Effects of oxytocin in different solutions on cord plasma bilirubin levels: systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

Kittiphum Vejsitthangkul[1], M.D.; Pimprapa Muenpirom[2], M.D.; Khakhanang Chantarayotha[3], M.D.; Benjaporn Namyotee[3], M.D.

[1]Udon Thani Hospital, Thailand; [2]Roi Et Hospital, Thailand; [3]Khon Kaen Hospital, Thailand.

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Correspondence to: Chutharat Thanchonnang; chuth.pp@gmail.com

ABSTRACT

OBJECTIVE

To identify the effects of oxytocin in different solutions on cord plasma bilirubin levels.

METHODS

We searched systematically for studies through PubMed, the Cochrane Library, Scopus, Clinicaltrials.gov, Trip Database and Google Scholar as well as hand-searching to identify relevant randomized controlled trials (RCTs) that compared the cord plasma bilirubin levels of solutions of oxytocin infusion in 5% glucose in water and in 0.9% NaCl solution as the primary outcome. The secondary outcomes included their effects on neonatal plasma bilirubin levels day 2-3 and cord plasma sodium levels.

RESULTS

We identified and included two RCTs with 269 full-term pregnant women with singleton pregnancy. Cord plasma bilirubin levels was not significantly different between using oxytocin in either 5% glucose in water or 0.9% NaCl solution (mean difference (MD), -0.03; 95% confidence interval (CI) [-0.52 to 0.46], I^2=93%). Neonatal plasma bilirubin levels in day 2-3 was also not significantly different between using oxytocin in either 5% glucose in water or 0.9% NaCl solution (MD, 0.27; 95% CI, [-1.59 to 2.13], I^2=97%). Cord plasma sodium levels of using oxytocin in 5% glucose in water was significantly lower than that of in 0.9% NaCl solution group (MD, -2.00; 95% CI, [-3.57 to -0.44], I^2=95%).

CONCLUSION

There was no statistically significant difference in cord plasma bilirubin levels between using oxytocin in 5% glucose in water and in 0.9% NaCl solution.

BACKGROUND

Induction of labor is a procedure that stimulates uterine contractions during pregnancy, then labor begins later and leads to a vaginal childbirth.[1,2] In 2006, It accounted for 22.5% of the total labor in United States.[3] Nowaday, we have many methods used for induction of labor such as breast stimulation, amniotomy, membrane stripping and using synthetic oxytocin.[2,4] Oxytocin is widely used in obstetrics not only to induce labor, but it is also used for augmentation of labor and postpartum hemorrhage prevention.[7-10] In the Southern Sweden, oxytocin was used in 33.2% of pregnant women for induction of labor between 2001 and 2002.[6]

Oxytocin has antidiuretic hormone-like effect that increases the permeability to water of the cell membrane and increases red blood cell fragility.[5,6] Oxytocin-induced labor is associated with increasing adverse effects in neonates such as hyponatremia, neonatal seizures and retinal hemorrhage.[11-13] Using oxytocin for induction of labor was reported as one of the factors that causes neonatal hyperbilirubinemia,[14,15] one of the most common medical problems in 50% term infants that leads to neurotoxicity in severe condition.[16,17]

Oxytocin can be diluted in either 5% glucose in water or 0.9% NaCl solution before administration.[18-20] In 1993, a Nigerian RCT with 164 pregnant women reported that cord plasma bilirubin level was significantly higher in infants of mothers with oxytocin in 5% glucose in water than those with 0.9% NaCl solution and the control group; without any intravenous fluid infusion and oxytocin.[21] However, another Turkish RCT in 2003 reported that cord plasma bilirubin levels in 105 infants was not statistically different among the three groups, oxytocin in 5% glucose in water group, oxytocin in 0.9% NaCl solution group and control group; without any intravenous fluid infusion and oxytocin.[22] Regarding the controversy mentioned above, the aim of this systematic review is to determine the effects of oxytocin in 5% glucose in water and in 0.9% NaCl solution on cord plasma bilirubin levels.

