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High dose vs. low dose oxytocin for labor augmentation: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Objectives: To compare the safety and efficacy between high dose and low dose oxytocin administration for labor augmentation.

Methods: We searched for the available studies during March 2020 in PubMed, Cochrane Library, Scopus, and ISI Web of science. All randomized clinical trials (RCTs) that assessed safety and efficacy of high dose vs. low dose oxytocin for labor augmentation were considered. The extracted data were entered into RevMan software. Dichotomous and continuous data were pooled as odds ratio (OR) and mean difference (MD) respectively, with the corresponding 95% confidence intervals (CI). Our main outcomes were cesarean delivery rate, spontaneous vaginal delivery rate, uterine hyperstimulation and tachysystole, and labor duration from oxytocin infusion.

Results: Eight RCTs with 3,154 patients were included. High dose oxytocin did not reduce cesarean delivery rate compared to low dose oxytocin (OR=0.76, 95% CI [0.52, 1.10], p=0.15). After solving the reported heterogeneity, high dose oxytocin did not increase the rate of spontaneous vaginal deliveries vs. low dose oxytocin (OR=1.06, 95% CI [0.84, 1.32], p=0.64). Low dose oxytocin was linked to a significant decline in uterine hyperstimulation and tachysystole (p>0.001). A reduction in labor duration was found in high dose oxytocin group over low oxytocin regimen (MD=−1.02 h, 95% CI [−1.77, −0.27], p=0.008).

Conclusions: We found no advantages for high dose oxytocin over low dose oxytocin in labor augmentation except in reducing labor duration. Low dose oxytocin is safer as it decreases the incidence of uterine hyperstimulation and tachysystole. More trials are needed to confirm our findings.

Keywords: cesarean delivery; labor augmentation; oxytocin.

Introduction

Prolonged labor is a substantial reason for maternal and perinatal morbidity and mortality. The causes of prolonged labor include abnormal fetal presentation, inadequate bony pelvis, poor uterine contractions, and maternal soft tissue abnormalities [1, 2]. Prolonged or delayed labor has become one of the main indications for cesarean section. Cesarean section is a very common procedure nowadays, thus, exploring less invasive interventions is very crucial to limit the rates of cesarean delivery [1]. Labor augmentation has commonly been used when poor uterine contractions are responsible for the delayed labor [3, 4]. It stimulates the uterus to increase the duration, frequency, and intensity of contractions after spontaneous labor onset. Intravenous oxytocin infusion and amniotomy are traditional methods used for labor augmentation [3].

Oxytocin is a nonapeptide hormone produced in the hypothalamus, paraventricular, and supra-optic nuclei [5]. It is carried alongside the neuronal axons from the hypothalamus to be liberated from the posterior pituitary gland

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directly into the circulation. Synthetic oxytocin (pitocin) is one of the most frequently used medications to augment labor, which has been recommended by O'Driscoll in 1960 [6]. The chief goals of oxytocin administration during labor are to obtain efficient uterine contractions, induce cervical changes, and accelerate the labor in order to facilitate fetal delivery [6].

However, oxytocin administration causes different maternal adverse events including headache, vomiting, nausea, bradycardia, tachycardia, and cardiac arrhythmia. In addition, oxytocin can induce fetal distress that can lead to asphyxia, fetal or neonatal death, and hyponatremia in neonates [7]. A case-control study compared 666 cases of postpartum hemorrhage with controls of 153,645 women and reported that oxytocin administration during labor was linked to a significant increase in the risk of postpartum hemorrhage [8].

There is a great controversy regarding the optimal dose of oxytocin for its administration in labor augmentation. Although high dose oxytocin reduces the duration of labor, it can lead to uterine hypertonicity, uterine rupture, and fetal hypoxia. On the other hand, although low dose oxytocin seems to be safer, it may be not efficient enough for labor delay management [9].

