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A Comparison of the effects of Morphine and Buprenorphine on full-term and near-term neonates with neonatal abstinence syndrome

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Abstract

Background: Since there is insufficient data to compare the relative efficacy of commonly prescribed opioids (morphine and buprenorphine), the present study aimed to compare the effect of morphine and buprenorphine on term and near-term neonates with neonatal abstinence syndrome.

Methods: This double-blind randomized clinical trial was performed on 60 neonates whose mothers were addicted to drugs (opium and its derivatives) and the neonate had symptoms of withdrawal syndrome. They were all. Admitted to Valiasr Hospital in Birjand. Neonatal assessment was based on Finnegan score. The neonates were randomly assigned in two groups of buprenorphine (n = 30) and morphine (n = 30). The Chi square test, Fisher exact test, student t test and Mann-Whitney U test were used for comparing the background characteristics and treatment outcomes between the two groups.

Results: In the present study, a total of 53.3% of the patients in both groups were boys and the rest were girls. The mean lengths of hospital stay in the buprenorphine and morphine groups were 5.97 ± 3.38 and 7.53 ± 4.83 days, respectively (p=0.15). Also, apnea was observed in 33.3% of the total neonates in the buprenorphine group and 43.3% of the neonates in the morphine group (p=0.43). The two groups were homogenous in regards to apnea complications, oral intolerance, hypotension and blood culture result (p>0.05)

Conclusion: The results of the present study showed no significant difference in the outcomes of treatment and reduction of treatment complications between the buprenorphine and morphine-treated neonates.

Key Words: Buprenorphine, Morphine, Neonatal Abstinence Syndrome.

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1- INTRODUCTION

The opioid crisis is a growing social and public health phenomenon (1) and substance abuse is one of the serious problems of civilized man at the beginning of the third millennium. Large-scale complications of substance abuse severely affect the physical and mental life of the individual as well as the family, culture, economy, and society. Substance abuse has been a complex problem throughout history and now internationally (1-3).

According to the United Nations Report on Substance Abuse, more than 200 million people, or 4.2% of the world's population, are addicted to drugs (1). On the other hand, according to the World Health Organization, women comprise 40% of those with a lifetime drug abuse (4).

Most people perceive substance abuse as a male phenomenon. Although the prevalence of substance use disorder is reported to be lower among women than men, the addiction rate is faster in them and has become a serious growing threat today (5). In this regard, a study by Pacurucu-Castillo et al. (2019) showed that although there is one addicted woman for every 4-5 men addicted to opiates, the ratio of demand for opioid pain relievers in men and women is 1:7, respectively (1).

Women's addiction causes problems at the family level, especially since most of these women are of childbearing age and the mother's addiction causes many problems for the neonates (4, 6). Since drugs easily cross the placental barrier, chronic use of prescribed medications or drug use during pregnancy can affect postpartum outcomes. More importantly, substance use during pregnancy causes fetal drug dependence and leads to a set of physiological and behavioral symptoms, which are called neonatal abstinence syndrome (NAS) (7-9). Due to women's addiction, NAS has increased dramatically and has become a major health problem.

Results of a study carried out in the United States in 2018 showed that the incidence of NAS increased fivefold from 2000 to 2014 and increased from 0.8 to 1.5 per 1,000 hospital births (10). NAS symptoms generally occur within the first 24 hours of life in neonates with short-term intrauterine opioids exposure and 72-96 hours of life in neonates with long-term intrauterine opioid exposure (11).

The risk of hospital admission rate is more than twice among neonates with NAS (9, 11-13). They also suffer from many problems such as tremors, loud crying (9, 11), restlessness, trouble sleeping (11), seizures (9), irritability, intolerance, vomiting, loose stools, tachycardia, and respiratory distress. On the other hand, it has been suggested that there is a risk of ADHD in old age among neonates with withdrawal syndrome (11, 14, 15). In addition, NAS symptoms have a clinical effect on nutrition and have negative effects on growth and development (9, 11).

