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Research Article

Probiotics as a Complementary Method in Accelerating the Treatment of Opioid Poisoning: A Clinical Trial with *Lactobacillus* and *Bifidobacterium* Strains

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ABSTRACT

Introduction: The amount of opioids used in Iran is estimated at one million and two hundred thousand people. Probiotic force-feeding containing *Lactobacillus acidophilus* and *Bifidobacterium bifidum* can increase the effectiveness of initial treatment and intravenous naloxone as an antidote and accelerate recovery.

Materials and methods: In this randomized controlled clinical trial study, 30 patients with acute opioid poisoning were studied. In addition to treatment with naloxone and other control therapies, half of the patients were treated with probiotics and the other half with placebo. Patients were randomly assigned to one of the two case or control groups and the case group underwent standard probiotic force-feeding every eight hours for seven days. Data from the study were analyzed by SPSS software version 16. Results: The results of the present study showed that one week of treatment with probiotics caused a significant increase in glutathione antioxidant levels compared to before the intervention. In contrast, glutathione levels in the placebo group decreased considerably. Vitamin B6 levels after treatment with probiotics increased meaningfully compared to before the intervention, while in the placebo group, this amount decreased significantly compared to before the intervention. The difference in the mean level of serum glutathione and vitamin B6 in both groups (probiotics and placebo) was statistically significant before and after the intervention ($P<0.0001$).

Conclusion: Taking probiotics containing *Lactobacilli* and *Bifidobacterium* in combination with routine opioid poisoning treatments can improve the signs and symptoms of acute poisoning and increase the effectiveness of naloxone.

Keywords: Probiotic; *Lactobacillus*; *Bifidobacterium*; Acute poisoning; Opioid

INTRODUCTION

Drug poisoning is one of the most important and common types of medical emergencies that require special attention and timely interventions to treat patients and if necessary, the use of methods such as anti-dote and gastrointestinal lavage, etc., [1]. Rapid interventions for some types of poisoning that have more critical conditions and also in cases of multi-drug poisoning need more attention [2]. About 76% of patients in Iran, the treatment of drug poisoning are well done in the emergency room and patients with the relatively good general condition are discharged from the hospital in a short time [3]. However, in some cases, patients need to stay longer and receive more supportive treatments, and the common treatments used will not be effective [4]. Opioid poisoning is one of the most common types of poisoning and accounts for about 10% of all poisonings. Opioid poisoning due to overdose or causes such as suicide often leads to being life-threatening. Because the interval between drug intoxication and mortality from complications, especially respiratory depression, is short, there is little time to treat anti-toxicity and improves the condition of these patients. Therefore, today, various treatment methods are used for emergency treatment of these poisonings, each of which has its effectiveness and efficiency [5-7]. Narcotic drugs have numerous properties that have various effects on different systems of the body [8,9]. These drugs can cause distinctive functional symptoms in the respiratory system, central nervous system, cardiovascular system [10-12].

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Intestinal bacteria affect neural circuits that are particularly involved in addictive behaviors. Examining the clinical and preclinical evidence for the effects of opioid use on intestinal bacteria, and the effects of intestinal bacteria on behavioral responses to drugs supports a two-way relationship between intestinal microbiota and opioid-related behaviors. Therefore, it is necessary to study the possible mechanisms of communication between the intestine and the brain in situations such as addiction, which causes a person to suffer from various physical and psychological disorders [13].

The normal microbial flora of the human intestine changes in the diet, the use of antibiotics, maternal pregnancy, type of delivery (cesarean and normal), drug use, and many other factors. Communication between the brain and the gut is two-way communication. Just as the brain regulates gastroenteric function, enteric microbiota can also affect brain function. The normal microbial flora of the gut stimulates the production of various metabolites and stimulates the production of various hormones, resulting in effects on the hypothalamus, amygdala, and hypopharynx [14].

The idea of the effectiveness of probiotics as adjunctive therapy in the acute phase of opioid intoxication is rooted in some studies that have examined the relationship between prevotella and *bifidobacterium* strains in the gut and their modification by opioid use. The results of these studies indicate that the existing microbial balance will increase *bifidobacterium* [15]. So we can expect that by making changes in this balance with the use of probiotics, we can have a faster outcome in the treatment of drug poisoning and reduce mortality. This study aimed to determine the effect of probiotic use in accelerating the treatment of opioid intoxication.

MATERIALS AND METHODS

The present study was conducted as a randomized clinical trial with a control group on patients poisoned with opioids in the Intensive Care Unit (ICU) of Loghman hakim hospital in 2019. Probiotics were purchased from Zisttakhmir.

