2019

Is Sublingual Buprenorphine Treatment Effective and Efficient When Compared to Traditional Neonatal Opium Solution (Morphine) in Treating Newborns with Neonatal Abstinence Syndrome?

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Is Sublingual Buprenorphine Treatment Effective and Efficient When Compared to Traditional Neonatal Opium Solution (morphine) in Treating Newborns with Neonatal Abstinence Syndrome?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 14, 2018

ABSTRACT

Objective: The objective of this selective EBM review is to determine whether sublingual buprenorphine treatment is effective and efficient when compared to traditional neonatal opium solution (morphine) in treating newborns with neonatal abstinence syndrome (NAS).

Study Design: Review of one randomized active-control clinical trial, one randomized double-blind, double-dummy clinical trial, and one retrospective cohort analysis.

Data Sources: All articles were published in English between the years of 2011 and 2017. Articles were obtained from peer-reviewed journals and databases using PubMed and Embase.

Outcomes: Outcomes measured were length of stay using the neonates birth date and hospital discharge date as well as duration of treatment using the cessation date of treatment once MOTHER NAS score <8.

Results: Kraft et al. (2011) found a statistically significant decrease in hospital stay and duration of treatment with buprenorphine when compared to morphine treatment of NAS. Further study by Kraft et al. (2017) again found a statistically significant decrease in hospital stay and duration of treatment with buprenorphine compared to morphine. Hall et al. (2016) found in their retrospective cohort study that patients treated with buprenorphine had a shorter hospital stay and a shorter duration of treatment when compared to patients who were treated with morphine or methadone.

Conclusions: All three studies confirm that buprenorphine treatment is both effective and efficient when compared to traditional neonatal opium solution (morphine) in treating newborns with neonatal abstinence syndrome. Further studies should place focus on treatment weaning the mother from the offending substance and its effect on the incidence of NAS, length of stay in the hospital, and possible elimination of pharmacologic intervention in neonates.

Keywords: neonatal abstinence syndrome, sublingual buprenorphine

INTRODUCTION

Neonatal abstinence syndrome (NAS) occurs in newborns who were exposed to drugs in utero and results in the presence of signs and symptoms of withdrawal. Presentation of NAS includes tremors, irritability, high-pitched crying, increased muscle tone, vomiting, poor sleep, diarrhea, tachypnea, sweating and low-grade fever. In addition to withdrawal, the newborns are also at risk for poor intrauterine growth, premature birth, seizures, and birth defects. It is evident that this is an unfortunate series of events and difficult way to begin life.

The current opioid crisis that has plagues adults in the US today has sadly affected the neonate population as well. The incidence of NAS has significantly risen over the last 10 years, with the number of neonates admitted to the NICU with NAS increasing 10-fold from 2005 to 2011.[1] In 2009, NAS averaged $53,400 in hospital charges with an associated average hospital stay of 16.4 days, whereas, uncomplicated births average $9,500 and 3.3 days in the hospital.[2] A recorded 9,674 neonates were kept in the hospital after birth for NAS in 2009.[3]

This influx in neonatal patients has put an extensive amount of stress on the neonatologist's workload. The high demand for specialized physicians, and the subsequent low supply has provided a window of opportunity for physician assistants.[4] With some additional training, PAs can serve a vital role in the care of critically ill neonates and their families.[4] They have the ability to review labs, intubate neonates, accompany critical patients to procedures, initiate treatment, and provide an integral role in providing direction and communication in patient care.[5]

The exact pathophysiologic mechanism of opioid withdrawal in an infant is unknown. However, it is known that the low molecular weight water-soluble opioids, as well as the synthetic opiates, are easily able to cross the placenta and effect the fetus.[1] The locus coeruleus

of the pons is the most important and sensitive center in opioid withdrawal. Lack of opioids is sensed, and an increased production of norepinephrine occurs, which causes many of the signs of NAS.[1]

Treatment for NAS includes non-pharmacologic as well as pharmacologic regimens. Non-pharmacologic therapies include swaddling, frequent feeds, pacifiers, music, and massage therapy. Pharmacologic treatments consist of morphine, methadone, phenobarbital, clonidine, and buprenorphine. Most treatment options for opioid withdrawal, as listed above, are for use in adults. The standard of care for NAS has been morphine, but it has its own side effects and a longer treatment duration. Buprenorphine has been routinely used in adults for abstinence therapy and symptom control with lower rates of respiratory depression. This finding comes as a highly attractive treatment option for neonates since NAS already puts a significant amount of stress on the newborn.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not sublingual buprenorphine treatment is effective and efficient when compared to traditional neonatal opium solution (morphine) in treating newborns with neonatal abstinence syndrome (NAS).

METHODS

Two randomized control trials and one retrospective cohort analysis were selected for this review. The population included newborns with neonatal abstinence syndrome with intervention consisting of sublingual buprenorphine treatment. All three studies had a treatment group using buprenorphine and an experimental group who received neonatal opium solution (morphine). Outcomes measured were the efficacy of buprenorphine as measured by the duration of treatment and the efficiency as measured by the length of stay in the hospital.