Xenakis et al. [10] found a significant increase in spontaneous vaginal deliveries and a significant reduction in cesarean section rates with high dose oxytocin administration for augmentation of labor. However, a recent study found no benefits from high dose oxytocin utilization in augmentation of labor when compared to low dose oxytocin as high dose oxytocin did not reduce the rates of cesarean deliveries [11]. We aimed to update the available evidence from the recently published randomized clinical trials (RCTs) about the safety and efficacy of high dose vs. low dose oxytocin concerning labor augmentation.

Methods

We performed this systematic review and meta-analysis in strict accordance with the Cochrane Handbook for Systematic Reviews of Interventions [12]. The PRISMA statement guidelines were followed during the preparation of this review and meta-analysis [13].

Search strategy

We performed a comprehensive search for the available RCTs in PubMed, Cochrane Library, Scopus, and ISI Web of science during March 2020. We used a combination of the following MeSH terms: (High dose OR High-dose) AND (Low dose OR Low-dose) AND (Oxytocin OR Pitocin) AND (Labor OR Delivery OR Labour OR Birth). Two investigators (RA & AA) performed the search strategy. We conducted a manual search of the references of included studies for retrieval of further studies that were not identified by database searching.

Eligibility criteria

We included RCTs that met the following inclusion criteria: (1) population: pregnant women in spontaneous labor needing oxytocin augmentation due to delayed or slow progress of labor; (2) intervention: high dose oxytocin which is defined as starting dose and increments of equal to or more than 4 mU per minute; (3) comparator: low dose oxytocin which is defined as starting dose and an increment of less than 4 mU per minute; (4) outcome parameters: cesarean delivery (CD) rate, spontaneous vaginal delivery rate, instrumental vaginal delivery rate, duration of labor from oxytocin infusion in hours, uterine hyperstimulation, uterine tachysystole, postpartum hemorrhage, neonatal intensive care unit (NICU) admission, and perinatal and neonatal mortality and (5) study design: RCTs.

We selected the appropriate doses of oxytocin that met our inclusion criteria based on a previously published review in 2013 [14]. We excluded different studies for the following reasons: (1) *in vitro* and animal studies; (2) non-randomized trials; (3) if the dose of oxytocin was not stated in one or both groups; (4) reviews or letter to editors and (5) studies containing data were unreliable for extraction and analysis.

Uterine hyperstimulation was meant by single contractions lasting 2 min or more or five or more contractions during 10 min [15]. Uterine tachysystole was defined as ≥6 contractions per 10 min [16]. Postpartum hemorrhage was defined as blood loss of more than 500 or 1,000 mL during the first 24 h after delivery [17].

Study selection

Eligibility screening was conducted in a two step-wise manner (title/abstract screening and full-text screening). Title and abstract of all recognized articles were screened separately by two reviewers (AA & MS) to assess their relevance to the meta-analysis. In case of disagreement, the full text was retrieved and reviewed by a senior author (AA) for a final decision.

Data extraction and analysis

Two authors (AA and MB) extracted data on a standardized data collection sheet. We extracted the data as the following: list of authors, year of publication, sample size, study location, and summary of the included studies. Likewise, we extracted our outcomes as previously reported.

After that, all data were entered into RevMan software for meta-analysis. Dichotomous and continuous data were pooled as odds ratio (OR) and mean difference (MD) respectively, with the corresponding 95% confidence intervals (CI) in the Mental-Haenszel method.

We assessed the statistical heterogeneity between the studies by using I-squared (I^2) statistics and values of ≥50% were indicative of high heterogeneity [18]. When heterogeneity was significant, we used the random-effects model for meta-analysis. Fixed effect model was utilized when there was no significant heterogeneity. Pooled analyses of data from all studies were performed for outcomes. We removed the reported heterogeneity if found by performing a sensitivity analysis

where we excluded one study at a time and assessed the impact of removing each study on the summary results and the heterogeneity.