Sample size according to the pilot study and based on the formula, with considering alpha (first error of the study) at the rate of 0.05, beta (second error of the study) 0.1, P1 (probiotic effectiveness in the pilot study) 0.7 and P2 (placebo efficacy in the pilot study) 0.2, were calculated.

30 patients in two groups of 15 people, including the probiotic group and control group entered the study. Patients with concomitant poisoning with other substances, dissatisfactions of companions to participate in the study, or death of the patient were excluded from the study before the start of treatment.

Patients were randomly divided into one of two experimental or control groups using the block method, in the form of triple blocks. In addition to the usual treatment methods, the experimental group underwent oral administration of two standard probiotic sachets every eight hours for seven days.

Levels of glutathione, B6, and antioxidants were measured before and after the intervention using appropriate laboratory kits. An information form was prepared and patient information, including background information (age and gender), information on intoxication (duration of intoxication and intoxicating substance) and results of preclinical tests before and after the intervention as well as clinical indicators (level of consciousness and cognitive function of patients) were recorded in it.

Ethical approval

This study was approved by the institutional ethics board of Shahid Beheshti University of Medical Sciences (No: IR.SBMU.RETECH.REC.1398.428) and participants signed informed written consent forms.

Statistical analysis

Final data were analyzed using SPSS software version 16. The normal distribution of data was determined by the Kolmogorov-smirnov test. Then central and descriptive indices were calculated and expressed. Parametric tests such as independent t-test or parametric bread tests such as Mann-Whitney and Chi-square were also used. The significance level was considered $P<0.05$ for all samples.

RESULTS

The mean age in the probiotic group was 45.2 ± 18.33 years. The youngest patient in this group was 16 years old, and the oldest was 84 years old. In the placebo group, the mean age was 35.8 ± 18.67 years. The youngest patient in the control group was 16 years old, and the oldest was 73 years old. In the probiotic group, 11 patients (73.3%) were male and four patients (26.7%) were female, and in the placebo group, 12 patients (80%) were male and three patients (20%) were female.

The mean level of consciousness or GCS (Glasgow Coma Scale) in the probiotic group was 7.67 ± 1.29. The lowest GCS rated among patients was 5, and the highest was 9. In the placebo group, the mean GCS was 8.13 ± 1.72. The lowest GCS rated among patients was 5, and the highest was 12. The mean APACHE (Acute Physiology and Chronic Health Evaluation) in the probiotic group was 20.66 ± 5.65 and in the placebo group, the mean APACHE was 21 ± 6.17. No significant differences were observed between the two groups in terms of age, gender, GCS and APACHE scale.

The most toxic substance among the probiotic group was methadone (33.3%) followed by concomitant use of opium and methadone (26.7%). In contrast, in the placebo group, the most common cause of poisoning was methadone (40%) followed by tramadol (33.3%) (Table 1).

Table 1: Cause of poisoning in patients in the probiotic and placebo groups.

Cause of poisoning	Probiotic group (N=15)	Control group (N=15)	All patients (N=30)	P-value
Methadone	5 (33.3%)	6 (40%)	11 (36.7%)	0.161
Opium	3 (20%)	3 (20%)	6 (20%)	
Tramadol	1 (6.7%)	5 (33.3%)	6 (20%)	
Opium and methadone	4 (26.7%)	1 (6.7%)	5 (16.6%)	
Methadone and tramadol	2 (13.3%)	0 (0%)	2 (6.7%)	

Biochemical and hematological parameters before and after the intervention among patients in the experimental group and placebo are shown in Table 2. The results showed that in the probiotic and placebo groups, RBC (Red Blood Cell), Hemoglobin (Hgb), Hematocrit (HCT) and Potassium (K) levels after the intervention was significantly decreased (P<0.05). Also, the results showed that in the probiotic and placebo groups, PH level after the intervention was significantly increased (P<0.05).

Table 2: Hematology, biochemical and Blood Gases Index results in patients in the probiotic and placebo groups.

