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LACTULOSE VERSUS NALOXONE FOR OPIOID-INDUCED CONSTIPATION IN THE POISONING INTENSIVE CARE UNIT

RAHIMI et al. Lactulose Versus Naloxone

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Abstract
Background: Constipation caused by opioids (OIC) is prevalent among critically poisoned patients and can result in complications that prolong hospitalization and, in rare cases, cause bowel perforation. The aim of this research is to evaluate the safety and efficacy of lactulose and naloxone in treating OIC in the intensive care unit (ICU) for poisoning.
Methods: This study was a randomized and double-blind clinical trial on patients with opioid poisoning who suffered from constipation for 14 months. The patients were divided into two groups, one group receiving lactulose (30 cc daily) and the other receiving naloxone (8 mg Three times a day). The parameters of age, gender, type of opioid used, APACHE II, GCS score, defecation time and a number of laboratory variables were recorded. All data was collected and analyzed by SPSS software.
Results: Out of the participants in the lactulose group, 85.37% were males and 14.63% were females. In the naloxone group, 94.9% were males and 5.1% were females. The average age in the lactulose group was 44±16.2 years, while in the naloxone group it was 48.13±19.1 years. The average defecation time was 30.8±23.1 hours in the naloxone group and 25±11.5 hours in the lactulose group. Six patients (15%) in the naloxone group experienced treatment failure. Symptoms of withdrawal syndrome were experienced by 15 patients (39.5%) in naloxone group.
Conclusions: The evidence suggests that lactulose is a superior choice because it does not carry the risk of withdrawal syndrome or treatment ineffectiveness.
Keywords: Constipation**,** Defecation time**,** Lactulose, Naloxone, Opioid

Introduction:

There are various factors that can lead to constipation, including underlying medical conditions, lifestyle choices, and medications (1, 2). Chronic constipation can lead to serious complications such as hemorrhoids, bowel obstruction, and even death. Additionally, it can cause upper gut problems like gastroesophageal reflux disease (3, 4). Opioid therapy for pain often leads to opioid bowel dysfunction (OBD) due to the impact on the gastrointestinal (GI) tract via mu-opioid receptors. The most prevalent type of OBD is OIC, which can endure for the duration of the treatment (5-7). The prevalence of OIC is estimated to be between 40% to 95%, with varying degrees of distress and duration of unpleasant symptoms among patients (2, 8).

The primary treatment methods for constipation are oral laxatives and stool softeners, but for individuals taking chronic opioids, the drugs may directly cause persistent constipation, making laxatives alone insufficient. Additionally, opioid-induced constipation does not usually result in tolerance. In 2008, the Food and Drug Administration (FDA) approved methylnaltrexone, an opioid receptor antagonist, for treating OIC (9-12). The most commonly used approach for treating opioid-induced constipation involves the use of both a stimulant and a stool softener. Gastrointestinal stimulants like Senna or bisacodyl work by increasing muscle contractions triggered by an enteric reflex. Stool softeners operate through one of three mechanisms. Surfactants, such as docusate, are emulsifiers that help mix fat and water in the feces. Lubricants like mineral oil slow down the absorption of water from stools in the colon, thus making them softer. Osmotics like lactulose attract water into the colon, thereby hydrating the stools (2, 13).

To prevent oxycodone -induced constipation, a combination of oxycodone and naloxone has been taken orally. When taken orally, naloxone has very low bioavailability (less than 2%) because it is extensively metabolized in the liver. As a result, oral naloxone only binds to peripheral opioid receptors in the gastrointestinal tract at pharmacologically relevant concentrations. This binding inhibits oxycodone's ability to affect gastrointestinal function, thereby reducing the risk of OIC (14, 15).

Numerous researches have proven that naloxone is a secure and efficient treatment for OIC in the ICU (16-19). The purpose of the study design was to compare the effectiveness of lactulose and naloxone in the treatment of opioid-induced constipation.

Methods:

In this clinical trial, a randomized and double-blind approach was used to study patients who suffered from constipation (3 days without defecation) due to opioid use. The study was conducted in the poisoning intensive care unit of xxx Hospital in Tehran from November 2022-December 2023. The patients were divided into two groups using simple randomization, with one group receiving lactulose and the other receiving naloxone.

The lactulose group received a daily dose of 30 cc, while the naloxone group received 8 mg (20 cc) three times a day. The time taken for the first defecation after treatment initiation was recorded for both groups, with patients being monitored for 72 hours. Failure to defecate during this period was considered as treatment failure.

Patients were excluded from the study if they consumed substances that caused constipation concurrently, if they did not provide consent to participate, or if they had underlying conditions such as intestinal obstruction, rheumatological or neurological disorders, shock, or iron deficiency anemia. The parameters of age, gender, type of opioid used, Acute physiology and chronic health evaluation (APACHE II), Glasgow Coma Scale (GCS) score, drug dose, frequency of drug use, defecation time and a number of laboratory variables were recorded.