METHODS

This study is a systematic review to determine the effects of oxytocin in different solutions on cord plasma bilirubin levels. It was conducted according to Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 and followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[23,24]

DATA SOURCES

We searched systematically for studies through PubMed, the Cochrane Library, Scopus, Clinicaltrials.gov, Trip Database and Google Scholar to identify the articles. Searching in Pubmed and the Cochrane Library were undertaken using MeSH terms: (i) "jaundice, neonatal" OR "hyperbilirubinemia, neonatal" AND "oxytocin" AND "solution" OR "diluent", (ii) "neonatal" AND "bilirubin" AND "oxytocin" AND "solution" OR "diluent". We used PICO search to identify articles in Trip database ("oxytocin" AND "solution" OR "dilution for I, "neonatal serum bilirubin" OR "neonatal jaundice" OR "neonatal hyperbilirubinemia" for O, no filling for P and C) and we used various combinations of following keywords in the other databases: neonatal,

Table 1. Characteristics of included studies

First author's name	Year	Country	During of trial	Number of participants			Cord blood					
				5% glucose in water	0.9% NaCl solution	Control group	Mean neonatal plasma bilirubin (SD)			Mean neonatal plasma sodium(SD)		
							5% glucose in water	0.9% NaCl solution	Control group	5% glucose in water	0.9% NaCl solution	Control group
A.O. Omigbodun	1993	Nigeria	N/A	40	42	82						
Day 0							1.0 (0.7)	0.8 (0.5)	0.8 (0.5)	130.1 (6.5)	132.9 (4.2)	132.5 (6.3)
Day 2-3							5.8 (3.9)	4.6 (2.7)	4.4 (2.7)	N/A	N/A	N/A
Engin Oral	2003	Turkey	January to December in 1995.	36	29	40						
Day 0							1.6 (0.8)	1.9 (0.9)	1.7 (0.5)	139.8 (5.9)	141.0 (4.7)	140.0 (3.6)
Day 2-3							5.2 (2.0)	5.9 (3.1)	6.82 (3.2)	N/A	N/A	N/A

bilirubin, neonatal jaundice, neonatal hyperbilirubinemia, oxytocin, solution and diluent. We latter performed hand-searching by exploring references of the preliminary included articles from database searching and manually searched for additional relevant studies.

STUDY SELECTION

The selection of identified articles included two steps. For the first step, we screened titles and abstracts by four independent reviewers. The second step, all selected articles were read in full text by four reviewers then we assessed and selected studies by inclusion criteria and exclusion criteria for using data in this systematic review. Controversies among the four reviewers were resolved by consensus of the fifth author.

INCLUSION CRITERIA

STUDY DESIGN

We included all RCTs comparing the cord plasma bilirubin levels of the infants of the mothers using either oxytocin in 5% glucose in water or in 0.9% NaCl solution.