Variables	Therapeutic intervention	Probiotic (N=15)	Placebo (N=15)	P-value A	P-value B
Hematology (Mean ± SD)					
RBC (× 10^6/mm^3)	Before	4.49 ± 0.73	4.76 ± 0.71	P<0.0001	P<0.0001
	After	3.85 ± 0.63	3.83 ± 0.72		
Hgb (g/dl)	Before	13.41 ± 2.34	14.3 ± 2.3	P<0.0001	P<0.0001
	After	11.21 ± 1.97	11.4 ± 2.1		
HCT (%)	Before	41.84 ± 6.7	41.4 ± 7.22	P<0.0001	P<0.0001
	After	35.2 ± 5.38	35.27 ± 6.52		
MCV	Before	92.05 ± 5.65	93.18 ± 7.1	0.496	0.336
	After	91.38 ± 4.41	92.11 ± 5.65		
MCH	Before	28.04 ± 7.31	30.18 ± 2.86	0.177	0.447
	After	29.07 ± 1.89	29.77 ± 1.69		
MCHC	Before	32.45 ± 1.61	32.38 ± 1.76	0.144	0.954
	After	31.83 ± 1.82	32.35 ± 1.35		
WBC (× 10^3/mm^3)	Before	11.44 ± 3.65	12.34 ± 5.46	0.388	0.406
	After	10.38 ± 3.29	11.04 ± 4.98		
Neutrophils (%)	Before	81.57 ± 6.86	74.5 ± 17.64	0.34	0.67
	After	76.99 ± 8.9	76.67 ± 11.6		
Lymphocytes (%)	Before	13.45 ± 5.67	19.64 ± 15.63	0.693	0.417
	After	15.05 ± 6.4	15.87 ± 9.9		
PLT	Before	197.9 ± 55.5	231.4 ± 74.4	0.167	0.293
	After	223.6 ± 67.8	208.6 ± 81.7		
Biochemical (Mean ± SD)					
Glutathione	Before	2.08 ± 0.25	2.21 ± 0.15	0.014	P<0.0001
	After	2.29 ± 0.29	1.84 ± 0.38		
Vitamin B6	Before	30.23 ± 1.8	30.99 ± 1.36	P<0.0001	P<0.0001
	After	31.87 ± 2.3	29.61 ± 1.35		
Glucose (mg/dl)	Before	135.2 ± 68.31	120.33 ± 58.8	0.319	0.513
	After	118.3 ± 52.2	137.87 ± 77.59		
Urea (mg/dl)	Before	58.0 ± 32.75	58/0 ± 37.43	0.948	0.46
	After	57.06 ± 51.2	72.4 ± 80.53		
Creatinine (mg/dl)	Before	1.69 ± 0.72	1.7 ± 0.72	0.54	0.864
	After	1.43 ± 1.67	1.77 ± 2.1		
Na (mEq/l)	Before	137.2 ± 4.7	137.8 ± 3.64	0.191	0.69
	After	135.4 ± 3.43	137.3 ± 4.04		
K (mEq/l)	Before	4.47 ± 1.13	4.99 ± 1.23	0.005	0.002
	After	3.66 ± 0.49	3.84 ± 0.48		
Biochemical (Mean ± SD)					
PCO_2	Before	60.6 ± 19.01	60.54 ± 24.71	0.001	0.068
	After	38.94 ± 9.29	46.4 ± 18.9		
PO_2	Before	37.32 ± 19.56	37.07 ± 15.47	0.087	0.029
	After	49.6 ± 24.05	52.18 ± 25.01		
HCo_3	Before	22.04 ± 6.14	22.57 ± 4.79	0.392	0.14
	After	23.6 ± 4.87	24.9 ± 6.1		
Oxygen Saturation %	Before	50.7 ± 19.24	59.46 ± 27.97	0.001	0.081
	After	73.64 ± 19.22	75.37 ± 17.04		
PH	Before	7.22 ± 0.07	7.22 ± 0.11	P<0.0001	0.002
	After	7.38 ± 0.09	7.34 ± 0.1		

A: Comparison of mean before and after intervention in the probiotic group

B: Comparison of mean before and after intervention in the placebo group

The mean serum level of glutathione after intervention increased significantly in the probiotic group (P=0.014). In contrast, this amount decreased significantly in the placebo group (P<0.0001). The mean serum level of Vitamin B6 after intervention increased significantly in the probiotic group (P<0.0001). In contrast, this amount decreased significantly in the placebo group (P<0.0001).

Mean serum PCO_2 decreased significantly in the probiotic group after the intervention (P=0.001). In contrast, this amount in the placebo group was not significantly different from before the intervention. Mean serum PO_2 increased significantly in the placebo group after the intervention (P=0.029). In contrast, this amount in the probiotic group was not significantly different from before the intervention.

The mean percentage of oxygen saturation in the probiotic group decreased significantly after the intervention (P=0.001). In contrast, this value in the placebo group was not significantly different from before the intervention.

