = 39)	19	48.7	20	51.3	0.789*
	Female (n = 25)	13	52	12	48	
Hypertension	No (n = 61)	31	50.8	30	49.2	0.554*
	Yes (n = 3)	1	33.3	2	66.7	
Diabetes	No (n = 59)	29	49.2	30	50.8	0.641*
	Yes (n = 5)	3	60	2	40	
Variable		**Mean**	**SD**	**Mean**	**SD**	***P* value**
Age (y)		43.09	17.18	44.21	15.15	0.782**
Height (cm)		170.65	8.69	173.31	3.74	0.155***
Weight (kg)		61.90	11.13	68.62	8.87	0.600***

*Chi-square; **Independent t-test; ***Mann-Whitney.

Table 2. Comparison of clinical data between control and intervention groups at admission time and after the intervention completion

Variable	Baseline		*P* value	After intervention		*P* value
	Control	Intervention		Control	Intervention	
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
MAP (mm Hg)	90.20 ± 8.73	88.74 ± 10.29	0.711*	91.51 ± 6.73	89.74 ± 6.38	0.220*
RR (n)	12.53 ± 2.44	11.44 ± 2.21	0.066**	14.84 ± 2.12	14.13 ± 1.40	0.056*
PR (n)	79.09 ± 9.53	89.38 ± 8.33	<0.001*	75.53 ± 8.57	79.63 ± 8.51	0.044*
T (°C)	36.72 ± 0.36	36.85 ± 0.47	0.330*	36.79 ± 0.31	36.95 ± 0.52	0.264*
PH	7.33 ± 0.07	7.31 ± 0.12	0.830*	7.39 ± 0.04	7.41 ± 0.05	0.452**
PCO_2 (mm Hg)	49.53 ± 8.40	50.38 ± 9.33	0.703**	44.80 ± 7.65	40.22 ± 6.93	0.015**
PO_2 (mm Hg)	44.65 ± 8.89	44.48 ± 5.95	0.931**	48.82 ± 5.55	55.72 ± 8.12	<0.001**
HCO_3 (mEq/L)	25.04 ± 4.01	23.19 ± 4.29	0.080**	29.92 ± 3.71	25.38 ± 4.77	0.072*
AST (IU/L)	30.91 ± 8.46	45.44 ± 6.70	<0.001**	28.81 ± 6.18	23.34 ± 1.41	<0.001*
ALT (IU/L)	44.88 ± 10.21	49.91 ± 14.84	0.119**	34.84 ± 8.49	25.24 ± 6.68	<0.001*
ALP (IU/L)	228.6 ± 40.1	242.3 ± 43.6	0.059*	179.2 ± 41.6	138.9 ± 18.06	<0.001*

SD: Standard deviation; MAP: Moderate arterial pressure; RR: Respiratory rate; PR: Pulse rate; T: Temperature; PCO2: Partial pressure of carbon dioxide; PO2: Partial pressure of oxygen; HCO3: Bicarbonate; AST: Aspartate transaminase; ALT: Alanine transaminase; ALP: Alkaline phosphatase. *Mann-Whitney; **Independent t-test.

Table 3. Comparative analysis of clinical characteristics within control and intervention groups at admission and after intervention-completion times