Statistical analysis

The data was analyzed using IBM SPSS 23 software. The dispersion and descriptive indices of the variables were investigated. The Chi-square test was used to compare qualitative variables. The independent t-test and Mann-Whitney Test were also used to compare groups. Kolmogorov-Smirnov test was used to check the normality of data distribution. A significance level of $P \leq 0.05$ was considered.

Results:

The study consisted of a total of 80 individuals, with 39 of them being treated with naloxone and the remaining 41 receiving lactulose. In the lactulose group, there were 35 (85.37%) males and 6 (14.63%) females, while in the naloxone group, there were 37 (94.9%) males and 2 (5.1%) females. The average age in lactulose group was 44±16.2 and in naloxone group was 48.13±19.1 years. There was no significant difference between the two groups in age and gender distribution. Table 1 displays the mean values of the body temperature, systolic and diastolic blood pressure, heart rate, APACHE II score, GCS score, and weight for patients in two different groups.

None of the patients had a history of abdominal and pelvic surgery in the last month. In the lactulose group, 26 individuals required intubation, while in the naloxone group, only 3 individuals needed to be intubated. Fifteen (39.5%) patients who were given naloxone experienced symptoms of withdrawal syndrome, and the treatment had to be discontinued after 7 doses in one patient because their vital signs became unstable. The most consumed opioids in both lactulose and naloxone groups were methadone (53.7% vs. 23.1%) and opium (19.5% vs. 23.1%) (Figure 1).

The results of the Mann-Whitney test showed that there is no significant difference between the two groups in defecation time (P=0.769). However, the mode of the data was 16 in the naloxone group and 26 in the lactulose group. The average defecation time was 30.8±23.1 hours in the naloxone group and 25±11.5 hours in the lactulose group. Out of the total number of cases, 6 (15%) in the naloxone group experienced treatment failure, while no cases of treatment failure were observed in the lactulose group.

The effect size was determined using Cohen's d method. The calculated effect size d is 0.32 (medium effect size), which falls within the small range. This suggests that the difference in means between naloxone and lactulose is of

small magnitude. Based on t-test power calculator, the power (the likelihood of accurately rejecting the null hypothesis) equal to 0.268 was obtained (df=70, noncentrality parameter: 1.357, critical t: 1.994).

Discussion and conclusion:

Although opioids can effectively manage moderate-to-severe pain, up to 18.9% of patients discontinue opioid therapy due to the side effects associated with the drugs. OIC, which is a common side effect of pain therapy, can often result in the discontinuation of opioid therapy due to its significant negative impact on the quality of life (20). In this study, we compared the effectiveness of lactulose and naloxone in the treatment of constipation caused by opioid poisoning. There was no significant difference in the average defecation time in the two groups. Out of the patients who received naloxone, 15 individuals (39.5%) exhibited signs of withdrawal syndrome. Six patients (15%) in the group treated with naloxone had treatment failure, whereas there were no instances of treatment failure in the group treated with lactulose.

Lactulose, a disaccharide that cannot be digested, has been utilized in the medical field. Depending on the prescribed amount, oral lactulose can function as a prebiotic, an osmotic laxative, or a detoxifying agent (21). There is limited information regarding the use of laxatives for treating OIC, and there is hardly any evidence from studies that involve placebos or comparisons (22). One instance involves the examination of Senna and lactulose's impact on cancer patients who are undergoing opioid treatment, but the findings indicated that there was no notable contrast between the two (23). Friedman and colleagues conducted a comparison between lactulose and polyethylene glycol to determine their effects. They discovered that the use of polyethylene glycol/electrolyte solution resulted in the loosest stool consistency, resembling diarrhea. Additionally, it is probable that polyethylene glycol/electrolyte solution is the most economical option. Both experimental groups showed no significant differences in reducing the formation of hard stool (24).

Previous studies have investigated the dosage of oral naloxone for the treatment of opioid-induced constipation (25-27). Caitlin et al in a study on patients aged 18 to 89 years admitted to the medical intensive care unit found that enteral naloxone was safe for the treatment of opioid-induced constipation. They reported that the median duration for bowel movement was 24.4 hours. The median count of naloxone doses administered before achieving bowel movement was 3 (18).

There was a lack of comparative or placebo-controlled studies. A systematic review and meta-analysis conducted in 2020 showed that only 6 blinded and randomized controlled trials studies have been conducted on naloxone for the treatment of opioid-induced constipation (28). The oxycodone/naloxone combination was the subject of four conducted studies (14, 15, 29, 30). A study was done on sustained release naloxone (31).

Meissner examined 202 individuals suffering from long-term pain who were given sustained oral oxycodone for treatment. They were randomly divided into groups and given either 10, 20, or 40 mg/day of naloxone or a placebo. The study found that bowel function improved as the dosage of naloxone increased. In particular, the participants who received 20 mg and 40 mg of naloxone showed significant improvement in bowel function compared to those who received the placebo. However, there was a tendency for a higher incidence of diarrhea with higher doses of naloxone (32).