Quality of included studies and risk of bias assessment

We assessed the risk of bias in our included RCTs by using the revised version of the Cochrane Randomized Bias Risk Assessment Tool (RoB 2.0) [19], which contains five domains: (1) bias of the randomization process; (2) bias due to deviations from the intended interventions; (3) bias due to missing outcome data; (4) bias in the measurement of the outcomes; and (5) selection bias of the reported outcomes. If all domains were of low risk, the study was considered to be of low risk of bias. If one of these domains displayed high risk of bias, the study was believed to be of high risk of bias. If one of the above mentioned domains was unclear, the study would be stated as unclear risk of bias (some concerns). Two reviewers (AA & MS) performed the quality assessment of the included studies where any discrepancies were resolved by discussion between each of them.

Publication bias

According to Egger and colleagues, assessment of publication bias using the funnel plot method and Egger's test was unreliable for fewer than 10 included studies. Therefore, in the present study, we could not assess for publication bias due to a small number of included studies [20, 21].

Results

Search results and characteristics of included studies

Our search strategy resulted in 685 studies. After title and abstract screening, 25 articles were reliable for full-text screening. We excluded 17 of them in which eight articles did not meet our inclusion criteria, four articles were observational studies, and five articles were reviews. Finally, eight studies matched our inclusion criteria and were included in the final analysis. The PRISMA flow diagram for study selection is shown in Figure 1. Supplementary Material (file no. 1) shows a table for the keywords used in different databases and the reasons for the exclusion of any paper.

A total of eight RCTs [10, 11, 22–27] met our inclusion criteria, which included 3,154 patients. The included studies compared high dose oxytocin vs. low dose oxytocin for labor augmentation. The studies included different women needed for labor augmentation by oxytocin through the following criteria as handled by the physicians: arrest of cervical dilation as assessed by partogram during the first stage of labor, insufficient uterine

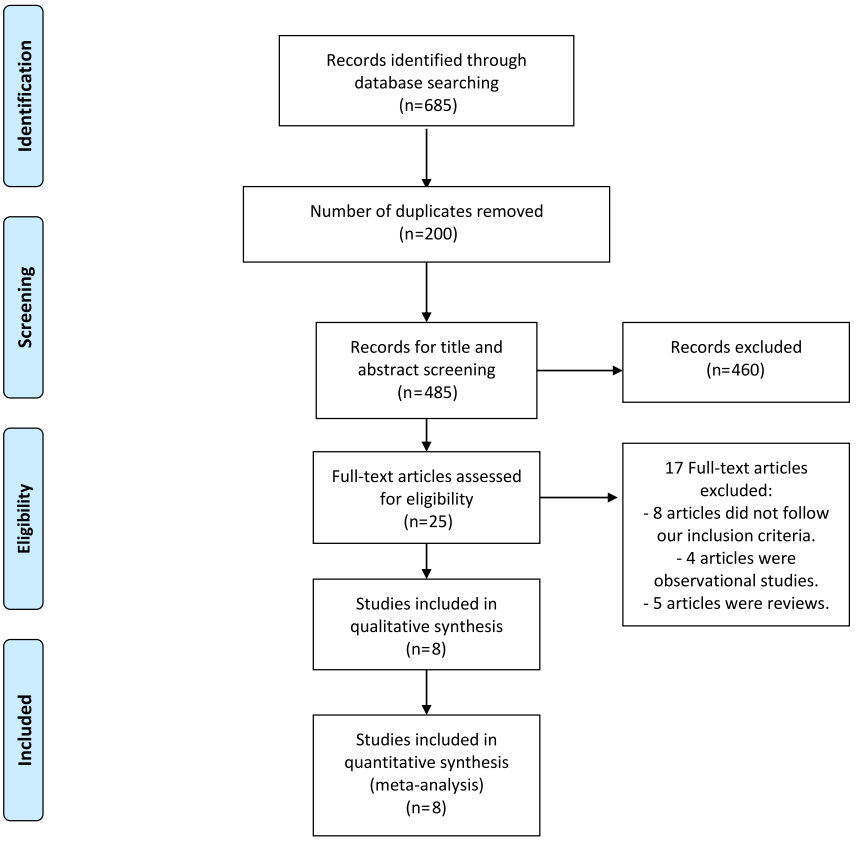

Figure 1: PRISMA flow chart of the study selection process.

contractions, and delayed fetal descent during the second stage of labor. The summary of the included studies was shown in Table 1.