Pharmacological treatments and various measures are used to reduce and eliminate NAS complications. Non-pharmacological measures should be taken in all neonates who undergo prenatal opioid exposure. These measures include neonate-mother room-sharing, encouraging breastfeeding, minimizing stimuli, and etc. (9). However, some studies have shown that most neonates with NAS need medical intervention to control the withdrawal symptoms (9, 12, 16), and the neonates recover as the drugs are excreted from the body (9). In a study on 10,327 neonates, Tulia et al. (17) showed that the proportion of NAS neonates undergoing pharmacological treatments increased from 74% in 2004-2005 to 87% in 2012-2013 (17). Taleghani et al. also stated that the American Academy of Pediatrics (AAP) and a systematic review identified opioid replacement as the ideal treatment for NAS. Besides, the American College of Obstetricians and Gynecologists (ACOG)

recommends methadone or buprenorphine treatment in opioid-dependent women during pregnancy (12). Various studies (12, 18, 19) have shown that buprenorphine is associated with shorter treatment duration and minimal side effects on NAS patients, because the mechanisms of action of buprenorphine, as a mu agonist and partial kappa opioid receptor agonist in the central nervous system, support its potential biological and scientific use in NAS. Thus, buprenorphine can be used as a first-line treatment for all neonates exposed to intrauterine opioids (12).

Since there is insufficient data to compare the relative efficacy of commonly prescribed opioids (morphine and buprenorphine) on the one hand, and to evaluate the best low-cost and least complicated treatments of withdrawal syndrome on the other hand, the present study compares the effects of morphine and buprenorphine on full-term and near-term neonates with NAS admitted to Valiasr Hospital in Birjand.

2- MATERIALS AND METHODS

2-1. Study design and setting

This double-blind randomized clinical trial was performed on 60 neonates admitted to Valiasr Hospital in Birjand. Mothers were addicted to drugs (opium and its derivatives) and the neonate had withdrawal symptoms.

2-2. Sample size estimation

The sample size was calculated as 30 people in each group based on the study by Bada et al. (20) and using the formula for comparing the means in two independent groups with 99% confidence interval and a test power of 97% taking into account the mean treatment duration (39 days for morphine vs. 28 days for clonidine).

$$n = \frac{(z(1-\alpha/2) + z(1-\beta))^2(\epsilon 1^2 + \epsilon 2^2)}{(\mu 1 - \mu 2)^2}$$

2-3. Treatment groups

The neonatal assessment was according to the modified Finnegan score (21). It was taken into account in the drug treatment that the neonate's post-feeding on the modified neonatal abstinence scale had to be ≥9 in two consecutive evaluations and there were no other confounding factors. Moreover, the neonates were randomly assigned to buprenorphine (n=30) and morphine groups (n=30) with the allocation ratio of 1:1, which were homogeneous in terms of sex, weight, age of hospitalization, maternal age, and duration of drug use.

2-4. Inclusion and exclusion criteria

Inclusion criteria were postpartum age< 7 days, gestational age ≥35 weeks, prenatal contact with narcotics (history of opium use and its derivatives during pregnancy and mother's confession for opium use during pregnancy), symptomatic patient (no breastfeeding, vomiting, fever, tremor, hyperreflexia, getting less than 1-2 and 3 hours of sleep), and 3 consecutive Finnegan scores≥8 evaluated in three separate hours or 2 consecutive Finnegan scores ≥ 12, no seizures, no major congenital anomalies, no hemodynamic instability and blood pressure, no major medical problems associated with withdrawal syndrome, and obtaining consent of the neonate’s legal guardian. All neonates were under behavioral interventions, including swaddling and pacifier use, and a low-light and low-noise NICU.

When the Finnegan score was still high despite behavioral interventions, the decision was made to start pharmacological treatment and the neonate received the studied drugs randomly.