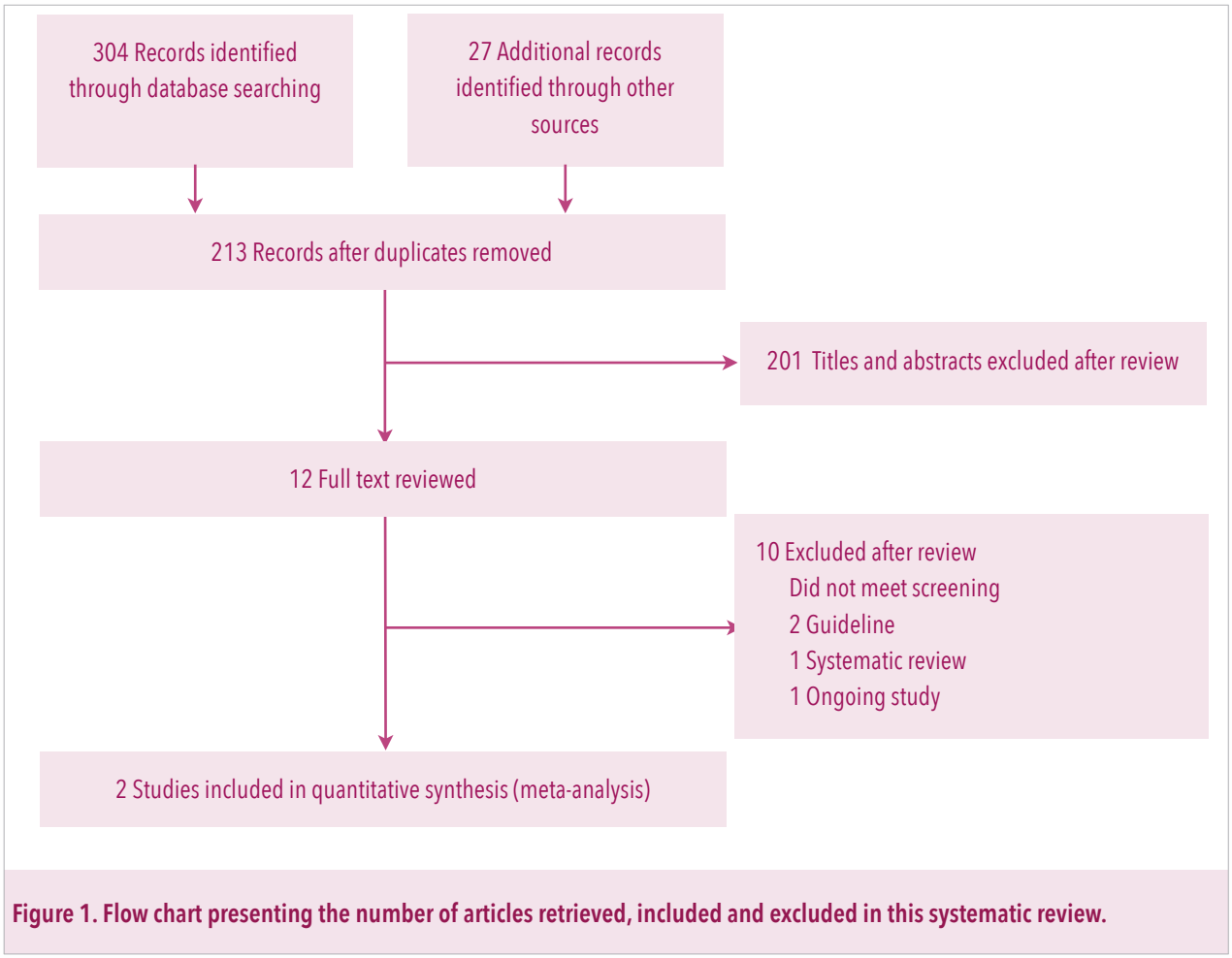

Figure 1. Flow chart presenting the number of articles retrieved, included and excluded in this systematic review.

PARTICIPANTS

The participants were pregnant women with gestational age 37 weeks or greater with singleton pregnancy.

INTERVENTIONS

Oxytocin diluted in either 5% glucose in water or in 0.9% NaCl solution.

CONTROLS

No any intravenous fluid solutions or oxytocin infusion.

OUTCOMES

The primary outcome was cord plasma bilirubin levels of the infants and the secondary outcomes were neonatal plasma bilirubin levels in day 2-3 and cord plasma sodium levels of the infants.

EXCLUSION CRITERIA

We excluded studies with patients with hemolytic disease (e.g., glucose-6-phosphate dehydrogenase deficiency and Rhesus and ABO incompatibility), medical complication of pregnancy (e.g., hypertension, diabetes mellitus, pyrexia, jaundice

Table 2. Jadad Score

	A.O. Omigbodun et al., 1993	Engin Oral et al., 2003
Was the study described as randomized?	1	1
Was the method used to generate the sequence of randomization described and was it appropriate?	1	1
Was the study described as double-blind?	0	0
Was the method of double-blind described and was it appropriate?	0	0
Was there a description of withdrawals and dropouts?	1	1
Score	3	3

and anemia) and fetal problems (e.g., intrauterine growth restriction, macrosomia and fetal anomaly).

