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ORIGINAL ARTICLE

Lactulose Versus Naloxone for Opioid-Induced Constipation in Intensive Care

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ABSTRACT

Objectives: Constipation caused by opioid-induced constipation (OIC) is prevalent among critically poisoned patients and can result in complications that prolong hospitalization and, in rare cases, cause bowel perforatio This research aimed to evaluate the safety and efficacy of lactulose and naloxone in the treatment of OIC in the intensive care unit for poisoning.

Materials and Methods: This was a randomized, double-blind, clinical trial of patients with opioid poisoning who experienced constipation for 14 months. Patients were divided into two groups: one 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, Acute Physiology and Chronic Health Evaluation II score, Glasgow Coma Scale score, defecation time, and number of laboratory variables were recorded. All data were collected and analyzed using SPSS software.

Results: Of the participants in the lactulose group, 85.37% were male and 14.63% were female. In the naloxone group, 94.9% of patients were male and 5.1% were female. The average age of the lactulose group was 44 ± 16.2 and in the naloxone group 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%) patients in the naloxone group.

Conclusion: The evidence suggests that lactulose is a superior treatment choice because it does not carry the risk of withdrawal syndrome or treatment ineffectiveness.

Keywords: Constipation, defecation time, lactulose, naloxone, opioid

INTRODUCTION

Various factors can lead to constipation, including underlying medical conditions, lifestyle choices, and medications.[1,2] Chronic constipation can lead to serious complications, such as hemorrhage, 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) because of its impact on the gastrointestinal (GI) tract *via* mu-opioid receptors. The most prevalent type of OBD is opioid-induced constipation (OIC), which can last for the duration of the treatment.[5-7] The prevalence of OIC is estimated to be between 40% and 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. However, in individuals taking chronic opioids, these drugs may directly cause persistent constipation, making laxatives alone insufficient. In addition, OIC does not usually result in tolerance. In 2008, the Food

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and Drug Administration approved methylnaltrexone, an opioid receptor antagonist, for treating OIC.[9-12] The most commonly used approach for treating OIC involves the use of both a stimulant and stool softener. GI stimulants like Senna or bisacodyl work by increasing muscle contractions triggered by an enteric reflex. Stool softeners operate by one of three mechanisms. Surfactants, such as docusate, are emulsifiers that help mix fat and water in feces. Lubricants like mineral oil, slow down the absorption of water from stool 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 is consumed 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 binds only to peripheral opioid receptors in the GI tract at pharmacologically relevant concentrations. This binding inhibits oxycodone's ability to affect GI function, thereby reducing the risk of OIC.[14,15]

Numerous studies have demonstrated that naloxone is a secure and efficient treatment for OIC in the ICU.[16-19] The purpose of this study was to compare the effectiveness of lactulose and naloxone in the treatment of OIC.

MATERIALS AND METHODS

In this clinical trial, a randomized, double-blind approach was used to study patients who experienced constipation (3 days without defecation) due to opioid use. The study was conducted in the poisoning intensive care unit of Loghman Hakim Hospital in Tehran between November 2022 and December 2023. 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, whereas the naloxone group received 8 mg (20 cc) three times a day. The time to first defecation after treatment initiation was recorded for both groups, with patients monitored for 72 hours. Failure to defecate during this period was considered treatment failure.

Patients were excluded from the study if they concurrently consumed substances that caused constipation, did not provide consent to participate, or 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 II score (APACHE II), Glasgow Coma Scale (GCS) score, drug dose, frequency of drug use, defecation time, and number of laboratory variables were recorded.

This study was approved by the institutional ethics board of Shahid Beheshti University of Medical Sciences (approval number: IR.SBMU.RETECH.REC.1400.1024, date: 02.06.2022). This article was also registered in the Iranian Registry of Clinical Trials with number: IRCT20210720051946N4.

Statistical analysis

The data were 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 *U* test were also used to compare groups. Kolmogorov-Smirnov test was used to assess the normality of data distribution. A significance level of $p \leq 0.05$ was considered.

RESULTS

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

Table 1. Vital and fundamental details regarding patients who underwent 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*

*$p < 0.05$, SD: Standard deviation, APACHE: Acute Physiology and Chronic Health Evaluation, GCS: Glasgow Coma Scale

None of the patients had a history of abdominal or pelvic surgery within the last month. In the lactulose group, 26 individuals required intubation, whereas in the naloxone group, only 3 individuals required intubation. Fifteen (39.5%) patients who received 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 the 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 *U* test showed that there is no significant difference between the two groups in defecation time (p= 0.769). However, the mode of 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. Of the total number of cases, 6 (15%) patients in the naloxone group experienced treatment failure, whereas no treatment failure was observed in the lactulose group.

