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Investigating the effect of adding silymarin to the standard treatment of naloxone in methadone intoxication; a double-blind clinical trial

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ABSTRACT

Introduction: In cases of methadone intoxication, the drug is mainly processed by the liver, however, its elimination through the kidneys is also crucial. On the other hand, naloxone therapy is a gold standard treatment for opioid intoxication, the addition of other drugs can improve its benefits and reduce side effects.

Objectives: This study aimed to assess the effectiveness of adding silymarin to the standard treatment of naloxone in patients with methadone intoxication, to improve patient outcomes and reduce the risk of complications associated with alone naloxone therapy.

Patients and Methods: This clinical trial study aimed to investigate the efficacy of silymarin in combination with standard treatment for methadone intoxication patients. The study employed a control group, which received standard treatment with naloxone, and an intervention group, which received both naloxone and silymarin. Liver functional tests (LFTs), kidney functional tests, malondialdehyde (MDA), and ferric-reducing ability of plasma (FRAP) were measured at admission and post-intervention times to compare the outcomes between the two groups. Statistical analyses, including chi-square, independent and paired *t* tests, Wilcoxon, and Mann-Whitney tests were conducted to identify significant differences between the groups.

Results: Results indicated that 32 and 33 patients were included in the naloxone and naloxone + silymarin groups, respectively. The results showed that the changes in kidney functional tests such as blood urea nitrogen (BUN) and creatinine (Cr), MDA, and FRAP were not statistically significant between the two groups. However, the changes in LFTs, including, aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP), were statistically significant. Notably, the LFT changes were more pronounced in the group receiving both naloxone and silymarin, indicating a greater reduction in liver enzymes in this combined treatment group.

Conclusion: The addition of silymarin to standard naloxone treatment for methadone intoxication patients could improve liver function, as the combined therapy showed a more pronounced reduction in liver enzyme levels compared to standard treatment alone; however, this combination treatment could not change the kidney function and oxidative stress markers.

Trial Registration: The trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT20210216050377N1; ethical code from Shahrekord University of Medical Sciences; IR.SKUMS.REC.1400.048). This study was also registered in Research Registry website with Unique Identifying Number (UIN) of researchregistry10395.

Implication for health policy/practice/research/medical education:
In this clinical trial study, we found that incorporating silymarin into standard naloxone treatment for methadone intoxication patients could improve liver function, which may lead to more effective management of liver-related complications. This finding could inform policy changes and clinical guidelines for the treatment of methadone intoxication, particularly in settings where liver dysfunction impacts kidney function; for example, it can lead to the accumulation of bilirubin and other substances that can cause kidney damage. Additionally, these findings highlight the need for further research to fully elucidate the mechanisms by which silymarin exerts its beneficial effects on liver function and to explore its potential as a complementary therapy in other clinical contexts.

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Clinical Trial

Introduction

Methadone, a synthetic opioid, was first developed in the 1940s as a painkiller. Today, it is the most widely used treatment for opioid dependence globally, having been employed for over 40 years under the methadone maintenance treatment (MMT) program (1). According to the search results, previous studies have found that MMT programs are effective in reducing crime, illegal medication use, morbidity, and mortality, while also improving social actions and quality of life for individuals compared to other opioids (2-5).

Methadone intoxication is a significant public health concern due to its widespread availability and increasing prevalence of drug addiction (6). Methadone is derived from heroin and often used to treat opioid use disorders, but its long-acting nature and potential for overdose can lead to severe and life-threatening consequences (7). This substance is predominantly eliminated through hepatic metabolism; however, its renal clearance is important. When kidney function declines, the ability to excrete methadone diminishes, resulting in higher plasma concentrations of the drug (8). In recent years, methadone poisoning has become a common cause of hospitalizations in intensive care units (ICUs), particularly among young children (9), with the majority of cases occurring due to accidental ingestion of the syrup form of the drug (10). Furthermore, the availability of methadone in pharmacies and its use by parents attempting to overcome addiction can contribute to the rising number of cases (11). Additionally, the severity of methadone intoxication can manifest in various ways, including respiratory depression, coma, vomiting, seizures, nausea, cardiac arrhythmia, and toxic-hypoxic encephalopathy, which underscores the need for effective treatment strategies, such as intestinal lavage and naloxone tapering methods (12).