Risk of bias assessment

The articles were assessed for the risk of bias after the selection and inclusion of the studies. The results of the risk of bias assessment for the randomized studies are shown in Table 2 and the judgments are shown in the Supplementary Material (file no.2). The overall risk of bias was ranked as low risk of bias in only three studies [11, 24, 27]. The overall risk of bias was at high risk of bias in four studies [10, 22, 23, 26]. Only one study had some concerns regarding the overall risk of bias [25].

Outcomes

Cesarean delivery rate

We did not find a statistically significant difference between both doses of oxytocin regarding cesarean delivery rate (OR=0.76, 95% CI [0.52, 1.10], p=0.15) as shown in Figure 2. The pooled studies were heterogeneous (p=0.05, I^2=50%). We reduced the heterogeneity by removing Xenakis et al. study [10] (p=0.54, I^2=0%) showing no statistically significant difference between both doses of oxytocin in spontaneous vaginal delivery rate (OR=0.95, 95% CI [0.75, 1.22], p=0.70).

Spontaneous vaginal delivery rate

High dose oxytocin was associated with a statistically significant increase in the rate of spontaneous vaginal delivery in comparison with low dose oxytocin (OR= 1.66, 95% CI [1.03, 2.66], p=0.04) as shown in Figure 3A. However, the pooled studies were heterogeneous (p=0.004, I^2=71%). We reduced the heterogeneity by removing Xenakis et al. and Liu et al. studies [10, 23] (p=0.80, I^2=0%) showing no statistically significant difference between both doses of oxytocin in spontaneous vaginal delivery rate (OR= 1.06, 95% CI [0.84, 1.32], p=0.64) as shown in Figure 3B.

Instrumental vaginal delivery rate

There was no statistically significant difference between high dose and low dose oxytocin regimens in instrumental vaginal delivery rate (OR=0.82, 95% CI [0.65, 1.04], p=0.10) as shown in Figure 4. The pooled studies were homogeneous (p=0.17, I^2=36%).

Uterine hyperstimulation

High dose oxytocin was linked to a statistically significant increase in uterine hyperstimulation incidence compared to low dose oxytocin (OR= 2.09, 95% CI [1.56, 2.81], p>0.001) as shown in Figure 5. The pooled studies were homogeneous (p=0.08, I^2=46%).

Uterine tachysystole

High dose oxytocin was linked to a statistically significant increase in uterine tachysystole incidence compared to low dose oxytocin (OR=3.04, 95% CI [2.39, 3.87], p>0.001) as shown in Figure 6. The pooled studies were homogeneous (p=0.16, I^2=50%).

Postpartum hemorrhage

We did not find any statistically significant difference between both doses of oxytocin regarding postpartum hemorrhage (OR= 0.99, 95% CI [0.81, 1.21], p=0.89) as shown in Figure 7. The pooled studies were homogeneous (p=0.25, I^2=27%).

NICU admission

There was no statistically significant difference between both doses of oxytocin regarding NICU admission (OR=1.12, 95% CI [0.81, 1.54], p=0.50) as shown in Figure 8. The pooled studies were homogeneous (p=0.18, I^2=42%).

Labor duration from oxytocin infusion till delivery

High dose oxytocin was linked to a statistically significant decline in labor duration from oxytocin infusion till delivery when compared to low dose oxytocin group (MD=−1.02 h, 95% CI [−1.77, −0.27], p=0.008) as shown in Figure 9. The pooled studies were heterogeneous (p>0.001, I^2=95%). We solved the heterogeneity by excluding Jamal et al. study [25] (p=0.15, I^2=52%) showing further decline in labor duration from infusion till delivery among high dose oxytocin group (MD=−0.62 h, 95% CI [−0.88, −0.36], p>0.001).

