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Is clonidine effective in reducing duration of treatment in infants admitted for neonatal abstinence syndrome?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not clonidine is effective in reducing duration of treatment in infants admitted for neonatal abstinence syndrome (NAS).

Study Design: Review of two randomized control trials and one retrospective cohort design.

Data Sources: All articles were published in English in peer reviewed journals between the years of 2015 and 2019. Articles were obtained from peer reviewed journals and databased using PubMed and Cochrane Library.

Outcomes: Outcomes measured were duration of treatment and duration of treatment of morphine, measured in days.

Results: The infants treated with clonidine in Bada et al. required a statistically significantly shorter duration of treatment than those treated with morphine ($p=0.02$). Surran et al. found that infants who received morphine/clonidine had a statistically significant longer duration of treatment of morphine than the comparison group of infants treated with morphine/phenobarbital ($p=0.001$). Gullickson et al. reported a statistically significant increase in the duration of treatment for those who received morphine/clonidine compared to those who only received morphine ($p=0.004$).

Conclusions: Based on the conflicting findings of the three trials, it is unknown if clonidine is efficacious in reducing the duration of treatment in infants with NAS. As NAS becomes more prevalent in the United States, more research needs to be done to more fully define clonidine's role in treatment.

Keywords: clonidine, neonatal abstinence syndrome, morphine

INTRODUCTION

Neonatal abstinence syndrome (NAS) is the unfortunate consequence for approximately 55% to 95% of newborns with prenatal opiate exposure.[1] Though rarely a fatal condition, NAS can cause a wide variety of devastating signs and symptoms in a newborn, usually requiring hospital-stay prolonging treatments. This evidence based review evaluates two RCTs and one retrospective cohort comparing the efficacy of clonidine in reducing the duration of treatment in infants with NAS.

The incidence of NAS has increased throughout the United States in recent years. Data suggest that in the United States, approximately 80 newborns are diagnosed with NAS per day.[2] The increase in the incidence of NAS has been associated with an increase in health care costs. NAS patients' hospital stays cost about nine times as much as a newborn without NAS[2], about $9,200 compared to $1,200. This is largely because patients with NAS need to stay in the hospital longer to receive treatment. In 2017, the HCUP reported 27,085 NAS newborn hospitalizations.[2] That study also found that the average length of hospital stay for newborns with NAS was between 11 and 12 days, compared to two days for those without.[2]

NAS is a multisystemic disorder that most notably causes autonomic dysregulation. The sudden withdrawal results in an increase in neurological excitability and neurotransmitter production which causes a variety of signs.[3] Signs include excessive irritability and crying, seizures, sleep problems, hyperthermia, gastrointestinal problems, poor feeding, and tremors. However, the exact cellular mechanisms of the condition remain widely unknown.[3]

Non-pharmacologic treatments are implemented to support pharmacotherapy or can be used exclusively in mild cases of NAS. Examples include: gentle handling, swaddling, feeding on demand, dimmed lights, minimal noise, cuddling, maternal involvement, breastfeeding,

pacifiers, music therapy, and continuous monitoring.[3] Morphine has historically been the standard first-line pharmacologic treatment for NAS. However, the longer-term safety of opiates in the treatment of NAS remains unknown, as such, alternatives need to be considered.[4]

Clonidine is being studied for its potential role in the treatment of NAS as a non-opiate alternative or adjunct to the standard morphine regimen. Clonidine is an alpha-2 adrenergic agonist that works by inhibiting neurotransmitter production, which then decreases signs of NAS.[4] It has been shown to be effective in reducing withdrawal symptoms in adults, which prompted questions about its potential as a treatment for infants as well.[5]

OBJECTIVE

The objective of this selective EBM review is to determine whether or not clonidine is effective in reducing duration of treatment in infants admitted for Neonatal Abstinence Syndrome (NAS).

METHODS

The articles were selected based on relevance to the clinical question and outcomes measured. All were published in peer-reviewed journals. The articles were obtained from searches of PubMed and Cochrane Library. Keywords used in searches included “clonidine” and “neonatal abstinence syndrome” and “morphine.” Inclusion criteria included: primary research studies, published in English, after October 10, 2010. The exclusion criteria included: published before October 6, 2010, and secondary research design. Two randomized control trials and one retrospective cohort design were selected for analysis.

