

Safety, Tolerability, and Efficacy of Acupuncture in Management of Neonatal Abstinence Syndrome (NAS): A Systematic Review

Sara Ghahremani¹, Farideh Asadzadeh², Forough Rakhshanizadeh³, Sepideh Fanaei⁴, Iman Hashemi Petroudi⁴, Faezeh Ghorbani⁵, *Masumeh Ghazanfarpour⁵, Zeinab Sadat Hoseini⁶

¹Assistant Professor of Pediatrics, Department of Pediatrics, Faculty Of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. ²Department of Pediatrics, Mashhad University of Medical Sciences, Mashhad, Iran. ³Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical sciences, Mashhad, Iran. ⁴Department of Anesthesiology, Mashhad University of medical sciences, Mashhad, Iran. ⁵Department of Nursing and Midwifery, Razi School of Nursing and Midwifery, Kerman University of Medical Sciences, Kerman, Iran. ⁶Student Research Committee, Faculty of Medicine, Islamic Azad University of Mashhad, Mashhad, Iran.

Abstract

Background: The Neonatal Abstinence Syndrome (NAS) has been treated so far by various drugs, such as opioids and non-opioids. There is some concern about NAS babies who receive chemical drug treatment. Some researchers mentioned that shorter pharmacological treatment and less lengthy hospitalization are associated with several secondary advantages. The aim of this study was to assess safety, tolerability, and efficacy of acupuncture in management of Neonatal Abstinence Syndrome in infants.

Materials and Methods: An extensive search was done in databases of Medline, EMBASE, Scopus, Cochrane, and Web of Science until August 2018. Two independent researchers screened articles, in the next step, full texts of probably relevant articles were summarized and categorized based on the evaluated outcomes and overall effect size was presented.

Results: Five studies were included in the systematic review. Auricular acupuncture when implemented as adjunct pulse non pharmacologic in management of NAS is safe, feasible, and acceptable. However, Auricular acupressure did not show any significant effect on pharmacological therapy, length of hospital stay and average NAS scores. Treatment with Laser acupuncture as adjunct in management of infants with NAS were associated with several advantages. These include improvement in feeling (better relaxation and higher calorie intake), decreased Finnegan scores, shorter duration of treatment with morphine, and shorter duration of hospitalization. In terms of safety, treatment with laser acupuncture as adjunctive were well-tolerated.

Conclusion: The findings of this systematic review showed that infants with NAS secondary to maternal opiate usage may receive more benefits of treatment with acupuncture in combination with pharmacologic therapy compared to pharmacologic therapy alone. In these findings should be interpreted in light of mentioned limitation.

Key Words: Acupuncture, Acupressure, Efficacy, Neonatal Abstinence Syndrome.

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*Corresponding Author:

Dr. Masumeh Ghazanfarpour, Department of Nursing and Midwifery, Razi School of Nursing and Midwifery, Kerman University of Medical Sciences, Kerman, Iran.

Email: masumeh.ghazanfarpour@yahoo.com

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1- INTRODUCTION

Neonatal Abstinence Syndrome (NAS) is a term for a group of conditions caused when a newborn is exposed to addictive illegal drugs while in the pregnant mother. It is vital to attempt early diagnosis and treatment of NAS due to its serious and potentially life-threatening complications (3, 4). Studies have shown that the exposure to antenatal opiate could influence the development of brain and subsequently cause problems regarding reduced corticogenesis, neurogenesis, and synaptogenesis and changes in the ontogeny of the stress axis and immune response, decreased head circumference and small brain volume (5). The hospitalization of numerous newborns persists for weeks in treating withdrawal, and so this increases maternal guilt and reduces maternal bonding. The mild symptoms can be distinguished from severe ones using Finnegan Neonatal Abstinence Scoring Tool (FNAST), providing conditions for assessing effective treatment (6). The majority of NAS need pharmacotherapy (7) such as opioids like diluted deodorized tincture of opium (dDTO), morphine, methadone and buprenorphine and non-opioids like the noradrenergic antagonist (clonidine), and phenobarbital (8-11), among which, the widely used medications for opioid withdrawal are dDTO, and morphine sulfate (63%), and then methadone (20%). Phenobarbital is the second line drug in treating opioid-exposed infants (12). There is some concern about NAS babies who receive drug treatment during the first few months of their life, a period of fast-growth of the brain after birth. Potential damages to brain development due to exposure to drugs indicate the need to evaluate the use of non-opiate abused drugs such as clonidine as an alternative to the treatment of opiate for infants with NAS (3). Some authors mentioned that shorter pharmacological

treatment and less length of hospitalization are associated with several secondary including a reduction in adverse effects of oral morphine therapy, a reduction in costs of hospital stays and it promotes bonding with parents (13). A few studies assessed the effect acupuncture or acupressure in combination with usual pharmacological treatment on NAS with two Randomized controlled trials (RCTs) (12, 13), a case report (14), and a case series (15). Therefore, it is important to reach a conclusion from all of the few existing studies. The aim of this study was to assess safety, tolerability, and efficacy of acupuncture in management of Neonatal Abstinence Syndrome in infants.