Perinatal and neonatal mortality

There was no statistically significant difference between low dose and high dose oxytocin groups in perinatal and

Table 1: Summary of the included studies.

Study ID	Study location	Study groups	Oxytocin dose	Delayed labor definition	Sample size, n	Participants	Maternal age, years Mean (SD)	Gestational age, weeks Mean (SD)	Main findings
Selin et al. 2019	Sweden	High dose oxytocin	The infusion started with 6.6 mU/min and could be increased every 20 min by 6.6 mU.	Delayed labor was defined in accordance with the Swedish National recommendations by using a three-hour partogram action line for delay during the first stage of labor or an arrest of the descent of the fetal head for one to two hours during the second stage of labor.	647	Nulliparous women with normal singleton pregnancies at term (37 + 0 to 41 + 6 gestational weeks), cephalic presentation, spontaneous onset of labor, active phase of labor (regular painful contractions and effaced cervix and dilation between 3 and 4 cm), confirmed delayed labor progress, and ruptured membranes.	29 (4.8)	40.3 (1.06)	They found no advantages for routine use of high dose oxytocin in labor delay when compared to low dose oxytocin.
		Low dose oxytocin	The infusion started with 3.3 mU/min and could be increased every 20 min by 3.3 mU to a maximum dose of 29.7 mU/min		648		29 (4.6)	40.24 (0.99)	
Liu et al. 2018	China	High dose oxytocin	The infusion started with 8 mU/min and could be increased by 4 mU/min	Delayed labor was diagnosed when there was arrest in labor progress per the partogram.	162	Primiparous women with cervical dilation at least 28 mm with no augmentation, the absence of any pregnancy complications, singleton pregnancy, with an arrested labor progress per the partogram with a need for oxytocin for augmentation of labor.	25.53 (2.46)	39.7 (0.6)	They concluded high-dose and pulsatile oxytocin had reduced the risks of operative delivery in comparison with continuous administration.
		Low dose oxytocin	The infusion started with 2 mU/min and could be increased 1 mU/min		162		25.46 (1.95)	40.1 (0.7)	
Jamal et al. 2004	Iran	High dose oxytocin	The infusion started with 4.5 mU/min and could be increased by 4.5 mU/min every 30 min	Delayed labor was diagnosed by ineffective uterine contractions in the beginning of active labor.	100	All patients with cervical dilatation of 3 cm or greater and gestational age 37 weeks and more.	25.4 (4.9)	39.1 (1.3)	They concluded high dose oxytocin significantly reduced labor duration without any maternal and fetal adverse events.
		Low dose oxytocin	The infusion started with 1.5 mU/min initially and could be increased by 1.5 mU/min every 30 min		100		26.3 (5.1)	38 (1.3)	
Xenakis et al. 1995	United States (US)	High dose oxytocin	It was initiated at 4 mU/min and increased by 4 mU/min every 15 min until adequate uterine contractility was achieved	Delayed labor was diagnosed in case of arrest of dilatation or arrest of descent.	154	Nulliparous and multiparous patients who were admitted to the labor and delivery suite at > 37 weeks of gestation and who were in active labor were eligible for participation.	24.4 (5.9)	40.2 (1.6)	They concluded high dose oxytocin significantly lowered labor duration with decline in the need for cesarean section.
		Low dose oxytocin	Initial oxytocin at 1 mU/minute, the dose being increased by 1 mU/min		156		24.2 (6.9)	39.9 (2)	

Table 1: (continued)