Naloxone, a medication that reverses opioid overdoses, has been increasingly administered to treat opioid intoxication (13). Naloxone therapy in methadone intoxication is a topic of growing interest due to the increasing use of methadone for opioid use disorder and the potential for overdose. A case report published in 2023 described a patient who was hospitalized for phenibut intoxication while on regular methadone substitution therapy. The patient was given naloxone, which initially improved their symptoms but later led to agitation and the need for administration of haloperidol (14). Therefore, due to the potential side effects of naloxone therapy, its combination with other drugs seems to be necessary.

Silymarin, a flavonoid compound extracted from the milk thistle plant, has been studied for its potential therapeutic effects in various conditions, including liver disease and oxidative stress (15). Based on our knowledge, no study has been conducted to assess the use of silymarin in methadone poisoning. Therefore, while there is limited research on the role of silymarin in methadone intoxication, existing studies suggest that careful management of naloxone administration is crucial in managing the symptoms of methadone overdose.

Objectives

This study aimed to investigate the effectiveness of adding silymarin to the standard treatment of naloxone in patients with methadone intoxication, as compared to the standard treatment alone, in a double-blind clinical trial.

Patients and Methods

Study design and participants

This study is a randomized, double-blind clinical trial conducted from May 19, 2021 to December 20, 2021 at Kashani hospital in Shahrekord, focusing on patients with methadone overdose. The trial aimed to investigate the efficacy of adding silymarin to the standard treatment of naloxone methadone overdose, ensuring the highest level of scientific rigor through the use of a randomized and double-blind design. By controlling for extraneous variables and concealing treatment assignments from participants and researchers, the study minimized the risk of bias and enhanced the validity of its findings.

Inclusion criteria

We included patients without applying age restrictions who were referred to the emergency department of Kashani hospital with a confirmed diagnosis of methadone poisoning for the study. The methadone poisoning diagnosis was confirmed by the classical clinical triad (decreased level of consciousness, meiotic pupils, and decreased blood oxygen levels) as well as positive urine methadone levels. Patients with a Glasgow Coma Scale (GCS) score of 8 or higher and those who were able to provide informed consent were the other terms of inclusion criteria.

Exclusion criteria

- Informed consent: patients who refused to provide informed consent to continue participating in the study were excluded from further participation.
- Worsening of condition: patients whose condition deteriorated during the study were removed from the study and provided with emergency care to ensure their health and well-being were not compromised.
- Interfering substances: patients who used supplements or medications with similar effects or that interfered with the efficacy of naloxone and silymarin during the study were excluded from further participation.
- Silymarin or naloxone allergy: patients with a documented history of allergy to silymarin or naloxone were excluded from the study due to the potential risk of adverse reactions.

Sample size

To determine the sample size for this clinical trial study

considering the sample size in similar studies, we used the two-sample *t* test formula. Assuming a conservative estimate of the standard deviation (σ) as 1.0 and the effect size (d) as 0.5, we can calculate the sample size using the formula. Plugging in the values, we get approximately 64.5, which we round up to the nearest whole number, resulting in a total sample size of 65. This means that the study should include at least 65 patients in total, with 32 patients in the control group and 33 in the intervention group, to achieve the desired level of significance and power.

Randomization and allocation

In this clinical trial study, the lottery method of randomization involves generating a random sequence of treatment assignments using a random number generator or a lottery system. The study involved 65 patients and two treatments, the researcher generated a list of 65 random numbers, each corresponding to one of the treatments. The patients were then assigned to the one of treatment groups based on the order of their random numbers, ensuring that each treatment was assigned to a patient in a random and unbiased manner. This method ensures that the treatment assignments are truly random and independent of any potential confounding variables, which helps to increase the validity and reliability of the study's results.

Blinding

In the study, a double-blind design was employed to ensure the integrity of the results. This meant that both the patients participating in the trial and the researchers conducting the study were unaware of the treatment assignments. This approach helped to minimize the potential for bias and ensured that the outcomes were solely based on the efficacy of the treatments being tested, rather than any personal preferences or expectations.

Data collection and intervention

At the beginning of the study and before any intervention, the purpose of the study was explained to the patients, and written informed consent was taken. Demographic characteristics, including gender, age, body mass index (BMI), and underlying disease history, were collected by asking the patients. A blood sample was taken, and laboratory tests, including kidney functional tests such as blood urea nitrogen (BUN) and creatinine (Cr), liver functional tests (LFTs), malondialdehyde (MDA), and ferric-reducing ability of plasma (FRAP) were conducted. The MDA and FRAP tests were conducted using spectrophotometry (Spectrophotometer UV-2100, Unico, New Jersey, USA).

