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Digoxin for preventing or treating neonatal respiratory distress syndrome (Review)

Soll R, Özek E

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[Intervention Review]

Digoxin for preventing or treating neonatal respiratory distress syndrome

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ABSTRACT

Background

Lendrum 1955 suggested that pulmonary edema secondary to congestive heart failure may contribute to neonatal respiratory distress syndrome (RDS). Based on this hypothesis, investigators began to use digitalis glycosides to improve myocardial contractility and decrease congestive heart failure. The first use of digitalis glycosides in infants with RDS was reported by Stahlman 1959. Stahlman reported a reduction in mortality in an uncontrolled trial of digitalis in infants with RDS.

Objectives

To assess the effect of digoxin on mortality in premature infants at risk for or with RDS.

Search methods

Searches were made of the Oxford Database of Perinatal Trials, Medline (MeSH terms: digoxin; limits: age groups, newborn infants; publication type, clinical trial), previous reviews including cross references, abstracts, conference and symposia proceedings, expert informants, and journal handsearching in the English language.

When updated in December 2008, the search was expanded to include Medline, CINHAL, and Embase (MeSH terms and text words: digoxin or digitalis; limits: age group, all infants; publication type: clinical trial).

Selection criteria

Randomized and quazi-randomized controlled trials of digoxin in either the prevention or treatment of RDS are included in this overview.

Data collection and analysis

Data regarding clinical outcomes were excerpted from the trial reports by one review author (RS) and checked by the second review author (EO). Data were analyzed according to the standards of the Cochrane Neonatal Review Group.

Main results

Two randomized controlled trials have studied the effects of digoxin in the prevention and treatment of RDS. No improvement in respiratory status or mortality was noted. Meta-analysis of the effect of digoxin given to infants at risk of or with RDS on mortality does not suggest any benefit of digoxin treatment (typical relative risk 1.27 95% CI 0.78 to 2.07; typical risk difference 0.06, 95% CI -0.06 to 0.17).

Authors' conclusions

Although hemodynamic disturbances play a role in the overall pathogenesis of respiratory distress syndrome, the specific contribution of early congestive heart failure (unrelated to hemodynamically significant patent ductus arteriosus) does not appear to be a significant factor in RDS. Treatment with digoxin has no proven value in infants solely affected with RDS.

PLAIN LANGUAGE SUMMARY

Digoxin for preventing or treating neonatal respiratory distress syndrome

There is no evidence that the administration of digoxin helps babies with neonatal respiratory distress syndrome.
Sometimes a newborn baby has lungs that are not expanded properly. This is most common in preterm babies (born before 34 weeks) and is known as respiratory distress syndrome (RDS). Congestive heart failure may lead to fluid accumulation in the lungs, contributing to RDS. The drug digoxin has been used for congestive heart failure and has been suggested for RDS. The review found no evidence from trials that digoxin reduces congestive heart failure, prevents RDS or improves the outcome of preterm babies with RDS.

BACKGROUND

In 1955 Lendrum (Lendrum 1955) suggested that pulmonary edema secondary to congestive heart failure may contribute to neonatal respiratory distress syndrome (RDS). Based on this hypothesis, investigators began to use digitalis glycosides to improve myocardial contractility and decrease congestive heart failure. The first use of digitalis glycosides in infants with RDS was reported by Stahlman 1959. Stahlman reported a reduction in mortality in an uncontrolled trial of digitalis in infants with RDS. This experience led to two randomized controlled trials of digoxin in the prevention and treatment of RDS.

The following analysis is a systematic review of the randomized controlled trials that compared digoxin administration to placebo treatment in infants at risk for or with established respiratory distress syndrome.

OBJECTIVES

Primary objectives:

To assess the effect of digoxin on mortality in premature infants at risk for or with RDS.

Secondary objectives:

To assess the effect of digoxin on morbidity in infants at risk for or with RDS.

Subgroups analyses (if available):

- premature infants less than 30 weeks gestation;
- infants with established RDS.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and quazi-randomized controlled trials comparing digoxin to placebo treatment.

Types of participants

Premature infants (< 37 weeks gestation) at risk of developing respiratory distress syndrome (infants delivered by cesarean section, infants of diabetic mothers, and low birth weight infants) or infants with a clinical diagnosis of RDS.

Types of interventions

Infants were randomized to receive digoxin (initial digitalizing dose followed by 72 hours of maintenance therapy) or placebo treatment.

Types of outcome measures

Primary outcomes

- Neonatal mortality (at or before 28 days).
- Mortality prior to hospital discharge.

