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Original Research Article

METHADONE AND MORPHINE FOR THE TREATMENT OF NEONATAL ABSTINENCE SYNDROME: A COMPARISON OF SAFETY AND EFFICACY

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Abstract: *This study was designed to compare the safety and efficacy of morphine and methadone for treating NAS. A randomized, double-blind study was conducted at The Children's Hospital & The Institute of Child Health Multan from December 2021 to December 2022. A total of 180 pregnant women were enrolled in the study, of which 114 needed treatment and were randomized (1:1) to receive morphine or methadone. Standardized Finnegan Score (FS) was used to assess infants every four hours. Methadone alternating with placebo or neonatal diluted morphine was administered to infants every four hours. The primary endpoint of the study was the duration of the hospital stay. Both the methadone and morphine groups had similar risk factors and demographic variables. There was a total of 14 adverse events equally distributed in both groups. After adjusting for the type of opioid used by the mother, it was found that the mean relative duration of hospital stay was 13% (which corresponds to the difference of 2.8 days) lower in the methadone group compared to morphine. The duration of treatment was 15% (which corresponds to a difference of 2.2 days) lower in the methadone group than in morphine. The median hospital stay with methadone was 15 days compared to 19 days with morphine (P = .005). Based on the results, it can be concluded that for the treatment of NAS, methadone had better short-term outcomes than morphine.*

Keywords: Neonatal Abstinence Syndrome, Morphine, Methadone

Introduction

Opioids are prescribed for controlling chronic pain during pregnancy. Above 5% of pregnant women experience adverse effects due to the misuse of opioids (Sujan et al., 2022). As the consumption of psychotropic medications and opioids among pregnant women has increased, thus occurrence of neonatal abstinence syndrome (NAS) has increased (Maalouf et al., 2019). Neonatal abstinence syndrome involves the combination of signs of central and autonomic nervous dysfunction in infants exposed to the effects of opioids in utero (Favara et al., 2019; Hwang et al., 2020).NAS is treated using different approaches without a single universal approach. Commonly used treatments are opioids, methadone, or neonatal morphine solution (Patrick et al., 2020). If the patient does not respond to opioids, a second drug is added.

Nevertheless, these treatment approaches are significantly heterogeneous, and the efficacy and safety of these drugs are not well established. A study found that the mean duration of treatment for NAS was reduced considerably with the use of methadone (15 days) as compared to morphine (21 days) (Ghazanfarpour et al., 2019). Other studies showed that with single-drug regimes, there was no difference in potential advantages or short-term outcomes of morphine or methadone (Burke and Beckwith, 2017; Young et al., 2015). Depending on the infant's weight, some doctors advise using opioids. On the other hand, some prescribe opioids based on the severity of the illness, as demonstrated by the Finnegan Neonatal Abstinence Scoring System. (Jones and Kraft, 2019). This study aims to evaluate the effectiveness and security of weight- and sign-based withdrawal control techniques. This study compares the efficacy and safety of morphine and methadone in treating NAS.

Methodology

A randomized, double-blind study was conducted at The Children's Hospital & The Institute of Child Health Multan from December 2021 to December

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2022. The study included mothers who were treated for opioid use disorder with buprenorphine or methadone or for chronic pain with opioids. Mothers who consumed alcohol and had a chronic illness or infectious disease were excluded. A total of 180 pregnant women were enrolled in the study, of which 114 needed treatment and were randomized (1:1) to receive morphine or methadone. The informed consent of the participants was recorded. The ethical board of the hospital approved the study. All mothers underwent urine toxicology testing at the time of delivery. Infants were delivered after 37 weeks of gestation (pre-mature deliveries were excluded) with no evidence of genetic disorders, significant congenital abnormalities, or sepsis. Meconium and urine toxicology tests were performed on all infants at birth. Standardized Finnegan Score (FS) assesses infants every four hours(Jilani et al., 2021). The pharmacological intervention was started if FS > 8 on two consecutive assessments or > 12 on one assessment. The dose approach based on FS and weight are summarized in Table I. Methadone alternating with placebo, or neonatal diluted morphine was administered to infants every four hours (each staff member administered drugs every eight hours to ensure blinding). The morphine, methadone, and placebo looked identical to maintaining blinding. If FS > 8 on two consecutive assessments or > 12 on one assessment continued, the dose was increased. If FS did not drop despite increasing the amount to the predetermined maximal level, phenobarbital (20mg/kg loading dose, then 4 to 5 mg/kg daily) was given. The dose was increased until withdrawal was controlled. Study drugs (morphine or methadone) were then reduced by 10% every twelve to forty-eight hours (FSs<8). Treatment ended at 20% of the starting dose. The primary endpoint of the study was the duration of the hospital stay. Secondary endpoints were the duration of treatment with the study drug, weight gain during the hospital stay, the requirement for supplemental medication, and the dose increase of the study drug. SPSS version 23.0 was used to analyze the data. We used linear, logistic, and binominal regression to assess weight growth, binary data, and count data. It was investigated to see if the mother's opioid use would affect the course of treatment. The Wilcoxon test was used in unadjusted analyses to compare the treatment group medians. Statistical significance was defined as P 0.05.

