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Morphine vs methadone in the treatment of neonatal abstinence syndrome

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Morphine vs methadone in the treatment of neonatal abstinence syndrome.

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COMMENTARY, limited to 500 words

Misuse of opioids during pregnancy affects more than 5% of pregnancies in the United States (1). Infants exposed to alcohol or drugs in utero are at risk of developing neonatal abstinence syndrome (NAS). Several different approaches are used to treat NAS, and no universal standard exists. Morphine and methadone are commonly used pharmacological treatments (2).

This randomized, double-blind, intention-to-treat trial compared the short-term safety and efficacy of treatment with morphine versus methadone in infants with NAS.

Although 183 patients were consented, recruitment did not meet the sample size target as 66 infants did not require pharmacotherapy. Therefore, only 117 patients were randomized to treatment groups. Analysis was performed according to the intention-to-treat principle, projected to detect a difference in primary outcome of hospital length of stay (LOS) of 2.3 days. Secondary outcomes were considered exploratory given they were not accounted for in initial power calculations.

No significant difference was found in the primary outcome of hospital LOS with unadjusted analysis. Adjusted analysis showed a reduction in mean LOS of approximately 2.9 days with the use of methadone, compared with morphine. Recruitment did not meet the sample size target; therefore, power to detect the pre-specified difference in LOS was diminished.

However, when compared to the observational arm, the randomized group had shorter LOS, LOS due to NAS, and treatment length suggesting that protocolization of care practices itself may lead to improved outcomes.

The study was delayed initially given a lack of commercially available preservative free formulation of methadone suitable for infants. Recruitment was challenging with significant numbers of parents declining randomization citing reasons including fear of social or legal ramifications. Increasing focus on non-pharmacological management of NAS, such as the Eat, Sleep, Console assessment approach (3), was apparent over the course of the study with an overall decline in pharmacotherapy requirement. Recruitment ceased before the planned sample size was attained for reasons not explicitly stated.

Previous studies have similarly suggested shorter median treatment times using methadone for NAS, compared with morphine. A retrospective study by Patrick *et al.* involving 1424 infants from 14 centres showed methadone to be associated with reduced LOS, compared with morphine (4). Brown *et al.*, in a single-centre study of 31 infants demonstrated a shorter duration of pharmacotherapy with the use of methadone, compared with morphine (5). Contrary to these studies, a small retrospective study of 26 neonates by Young *et al.* found that methadone was associated with longer LOS, compared with morphine (6). A recent systemic review of 18 trials comparing a number of pharmacotherapies used in treatment of NAS suggested that buprenorphine is the optimal treatment with morphine the lowest ranked pharmacotherapy in terms of LOS and treatment time (7).

This study suggested treatment of NAS with methadone was somewhat better than morphine in terms of short-term outcomes and LOS. The long-term neurodevelopmental outcomes associated with methadone use are unclear and require further investigation.

Standardization of pharmacotherapy approaches to NAS would require further appropriately powered trials and evidence of long-term outcomes. Indeed, with increasing success with non-pharmacological management of NAS, the pharmacological options may become less relevant.

URL LINK

URL TO THE FULL REVIEW ON THE EBNEO WEBSITE

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CONFLICTS OF INTEREST

None

REFERENCES, only for the Commentary section and limited to 9

1. Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med* 2010; 363: 2320-2331.
2. Hudak ML, Tan RC; Committee on Drugs; Committee on Fetus and Newborn; American Academy of Pediatrics. Neonatal drug withdrawal. *Pediatrics* 2012; 129: e540-e560.
3. Grossman MR, Lipshaw MJ, Osborn RR, Berkwitt AK. A Novel Approach to Assessing Infants With Neonatal Abstinence Syndrome. *Hospital Pediatrics* 2018; 8: 1-6
4. Patrick SW, Kaplan HC, Passarella M, Davis MM, Lorch SA. Variation in treatment of neonatal abstinence syndrome in US children's hospitals, 2004-2011. *J Perinatol* 2014; 34: 867-872.
5. Brown MS, Hayes MJ, Thornton LM. Methadone versus morphine for treatment of neonatal abstinence syndrome: a prospective randomized clinical trial. *J Perinatol* 2015; 35: 278-283.

6. Young ME, Hager SJ, Spurlock DJr. Retrospective chart review comparing morphine and methadone in neonates treated for neonatal abstinence syndrome. *Am J Health Syst Pharm* 2015;7 2(suppl 3):S162-S167.
7. Disher T, Gullickson C, Singh B. Pharmacological Treatments for Neonatal Abstinence Syndrome. *JAMA Pediatr* 2019; 173:234-243