Variable	Control group		*P* value	intervention group		*P* value
	Before	After		Before	After	
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
MAP (mm Hg)	90.20 ± 8.73	91.51 ± 6.73	0.648*	88.74 ± 10.29	89.74 ± 6.38	0.945*
RR (n)	12.53 ± 2.44	14.84 ± 2.12	<0.001*	11.44 ± 2.21	14.13 ± 1.40	<0.001**
PR (n)	79.09 ± 9.53	75.53 ± 8.57	0.213*	89.38 ± 8.33	79.63 ± 8.51	<0.001
T (°C)	36.72 ± 0.36	36.79 ± 0.31	0.209*	36.85 ± 0.47	36.95 ± 0.52	0.536
PH	7.33 ± 0.07	7.39 ± 0.04	<0.001**	7.31 ± 0.12	7.41 ± 0.05	<0.001*
PCO_2 (mm Hg)	49.53 ± 8.40	44.80 ± 7.65	0.002*	50.38 ± 9.33	40.22 ± 6.93	<0.001**
PO_2 (mm Hg)	44.65 ± 8.89	48.82 ± 5.55	0.052**	44.48 ± 5.95	55.72 ± 8.12	<0.001*
HCO_3 (mEq/L)	25.04 ± 4.01	29.92 ± 3.71	0.152*	23.19 ± 4.29	25.38 ± 4.77	0.016**
AST (IU/L)	30.91 ± 8.46	28.81 ± 6.18	0.338*	45.44 ± 6.70	23.34 ± 1.41	<0.001*
ALT (IU/L)	44.88 ± 10.21	34.84 ± 8.49	<0.001**	49.91 ± 14.84	25.24 ± 6.68	<0.001*
ALP (IU/L)	228.6 ± 40.1	179.2 ± 41.6	<0.001*	242.3 ± 43.6	138.9 ± 18.06	<0.001*

SD: Standard deviation; MAP: Moderate arterial pressure; RR: Respiratory rate; PR: Pulse rate; T: Temperature; PCO2: Partial pressure of carbon dioxide; PO2: Partial pressure of oxygen; HCO3: Bicarbonate; AST: Aspartate transaminase; ALT: Alanine transaminase; ALP: Alkaline phosphatase. *Wilcoxon, **Paired t-test.

data between the intervention group, which received NAC administration, and the control group revealed different patterns. The mean differences in changes of MAP, RR, T, pH, and HCO3 between the two groups were not statistically significant. In contrast, the mean differences in changes of PR, PCO2, PO2, ALT, AST, and ALP were statistically significant. This analysis revealed significant reductions in PR, PCO2, and LFTs including ALT, AST, and ALP in the intervention group compared to the control group. In contrast, the PO2 showed a positive change, with the intervention group exhibiting a greater increase compared to the control group (Table 4).

Discussion

Methadone, a long-acting synthetic agonist of opioid receptors, is commonly employed within the framework of diverse opioid-driven addiction cessation programs. Its therapeutic utility is predicated on its ability to bind to opioid receptors, thereby mitigating the symptoms of withdrawal and facilitating the management of opioid dependence. This pharmacological property has made methadone an integral component of various treatment regimens aimed at addressing opioid addiction, including maintenance therapy and detoxification protocols (19). It is used in medication-assisted treatment for opioid use disorder and helps reduce opioid cravings and withdrawal symptoms (20). Methadone has a high potential for abuse and can lead to physical dependence, which makes it a risk factor for methadone abuse and intoxication in the consumer (21). NAC is a safe and well-tolerated glutamatergic agent that has shown promise as a potential pharmacotherapy for substance use disorders (22). It can restore homeostasis to brain glutamate disrupted in addiction, thereby reducing craving and the risk of relapse. Additionally, NAC has antioxidant properties that may protect against methadone-induced toxicity (23). In this study, we evaluated the therapeutic potential of NAC in combination with naloxone for the management of methadone intoxication, examining its effects on various hemodynamic parameters and LFTs.

The results of our study on NAC treatment for methadone poisoning revealed significant differences in several key parameters. The combination of NAC and naloxone treatment demonstrated significant reductions in PR, PCO2, and LFTs, including ALT, AST, and ALP, compared to the naloxone alone. Conversely, the PO2 showed a positive change, with a greater increase in the NAC and naloxone group. These findings suggest that NAC had a positive impact on the treatment of methadone poisoning, particularly in terms of improving liver function and respiratory parameters. The reduction in LFTs such as ALT, AST, and ALP indicated that NAC may have helped to mitigate liver damage caused by methadone poisoning. Similarly, the decrease in PCO2 and increase in PO2 suggest that NAC may have improved respiratory function, which is critical in managing methadone poisoning.