The population studied was infants admitted for treatment of Neonatal Abstinence Syndrome with prenatal opiate exposure. The three trials all implemented an interventional treatment of clonidine, which was compared to either morphine alone, or morphine and

phenobarbital.[1,4,5] The outcomes included the duration of treatment and the duration of treatment of morphine. [1,4,5]

Table 1. Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Bada[4] (2015)	RCT	31	<7 days old	<7 days old, GA ≥35 wks, prenatal opioid exposure, symptomatic with Finnegan Scores ≥ 8, likely to survive	Prenatal cocaine exposure, seizures, major congenital malformation, BP instabilities, major medical condition other than NAS	0	Regimen of clonidine 5µg/kg/day with daily dose escalation until sx were controlled. Weaning off medication once sx were controlled for 48h.
Surran[1] (2013)	RCT	68	≤15 days old	≤15 days old, prenatal opioid exposure, moderate to severe NAS with Modified Finnegan Scores ≥ 8, medically stable	GA <35 wks, IUGR, congenital anomalies, in utero exposure to BZD, medically unstable	2	Regimen of morphine sulfate 0.4mg/ml and clonidine 10mcg/ml with doses dependent on severity. Morphine then clonidine weaned once sx controlled.
Gullick-son[5] (2019)	Retrospective Cohort	174	Average GA: 38.1 weeks for M+C. 36.2weeks for M group	Prenatal opioid exposure, born 2006-2015 treated at IWK Health Centre, symptomatic, with coded Finnegan score or ICD-10 P96.1	Infants with iatrogenic W/D, or treated with regimen other than morphine or morphine + clonidine	0	Regimen of morphine (mg/kg q3h) and clonidine (mcg q3h) with doses dependent on severity. Morphine then clonidine weaned once sx controlled.

OUTCOMES MEASURED

This review analyzes clonidine's potential efficacy in reducing the duration of treatment in infants admitted for Neonatal Abstinence Syndrome. The outcome studied for Gullickson et al. and Bada et al. was the duration of treatment, measured in days.[4,5] The outcome studied for Surran et al., where both the intervention and comparison groups included morphine, was the duration of treatment of morphine, measured in days.[1] Surran et al. chose their primary outcome to be the duration of morphine treatment instead of the total duration of treatment because infants in the comparison groups weaned off their phenobarbital at home, which made tracking the total endpoint of treatment more difficult.[1]

RESULTS

Bada et al. randomized 31 infants with NAS into two control groups to receive either morphine 0.4mg/kg/day or clonidine 5μg/kg/day with daily dose escalation until control of symptoms was achieved.[4] After 48 hours of symptom control, infants' doses were weaned by 10% every other day until treatment could be safely stopped.[4] The study was double-blind, and all clinical and research personnel other than the clinical pharmacists were unaware of infants' medication assignments.[4] The infants included in the study all were <7 days old, GA ≥35 wks, with prenatal opioid exposure, and symptomatic with Finnegan Scores ≥8. The total inclusion and exclusion criteria for the study are outlined in Table 1. The Wilcoxon rank-sum test was used to analyze differences between the two treatment groups. There were no significant differences in the characteristics of infants in the two groups in regards to birth weight, gestational age, APGAR score, sex, postnatal age, and Finnegan score.[4] The duration of treatment was significantly different between the two groups with the clonidine group having a shorter duration than morphine as shown in Table 2.[4] One patient in the clonidine group was

excluded from the analysis due to the clinical staff's deviation from the protocol for that patient.[4] No adverse effects such as abnormal BP or arrhythmias were found in any infants who received clonidine.[4]

Table 2. Outcomes of Morphine and Clonidine

Intervention	Mean Duration of Treatment (days)	Standard Deviation	P-value
Clonidine	32	20.4	0.02*
Morphine	42.7	17.8	
*= Statistically significant (P < 0.05)			

Surran et al. conducted a randomized control trial on infants ≤15 days old, with prenatal opioid exposure, and moderate to severe NAS.[1] The study was non-blinded due to different monitoring requirements for the two treatment groups.[1] However, the randomization was concealed from the clinical research team, and the clinicians followed an exact protocol in regards to dosing and weaning procedures.[1] The study compared the duration of treatment of morphine in infants who received clonidine/morphine versus phenobarbital/morphine.[1] Complete inclusion and exclusion criteria for participants are detailed in Table 1. The Wilcoxon rank-sum test was used to analyze differences between the two treatment groups. The study reported no significant differences in characteristics in the two groups in regards to gestational age, birth weight, and 5 minute APGAR score.[1] There was a significant difference in Modified Finnegan score and maternal oxycodone dose.[1] All patients in this study were analyzed in the groups in which they were randomized.[1] Two patients in the clonidine/morphine group were withdrawn from the study: one due to BZD exposure in utero and one due to a seizure condition, both discovered after the start of the study.[1] There were no reported adverse effects from clonidine in any patients who received it.[1] Overall, the results of the study with univariable analysis showed

that the phenobarbital/morphine group required significantly less duration of treatment than the clonidine/morphine group, as shown in Table 3.[1]