2- MATERIALS AND METHODS

The main purpose of the current systematic review was to find the required therapeutic approaches for neonatal abstinence syndrome.

2-1. Search strategy

The present study was conducted based on the Cochran's guidelines. An extensive search was performed on the Medline, EMBASE, Scopus, Cochrane, and Web of Science until August 2018. The search query in Medline (via PubMed) is shown in **Table.1**. In addition, a manual search was conducted in Google motor engine, Google Scholar, and bibliography of related articles and reviews.

2-2. Inclusion criteria

This systematic review included all types of included studies (such as Randomized control trials, or randomized clinical trials [RCTs], case report, and case series) in English studying the impact of different methods of acupuncture in neonates for improving the NAS. No restriction was considered for the control group.

2-3. Data extraction

Two separate authors reviewed the searched articles. Thus, title and abstract were read to select the relevant articles, and then full-text of the related articles was downloaded to evaluate in more detail. The listed references of the included articles were reviewed to find additional related articles. The information of articles

was tabulated in summary, including the author's name, time of study, design (with details), and type of opioid exposure in uterus, intervention and control groups, assessment tool of NAS severity, and primary outcome of studies. Finally, the data were reported qualitatively (13, 16-19) (**Table.2**).

Table-1: Search strategy for Medline (via PubMed).

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((("neonatal abstinence syndrome"[MeSH Terms] OR ("neonatal"[All Fields] AND "abstinence"[All Fields] AND "syndrome"[All Fields]) OR "neonatal abstinence syndrome"[All Fields]) OR ("neonatal abstinence syndrome"[MeSH Terms] OR ("neonatal"[All Fields] AND "abstinence"[All Fields] AND "syndrome"[All Fields]) OR "neonatal abstinence syndrome"[All Fields] OR ("neonatal"[All Fields] AND "withdrawal"[All Fields] AND "syndrome"[All Fields]) OR "neonatal withdrawal syndrome"[All Fields])) AND (("acupuncture"[MeSH Terms] OR "acupuncture"[All Fields] OR "acupuncture therapy"[MeSH Terms] OR ("acupuncture"[All Fields] AND "therapy"[All Fields]) OR "acupuncture therapy"[All Fields]) OR ("acupressure"[MeSH Terms] OR "acupressure"[All Fields])).
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2-4. Outcome measures

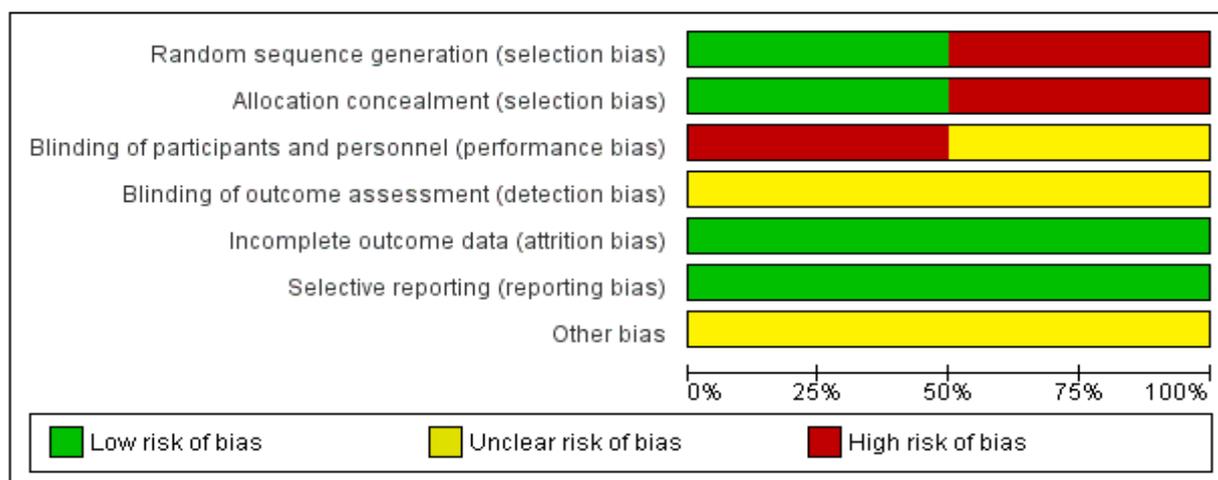
Outcome measures were considered to be type of treatment, duration of treatment, duration of hospitalization, drug safety, and drug complication.