A comprehensive review of the existing literature did not yield any studies specifically examining the effect of NAC on the treatment of methadone poisoning. However, a similar study by McKetin et al investigated the efficacy of NAC in managing methamphetamine dependence. Their findings indicated that NAC treatment did not significantly reduce drug dependence in patients with methamphetamine dependence (23). In a study by LaRowe et al, the results demonstrated that NAC is a tolerable treatment in healthy, cocaine-dependent patients and may reduce their withdrawal symptoms and cravings (24). Also, our results are consistent with previous studies that have demonstrated the therapeutic potential of NAC in various conditions. For example, NAC has been shown to have antioxidant and anti-inflammatory effects, which

Table 4. Comparison of mean changes in clinical data during the times of admission until intervention completion between control and intervention groups

Variable	Control group		Intervention group		Mean difference		*P* value
	Mean	SD	Mean	SD	Mean	Standard error	
MAP (mm Hg)	+ 1.30	7.88	+ 1.87	10.22	0.57	2.28	0.925*
RR (n)	+ 2.31	2.81	+ 2.68	2.34	0.37	0.64	0.565**
PR (n)	- 3.56	12.88	- 9.75	10.90	6.18	2.98	0.013*
T (C)	+ 0.06	0.33	+ 0.09	0.68	0.03	0.13	0.861*
PH	+ 0.05	0.06	+ 0.09	0.12	0.04	0.02	0.358*
PCO_2 (mm Hg)	- 4.73	7.96	- 10. 16	11.91	5.43	2.53	0.036**
PO_2 (mm Hg)	+ 4.17	11.66	+ 11.23	11.75	7.06	2.92	0.019**
HCO_3 (mEq/L)	+ 0.87	5.22	+ 2.19	4.85	1.32	1.26	0.301**
AST (IU/L)	- 2.10	9.68	- 22.09	6.51	19.99	2.06	<0.001**
ALT (IU/L)	-10.03	11.88	-24.66	14.90	14.63	3.36	<0.001**
ALP (IU/L)	- 49.40	39.30	- 103.41	46.20	54.01	10.72	<0.001**

SD: Standard deviation; MAP: Moderate arterial pressure; RR: Respiratory rate; PR: Pulse rate; T: Temperature; PCO2: Partial pressure of carbon dioxide; PO2: Partial pressure of oxygen; HCO3: Bicarbonate; AST: Aspartate transaminase; ALT: Alanine transaminase; ALP: Alkaline phosphatase. *Mann-Whitney; **Independent t-test.

can help to protect against oxidative stress and tissue damage (25).

Overall, this study highlights the potential benefits of NAC in the treatment of methadone poisoning, particularly in terms of improving liver function and respiratory parameters. The findings support the use of NAC as a therapeutic agent in managing methadone poisoning and suggest that it may be a valuable adjunct to standard treatment regimens. While a clinical trial is still needed to approve the efficacy of NAC in the treatment of methadone intoxication, the preliminary evidence suggests that NAC may be a useful adjunct therapy in the management of methadone poisoning. However, further research is needed to definitively establish the efficacy and nature of the benefit of NAC in treating methadone poisoning.

Conclusion

The comparative analysis of hemodynamic and biochemical parameters between the control and intervention groups revealed significant differences in PR, PCO2, PO2, and LFTs. The intervention group demonstrated significant reductions in PR, PCO2, and LFTs, including ALT, AST, and ALP, compared to the control group. Conversely, the PO2 showed a positive change, with the intervention group exhibiting a greater increase compared to the control group. These findings suggest that NAC had a positive impact on the treatment of methadone poisoning, particularly in terms of improving liver function and respiratory parameters.

Limitations of the study

This study was conducted on a limited number of the patients. We suggest larger studies on this subject.

Authors' contribution

Conceptualization: Pantea Ramezannezhad.
Data curation: Zahra Karimi Taghanaki.
Formal analysis: Esfandiar Heidarian.
Investigation: Pantea Ramezannezhad and Zahra Karimi Taghanaki.
Methodology: Esfandiar Heidarian.
Project management: Pantea Ramezannezhad.
Resources: All authors.
Supervision: Zahra Karimi Taghanaki.
Validation: Elham Raeisi.
Writing—original draft: All authors.
Writing—reviewing and editing: All authors.