DATA EXTRACTION AND QUALITY ASSESSMENT

From each study, we extracted data regarding the first author's name, year of publication, country where the study was done, during of trial, number of participant, and outcome. We extracted data into simple standard forms. Four reviewers independently assessed the quality of the studies by using Jadad score and the Cochrane Collaboration's tool, recommended by Cochrane Handbook for Systematic Reviews of Interventions. [23] The Cochrane Collaboration's tool classifies the study's biases into three groups (low risk, high risk and unclear risk) and regards the following evaluation: random sequence generation, allocation concealment, blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data, selective reporting and other biases.

STATISTICAL ANALYSIS

All analyses were performed with Review Manager 5.3 statistical software to assess the effects of oxytocin in different solutions on cord plasma bilirubin levels. We calculated mean difference (MD) of discrepancies of all outcomes between 5% glucose in water and control group and that of between 0.9% NaCl solution and control group with 95% confidence interval (CI) for continuous data. The I^2 statistics were used to evaluate statistical heterogeneities across the studies. The statistical test of heterogeneity was significant if $P<0.1$ and heterogeneity was high if the I^2 statistics was more than 50%. We used a random-effect model for the meta-analysis when heterogeneity was statistical significance and also used a fixed-effect model when heterogeneity was not statistical significance. We created funnel plots showing the standard error and the effect size to identify the potential of publication bias in our review.

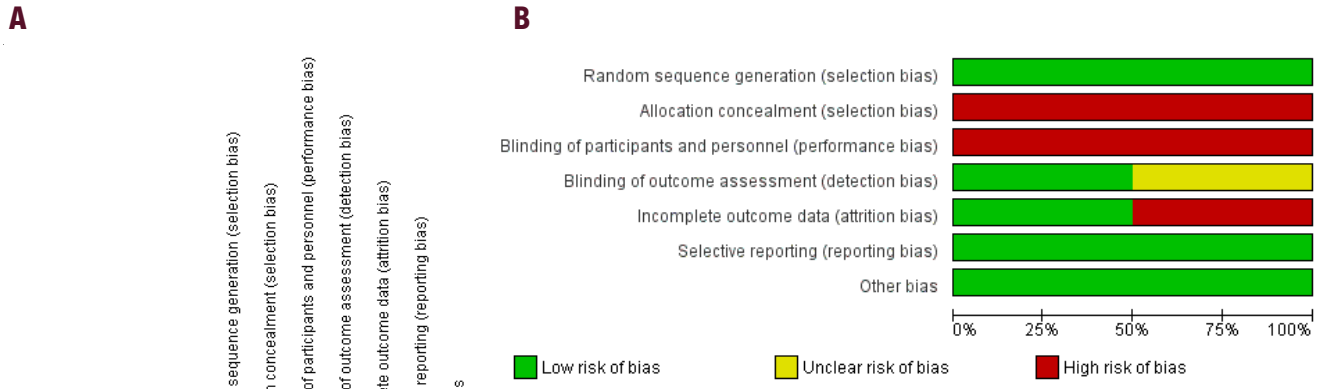

Figure 2. Risk of bias
Panel A, Risk of biases summary and Panel B, Risk of bias graph

RESULTS

STUDY CHARACTERISTICS

We identified 331 studies; 304 from database searching and 27 from hand-searching, 118 were excluded because they were duplicated (Figure 1). Of the remaining 213 studies, 201 were excluded because their titles and abstracts were not relevant to the diluents of oxytocin or neonatal bilirubin levels. Then, we reviewed 12 full texts and excluded ten studies; six did not meet screening criteria, two were guidelines, one was a systematic review and one was an ongoing trial. Finally, two eligible trials were included in our systematic review. The included two trials were set in Nigeria and Turkey and their characteristics were summarized in Table 1.