The control group received standard treatment involving naloxone therapy. Initially, a serum sample was taken, and treatment measures were initiated. In non-addicted patients, 0.4 mg of naloxone was injected intravenously (IV) every five minutes until oxygen saturation levels reached above 93%. In addicted patients, 0.05 mg was administered every five minutes. Following this treatment, a maintenance dose infusion with 2/3 of the wake-up dose was started for all patients and continued for 24 hours. The naloxone dose was then tapered by halving it every six hours until it reached zero. Given methadone's half-life of 25-52 hours, patients were monitored for 24 hours after naloxone cessation to ensure they did not exhibit any symptoms (16,17).

In the intervention group, patients received both standard treatments involving naloxone and silymarin as part of their treatment regimen. Specifically, patients in this group were administered 140 mg of silymarin tablets under the brand name Livergol (Goldaru Pharmaceutical Company) three times a day for three days in addition to naloxone therapy (18, 19). After the intervention, a second blood sample was obtained from each patient on the third day of naloxone treatment, and all relevant tests were rechecked. This modality allowed for a comprehensive comparison of primary variables within each group as well as between the two groups before and after the intervention.

Statistical analysis

The data were analyzed using SPSS version 27. For qualitative data, the chi-square and Fisher's exact tests were conducted to compare the control and intervention groups. The Wilcoxon rank-sum or paired *t* test and Mann-Whitney U or independent *t* test, based on the data distribution were conducted for quantitative data analysis. To determine normality, the Kolmogorov-Smirnov test was conducted. The *P* value <0.05 was considered significant.

Results

In the initial evaluation of eligible participants, 118 methadone-intoxicated patients were enrolled. However, 46 patients were excluded from the study due to various reasons, including not meeting inclusion criteria, declining to participate, and other reasons. Of the remaining 72 patients, 37 were randomly allocated to the intervention group and 35 to the control group. Both groups received the standard treatment of naloxone, with the intervention group also receiving silymarin. Two patients in the intervention group were excluded due to unwillingness to continue the study. In the evaluation for follow-up, two patients in the control group and one in the intervention group were lost to follow-up due to death or referral to another hospital. Additionally, one patient in both groups was lost to follow-up due to discharge by personal consent. Finally, 33 patients in the intervention group and 32 in the control group were included in the final data analysis (Figure 1).

The demographic characteristics of the participants were analyzed to identify any potential differences