Conflicts of interest

The authors declare no conflict of interest.

Ethical issues

The research was conducted in accordance with the principles of the Declaration of Helsinki. This study resulted from the internal medicine residential thesis of Zahra Karimi Taghanaki (Thesis #5554), with the Ethical code (#IR.SKUMS.REC.1399.244), approved by the ethics committee of Shahrekord University of Medical Sciences, Shahrekord, Iran. The study protocol was also registered as a clinical trial at the Iranian Registry of Clinical Trials (identifier: IRCT20210222050462N1; https://irct.behdasht.gov.ir/trial/55313). Accordingly, written informed consent was taken from all participants before any intervention. Besides, the authors have ultimately observed ethical issues (including plagiarism, data fabrication, and double publication).

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References

1. Stoicea N, Costa A, Periel L, Uribe A, Weaver T, Bergese SD. Current perspectives on the opioid crisis in the US healthcare system: A comprehensive literature review. Medicine (Baltimore). 2019;98:e15425. doi: 10.1097/md.0000000000015425.
2. Pergolizzi JV, Varrassi G, Paladini A, LeQuang J. Stopping or Decreasing Opioid Therapy in Patients on Chronic Opioid Therapy. Pain Ther. 2019;8:163-76. doi: 10.1007/s40122-019-00135-6.
3. Urits I, Patel A, Zusman R, Virgen CG, Mousa M, Berger AA, et al. A Comprehensive Update of Lofexidine for the Management of Opioid Withdrawal Symptoms. Psychopharmacol Bull. 2020;50:76-96.
4. Rodriguez CE, Klie KA. Pharmacological treatment of opioid use disorder in pregnancy. Semin Perinatol. 2019;43:141-8. doi: 10.1053/j.semperi.2019.01.003.
5. Calcaterra SL, Bach P, Chadi A, Chadi N, Kimmel SD, Morford KL, et al. Methadone Matters: What the United States Can Learn from the Global Effort to Treat Opioid Addiction. J Gen Intern Med. 2019;34:1039-42. doi: 10.1007/s11606-018-4801-3.
6. Kozak Z, Ciccarone D, Thrul J, Cole TO, Pappas AL, Greenblatt AD, et al. Harm reduction behaviors are associated with carrying naloxone among patients on methadone treatment. Harm Reduct J. 2023;20:17. doi: 10.1186/s12954-023-00745-6.
7. Sameed M, Teague H. Use of nebulized naloxone to reverse methadone overdose - A case report and review of literature. J Community Hosp Intern Med Perspect. 2019;9:422-4. doi: 10.1080/20009666.2019.1659664.
8. Petrich M, Battin M, Walker E, Brown M, Abdelwahab M, Ma'ayeh M, et al. Comparison of neonatal outcomes in pregnant women undergoing medication-assisted treatment of opioid use disorder with methadone or buprenorphine/naloxone. J Matern Fetal Neonatal Med. 2022;35:10481-6. doi: 10.1080/14767058.2022.2130238.
9. Musy SN, Ausserhofer D, Schwendimann R, Rothen HU, Jeitziner MM, Rutjes AW, et al. Trigger Tool-Based Automated Adverse Event Detection in Electronic Health Records: Systematic Review. J Med Internet Res. 2018;20:e198. doi: 10.2196/jmir.9901.
10. Fox LM, Hoffman RS, Vlahov D, Manini AF. Risk factors