The effect size was determined using Cohen's *d*-test. The calculated effect size d was 0.32 (medium effect size), which falls within the small range. This suggests that the difference between the means of naloxone and lactulose is small. Based on a *t*-test power calculator, a power (the likelihood of accurately rejecting the null hypothesis) of 0.268 was obtained (df = 70, non-centrality parameter: 1.357, critical t: 1.994).

DISCUSSION

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, often results in the discontinuation of opioid therapy due to its significant negative impact on 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 between the two groups. Of the patients who received naloxone, 15 individuals (39.5%) exhibited signs of withdrawal syndrome. Six patients (15%) in the naloxone group experienced treatment failure, whereas there were no cases of treatment failure in the lactulose group.

Lactulose is a disaccharide that cannot be digested and has been utilized in the medical field. Depending on the prescribed amount, oral lactulose can function as a prebiotic, osmotic laxative, or 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] Freedman et al.[24] compared the effects of 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, polyethylene glycol/electrolyte solution is probably 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 OIC.[25-27] Gibson and Pass[18] conducted a study on patients aged 18 to 89 years admitted to the medical intensive care unit and found that enteral naloxone was safe for the treatment of OIC. They reported that the median duration of bowel movements was 24.4 h. The median number of naloxone doses administered before achieving bowel movement was 3.[18]

There were no comparative or placebo-controlled studies. A systematic review and meta-analysis conducted in 2020 showed that only 6 blinded and randomized controlled trials have investigated naloxone for the treatment of OIC.[28] The combination of oxycodone and naloxone was the subject of four studies.[14,15,29,30] A study was conducted on sustained-release naloxone.[31]

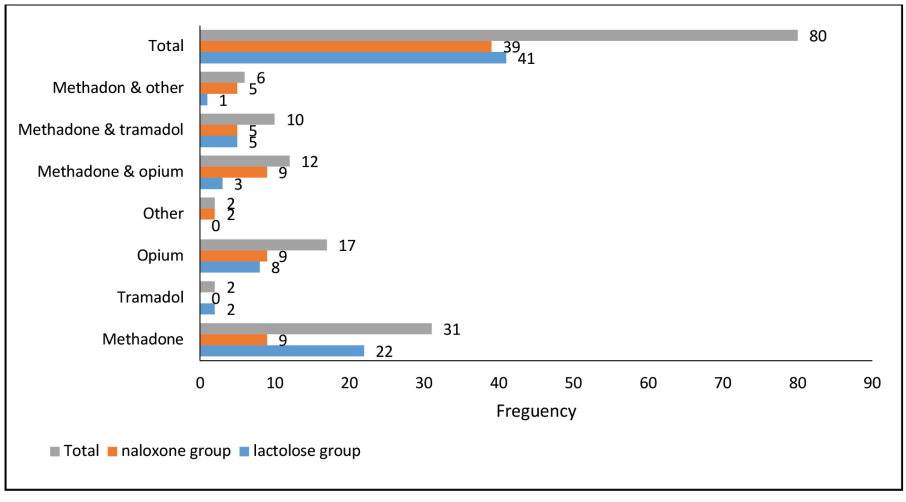

Figure 1. Type of opioids in the lactulose and naloxone groups

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

Unfortunately, no previous studies have compared the effects of naloxone and lactulose on improving OIC. Moreover, 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 the patient's body temperature and GCS scores in the 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 do not have any justification for this.

CONCLUSION

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

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Ethics

Ethics Committee Approval: This study was approved by the institutional ethics board of Shahid Beheshti University of Medical Sciences (approval number: IR.SBMU.RETECH.REC.1400.1024, date: 02.06.2022). This article was also registered in the Iranian Registry of Clinical Trials with number: IRCT20210720051946N4.

Informed Consent: Written consent was obtained from the participants.

Authorship Contributions

Surgical and Medical Practices: M.R., Concept: M.R., Design: M.R., Data Collection or Processing: M.R., M.D.A., M.H.A., Analysis or Interpretation: L.G., Literature Search: Ma.R., S.S., B.M., Writing: M.R., P.E.T.E.

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