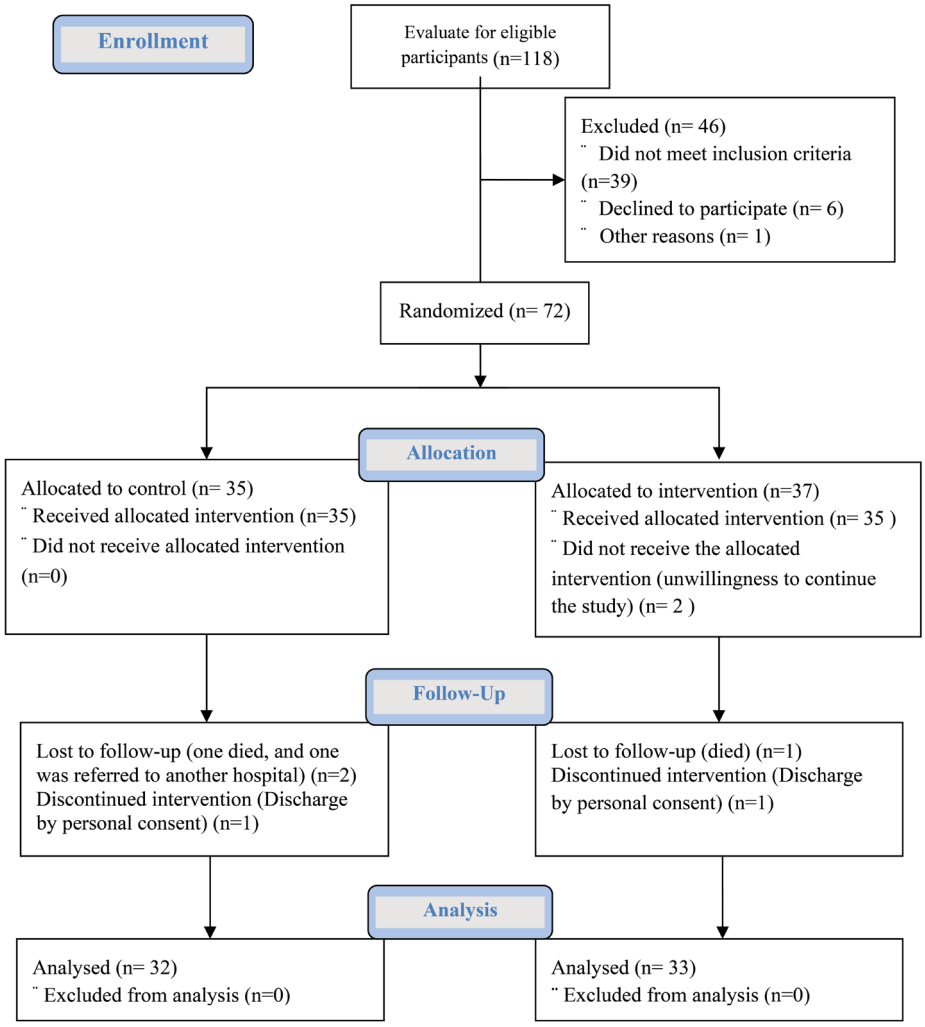

Figure 1. CONSORT flowchart of the study.

between the naloxone and naloxone + silymarin groups. Results indicated that the naloxone group consisted of 32 patients, with 19 males and 13 females, with a mean age of 35.75 ± 1.63 years. In contrast, the naloxone + silymarin group consisted of 33 patients, with 24 males and 9 females, with a mean age of 43.64 ± 17.66 years. Statistical analysis revealed that the frequency distribution of all demographic characteristics was similar and showed no significant statistical difference between the two groups (Table 1).

The laboratory tests analysis at the patients' admission time revealed that none of the laboratory tests, including kidney function tests, LFTs, MDA, and FRAP tests, showed a significant difference between the naloxone group and the silymarin + naloxone group. Similarly, the mean difference in kidney functional tests, ALT, MDA, and FRAP at the post-intervention time was non-significant between the two groups. However, the mean difference in AST and ALP was significant, indicating a potential impact of the silymarin addition on liver enzyme activity (Table 2).

The results demonstrated that in the naloxone group, the mean changes of BUN, Cr, and MDA between admission and post-intervention time points were not statistically significant. However, the differences in LFTs and FRAP were significant. In the naloxone + silymarin group, the mean changes of BUN and MDA between admission and post-intervention were not statistically significant, while the differences in LFTs, Cr, and FRAP were significant. These findings suggest that the addition of silymarin to the naloxone treatment may have had a more pronounced impact on certain laboratory parameters, such as liver function and antioxidant status, compared to naloxone alone (Table 3).

The comparative analysis of mean changes between the naloxone and naloxone + silymarin groups revealed that the mean changes in BUN, Cr, MDA, and FRAP were not statistically significant. In contrast, the mean changes in LFTs, including AST, ALT, and ALP, were significant. Specifically, the mean changes in LFT tests were significantly higher in the naloxone + silymarin group compared to the naloxone group, indicating a more pronounced reduction in liver enzyme activity in the combined treatment group. This suggests that

Table 1. Demographic information of participant patients in both groups

Variable	Sub-variable	Group				*P* value
		Control (Naloxone) (n = 32)		Naloxone + Silymarin (n = 33)		
		No.	%	No.	%	
Gender	Male	19	59.4	24	72.7	0.225*
	Female	13	40.6	9	27.3	
Smoking	No	21	65.6	23	69.7	0.726*
	Yes	11	34.4	10	30.3	
HTN	No	24	75	26	78.8	0.717*
	Yes	8	25	7	21.2	
		Mean	SD	Mean	SD	
BMI (kg/m^2)		22.67	3.21	23.37	3.11	0.225**
Age (year)		35.75	15.63	43.64	17.66	0.062**

HTN, Hypertension; BMI, Body mass index.
*Chi-square; **Independent *t* test.