2-5. Procedure

The drugs were the same in terms of appearance (volume, clarity, color, and odor). The drugs prescribed for neonates

included 2 mg buprenorphine tablets (Faran pharmaceutical Company) and 1 cc 10-mg morphine ampoule (Daroupakhsh Company). The drug was prepared in the following form: Morphine (1cc) was mixed with 24 distilled water drops or 10% dextrose water and then two drops per kilogram of body weight were given to the baby at the baseline. Also, each 2 mg buprenorphine tablet was mixed with 50 cc of 5% dextrose water and two drops per kilogram of this solution was given to the baby at the baseline. Placebo was prepared using 5% dextrose solution and all three solutions were kept in single-shaped bottles in the ward. On the other hand, all physicians and nurses involved in the study, except the physician in charge of the drug preparation, were unaware of the nature of the drug used. All patients received the initial dose in two different groups with treatment indications based on the Finnegan score. Morphine-treated neonates were given a starting dose of 0.4 mg / kg daily divided for every 4 hours. Subsequent doses of the drug were determined based on the Finnegan table number at each evaluation. The Finnegan score was calculated by the resident physician each time after proper feeding of the neonate and before the drug prescription while the neonates were swaddled and kept in a low-light place. The drug dose was increased by 10% in the case of Finnegan score< 12, and, the drug dose was reduced again by 10% for the next dose in the case of Finnegan score> 8. Also, the drug dose was not changed in the case of Finnegan score 8-10. If the lowest dose was below 0.1 mg / kg / day, morphine was discontinued and the neonate was monitored and discharged for 48 hours. However, if the symptoms were not improved by using maximum dose, 75 morphine drops kg/day and 30 buprenorphine drops kg/day, the second drug was added. The second drug was phenobarbital, which was the same for all neonates and was prescribed by the physician in the case of Finnegan score> 12 despite taking the maximum morphine dose.

All of the above cases were taken into account in the buprenorphine-treated group and the starting buprenorphine dose was 0.075 mg / kg / day and the maximum daily dose was 30 drops / kg / day. Phenobarbital was started when the Finnegan score remained above 12 despite the maximum dose. All neonates were admitted to the NICU, and continuous cardiovascular examination and blood pressure measurements were performed every 8 hours.

2-6. Data analysis

Descriptive statistics including mean and SD for continuous data and frequency and percentage for categorical data were used to describe demographic characteristics of patients in the two groups. Kolmogorov-Smirnov test was used to check normality distribution of the investigated variables. Chi square, fisher exact test, student t test and Mann–Whitney U test were used for comparing the demographic characteristics and treatment outcomes between the two groups. A P-value of ≤ 0.05 was considered as statistically significant. Data were analyzed using SPSS vol. 24.

3- RESULTS

At first, 69 neonates were included in this study, 9 of which were excluded due to different reasons. In the buprenorphine group, 5 neonates were excluded from the study (One case due to seizures and 4 cases due to parents 'dissatisfaction and parents' impatience). In the morphine group, 4 neonates were excluded from the study (one case due to seizures and the other 3 cases due to parental dissatisfaction).

A total of 53.3% of the patients in both groups were boys. The two groups were homogeneous in terms of sex, age at the time of admission, gestational age,

maternal age and duration of drug usage by the neonate (**Table 1**).

As shown in **Table 2**, the mean weight of the two groups was compared in the three time periods (at birth, upon admission, and upon discharge). It was revealed that there was not a significant difference between the two groups in the three times in terms of neonates' weight ($p>0.05$), but the neonates' weight was significantly reduced in both groups during the three investigated time points ($p<0.01$).

Table-1: Comparing the demographic characteristics of neonates in the two groups

Variable		Treatment group		Total (%)	Statistical test result
		Buprenorphine	Morphine		
Gender n (%)	Girl	14 (46.7)	14 (46.7)	28 (46.7)	$=^2\chi 0.02$ P=1
	Boy	16 (53.3)	16 (53.3)	32 (53.3)	
Continuous variables: mean (SD)					
Age at time of hospitalization		38.06±28.93	27.3±24.93	32.91±26.93	t=0.24 p=0.81
Gestational age (week)		1.62±37.73	1.69±36.90	1.68±37.32	t=1.96 p=0.06
Maternal age (week)		6.61±28.90	7.29±31.40	7.01±30.15	t=1.39 p=0.17
Duration of drug use by the neonate (day)		3.20±4.20	3.05±4.92	4.53±3.13	t= 0.89 p=0.38