2-5. Quality assessment

After conducting the search and eliminating duplicated reports, two independent researchers screened the title and abstracts of the studies, and then potentially relevant studies were selected. Any disagreement was solved by discussion. The quality of the studies was assessed using Cochrane's proposed guidelines (20). The risk of bias of the included studies was assessed by two authors independently using the criteria of the Cochrane Handbook for Systematic Reviews of Interventions (21) that evaluated: (a) random sequence generation; (b) allocation concealment; (c) blinding of participants and personnel; (d) blinding of outcome assessment; (e) incomplete outcome data; (f) selective reporting; and (g) other bias. In this assessment, each item was graded as 'low', 'high' or 'unclear' risk of bias. Only two studies were RCTs and are included in **Figure.1**.

Table-2: Summary of included studies.

Author, Reference Year, Country	Study design	No. of patients (Int./Control)	Opioid exposure in uterus	Intervention	Control	Drop out (%) (Int./Cont.)	Assessment tool	Results
Raith et al., 2014, (14)	Case report	One girl infant	Morphine	Laser acupuncture as adjunct in combination with morphine	---	0	Finnegan	Their results suggested an improvement in feeling (better relaxation and higher calorie intake). Also, Finnegan scores showed a decrease on the day after laser therapy.
Filippelli et al., 2012, (15)	Case series	54 infants	Every usual pharmacological treatment	Non-insertive acupuncture	---	0	Variable scale	Their result showed that restless infants calmed down during treatment. Babies had better feeding (higher calorie intake).
Schwartz et al., 2011, (17)	4-year prospective randomized controlled study	37/39	DTO or phenobarbital	Auricular acupressure + DTO or phenobarbital	DTO or phenobarbital	0	Finnegan scoring system	No significant difference was observed between two groups during pharmacological therapy, length of hospital stay and average NAS scores.
Weathers et al., 2015, (18)	Prospective study conducted over a 2-year period	20	Methadone is the primary pharmacologic agent used, with clonidine used as an adjunct if NAS severity is not well-controlled with methadone	Pharmacologic treatment, majority of infants were exposed to one method + Auricular acupressure	Pharmacologic treatment	0	Modified Finnegan	Auricular acupressure as adjunct is safe, feasible, and acceptable to both parents and providers.
Raith et al., 2015, (19)	Case-report	14/14	A morphine solution and a sedative.	Morphine solution and a sedative + Laser acupuncture	Morphine solution and a sedative	---	Finnegan	Improvement in feeling (better relaxation and higher calorie intake). Also, Finnegan scores showed a decrease.



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Raithe et al., 2015	+	+	-	?	+	+	?
Schwartz et al., 2011	-	-	?	?	+	+	?

Fig.1: Quality control of clinical trial studies.

3- RESULTS

Twenty-nine articles were removed as duplicates. Twenty-nine articles were screened and 24 articles were excluded. Five studies were included in qualitative

synthesis with two RCTs (17,19), a pilot study (18), a case report (14), and a case series (15). **Figure.2** showed the process of selecting studies included in the systematic review.