Table 2. Clinical data comparative analysis between naloxone (control) and naloxone + silymarin groups at pre- and post-intervention time points

Variable	Admission time (group)		*P* value	Post-intervention (group)		*P* value
	Control (Naloxone)	Naloxone + Silymarin		Naloxone	Naloxone + Silymarin	
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
BUN (mg/dL)	12.92 ± 1.82	13.81 ± 2.47	0.104*	12.65 ± 2.08	13.50 ± 2.12	0.110*
Cr (mg/dL)	1.05 ± 0.26	1.18 ± 0.28	0.073**	0.97 ± 0.21	1.03 ± 0.16	0.210*
AST (IU/L)	37.21 ± 10.00	40.78 ± 9.10	0.137*	29.96 ± 7.48	26.54 ± 4.70	0.032**
ALT (IU/L)	38.25 ± 5.06	40.84 ± 6.82	0.086*	29.65 ± 6.17	27.84 ± 8.10	0.317*
ALP (IU/L)	253.15 ± 44.60	273.72 ±38.66	0.051**	196.15± 41.6	174.2 ± 30.4	0.018*
MDA (µmol/L)	33.35 ± 7.74	30.72 ± 6.59	0.145*	31.68 ± 6.11	32.87 ± 6.67	0.458**
FRAP (µmol/L)	724.07 ± 91.74	731.01 ± 0.01	0.813*	650.60± 98.4	625.36±163.8	0.453*

SD, Standard deviation; BUN, Blood urea nitrogen; Cr, Creatinine; MDA, Malondialdehyde; FRA, Ferric-reducing ability of plasma; AST, Aspartate transaminase; ALT, Alanine transaminase; ALP, Alkaline phosphatase.
*Independent *t* test, **Mann-Whitney.

Table 3. The comparison of clinical data changes within the naloxone and naloxone + silymarin groups from admission to post-intervention times

Variable	Control (Naloxone) group		*P* value	Naloxone + Silymarin group		*P* value
	Admission time	Post-intervention		Admission time	Post-intervention	
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
BUN (mg/dL)	12.92 ± 1.82	12.65 ± 2.08	0.539*	13.81 ± 2.47	13.50 ± 2.12	0.601*
Cr (mg/dL)	1.05 ± 0.26	0.97 ± 0.21	0.234**	1.18 ± 0.28	1.03 ± 0.16	0.002**
AST (IU/L)	37.21 ± 10.00	29.96 ± 7.48	<0.001**	40.78 ± 9.10	26.54 ± 4.70	<0.001**
ALT (IU/L)	38.25 ± 5.06	29.65 ± 6.17	<0.001**	40.84 ± 6.82	27.84 ± 8.10	<0.001**
ALP (IU/L)	253.15± 44.60	196.15 ± 41.6	<0.001**	273.72± 38.6	174.21 ± 30.4	<0.001**
MDA (µmol/L)	33.35 ± 7.74	31.68 ± 6.11	0.275**	30.72 ± 6.59	32.87 ± 6.67	0.119**
FRAP (µmol/L)	724.07± 91.74	650.60 ± 98.4	<0.001*	731.01± 0.01	625.36±163.8	<0.001*

SD, Standard deviation; BUN, Blood urea nitrogen; Cr, Creatinine; MDA, Malondialdehyde; FRA, Ferric-reducing ability of plasma; AST, Aspartate transaminase; ALT, Alanine transaminase; ALP, Alkaline phosphatase.
*Paired *t* test, ** Wilcoxon.

the addition of silymarin to naloxone may have a more profound impact on liver function, potentially indicating improved liver health outcomes (Table 4).

Discussion

The findings of this clinical trial suggest that the addition of silymarin to the standard naloxone treatment for methadone intoxication patients may provide additional benefits in improving liver function. The study revealed a more pronounced reduction in liver enzyme levels in the group receiving the combined naloxone and silymarin treatment compared to those receiving only naloxone. This finding indicates that combination therapy may be more effective in mitigating the liver-related complications

Table 4. The comparative analysis of mean changes in the clinical characteristics from admission to post-intervention times between the naloxone and naloxone + silymarin groups