Results

A total of 180 pregnant women were enrolled in the study, of which 115 needed treatments; the study was conducted on 115 infants. The mean gestational age was 39.2 weeks, the mean birth weight was 3156 g, and 57 (49.5%) were male. Both the methadone and morphine groups had similar risk factors and demographic variables. The Methadone group had more infants initially admitted to the newborn unit. There were 14 adverse events (equally distributed in both groups), including emesis, hypothermia, poor feeding, lethargy, oxygen desaturation, bradycardia, and swallow breathing. One infant in the methadone group had serious hypothermia, lethargy, and apnea and was readmitted to the neonatal ICU. The drug dose was decreased, and controlled adverse events in all infants. According to unadjusted analyses, both groups' differences in primary and secondary endpoints were not statistically significant. After adjusting for the type of opioid used by the mother, it was found that the mean relative duration of hospital stay was 13% (which corresponds to the difference of 2.8 days) lower in the methadone group compared to morphine. The duration of treatment was 15% (which corresponds to the difference of 2.2 days) lower in the methadone group compared to morphine. The median hospital stay with methadone was 15 days compared to 19 days with morphine (P = .005). The use of phenobarbital in the methadone group was less than in the morphine group, but this difference was statistically insignificant (P = .07) (Table I, II).

Table I Treatment schedule of study drugs

Level	FS	Initial daily dose (mg/kg)
Morphine (0.2 mg/mL)		
1	8-10	0.3
2	11-13	0.5
3	14-16	0.7
4	≥17	0.9
Methadone (0.4 mg/mL)		
1	8-10	0.3
2	11-13	0.5
3	14-16	0.7
4	≥17	0.9

Discussion

Though opioids are recommended for treating NAS, there is no standard pharmacological therapy. Some studies show that in infants treated for NAS, methadone was associated with less duration of hospital stay and less duration of treatment (Chin Foo et al., 2021; Mangat et al., 2019). Our study also showed that methadone was more efficacious than morphine in treating NAS.

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Table II Clinical outcomes

Outcome	Methadone n=57	Morphine n=57	Comparison between drugs	
			Unadjusted P value	**Adjusted P value**
Duration of hospital stay (days)			0.005	0.046
Median	15	19		
Mean	21.9 ±14.0	23.1 ±8.7		
Duration of treatment (days)			0.15	0.01
Median	10.5	14		
Mean	14.6± 8.1	16.5 ±6.8		
Number of infants requiring phenobarbital (%)	9 (15.7%)	16(28.0%)	0.08	0.07
Number of infants needing increased dose (%)	21(36.8%)	27(47.3%)	0.14	0.10
Mean weight gain (g/d)	8.5±13.8	11.2±14.1	0.30	0.20

.Different response of these drugs to NAS is due to the unique properties of these drugs. Methadone's active R enantiomer has better μ-opioid receptor agonist activity than morphine; however, receptor affinity is lower. The higher volume of distribution, protein binding, and fat solubility increases its half-life and prolongs the dosing interval (Kreutzwiser and Tawfic, 2020). Methadone has a more variable dose regimen than morphine and can be administered every 8 to 24 hours as compared to morphine which is given every three to four hours. A study showed that lengthening the dosing interval of methadone reduces the duration of treatment and hospital stay by 2 days (Morrison et al., 2022). The treatment approach used in this study quickly improved signs of NAS and enabled rapid drug weaning. Adverse effects were recorded, which were equally distributed in both groups. As a result, the treatment approach was changed to allow rapid weaning of the drug (from 24 to 12 hours). Subsequent events were minimized after this change. The treatment protocol for NAS is significantly varied, and additional drugs like clonidine and phenobarbital complicate the establishment of standard protocol (Whalen et al., 2019). A previous study has shown that phenobarbital or clonidine administered along with morphine has little effect on the duration of hospital stays (Merhar et al., 2021). According to our study's weight and sign-based approach, phenobarbital was administered in case a predetermined opioid dose could not control withdrawal. Though the need for phenobarbital was reduced by methadone, following protocol alone lowered the need for the supplemental drug.

A recent study on the management of NAS has shown buprenorphine to be more effective than morphine (Kraft et al., 2017). However, a significant quantity of alcohol in buprenorphine preservation limited its widespread use. Most drugs administered to newborns have adult formulations containing preservatives, which are unsafe and may affect neurological development. In this study, pre-study work was done to ensure the sterility, purity, and stability of methadone preparation. It highlights the need for the development of safe formulations that are commercially available (Buckley et al., 2018). The limitation of this study is that FS was used to determine treatment needs in infants. This tool is subjective and may be affected by inter-observer variability.

Conclusion

Thus, it can be concluded that for the treatment of NAS, methadone had better short-term outcomes than morphine.

Conflict of interest

The authors declared no conflict of interest.

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