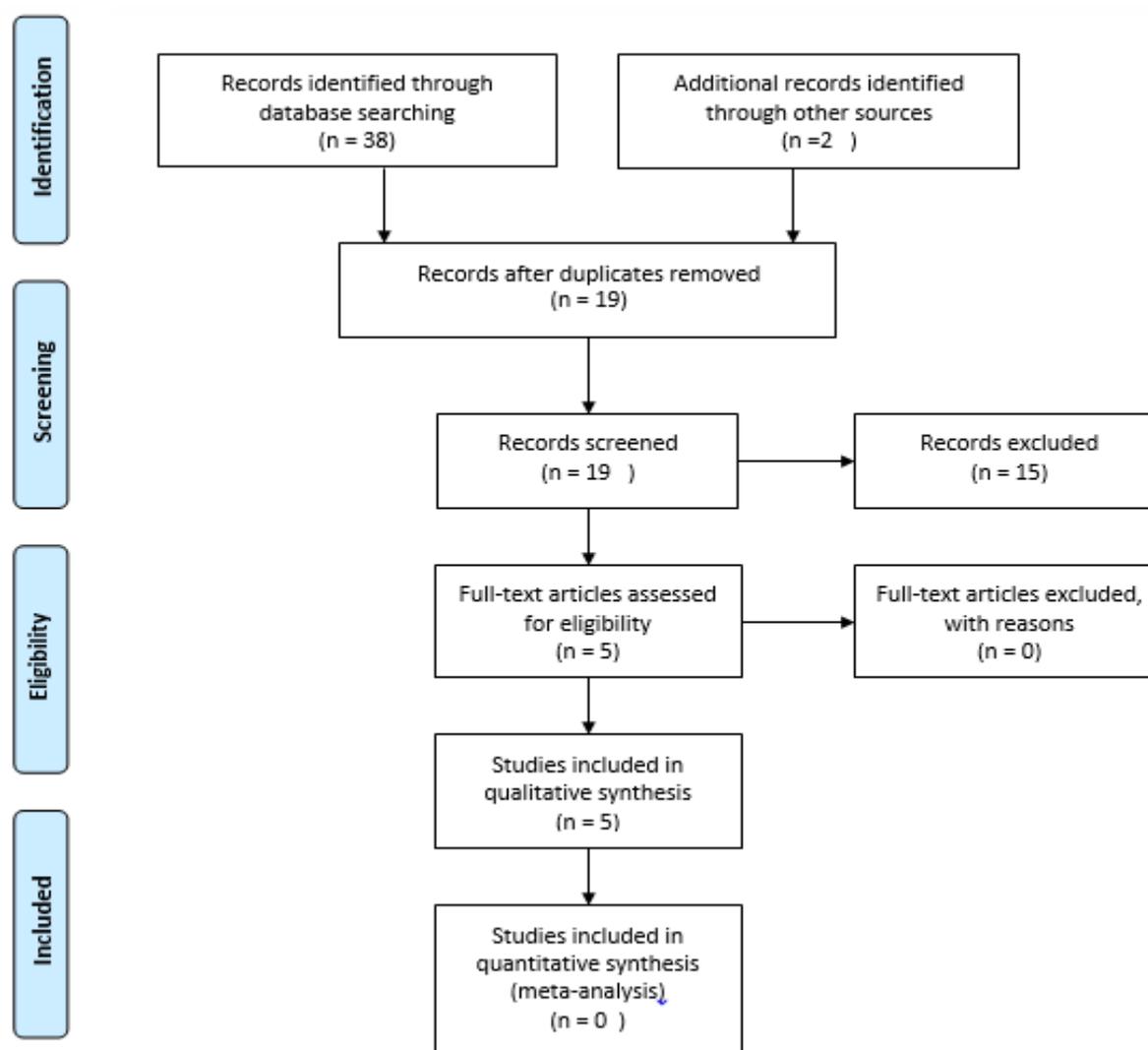


Fig.2: PRISMA flowchart of present systematic review.

3-1. Laser acupuncture

Recently, two studies involve the use of laser acupuncture as adjunct in combination with morphine. The first study done by Raith and Urlesberger was a case report of a full-term baby girl. The laser acupuncture was implemented on several sites on body and auricular about one hour after feeding and administration of morphine; their results suggested an improvement in feeling (better relaxation and higher calorie intake). Also, Finnegan scores showed a decrease on the day after laser therapy (14). The second study was conducted by the same authors, Raith et al;

in the randomized controlled trial, 28 infants were divided into two groups. The first group received laser acupuncture in combination with drug treatments of oral morphine solution and oral phenobarbital (group A), and the second group received drug treatment alone (control). Their results showed shorter duration of treatment when acupuncture was used in combination with morphine (28 vs. 30 days, $p=0.019$), and shorter duration of hospitalization (35 vs. 50 days, $p=0.048$) in group A compared to control group (19). In both studies (case report and RCTs), in terms of safety, treatment with laser acupuncture as adjunctive were well-

tolerated (no visible skin changes, no distress or discomfort) even some infants fell asleep. Also, authors mentioned that they did not receive an assessment or negative feedback of hospital staff or parents of infants (14, 19).

3-2. Auricular acupuncture

Weathers et al. performed a pilot study on 20 infants with NAS secondary to maternal parental opiate. Press needles were inserted into 3-4 sites. Needles remained for 3 ± 1 days then switched to right ear. Their results showed that auricular acupuncture when implemented as adjunct pulse non pharmacologic in management of NAS is safe, feasible, and acceptable (consent rate of) to both parents and providers (18).