Variable	Naloxone group		Naloxone + Silymarin group		Mean difference		*P* value
	Mean	SD	Mean	SD	Mean	Standard Error	
BUN (mg/dL)	- 0.26	2.25	- 0.30	3.36	0.04	0.71	0.952*
Cr (mg/dL)	- 0.07	0.36	- 0.14	0.24	0.07	0.07	0.395**
AST (IU/L)	- 7.25	7.21	- 14.24	9.94	6.99	2.16	0.002**
ALT (IU/L)	- 8.59	6.45	- 13.00	10.33	4.41	2.14	0.044**
ALP (IU/L)	- 57.00	59.03	- 99.51	48.95	42.51	13.43	0.003*
MDA (µmol/L)	- 1.67	8.49	+ 2.14	7.70	3.81	2.01	0.062*
FRAP (µmol/L)	- 73.47	75.76	- 105.65	164.66	32.18	31.96	0.318**

SD, Standard deviation; BUN, Blood urea nitrogen; Cr, Creatinine; MDA, Malondialdehyde; FRA, Ferric-reducing ability of plasma; AST, Aspartate transaminase; ALT, Alanine transaminase; ALP, Alkaline phosphatase.
*Independent *t* test, **Mann-Whitney.

associated with methadone intoxication. To the best of our knowledge, this study is the first human study that assesses the effect of silymarin in methadone intoxication patients. In previous studies, numerous advantageous impacts of silymarin have been recognized, encompassing antioxidative, anti-inflammatory, hepatoprotective, and anti-fibrotic attributes, alongside the regulation of insulin resistance (20,21). Consistent with our study, an animal study by Yemişen et al demonstrated the protective efficacy of silymarin on liver damage. They evaluated the efficacy of silymarin in liver damage in burned rats and found the beneficial effect of silymarin in reversing this type of liver damage (22). Our results are also consistent with another study that has demonstrated the protective effects of silymarin in liver toxicity. Abdelaal et al evaluated the effects of silymarin versus silymarin and green coffee extract on thioacetamide-induced liver injury in rats and found that the combination therapy improved liver function and antioxidant enzyme levels compared to silymarin alone (23). Similarly, another study on the hepatoprotective and antioxidant activities of *Dicranopteris linearis* leaf extract against paracetamol-induced liver intoxication in rats found that the extract attenuated liver damage and oxidative stress, suggesting its potential as a complementary therapy for liver protection (24).

Furthermore, in line with our study, several clinical trial studies have demonstrated the beneficial effects of silymarin on hepatoprotective activities. For instance, Luangchosiri et al conducted a randomized double-blinded placebo-controlled study to evaluate the effect of silymarin on antituberculosis drug-induced liver damage. They found that oral administration of silymarin significantly reduced liver injury, although the difference in glutathione, transaminase, and MDA levels between the control and intervention groups was not statistically significant (25). In contrast, a study by El-Kamary et al found no significant effect of silymarin on LFTs, such as ALT and AST; the authors reported that the administration of silymarin did not result in a statistically significant improvement in ALT and AST levels compared to the placebo group. This discrepancy in findings may be attributed to differences in the study populations, dosage, and duration of silymarin treatment, or the underlying liver pathologies being investigated (26).

Our findings also demonstrated that the addition of silymarin to the standard naloxone treatment for methadone intoxication patients did not significantly improve kidney function or reduce oxidative stress markers compared to naloxone alone. Specifically, the study found that the changes in kidney function tests, as well as oxidative stress markers such as MDA and FRAP, were not significantly different between the group receiving the combined naloxone and silymarin treatment and the group receiving only naloxone. The lack of significant effects on kidney function and oxidative stress markers suggests that the potential benefits of silymarin in methadone intoxication may be more specific to liver protection, rather than having a broader impact on other organ systems or systemic markers of oxidative stress. These findings highlight the need for further research to fully elucidate the mechanisms by which silymarin may exert its protective effects and to determine the optimal therapeutic approach for managing the various complications associated with methadone intoxication. Additional studies are warranted to explore the potential differential effects of silymarin on liver versus kidney function, as well as its impact on other relevant clinical outcomes. The findings of this study are particularly relevant in the context of methadone intoxication, where liver damage is a significant concern. The study highlights the potential of silymarin as a complementary therapy to the standard naloxone treatment, warranting further investigation to fully elucidate the clinical implications and optimize the management of methadone intoxication.

Overall, the results of this clinical trial suggest that the addition of silymarin to the standard naloxone treatment for methadone intoxication patients may provide additional benefits in improving liver function. The findings support the potential of silymarin as a

complementary therapy and warrant further investigation to fully elucidate its clinical implications and optimize the management of methadone intoxication.