Databases used to select adequate studies include PubMed and Embase. Keywords used during the search were "neonatal abstinence syndrome" and "buprenorphine". The three chosen studies were written in English and published between the years 2011-2017. Inclusion criteria for all three articles included randomized control trials and retrospective cohort analyses. Exclusion criteria, which all studies abided by, included studies that contained neonates without NAS and used methadone as the experimental therapy treatment. Table 1 displays detailed individual study components as well as inclusion and exclusion criteria. Statistical analysis of data included the mean change from baseline, median, confidence intervals, and p-values.

OUTCOMES MEASURED

This meta-review dissects the difference in length of stay in the hospital and the duration of treatment when comparing buprenorphine and morphine as treatment options. Length of stay was determined by the neonate's discharge date compared to their birth date. Duration of treatment was determined using the MOTHER NAS score. The MOTHER NAS score is a variation of the Finnegan scoring instrument.[6] The score ranges from 0 to 42, with the higher end signifying a greater severity (Table 2).[6] Cessation of treatment in patients was determined by a MOTHER score of <8.

RESULTS

Kraft et al. (2011) ran a randomized, open-label, active-control clinical trial comparing the standardized oral morphine to the experimental sublingual buprenorphine on 24 term infants with NAS in need of pharmacologic treatment.[3] Treatment was initiated in any full-term neonate (≥37 weeks' gestation) with a total MOTHER NAS score ≥24 after three consecutive counts, or a single score of ≥12.[3] Additional inclusion and exclusion criteria is indicated in Table 1.

Table 1 – Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Kraft[3] (2011)	Active-control RCT	24	≥ 37 weeks gestation	Infants with in utero exposure to opioids, requiring pharmacologic treatment for NAS	Exposure to benzodiazepines, maternal use of alcohol, medical illness, major congenital malformations, or breastfed infants.	0	Sublingual buprenorphine 15.9 mcg/kg in 3 doses; Morphine 0.4 mg/kg/d in 6 doses; adjunct Phenobarbital therapy when max dose of Buprenorphine (60 mcg/kg/d) or Morphine (1 mg/kg/d) is reached and NAS not controlled
Kraft[6] (2017)	Double-blind, double-dummy RCT	63	≥ 37 weeks gestation	Term infants exposed to opioids in utero with signs of NAS.	Major congenital malformations, birth weight of <2200g, a medical/neurologic illness, hypoglycemia requiring IV glucose, bilirubin level >20 mg/dL, maternal use of a benzodiazepine 30 days before birth, or seizures. Breastfeeding exclusion criteria amended during study.	5	Sublingual buprenorphine 15.9 mcg/kg in 3 doses; Morphine 0.4 mg/kg/d in 6 doses; Phenobarbital rescue dose when max dose of Buprenorphine (60 mcg/kg/d) or Morphine (1 mg/kg/d) is reached and NAS not controlled
Hall[7] (2016)	Retrospective Cohort Analysis	360	≥34 weeks gestation	Infants treated pharmacologically for NAS with an opioid during the 4-year period.	No infant had a major congenital malformation or experienced iatrogenic withdrawal.	0	Buprenorphine, Methadone, Methadone, adjunct phenobarbital therapy.

Table 2 – MOTHER NAS Scale; Scored Elements[6]

Signs and Symptoms	**Score**
Crying: Excessive high pitched Crying: Continuous high pitched	2 3
Sleeps <1 hour after feeding Sleeps <2 hours after feeding Sleeps <3 hours after feeding	3 2 1
Hyperactive Moro Reflex Markedly Hyperactive Moro Reflex	1 2
Mild Tremors: Disturbed Moderate-Severe Tremors: Undisturbed	1 2
Increased Muscle Tone	1-2
Excoriation	1-2
Generalized seizure (or convulsion)	8
Fever >37.3 C (99.2 F)	1
Sweating	1
Nasal Stuffiness	1
Frequent Yawning (≥4 successive times)	1
Sneezing (≥4 successive times)	1
Tachypnea (Respiratory Rate >60/min)	2
Poor feeding	2
Vomiting (or regurgitation)	2
Loose Stools	2
Failure to thrive (Current weight > 10% below birth weight 90%) (record daily weights)	2
Excessive irritability	1-3

Patients were randomized to traditional treatment of oral morphine and an experimental group of sublingual buprenorphine with 12 participants in each group.[3] This study adopted an intention-to-treat basis.[3] Using their continuous data, they determined that buprenorphine treatment had statistically significant improvements in both duration of treatment and length of hospital stay (Table 3).