Table-2: Comparing the mean weights of buprenorphine and morphine-treated neonates at birth, admission, and discharge

Weight (gr)	Treatment group		Mann-Whitney test result
	Buprenorphine mean± SD	Morphine mean± SD	
At birth	2586.5±637.48	2588.67±521.14	Z=0.16, P=0.87
Upon admission	2537.07±624.02	2541.33±530.75	Z=0.13, P=0.89
Upon discharge	2520.83±628.32	2513.17±542.79	Z=0.01, P=0.99
Kruskal-wallis test result	$\chi 2$ =18.9 P<0.001	$\chi 2$ =12.02 P=0.002	-

As presented in **Table 3**, the mean lengths of hospital stay in the buprenorphine and morphine groups were 5.97±3.38 and 7.53±4.83 days, respectively, but this difference between the two groups was not statistically significant (p=0.15).

Table-3: Comparing the mean hospital stay between the buprenorphine and morphine-treated neonates

Variable	Treatment group	Mean ± SD	Range	T-test statistics	P-value
Length of hospital stay	Buprenorphine	5.97 ±3.38	2-19 days	1.45	0.15
	Morphine	7.53 ± 4.83	2-19 days		

As **Table 4** represents, the two groups were homogenous regarding the apnea complications, oral intolerance, hypotension and blood culture (p>0.05). In each of the two groups, one patient needed a second drug (phenobarbital), but both patients were discharged based on the consent of their parents before the end of the treatment period and were excluded from our study.

Table-4: Determining and comparing the frequency of apnea complications, oral intolerance, hypotension and blood culture in buprenorphine and morphine-treated neonates

Variable		Treatment group		Total (%)	Statistical test result
		Buprenorphine N (%)	Morphine N (%)		
Apnea	No	20 (66.77)	17 (56.7)	37 (61.7)	$\chi2$=0.63
	Yes	10 (33.33)	13 (43.3)	33 (38.3)	P=0.43
Oral tolerance	No	1 (3.3)	0	1 (1.7)	Fexact=4.0
	Yes	21 (70.0)	15 (50.0)	36 (60.0)	1
	Relative	8 (26.7)	15 (50.0)	33 (38.3)	P=0.11
Hypotension	No	25 (83.3)	24 (80.0)	49 (81.7)	$\chi2$= 0.11
	Yes	5 (16.7)	6 (20.0)	11 (18.3)	P=0.74
Blood culture	No	28 (93.3)	28 (93.3)	56 (93.3)	P=1
	Yes	2 (6.7)	2 (6.7)	4 (6.7)	

4- DISCUSSION

The aim of the present study was to compare the effects of morphine and buprenorphine on 60 full-term and near-term neonates with neonatal abstinence syndrome admitted to Valiasr Hospital in Birjand.

The results of this study showed that the mean lengths of hospital stay in the buprenorphine and morphine groups were not statistically different. This result is consistent with the study by Nayeri et al. (22) and Jones et al. (23). However, Nayeri et al. (22) compared the effect of phenobarbital and morphine, and found no significant difference in morphine treatment and length of hospital stay. Jones et al. (23) also studied children exposed to buprenorphine and methadone. However, the results of both studies showed no relationship between the treatment and length of hospital stay. On the other hand, the results of the present study showed no significant difference in the length of hospital stay in both buprenorphine and morphine-treated groups; which was inconsistent with the results of the study by Taleghani et al. (12), Hall et al. (19), and Kraft et al. (24). It should be noted, however, that the study by Hall et al. (19) aimed to compare the effects of buprenorphine and traditional narcotics; which might have led to the difference in results. Furthermore, in a study at Thomas Jefferson Hospital in Philadelphia, Kraft et al. (24) showed that the mean duration of buprenorphine treatment was significantly shorter than that in the case of morphine treatment (15 days vs. 28 days, respectively). The present study was similar to the study by Walter Kraft et al. (24) in terms of the sample size. However, there was a slight difference in the method, and this slight difference in the method, race, and type of morphine and buprenorphine-producing companies may justify the differences in the results.