Conclusion

The findings of this clinical trial suggest that the addition of silymarin to the standard naloxone treatment for methadone intoxication patients may provide additional benefits in improving liver function. While the changes in kidney function tests, and oxidative stress markers such as MDA and FRAP, were not significantly different between the two groups, the study revealed a more pronounced reduction in liver enzyme levels in the group receiving the combined naloxone and silymarin treatment. This indicates that combination therapy may be more effective in mitigating the liver-related complications associated with methadone intoxication. The results highlight the potential of silymarin as a complementary therapy to the standard naloxone treatment, warranting further investigation to fully elucidate the clinical implications and optimize the management of methadone intoxication.

Limitations of the study

The study has several limitations; firstly, the sample size was relatively small, which may have limited the power to detect significant differences between the groups. Additionally, the study was conducted in a single center, which may not be representative of all patients with methadone intoxication. Furthermore, the study only measured LFTs, kidney functional tests, MDA, and FRAP, which may not capture the full range of potential benefits or adverse effects of the combined therapy. The study also did not control for potential confounding variables, such as patient demographics, comorbidities, or concomitant medications, which could have influenced the outcomes. Finally, the study was conducted in a controlled setting, which may not accurately reflect the real-world clinical practice where patients may receive varying levels of care and support.

Authors' contribution

Conceptualization: Maryam Hadipoor Chamgarani.
Data curation: Maryam Hadipoor Chamgarani, Pantea Ramezannezhad.
Formal analysis: Elham Raeisi.
Investigation: Pantea Ramezannezhad.
Methodology: Elham Raeisi and Esfandiar Heidarian.
Project Management: Pantea Ramezannezhad.
Resources: All authors.
Supervision: Maryam Hadipoor Chamgarani.
Validation: Esfandiar Heidarian.
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 under the tents of the Declaration of Helsinki. This study resulted from the thesis project of Maryam Hadipoor Chamgarani (Thesis#5550; Ethical code #IR.SKUMS.REC.1400.048), approved by the ethics committee of clinical biochemistry research center, basic health sciences institute, 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: IRCT20210216050377N1; https://irct.behdasht.gov.ir/trial/55314), and Research Registry website with Unique Identifying Number (UIN) of researchregistry10395. 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. Joseph H, Stancliff S, Langrod J. Methadone maintenance treatment (MMT): a review of historical and clinical issues. Mt Sinai J Med. 2000;67:347-64.
2. Marsch LA. The efficacy of methadone maintenance interventions in reducing illicit opiate use, HIV risk behavior and criminality: a meta-analysis. Addiction. 1998;93:515-32. doi: 10.1046/j.1360-0443.1998.9345157.x.
3. Bell J, Zador D. A risk-benefit analysis of methadone maintenance treatment. Drug Saf. 2000;22:179-90. doi: 10.2165/00002018-200022030-00002.
4. Dupont RL. Heroin addiction treatment and crime reduction. Am J Psychiatry. 1972;128:856-60. doi: 10.1176/ajp.128.7.856.
5. Martínez-Luna NG, Rodríguez-Cintas L, Esojo A, Palma-Álvarez RF, Robles-Martínez M, Grau-López L, et al. Harm reduction program use, psychopathology and medical severity in patients with methadone maintenance treatment. Adicciones. 2018;30:197-207. doi: 10.20882/adicciones.897.
6. Kharasch ED. Current Concepts in Methadone Metabolism and Transport. Clin Pharmacol Drug Dev. 2017;6:125-34. doi: 10.1002/cpdd.326.
7. Baehr C, Kelcher AH, Khaimraj A, Reed DE, Pandit SG, AuCoin D, et al. Monoclonal Antibodies Counteract Opioid-Induced Behavioral and Toxic Effects in Mice and Rats. J Pharmacol Exp Ther. 2020;375:469-77. doi: 10.1124/jpet.120.000124.
8. Vodovar D, Peyre H, Mégarbane B. Relationship between acute kidney injury and mortality in poisoning - a systematic review and metanalysis. Clin Toxicol (Phila). 2021;59:771-9. doi: 10.1080/15563650.2021.1928161.
9. Anderson M, Hawkins L, Eddleston M, Thompson JP, Vale JA, Thomas SH. Severe and fatal pharmaceutical poisoning in young children in the UK. Arch Dis Child. 2016;101:653-6. doi: 10.1136/archdischild-2015-309921.
10. Shinya H. A Case of child abuse disguised as drug