3-3. Auricular acupressure

Schwartz et al. compared auricular acupressure in combination with standard care with standard care alone in 4-year prospective randomized controlled study with seventy-six infants affected with NAS. Small needles were inserted on three to six ear locations. No significant difference ($p \leq 0.05$) was observed between two groups during pharmacological therapy, length of hospital stay and average NAS scores (17).

3-4. Non-insertive acupuncture (NIA)

Filippelli et al.'s study (15) was a case series, a retrospective chart review, 54 infants with NAS received one to six sessions of non-insertive acupuncture (NIA). Their result showed that restless infants calmed down during treatment. Babies had better feeding (higher calorie intake).

4- DISCUSSION

To the best of the authors' knowledge, this systematic review included all studies, regardless of study types that assessed the impact of different methods of

acupuncture in NAS for improving it. According to one pilot study with 20 infants, auricular acupuncture when implemented as non-pharmacologic adjunct in management of NAS is safe, feasible, and acceptable (18). However, according a 4-year prospective randomized controlled study with seventy-six infants affected with NAS, auricular acupressure did not show any significant effect on pharmacological therapy, length of hospital stay and average NAS scores (17).

Two studies involved the use of laser acupuncture as adjunct in combination with morphine. One study was a case report (14), and the other was RCTs (19). Treatment with Laser acupuncture as adjunct in management of infants with NAS was associated with several advantages. These include improvement in feeling (better relaxation and higher calorie intake), decreased Finnegan scores, shorter duration of treatment with morphine and shorter duration of hospitalization. In terms of safety, treatment with laser acupuncture as adjunctive was well-tolerated.

Auricular acupuncture as adjunct pulse non pharmacologic is safe, feasible, and acceptable (18). It seems that auricular acupuncture modifies the autonomic dysfunction by increasing parasympathetic nerves (18). Weathers et al., also mentioned that effectiveness of auricular acupuncture may be improved by other factors such as private patient rooms and availability of inpatient consultations (18).

Schwartz et al.'s study did not show any beneficial effect of Auricular acupressure on NAS (17). They believed that the observed difference between their results and those of other researches may be related to at least two factors: frequent interactions between the investigator and mothers, and nurses at the bedside, or differences in maternal opiate use (17). In terms of safety, treatment with laser acupuncture as adjunctive was well-

tolerated (14, 19). Some authors mentioned that shorter pharmacological treatment and less lengthy hospitalization are associated with several secondary advantages including a reduction in adverse effects of oral morphine therapy, a reduction in costs of hospital stays, and it promotes bonding with parents (13). Previous studies showed male infants showed a more severe NAS than females/than female infants. However, only one study among the studies compared control and intervention regarding gender (13). A study showed a relation between severity of NAS and taking heroin. However, this relation is unclear for at least two reasons. First, the relationship between severity of n Heroin consumed in conjunction with methadone and second, variations in the purity of each package and route of administration and maternal metabolism (17).

4-1. Study Limitations

There are several limitations that need to be addressed regarding these limitations: first, the number of studies was low with a case report, a case-series and pilot study and three clinical trials. Sample size of most of the studies included in the systematic review was small. Reasons for the small sample may be related to the lower incidence of NAS in some countries such as Austria; therefore, findings of some studies with small sample size may be changed if the sample size is more.

Second, one of reasons that we conducted a meta-analysis and subgroup analysis was mothers of infants received variable pharmacological treatment to manage NAS. The third limitation, most of the studies included in the systematic review reported maternal consumption of heroin and methadone based on self-report. Fourth limitation was some of the studies mentioned taking informed consent from parents is difficult due to issues related to illegal drug, child custody and

transportation (18). Therefore, this systematic review may be affected by these factors.

5- CONCLUSION

The finding of this systematic review showed that infants with NAS secondary to maternal opiate usage may receive more beneficial treatment with acupuncture in combination with pharmacologic therapy compared to pharmacologic therapy alone. Treatment with Laser acupuncture as adjunct was associated with better relaxation and higher calorie intake, decreased Finnegan scores, shorter duration of treatment with morphine and shorter duration of hospitalization. Also, auricular acupuncture is safe, feasible, and acceptable. Auricular acupressure was not effective in infants with NAS secondary to maternal opiate usage. In this study findings should be interpreted in light of the mentioned limitations.

6- CONFLICT OF INTEREST: None.

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