for severe respiratory depression from prescription opioid overdose. Addiction. 2018;113:59-66. doi: 10.1111/add.13925.
11. Choi NG, Choi BY, DiNitto DM, Marti CN, Baker SD. Naloxone therapy for prescription and illicit opioid poisoning cases aged 50+in the national poison data system, 2015-2020. Clin Toxicol (Phila). 2022;60:499-506. doi: 10.1080/15563650.2021.1981362.
12. Chang CT, Hsieh PJ, Lee HC, Lo CH, Tam KW, Loh EW. Effectiveness of N-acetylcysteine in Treating Clinical Symptoms of Substance Abuse and Dependence: A Meta-analysis of Randomized Controlled Trials. Clin Psychopharmacol Neurosci. 2021;19:282-93. doi: 10.9758/cpn.2021.19.2.282.
13. McKetin R, Dean OM, Turner A, Kelly PJ, Quinn B, Lubman DI, et al. A study protocol for the N-ICE trial: A randomised double-blind placebo-controlled study of the safety and efficacy of N-acetyl-cysteine (NAC) as a pharmacotherapy for methamphetamine ("ice") dependence. Trials. 2019;20:325. doi: 10.1186/s13063-019-3450-0.
14. Wang L, Xu Y, Zhao X, Zhu X, He X, Sun A, et al. Antagonistic effects of N-acetylcysteine on lead-induced apoptosis and oxidative stress in chicken embryo fibroblast cells. Heliyon. 2023;9:e21847. doi: 10.1016/j.heliyon.2023.e21847.
15. Shearer J, Mammen K, Bell J. The acceptability of combined methadone-naloxone treatment: Consumer and provider views on the potential utility of methadone-naloxone. Drug Alcohol Rev. 2010;29:138-43. doi: 10.1111/j.1465-3362.2009.00118.x.
16. McDonald R, Lorch U, Woodward J, Bosse B, Dooner H, Mundin G, et al. Pharmacokinetics of concentrated naloxone nasal spray for opioid overdose reversal: Phase I healthy volunteer study. Addiction. 2018;113:484-93. doi: 10.1111/add.14033.
17. Papazoglu C, Ang JR, Mandel M, Basak P, Jesmajian S. Acetaminophen overdose associated with double serum concentration peaks. J Community Hosp Intern Med Perspect. 2015;5:29589. doi: 10.3402/jchimp.v5.29589.
18. Hendrickson RG. What is the most appropriate dose of N-acetylcysteine after massive acetaminophen overdose? Clin Toxicol (Phila). 2019;57:686-91. doi: 10.1080/15563650.2019.1579914.
19. Ledingham E, Adams RS, Heaphy D, Duarte A, Reif S. Perspectives of adults with disabilities and opioid misuse: Qualitative findings illuminating experiences with stigma and substance use treatment. Disabil Health J. 2022;15:101292. doi: 10.1016/j.dhjo.2022.101292.
20. Mackay L, Bach P, Milloy MJ, Cui Z, Kerr T, Hayashi K. The relationship between crystal methamphetamine use and methadone retention in a prospective cohort of people who use drugs. Drug Alcohol Depend. 2021;225:108844. doi: 10.1016/j.drugalcdep.2021.108844.
21. Dupuy G, Cavalcanti L, Bourgogne E, Brichant-Petitjean C, Gomberoff L, Bloch V, et al. Are empty methadone bottles empty? An analytic study. Harm Reduct J. 2014;11:20. doi: 10.1186/1477-7517-11-20.
22. McClure EA, Gipson CD, Malcolm RJ, Kalivas PW, Gray KM. Potential role of N-acetylcysteine in the management of substance use disorders. CNS Drugs. 2014;28:95-106. doi: 10.1007/s40263-014-0142-x.
23. McKetin R, Dean OM, Baker AL, Carter G, Turner A, Kelly PJ, et al. A potential role for N-acetylcysteine in the management of methamphetamine dependence. Drug Alcohol Rev. 2017;36:153-9. doi: 10.1111/dar.12414.
24. LaRowe SD, Mardikian P, Malcolm R, Myrick H, Kalivas P, McFarland K, et al. Safety and tolerability of N-acetylcysteine in cocaine-dependent individuals. Am J Addict. 2006;15:105-10. doi: 10.1080/10550490500419169.
25. Rashid M, Chandran VP, Nair S, Muthu DS, Pappuraj J, Jacob KA, et al. N-Acetyl Cysteine in Rodenticide Poisoning: A Systematic Review and Meta-Analysis. Curr Rev Clin Exp Pharmacol. 2022;17:192-204. doi: 10.2174/2772432816666210825102726.