Secondary outcomes

- Respiratory distress (illness severity scores).
- Electrocardiographic abnormalities.
- Bronchopulmonary dysplasia (oxygen requirement at 28 days).
- Chronic lung disease (oxygen at 36 weeks postmenstrual age).
- Intraventricular hemorrhage.
- Necrotizing enterocolitis.
- Retinopathy of prematurity.
- Neurodevelopmental outcome.

Search methods for identification of studies

Searches were made of the Oxford Database of Perinatal Trials, Medline (MeSH terms: digoxin; limits: age groups, newborn infants; publication type, clinical trials), previous reviews including cross references, abstracts, conference and symposia proceedings, expert informants, and journal hand searching in the English language.

When updated in December 2008 and again in 2010, the search was expanded to include Medline, CINHAL, and Embase using the terms "digoxin" or "digitalis" and limited to "all infants" and "clinical trials".

Clinical trials registries were also searched for ongoing or recently completed trials (clinicaltrials.gov; controlled-trials.com; and who.int/ictrp)

Data collection and analysis

See: Collaborative Review Group search strategy. The standard search method of the Cochrane Neonatal Review Group was used.

Selection of studies

All randomized and quasi-randomized controlled trials fulfilling the selection criteria described in the previous section were included. Both investigators reviewed the results of the search and separately selected the studies for inclusion. The review authors resolved any disagreement by discussion.

Data extraction and management

Both review authors separately extracted, assessed and coded all data for each study using a form that was designed specifically for this review. For each included study, information was collected regarding the method of randomization, blinding, drug intervention, stratification, and whether the trial was conducted at a single center or multiple centers. Information regarding inclusion criteria, including gestational age, postnatal age at the time of treatment, and disease severity criteria was noted. Information on clinical outcome included only mortality. Differences in assessment were resolved by discussion. For each study, final data was entered into RevMan by one review author (RFS) and then checked by a second review author (EO). Any disagreements were resolved by discussion.

Assessment of risk of bias in included studies

The standard methods of the Cochrane Neonatal Review Group were employed. The methodological quality of the studies were assessed using the following key criteria: allocation concealment (blinding of randomization), blinding of intervention, completeness of follow-up, and blinding of outcome measurement/assessment. For each criterion, assessment was yes, no, can't tell. Two review authors separately assessed each study.

Any disagreement was resolved by discussion. This information was added to the Characteristics of Included Studies table.

In addition, for the update in 2010, the following issues were evaluated and entered into the Risk of Bias table:

1) Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated? For each included study, we categorized the method used to generate the allocation sequence as:

- adequate (any truly random process e.g. random number table; computer random number generator);

- inadequate (any non random process e.g. odd or even date of birth; hospital or clinic record number);

- unclear.

(2) Allocation concealment (checking for possible selection bias). Was allocation adequately concealed? For each included study, we categorized the method used to conceal the allocation sequence as:

- adequate (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);

- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);

- unclear.

(3) Blinding (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study? At study entry? At the time of outcome assessment? For each included study, we categorized the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or classes of outcomes. We categorized the methods as:

- adequate, inadequate or unclear for participants;

- adequate, inadequate or unclear for personnel;

- adequate, inadequate or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed? For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorized the methods as:

- adequate (< 20% missing data);

- inadequate (≥ 20% missing data):

- unclear.

(5) Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);

- inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);

- unclear.

(6) Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we described any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

- yes; no; or unclear.

If needed, we planned to explore the impact of the level of bias through undertaking sensitivity analyses.

Measures of treatment effect

The standard methods of the Neonatal Review Group were used. Statistical analyses were performed using Review Manager software. Categorical data were analyzed using relative risk (RR), risk difference (RD) and the number needed to treat (NNT). Continuous data were analyzed using weighted mean difference (WMD). The 95% Confidence interval (CI) was reported on all estimates.

Assessment of heterogeneity

We estimated the treatment effects of individual trials and examined heterogeneity between trials by inspecting the forest plots and quantifying the impact of heterogeneity using the I-squared statistic. If we detected statistical heterogeneity, we planned to explore the possible causes (for example, differences in study quality, participants, intervention regimens, or outcome assessments) using post hoc sub group analyses. We planned to use a fixed effects model for meta-analysis.

Data synthesis

Meta-analysis was performed using Review Manager software (RevMan 5), supplied by the Cochrane Collaboration. For estimates of typical relative risk and risk difference, we used the Mantel-Haenszel method. For measured quantities, we used the inverse variance method. All meta-analyses were done using the fixed effect model.