ASSESSING RISK OF BIAS

The two studies were assessed using Jadad score and the Cochrane Collaboration's tool for assessing risk of bias. One trial was assessed as having scores of 5 from the Jadad score while another study was scored 2 (Table 2). For the Cochrane Collaboration's tool, risk of bias was summarized in Figure 2.

RANDOM SEQUENCE GENERETION

Using the Cochrane Collaboration's tool for assessing risk of bias, both trials showed random sequence processes properly and were classified as "low risk".

ALLOCATION CONCEALMENT

Both trials did not show allocation concealment processes and were assumed to be open-label trials. They were classified as "high risk".

BLINDING OF PARTICIPANT AND PERSONNEL

Both trials were assumed to be open-label trials and were classified as "high risk"

BLINDING OF OUTCOME ASSESSMENT

The study in 1993 did not report details on blinding of the outcome assessment and was classified as "unclear" while another study stated

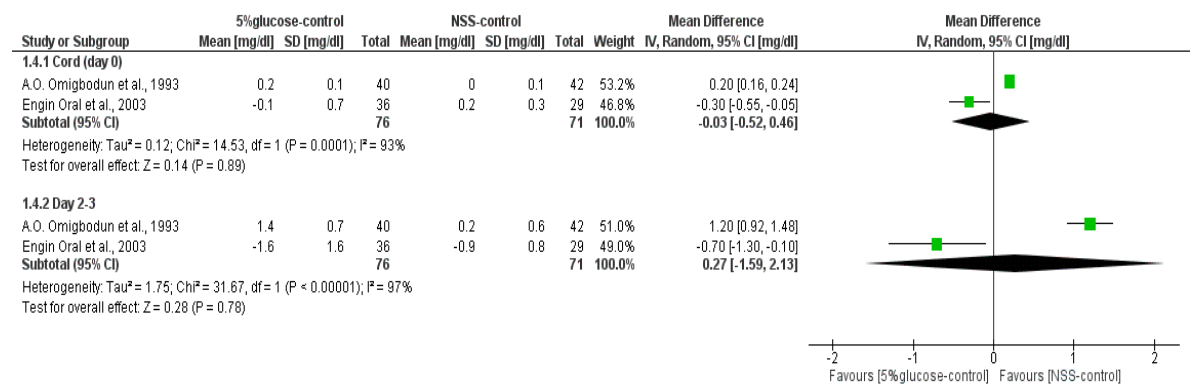

Figure 3. Estimates of mean differences of discrepancies on cord (day 0) and day 2-3 neonatal plasma bilirubin levels in 5% glucose in water and in 0.9% NaCl solution comparing with their controls.

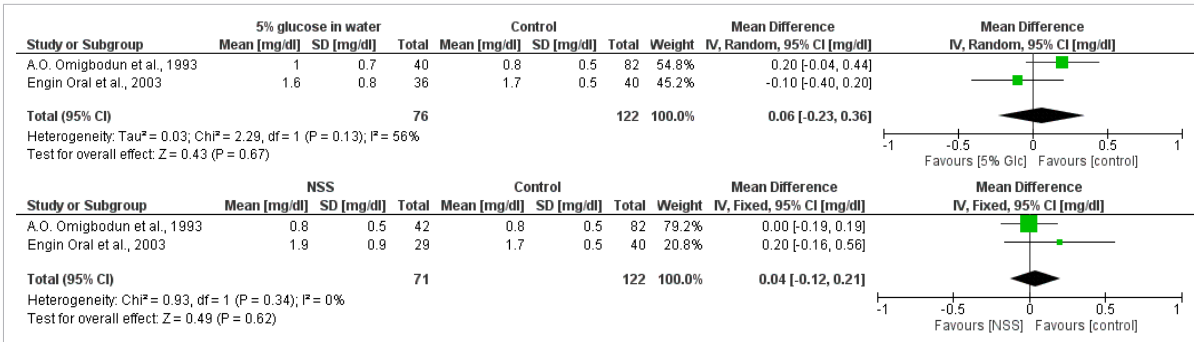

Figure 4. Estimates of discrepancies on cord (day 0) plasma bilirubin levels in 5% glucose in water and in 0.9% NaCl solution comparing with their controls.

the process properly and was classified as "low risk".