Some studies (12, 18, 19, 24-26) have shown that buprenorphine treatment shortens the treatment time and shortens the length of hospital stay, because

buprenorphine has many advantages over other drugs in the management of abstinence syndrome. In addition, the results of the study by Kraft et al. (26) showed that buprenorphine is significantly safer than oral morphine therapy. In that study, safety referred to the fact that buprenorphine is a partial mu agonist with long-lasting efficacy used in the treatment of abstinence syndrome, and reduces respiratory depression compared to other opioid agonists. Also, the duration of treatment and length of stay was reduced by about 30%.

The present study revealed no significant difference between buprenorphine and morphine groups in terms of the relative frequency of apnea and hypotension. There was no study comparing apnea in the buprenorphine and morphine groups, indicating that the present study is an innovative investigation in its field. However, it was generally noted in Kraft et al.'s study (24) that buprenorphine has a broad therapeutic index for respiratory problems and has a long half-life that may be useful in the treatment of NAS. However, neonatal apnea is not discussed in the previous studies and it was examined separately in other groups. Hamunen et al. (27) and Anders et al. (28) in their study found no occurrence of apnea and hypotension in the two investigated groups. However, it should be stated that Hamunen et al.'s study (27) was performed on children and the present study was conducted on neonates. Also, in their study on morphine-related apnea among premature neonates undergoing continuous positive airway pressure (CPAP), Anders et al. (28) showed no significant differences in apnea before and after morphine treatment. However, the difference between the findings of the above mentioned study (28) and the present one was related to the fact that the above study was performed on premature neonates and the results cannot be generalized to all neonates.

In their study on buprenorphine treatment for NAS management in methadone-exposed neonates, Taleghani et al. (12) demonstrated that buprenorphine treatment improved breastfeeding in neonates.

With regard to the need for a second drug (phenobarbital) in morphine and buprenorphine-treated neonates, it should be noted that one person needed a second drug (phenobarbital) in each of the two groups; however, both patients were discharged from the hospital against medical advice and were excluded from the present study. Moreover, since only one person needed an adjuvant drug, this finding was considered as having no statistical value. In this regard, the results of the study by Taleghani et al. (12) showed that although recent studies have not reported any difference between the use of adjuvant drug between buprenorphine and morphine-treated neonates, the results of the reported study (12) showed that buprenorphine-treated children need adjuvant drug more frequently. However, fewer buprenorphine-treated children needed to continue treatment after discharge from hospital compared to methadone-treated children. However, this difference is probably due to differences in the protocols used in our wards. While the results of a study by Kraft et al. (24) showed that 63 neonates (with a gestational age of 37 weeks) exposed to opioids in utero i received sublingual buprenorphine or oral morphine, the results of this study showed the efficacy and safety of sublingual buprenorphine for neonates with NAS who needed medical treatment. However, phenobarbital adjuvant therapy was used for neonates whose symptoms were not controlled using the maximum drug dose. While some studies such as the study by Nayeri et al. (22) in Tehran showed no need for adjuvant therapy between neonates of the two groups.

4-1. Limitations of the study

As the main limitations of the present study, we can mention the examination of neonates in one center, parents who didn't allow their neonate to complete treatment and withdraw from the project, and the short study period. Therefore, caution should be exercised while generalizing the findings of this research. A randomized prospective study is also proposed to compare different treatments for NAS.

5- CONCLUSION

The results of the present study showed no significant relationship between the buprenorphine and morphine treatments. However, the results of some studies have shown that buprenorphine treatment is an acceptable treatment as compared to morphine treatment for the treatment of NAS. Therefore, due to the small sample size in the present study, assessing this relationship requires stronger evidence by designing large-scale studies.

6- ACKNOWLEDGMENTS

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7- ETHICAL CONSIDERATION

Prior to the study, a written consent was obtained from the neonate's legal guardian and necessary explanations were given to the parents and the decision to start drug treatment and enter the study was based on the modified Finnegan scoring system (MFSS). The present study was approved by the Ethics Committee of Birjand University of Medical Sciences (ir.bums.REC.1397.168) with the clinical trial registration number (IRCT20181231042183N1).

8- CONFLICT OF INTERESTS

None.

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