DISCUSSION

Opioid drugs-prescription painkillers and illicit drugs-exert their pharmacological effects by engaging the endogenous opioid system, where they act as agonists in the μ-opioid receptor. Opioids are abused because of their analgesic effects and beneficial properties. People who are physically addicted or addicted to opiates may also use opiates to prevent withdrawal symptoms [16]. According to statistics from the United States, among people aged 12 or older in 2019, 3.7% (or 10.1 million people) misused opioids in the past year [17]. In Iran, studies show that opioid use is increasing in this country and is almost three times higher than in other countries. Approximately 1.2 million Iranians struggle with opioid dependence [18]. Non-prescribed consumption of methadone in the general population is less than opiates and some other available prescription opioids. Anyway, an increase in methadone-related poisoning and deaths present serious public health concerns [19].

The efficacy of probiotics in improving some poisonings has been proven [20-25], but its effect on drug poisoning has not been directly studied before. This study aimed to evaluate the impact of probiotics in accelerating the recovery of patients with drug intoxication.

The results of the present study showed that one week of treatment with probiotics caused a significant increase in glutathione antioxidant levels compared to before the intervention. In contrast, glutathione levels decreased significantly in the control group. In this regard, the results of a study by Mohammadian, et al. [26], in 2018 which reviewed the effect of probiotics on the response to oxidative stress and biochemical factors of fish blood serum in the face of lead metal in the diet, showed the amount of glutathione in all probiotic groups. There was a significant increase in all days after exposure to lead, which is similar to the results of the present study.

Another study on effect of probiotics supplementation on glucose and oxidative stress in type 2 diabetes mellitus showed that probiotics intake resulted in significant improvement in serum levels of FBS (SMD: -0.35, 95% CI: (-0.59, -0.12)), Total Antioxidant Status (TAS) (SMD: 0.33, 95% CI: (0.11, 0.55)), total glutathione (GSH) (SMD: 0.41, 95% CI: (0.26, 0.56)) and Malondialdehyde (MDA) (SMD: -0.54, 95% CI: (-0.83, -0.26)) [27].

A study was conducted to evaluate the effects of probiotic supplementation on movement and metabolic parameters in people with Parkinson's Disease (PD) in 2019. Their results showed that glutathione levels enhanced (+40.1 ± 81.5 *vs.* -12.1 ± 41.7 μmol/L, P=0.03) in comparison with the placebo [28].

Additionally, Kadry, et al. [29], and his colleague in Egypt in 2018, examining the effect of probiotic supplement therapy in the experimental model of cadmium chloride poisoning reported that poisoning with this substance considerably increases the levels of malondialdehyde and butyro cholinesterase and meaningfully decreases the levels of glutathione and superoxide dismutase was compared with the control group and improved treatment with probiotics.

A randomized, double-blind clinical trial involving 40 patients diagnosed with MDD was performed in 2016 [30]. Patients were randomly divided into two groups to receive probiotic supplements (n=20) or placebo (n=20) for 8 weeks. Their results showed that the use of probiotics led to a significant increase in total plasma glutathione levels (83.1 ± 1.8 *vs.* 190.7 ± 106.8 micromoles per liter, P=0.02) compared to placebo. The results of the above studies on glutathione levels are consistent with the results of the present study.

In the present study, it was found that the levels of vitamin B6 after treatment with probiotics increased meaningfully compared to before the intervention, while in the control group, this amount decreased significantly compared to before the intervention. In this regard, limited studies have examined the effect of probiotics on vitamin B6 levels. The results of a study by Fabian, et al. [31], which in 2008 in Austria examined the effect of probiotic yogurt consumption on B vitamins in young healthy women showed that, in general, probiotic yogurt consumption significantly increased vitamin B1 and vitamin A intake. B2, but had no consequential effect on vitamin B6 levels. Furthermore, in the current study, it was found that the levels of urea and creatinine in both groups did not show consequential differences.

The results of the current study showed the beneficial effects of probiotics on biochemical parameters of patients with acute opioid poisoning. Furthermore, evidence from laboratory studies shows that probiotics can partially counteract the harmful effects of drugs. In this regard, in an empirical study on rats conducted by Mohammadi, et al. [26], in 2018, probiotics can reverse the effects of reduced practical memory caused by morphine in mice. Besides, in a speculative study by Sakurai, et al. [32], in 2018, probiotics could effectively degrade opioid peptides. Therefore, this evidence indicates the beneficial effects of probiotics on inhibiting the effects of drugs in line with the present study results.

CONCLUSION

The present study results showed that one week of treatment with probiotics meaningfully increased the antioxidant levels of glutathione and vitamin B6 compared to before the intervention. In general, according to the present study results and similar studies in this field, it seems that probiotics, along with supportive therapies, can accelerate the recovery of patients with opioids poisoning. Finally, in this study, the difference in arterial blood gas levels and blood cell count parameters, and coagulation index in the probiotic-treated group was not significantly different from the control-treated group.

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CONFLICT OF INTERESTS

None declared.

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