INCOMPLETE OUTCOME DATA

Both of the included studies properly described all data of the outcomes and were classified as low risk.

SELECTIVE REPORTING

Both studies described all outcomes properly and were classified as "low risk".

OTHER POTENTIAL SOURCES OF BIAS

Both studies had no potential conflict of interest were classified as "low risk".

PRIMARY OUTCOME

MEAN CORD PLASMA BILIRUBIN LEVELS

The meta-analysis of the two trials showed no statistically significant difference between using oxytocin in 5% glucose in water and oxytocin in 0.9% NaCl solution regarding discrepancies of cord plasma bilirubin levels between both solutions and their controls (MD -0.03; 95% CI [-0.52 to 0.46], random-effect model) (Figure 3). The heterogeneity was measured as having I^2 equal to 93%.

The meta-analysis of the two trials also showed no statistically significant difference between using oxytocin in 5% glucose in water and the control regarding mean difference of cord plasma bilirubin levels (MD 0.06; 95% CI [-0.23 to 0.36], random-

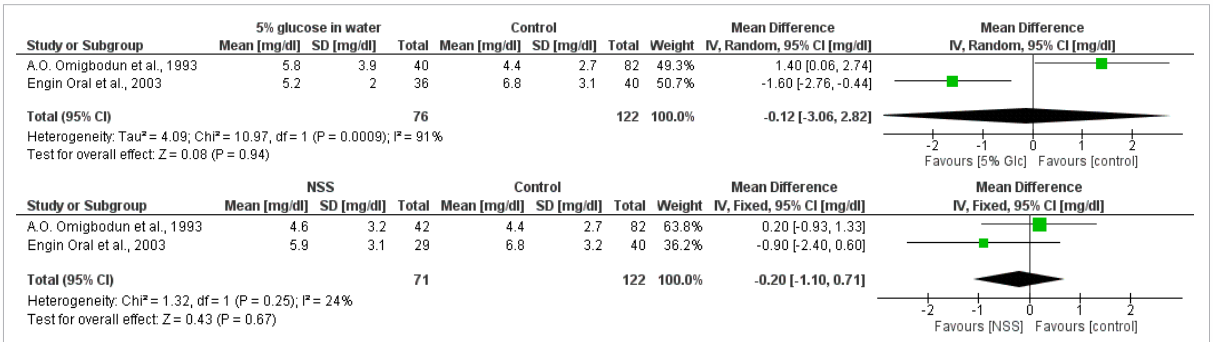

Figure 5. Estimates of discrepancies on day 2-3 neonatal plasma bilirubin levels in 5% glucose in water and in 0.9% NaCl solution comparing with their controls.