Subgroup analysis and investigation of heterogeneity

Subgroups analyses (if available):

- premature infants less than 30 weeks gestation.
- infants with established RDS.

RESULTS

Description of studies

Studies included in this review: Martin 1963 and Braudo 1969. Details of each study are given in the table "Characteristics of Included Studies" and references.

Martin 1963 studied the effect of digoxin in preventing RDS in a diverse group of newborns. Infants delivered by cesarean section, infants born to diabetic mothers, or infants with low birthweight (less than or equal to 5 1/2 lbs) were given digoxin during the first three days of life. No improvement in respiratory status or mortality was noted. Bradycardia, EKG abnormalities, and vomiting were more frequent in the digoxin treated infants.

Braudo 1969 studied the effects of digoxin in 77 infants with RDS. Infants were randomized to either a 72 hour course of digoxin or placebo treatment. No difference in mortality between treatment groups was noted. No adverse effects of digoxin were reported.

Risk of bias in included studies

Randomized controlled trials which compared the effect of digoxin to placebo treatment in infants either at risk of developing RDS or with clinical RDS are included in the analysis. Specific methodologic issues regarding the two studies included are discussed below:

Randomization:
Both included studies allocated assigned treatment by randomization. In both studies, randomization was accomplished using sealed envelopes at the participating center.

Blinding of treatment:
Treatment was blinded by the use of placebo injections. Neither the physicians nor the nurses caring for the infants knew which treatment the infants received.

Blinding of outcome assessment:
Investigators were blinded regarding treatment assignment and, therefore, blinded regarding outcome assessment.

Exclusion after randomization:
Minimal exclusions were noted after randomization.

Effects of interventions

Neither the study of Martin 1963 or Braudo 1969 noted an improvement with the administration of digoxin. Martin 1963 noted an increase in bradycardia, EKG abnormalities, and vomiting associated with digoxin administration.

The meta-analysis of the effect of digoxin in the prevention or treatment of respiratory distress syndrome suggests no benefit of digoxin treatment regarding mortality (typical relative risk 1.27, 95% CI 0.78 to 2.07; typical risk difference 0.06, 95% CI -0.06 to 0.17; I^2 14%)(Outcome 1.1).

DISCUSSION

In the 1950s, investigators believed that pulmonary edema secondary to congestive heart failure may contribute to neonatal RDS. Based on this hypothesis, investigators began to use digitalis glycosides to improve myocardial contractility and decrease congestive heart failure. Two randomized controlled trials which studied the effects of digoxin in the prevention of treatment of RDS are detailed in this analysis. Neither the study of Martin 1963 or Braudo 1969 were able to note any improvement associated with digoxin administration. Martin 1963 noted bradycardia and EKG abnormalities in infants who received digoxin.

Although these studies had very different criteria regarding entry and timing of treatment, neither study demonstrates any effect of digoxin in the treatment or prevention of RDS.

AUTHORS' CONCLUSIONS

Implications for practice

Although hemodynamic disturbances play a role in the overall pathogenesis of respiratory distress syndrome, the specific contribution of early congestive heart failure (unrelated to hemodynamically significant patent ductus arteriosus) does not appear to be a significant factor in RDS. Treatment with digoxin has no proven value in infants solely affected with RDS.

Implications for research

There is little reason to believe that further research on digoxin in the prevention or treatment of RDS is warranted.

ACKNOWLEDGEMENTS

We would like to thank Yolanda Montagne for updating the search strategy and performing the search.

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References to studies included in this review

Braudo 1969 *{published data only}*

Braudo M, Keith JD. The value of digitalis in the respiratory distress syndrome: a controlled study. *Journal of Pediatrics* 1969;**74**:310-4.

Martin 1963 *{published data only}*

Martin JK. A controlled trial of digoxin in the prevention of the respiratory distress syndrome. *Canadian Medical Association Journal* 1963;**89**:995-7.

Additional references

Lendrum 1955

Lendrum FC. The 'pulmonary hyaline membrane' as a manifestation of heart failure in the newborn infant. *Journal of Pediatrics* 1955;**47**:149-56.

Stahlman 1959

Stahlman MT. Adaptation to extra-uterine life. Report of 31st Ross Conference on Pediatric Research. Columbus, Ohio: Ross Laboratories, 1959.