intoxication: Abuse should suspected in cases of accidental drug ingestion. Chudoku Kenkyu. 2016;29:365-6.
11. 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.
12. Glaizal M, Gazin V, Aymard I, Messina-Gourlot C, Richard N, Mallaret M, et al. Suicidal poisonings with methadone in France: results of a two year national survey by the Toxicovigilance network. Clin Toxicol (Phila). 2012;50:841-6. doi: 10.3109/15563650.2012.731510.
13. Toderika Y, Williams S. Naloxone for Opioid Overdose and the Role of the Pharmacist. Consult Pharm. 2018;33:98-104. doi: 10.4140/TCP.n.2018.98.
14. 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.
15. Mastron JK, Siveen KS, Sethi G, Bishayee A. Silymarin and hepatocellular carcinoma: a systematic, comprehensive, and critical review. Anticancer Drugs. 2015;26:475-86. doi: 10.1097/cad.0000000000000211.
16. Carpenter J, Murray BP, Atti S, Moran TP, Yancey A, Morgan B. Naloxone Dosing After Opioid Overdose in the Era of Illicitly Manufactured Fentanyl. J Med Toxicol. 2020;16:41-8. doi: 10.1007/s13181-019-00735-w.
17. Shaw LV, Moe J, Purssell R, Buxton JA, Godwin J, Doyle-Waters MM, et al. Naloxone interventions in opioid overdoses: a systematic review protocol. Syst Rev. 2019;8:138. doi: 10.1186/s13643-019-1048-y.
18. Sornsuvit C, Hongwiset D, Yotsawimonwat S, Toonkum M, Thongsawat S, Taesotikul W. The Bioavailability and Pharmacokinetics of Silymarin SMEDDS Formulation Study in Healthy Thai Volunteers. Evid Based Complement Alternat Med. 2018;2018:1507834. doi: 10.1155/2018/1507834.
19. Chantarojanasiri T. Silymarin treatment and reduction of liver enzyme levels in non-alcoholic fatty liver disease: a case report. Drugs Context. 2023;12. doi: 10.7573/dic.2023-1-4.
20. Saller R, Melzer J, Reichling J, Brignoli R, Meier R. An updated systematic review of the pharmacology of silymarin. Forsch Komplementmed. 2007;14:70-80. doi: 10.1159/000100581.
21. Gillessen A, Schmidt HH. Silymarin as Supportive Treatment in Liver Diseases: A Narrative Review. Adv Ther. 2020;37:1279-301. doi: 10.1007/s12325-020-01251-y.
22. Yemişen E, Yarat A, Akbay TT, Toklu H, Şener G. The effect of silymarin on the liver in thermal burn injury. Mar Pharmaceutical J. 2014;18:56-61. doi: 10.12991/mpj.2014186120.
23. Abdelaal S, E Mousa HS, Ahmed SM. Effect of Silymarin versus Silymarin and green coffee extract on Thioacetamide induced liver injury in adult male albino rats (histological and Immunohistochemical study). Egyptian Journal of Histology. 2019;42:133-46. doi: 10.21608/ejh.2018.5079.1022.
24. Zakaria ZA, Kamisan FH, Kek TL, Salleh MZ. Hepatoprotective and antioxidant activities of Dicranopteris linearis leaf extract against paracetamol-induced liver intoxication in rats. Pharm Biol. 2020;58:478-89. doi: 10.1080/13880209.2020.1764058.
25. Luangchosiri C, Thakkinstian A, Chitphuk S, Stitchantrakul W, Petraksa S, Sobhonslidsuk A. A double-blinded randomized controlled trial of silymarin for the prevention of antituberculosis drug-induced liver injury. BMC Complement Altern Med. 2015;15:334. doi: 10.1186/s12906-015-0861-7.
26. El-Kamary SS, Shardell MD, Abdel-Hamid M, Ismail S, El-Ateek M, Metwally M, et al. A randomized controlled trial to assess the safety and efficacy of silymarin on symptoms, signs and biomarkers of acute hepatitis. Phytomedicine. 2009;16:391-400. doi: 10.1016/j.phymed.2009.02.002.