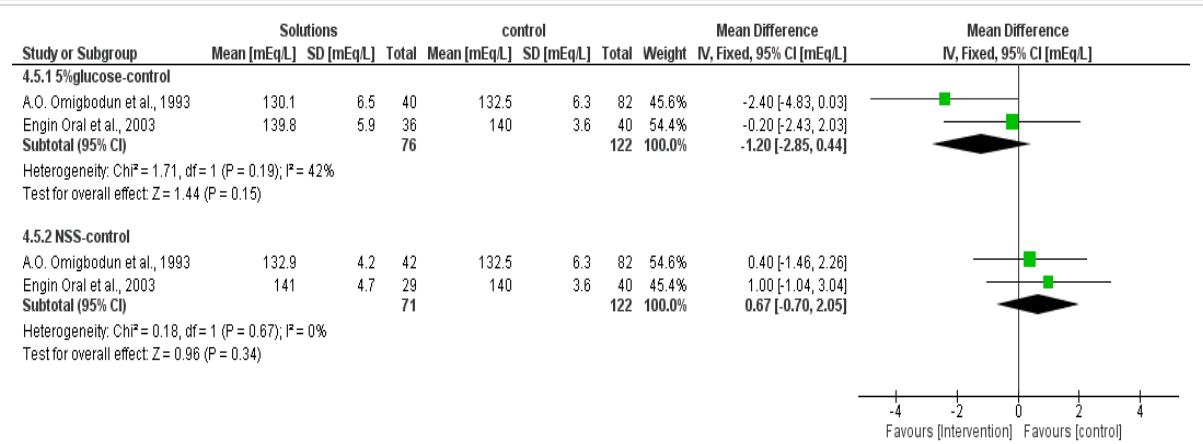

Figure 6. Estimates of mean differences of cord plasma sodium levels in 5% glucose in water and in 0.9% NaCl solution comparing with their controls.

effect model), the heterogeneity was measured as having I^2 equal to 56%, and it also showed that using oxytocin in 0.9% NaCl compared with the control had no statistically significant difference regarding mean difference of cord plasma bilirubin levels (MD 0.04; 95% CI [-0.12 to 0.21], fixed-effect model) (Figure 4), the heterogeneity was measured as having I^2 equal to 0%.

SECONDARY OUTCOMES

MEEN NEONATAL PLASMA BILIRUBIN LEVELS IN DAY 2-3

The meta-analysis of the two trials showed no statistically significant difference between using oxytocin in 5% glucose in water and oxytocin in 0.9% NaCl solution regarding discrepancies of neonatal plasma bilirubin levels in day 2-3 between both solutions and their controls (MD 0.27; 95% CI [-1.59 to 2.13], random-effect model) (Figure 3). The heterogeneity was measured as having I^2 equal to 97%.

The meta-analysis of the two trials also showed no statistically significant difference between using oxytocin in 5% glucose in water and the control regarding mean difference of neonatal plasma bilirubin levels in day 2-3 (MD -0.12; 95% CI [-3.06 to 2.82], random-effect model), the heterogeneity was measured as having I^2 equal to 91%, and it

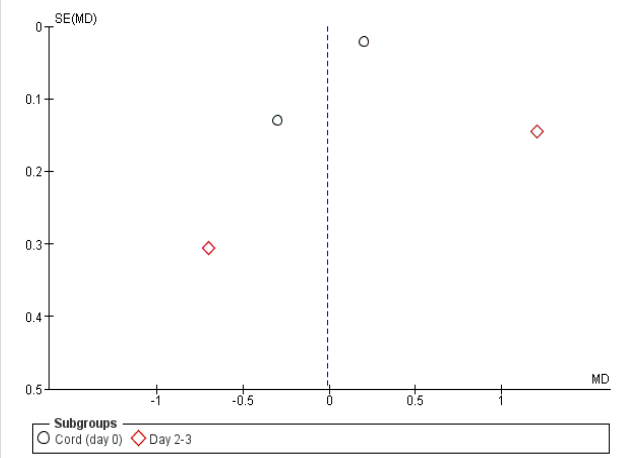

Figure 7. Funnel plot of comparison: mean differences of discrepancies on cord (day 0) and day 2-3 plasma bilirubin levels in both solutions comparing with the controls.

also showed that using oxytocin in 0.9% NaCl compared with the control had no statistically significant difference regarding mean difference of cord plasma bilirubin levels (MD -0.20; 95% CI [-1.10 to 0.71], fixed-effect model) (Figure 5), the heterogeneity was measured as having I^2 equal to 24%.