Unfortunately, no previous studies comparing the effects of naloxone and lactulose in improving opioid-induced constipation were found. Even naloxone was not compared with other laxatives. Nevertheless, several recommendations suggest that laxatives should be given to patients with cancer and non-cancer pain as a means of preventing or treating OIC (33-35).

A significant difference was observed between patients' body temperature and GCS in two groups. Unfortunately, before starting any treatment, vital signs were recorded and patients were randomly selected, and then we noticed this difference in the data analysis stage. We have no justification for this.

In conclusion, although there was no significant variation in the average defecation time when comparing naloxone and lactulose, it appears that lactulose is a better option due to its lack of risk for withdrawal syndrome and treatment failure.

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Table1. Vital and fundamental details regarding the patients who underwent the intervention

Variable	Naloxone group Mean±SD	Lactulose group Mean±SD	P-value
Gender Male	37 (94.9%)	35 (85.37%)	0.157
Age (year)	48.13±19.1	44±16.2	0.301
Temperature (°C)	36.9±0.34	37.37±0.4	0.001*
Systolic blood pressure (mmHg)	119.8±21.1	122.8±16.1	0.486
Diastolic blood pressure (mmHg)	74.4±12.2	78.8±12.9	0.124
Heart rate (Pulses/min)	89±17.7	88.5±25.4	0.925
Breathing rate (Breaths/min)	16.9±3.7	16.7±1.9	0.785
body weight (Kg)	87.9±30.3	84.2±17.3	0.649
APACHE II score	16.1±6.6	148.1±5.3	0.132
GCS Score	9.7±4.1	7.8±3.3	0.026*

*P<0.05

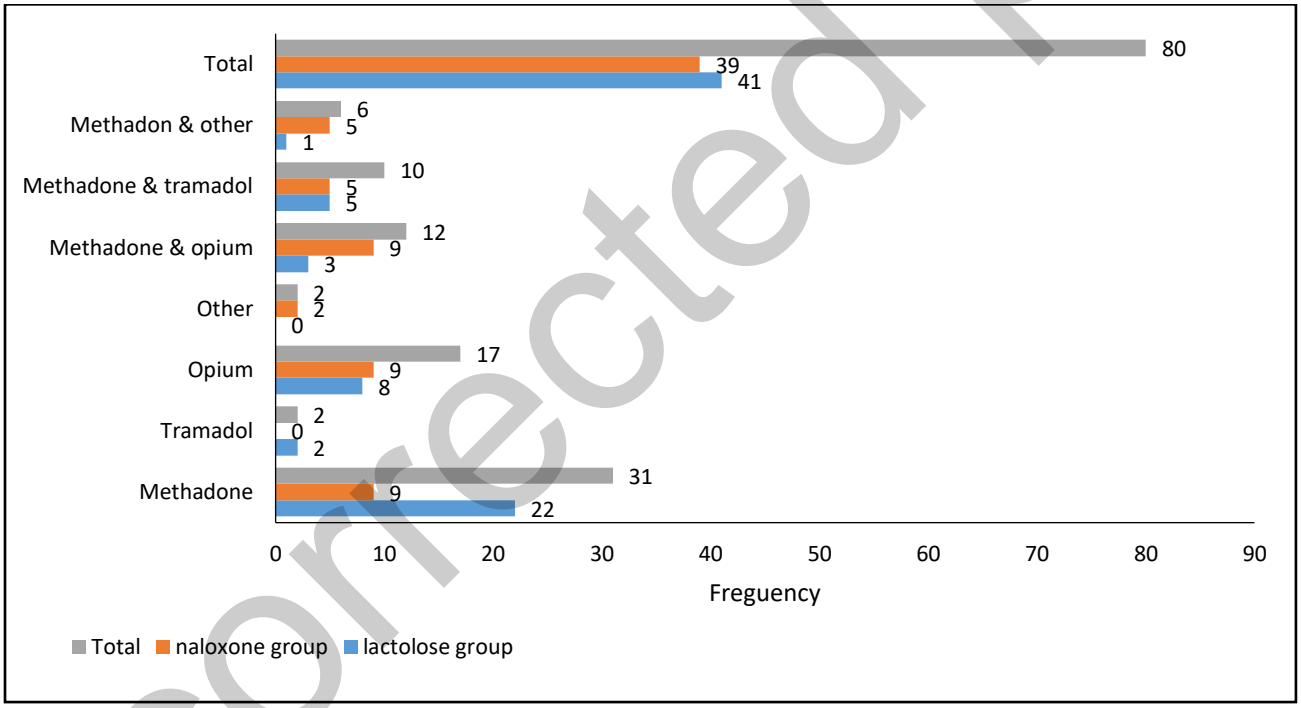

Figure1: Type of opioids in both lactulose and naloxone groups