References to other published versions of this review

Soll 1998

Soll R. Digoxin for preventing or treating neonatal respiratory distress syndrome. *Cochrane Database of Systematic Reviews* 1998, Issue 2. [DOI: 10.1002/14651858.CD001080]

Soll 2009

Soll R, Ozek E. Digoxin for preventing or treating neonatal respiratory distress syndrome. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: 10.1002/14651858.CD001080]

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Braudo 1969

Methods	Single center Blinding of Randomization: Yes (sealed envelopes) Blinding of Intervention: Yes (placebo IM injections) Complete Follow-up: Yes (87/88 enrolled) Blinding of Outcome measurement: Yes Stratification: None
Participants	Infants with clinical diagnosis of respiratory distress syndrome Silverman retraction score >3
Interventions	Digoxin vs. placebo treatment Digitalizing dose: 0.065 mg/kg Maintenance dose: 1/10 digitalizing dose 24 hours after start of treatment 1/10 digitalizing dose every 12 hours for 72 hours
Outcomes	Electrocardiographic abnormalities Mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Blinding of Randomization: Yes (sealed envelopes) Stratification: None
Blinding? All outcomes	Low risk	Blinding of Intervention: Yes (placebo IM injections) Blinding of Outcome measurement: Yes
Incomplete outcome data addressed?	Low risk	Complete Follow-up: Yes (87/88 enrolled)

Braudo 1969 *(Continued)*

All outcomes	

Martin 1963

Methods	Single center Blinding of Randomization: Yes (sealed envelopes) Blinding of Intervention: Yes (placebo IM injections) Complete Follow-up: Can't tell Blinding of Outcome measurement: Yes Stratification: None
Participants	Phase 1: Infants delivered by Cesarean section Infants of diabetic mothers Low birthweight infants (less than or equal to 5 1/2 lbs) Phase 2: Low birthweight infants (less than or equal to 5 1/2 lbs)
Interventions	Digoxin vs. glucose placebo Digitalizing dose: 0.03 mg/lb in two divided doses over 24 hours Maintenance dose: 0.01 mg/lb/day x 3 days
Outcomes	Respiratory and retraction score Electrocardiographic abnormalities Mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Blinding of Randomization: Yes (sealed envelopes) Stratification: None
Blinding? All outcomes	Low risk	Blinding of Intervention: Yes (placebo IM injections) Blinding of Outcome measurement: Yes
Incomplete outcome data addressed? All outcomes	Unclear risk	Complete Follow-up: Can't tell

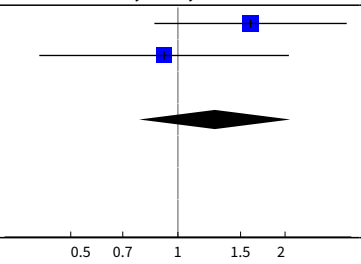
DATA AND ANALYSES

Comparison 1. Digoxin vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	2	212	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.78, 2.07]

Analysis 1.1. Comparison 1 Digoxin vs placebo, Outcome 1 Mortality.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Braudo 1969	18/44	11/43		51.73%	1.6[0.86,2.98]
Martin 1963	9/59	11/66		48.27%	0.92[0.41,2.05]
Total (95% CI)	**103**	**109**		**100%**	**1.27[0.78,2.07]**
Total events: 27 (Treatment), 22 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.16, df=1(P=0.28); I^2=13.84%					
Test for overall effect: Z=0.95(P=0.34)					



WHAT'S NEW

Date	Event	Description
6 December 2010	New citation required but conclusions have not changed	New co-author added - Eren Ozek
3 December 2010	New search has been performed	This updates the review "Digoxin for preventing or treating neonatal respiratory distress syndrome" published in the Cochrane Database of Systematic Reviews, Issue 2, 1998 (Soll 1998). Updated search in December 2010 found no new trials. Risk of bias tables included. No change in conclusions.

HISTORY

Protocol first published: Issue 2, 1998
Review first published: Issue 2, 1998

Date	Event	Description
29 January 1998	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Roger Soll drafted protocol, reviewed studies identified in search, excerpted data, and drafted the initial protocol and review.

Eren Özek replicated the search, separately excerpted data and reviewed the manuscript.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Neonatal Collaborative Review Group, NIH Contract #N01-MD-6-3253, USA.

INDEX TERMS

Medical Subject Headings (MeSH)

Cardiotonic Agents [*therapeutic use]; Digoxin [*therapeutic use]; Infant, Premature; Randomized Controlled Trials as Topic; Respiratory Distress Syndrome, Newborn [*drug therapy]

MeSH check words

Humans; Infant, Newborn