MEAN CORD PLASMA SODIUM LEVELS

The meta-analysis of the two trials showed that mean cord plasma sodium levels using oxytocin in 5% glucose in water compared with its control was not significantly reduced (MD -1.20; 95% CI [-2.85 to 0.44], fixed-effect model) (Figure 6), the heterogeneity was measured as having I^2 equal to 42%, while mean cord plasma sodium levels using oxytocin in 0.9% NaCl solution compared with its control was also not significantly reduced (MD 0.67; 95% CI [-0.70 to 2.05], fixed-effect model) (Figure 6), the heterogeneity was measured as having I^2 equal to 0%.

DISCUSSION

PRINCIPAL FINDINGS

Our systematic review showed that using oxytocin in 5% glucose in water and in 0.9% NaCl solution had similar effect on cord plasma bilirubin levels and neonatal plasma bilirubin levels in day 2-3. However, high heterogeneities were observed. Oxytocin in 5% glucose in water did not decrease cord plasma sodium levels compared with its control, and oxytocin in 0.9% NaCl solution did not decrease the cord plasma sodium levels compared with its control, either.

COMPARISON WITH OTHER STUDIES

We searched studies in many databases and we did not get cohort studies and case control studies associated with using oxytocin in different solutions and its effect. Our meta-analysis found that oxytocin in 5% glucose in water did not decrease cord plasma sodium levels. These findings contrasted with a previous RCT claimed that using oxytocin in 5% glucose in water decreased the cord plasma sodium levels,[26] the contrary might be due to that this RCT got 0 score from Jadad score (high risk of bias) and our study included two trials that had 3 score from Jadad score (fair risk of bias) and had more amount of participants, this RCT had 140 and our study had 269.

We also found that oxytocin in 0.9% NaCl solution did not decrease cord plasma sodium levels and a 1987's study reported that Hartmann's solution compared with control had no statistically significant difference on cord plasma sodium levels.[27] Thus, we assumed that the solutions had no effect on cord plasma sodium levels.

STRENGTHS AND LIMITATIONS

Our study was a systematic review, a high quality study design. To our knowledge, all relevants articles were identified. All processes of conducting the present review were followed the standard protocol of Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0.[23] Our review, however, had relatively small number of 269 participants from two studies that included in the meta-analysis. Both of the trials had fair quality after assessing for risk of bias using Jadad score, and limited quality using the Cochrane Collaboration's tool. Our outcomes regarding serum bilirubin had high heterogeneities. Thus, our conclusion can be definite.

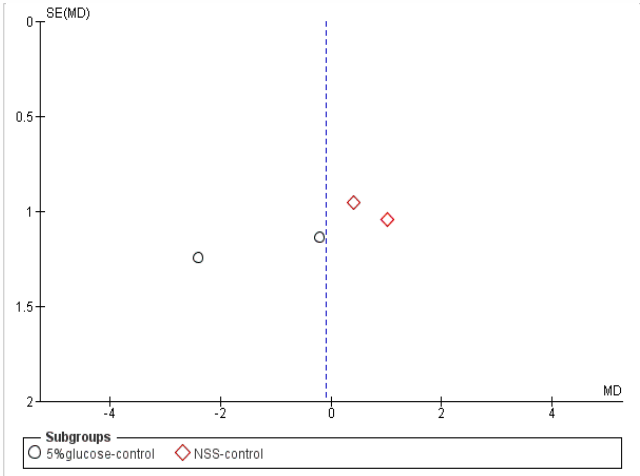

Figure 8. Funnel plot of comparison: mean differences of cord plasma sodium levels in both solutions comparing with the controls.

CONCLUSION

Oxytocin in 5% glucose in water and in 0.9% NaCl had no statistically significant difference in cord plasma bilirubin levels and neonatal plasma bilirubin levels in day 2-3. We also found that using oxytocin in 5% glucose in water and 0.9% NaCl solution had no statistically significant difference on cord plasma sodium levels compared with its own controls. However, our meta-analyses of the outcomes had high heterogeneities. Moreover, our systematic review was based on only two RCTs. Implication of our results should be careful. Further study should be a larger RCT regarding using oxytocin in these solutions for better estimation of their effects.

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COMPETING INTERESTS: This study has no competing on interest.
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