Table 3. Outcomes of Clonidine/Morphine and Phenobarbital/Morphine

Intervention	Mean Duration of Treatment of Morphine (days)	95% CI	P-value
Clonidine/Morphine	19.5	15.7, 23.2	0.001*
Phenobarbital/Morphine	12.4	10.1, 14.7	
*= Statistically significant (P < 0.05)			

A retrospective cohort analysis by Gullickson et al. studied symptomatic infants with prenatal opioid exposure treated at the IWK Health Center between 2006 and 2015 for NAS.[5] Their database identified 22 infants treated with morphine alone and 100 infants treated with morphine/clonidine who met the inclusion and exclusion criteria outlined in Table 1.[5] Fisher's exact test, t-test and Mann–Whitney U-test were used to analyze differences between the two treatment groups. There were no significant differences between the groups in regards to sex and birth weight, but there were significant differences between gestational age and 5 minute APGAR score.[5] The study also found a significant difference between the duration of treatment between the two treatment groups, with infants receiving morphine alone having a shorter duration of treatment than those who received morphine/clonidine.[5] No safety concerns or adverse effects were noted.

Table 4. Outcomes of Morphine and Clonidine/Morphine

Intervention	Mean Duration of Treatment (days)	Standard Deviation	P-value
Morphine	11.3	7.6	0.004*
Morphine/Clonidine	19.7	12.9	
*= Statistically significant (P < 0.01)			

DISCUSSION

Clonidine is an alpha-2 adrenergic agonist that works by an inhibitory mechanism to decrease sympathetic outflow from the CNS.[6] It is commonly used as adjunctive or alternative therapy in adults experiencing opioid withdrawal symptoms. Clonidine is also given to pediatrics for treatment of several different psychiatric disorders such as PTSD, conduct disorder, and ADHD.[6] The most common adverse reactions noted include sedation, weakness, bradycardia, irritability, headache, fatigue, dizziness, and abdominal pain.[6] Discontinuing clonidine abruptly can cause a rebound in withdrawal symptoms.[6] Therefore, clonidine must be gradually tapered over several days.

Clonidine's use in the treatment of NAS is a fairly new concept, with only limited research studying it's efficacy and safety. Limitations of research availability include no three blinded RCTs testing clonidine as monotherapy. The three primary research studies reviewed in this systematic review were not able to answer the question of clonidine's efficacy in reducing the duration of treatment of NAS either, as they came to conflicting conclusions.

There were several limitations listed in each of the studies that may have influenced the results and their generalizability. Bada et al. acknowledged their small sample size and failure to assess prenatal drug exposures by meconium assay as two limitation to the study.[4] They also noted that some infants finished their treatment at home, which required caregivers to identify withdrawal symptoms and properly carry out the weaning process.[4] It also required unmasking of the caregiver and primary care doctor.[4]

Surran et al. also mentioned limitations to their study due to lack of blinding.[1] There was no blinding of the treatment groups due to different monitoring and dosing protocols for the clonidine group.[1] They also noted that while the duration of the treatment of morphine was

shorter for those who were on phenobarbital/morphine, the total duration of treatment was much longer that group, which weaned phenobarbital at home for up to 8 months.[1]

Gullickson et al. was limited by location, as they only conducted their analysis from patients in one hospital in Canada.[5] They also noted that the clonidine/morphine group may have had a longer duration of treatment than morphine alone due consecutive weaning of morphine and then clonidine in the intervention group.[5] Another limitation of the Gullickson et al. study was the small sample size in the morphine group of 22 infants, compared to 100 in the morphine/clonidine group.[5]

Bada et al. was the only study to conduct follow-up monitoring for the participants in the study.[4] Twelve participants in each group were evaluated in 1 year follow-up visits. There were no significant differences found using the Wilcoxon rank-sum test between in the two treatment groups at that time in regards to language, physical growth, motor and cognitive ability.[4] After the 1 year visit, there was no further follow-up. More thorough follow up in regarding long term effects of clonidine should have also been considered by Bada et al. Gullickson et al. and Surran et al. should have investigated potential effects of the treatment after completion as well.

CONCLUSION

Based on the findings of this evidence-based systematic review, it is unknown if clonidine is effective in reducing the duration of treatment in infants with NAS. As NAS becomes more prevalent in the United States, more research needs to be done to more fully define clonidine's role in the treatment of NAS. Neonates are arguably the most vulnerable population, and those born with NAS face even more obstacles in just the first few days of life. More research needs to be conducted to ensure those with NAS have the best transition possible from the womb to the world outside. This research should focus on a multicenter trial of

clonidine as single-drug therapy in an infant's treatment of NAS since that was the only intervention that proved a shorter duration of treatment than morphine.[4] Further research should also include the long-term effects of clonidine in patients treated for NAS. Finally, future research studies should analyze the role of specific prenatal opiate agents, as well as non-opiate drugs, in response to different pharmacotherapies used to treat NAS.

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