Table 3 – Outcomes of Buprenorphine and Morphine

Outcome	**Buprenorphine (Mean ± SD)**	**Morphine (Mean ± SD)**	***P-value***
Length of Stay	32 ± 24	42 ± 13	0.05
Duration of Treatment	23 ± 12	38 ± 14	0.01

Expanding on their prior research, Kraft et al. (2017) took it upon themselves to perform Wish a double-blind, double-dummy clinical trial.[1] In this study, they had 63 full-term infants (≥37 weeks' gestation) randomly assigned to receive either sublingual buprenorphine or oral morphine to treat their NAS.[6] As with their previous study they used the same MOTHER NAS score guidelines, three consecutive scores totaling ≥24 or one single score ≥12.[6] Table 1 contains additional inclusion and exclusion criteria for the study. Throughout their research, they lost 5 participants, 3 from the buprenorphine group and 2 from the morphine group, all who were withdrawn by their parents due to concern for ineffective treatment.[6] The 5 withdrawn patients received open-label morphine due to the researchers following the intention-to-treat principle.[6] Again the researchers further proved, with more reliable study design, that buprenorphine therapy had a statistically significant improvement in shortening the duration of treatment and the length of hospital stay (Table 4).

Table 4 - Outcomes of Buprenorphine and Morphine with P-value and 95% CI

Outcome	**Buprenorphine (median); N=33**	**Morphine (median); N=30**	***P-value***	**Difference (95% CI)**
Length of Stay	21 (7 to 71)	33 (18 to 70)	<0.001	-12 (-22 to -7)
Duration of Treatment	15 (3 to 67)	28 (13 to 67)	<0.001	-13 (-21 to -7)

In a retrospective cohort analysis Hall et al. (2016) evaluated 360 infants treated for neonatal abstinence syndrome over a four-year period.[7] In June 2015, a standardized weaning protocol was put in place with sublingual buprenorphine as standard treatment despite the type of intrauterine opioid exposure.[7] Detailed inclusion and exclusion criteria are shown in Table 1. Overall, the study determined that neonates treated with buprenorphine treatment had a 3.0-day reduction in treatment duration and a 2.8-day reduction in hospital stay (Table 5).[7] Additionally,

they were able to determine that buprenorphine treatment resulted in hospital discharge of infants without need for adjunct therapy ($p < 0.001$).[7]

Table 5 – Retrospective Analysis of Outcomes for Treatment with Buprenorphine vs. Morphine Regardless of Intrauterine Exposure

Outcome	**Buprenorphine, Mean (95% CI); N=174**	**Morphine, Mean (95% CI); N=186**	***P-value***
Length of Stay	12.4 (11.3-13.6)	15.2 (14.1-16.4)	<0.001
Duration of Treatment	7.4 (6.3-8.5)	10.4 (9.3-11.5)	<0.001

DISCUSSION

The beginning of life for a neonate is stressful in the physiological sense. They have gone from a protective, life-sustaining, and nutrient providing uterine environment to the open world. Adding on additional stress from opioid withdrawal is the last thing a neonate needs to overcome. That being said, all three of the studies in this evidence-based systematic review demonstrate that treatment with buprenorphine allows for a shorter hospital stay and less time in treatment. While buprenorphine has been proven effective, it comes with its short-comings.

In both Kraft et al. (2011, 2017) studies, it was noted that a few patients receiving buprenorphine required supplemental treatment with phenobarbital to provide adequate disease stability.[3,6] It is unclear if the need for phenobarbital necessarily indicates treatment failure in the infant population.[3] Many factors go into neonatal withdrawal such as the type of abused agent used, strength and quantity of offending agent, and duration of intrauterine exposure.[8] With this in mind, it is no question that an infant may require supplemental treatment for symptom control.

Another item to consider is the type of intrauterine drug exposure included in the study. One might challenge the fact that both Kraft et al. (2011, 2017) studies excluded the use of benzodiazepines (Table 1). However, it should be noted that the Hall et al. (2016) retrospective study did not have any exclusion criteria for the offending agents and had the same significant

results for both measured outcomes (Table 5). This finding should further suggest that even when the type of intrauterine exposure was not controlled for, the outcome still presented buprenorphine as the better treatment option.

Limitations to this particular systemic review include the fact that two of the chosen studies were conducted by the same research group at the same hospital in Philadelphia, PA. It is known that the second study expanded on the limitations that they discovered in their first study, such as the number of participants and study control factors.[3] After improving their parameters and expanding their study size, they were still able to identify a positive outcome with buprenorphine over morphine treatment.[6] This duplication in research teams was recognized during the study selection process and an attempt was made to further support the systematic review by selecting a study from a different location, such as with Hall et al. (2016). In doing this, however, the strength of a randomized control trial was sacrificed and thus replaced with a retrospective cohort analysis.

CONCLUSION

This systemic review confirms that buprenorphine treatment is both effective and efficient when compared to traditional neonatal opium solution (morphine) in treating newborns with neonatal abstinence syndrome. Since the United States is undergoing such an epidemic with opioid abuse and addiction in the adult population, it is important not to forget about others that may subsequently suffer the consequence. These findings come at a crucial time for neonates born to mothers who battle with addiction. Further studies should be recommended in researching the safest amount of buprenorphine that a neonate can receive to try to limit or eliminate the need for supplemental phenobarbital. Additionally, it might be beneficial to focus on the mother and her access to adequate care both for prenatal and behavioral management.

Perhaps a study could explore the effectiveness of weaning a mother off the offending agents early in gestation and the resulting incidence in NAS, length of hospital stay, or if it omits a need for pharmacologic treatment altogether.

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