Study ID	Study location	Study groups	Oxytocin dose	Delayed labor definition	Sample size, n	Participants	Maternal age, years Mean (SD)	Gestational age, weeks Mean (SD)	Main findings
			every 30 min. If adequate contractility was not achieved by the end of 2 h, the oxytocin infusion was increased as needed by 1 mU/min every 30 min until adequate uterine contractility was obtained						
Bidgood et al. 1987	United Kingdom (UK)	High dose oxytocin	Oxytocin infusion was started at 7 mU/min and increased by 7 mU/min every 15 min	Delayed labor was confirmed when cervical dilatation was progressing at <0.5 cm/h.	19	Women were eligible for the study if they were in their first spontaneous labor, with vertex presentation and within 3 weeks of term.	NA	NA	They concluded the delay to delivery interval and the duration of the second stage of labor were significantly shorter in the high dose oxytocin group than in the low dose oxytocin group. However, no difference in cesarean section rates between both groups was found.
		Low dose oxytocin	Infusion was at an initial rate of 2 mU/min and increased by 2 mU/min every 15 min		21		NA	NA	
Kenyon et al. 2013	United Kingdom (UK)	High dose oxytocin	Initiation was 4 mU/minute, increasing every 30 min to 64 mU/minute	Delay was suspected as defined by the NICE intrapartum care guideline when cervical dilatation of <2 cm in 4 h occurred. On repeat vaginal examination 2 h later, delay was confirmed when progress of <1 cm in 2 h was found. This definition also takes into account the descent and rotation of the fetal head, and the strength, duration, and frequency of contractions.	47	Eligible women included were nulliparous women with a singleton pregnancy at term (37–42 weeks of gestation) with confirmed delay in spontaneous labor, as defined by the NICE intrapartum care guideline and with ruptured membranes.	NA	NA	They concluded no significant differences between high dose and low dose oxytocin in the rates of cesarean, vaginal, and instrumental deliveries with no evidence of increased harms for either mother or baby in both oxytocin regimes.
		Low dose oxytocin	Initiation was 2 mU/min, increasing every 30 min to 32 mU/minute		47		NA	NA	

Table 1: (continued)

Study ID	Study location	Study groups	Oxytocin dose	Delayed labor definition	Sample size, n	Participants	Maternal age, years Mean (SD)	Gestational age, weeks Mean (SD)	Main findings
Merrill et al. 1999	United States (US)	High dose oxytocin	Initiation was 4.5 mU/minute initially, increased by 4.5 ml/minute every 30 min	Delayed labor was diagnosed when there were insufficient uterine contractions.	249	Any patient beyond 24 weeks' gestation with a living fetus with cervical dilatation of 3 cm or greater with at least 10 uterine contractions per hour.	25.4(0.4)	39.1 (0.1)	High dose oxytocin was associated with significantly shorter labor without any demonstrable adverse fetal or neonatal effects.
		Low dose oxytocin	Initiation was 1.5 mU/minute initially, increased by 1.5 mU/minute every 30 min		242		25.4(0.4)	38.9 (0.1)	
Neerukonda et al. 2018	India	High dose oxytocin	Initiation was at 4 mU/min with incremental dose at 4 mU/min	Delayed labor was diagnosed when there was inadequate labor progress or uterine contractions.	200	All the patients with singleton pregnancy in spontaneous onset of active labor at 37 or more weeks of gestation with inadequate labor progress or contractions, admitted for labor and delivery.	24.12 (3.55)	38.9 (0.88)	They concluded high dose oxytocin effectively reduced oxytocin augmentation to delivery interval when compared to low dose group with no differences in the rates of cesarean deliveries between both groups.
		Low dose oxytocin	Initation was at 1 mU/min with incremental dose at 1–2 mU/min		200		24.45 (3.29)	39.04 (0.86)	

NA, not available.

Table 2: Results of bias risk assessment of randomized clinical trials by the RoB 2.0 tool.

Risk by domains						
Authors	**Randomization**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported result**	**Overall bias**
Selin et al. 2019	Low	Low	Low	Low	Low	Low
Kenyon et al. 2013	Low	Low	Low	Low	Low	Low
Neerukonda et al. 2018	Low	High	Low	High	Low	High
Xenakis et al. 1995	High	High	Low	High	Some concerns	High
Merrill et al. 1999	Low	Low	Low	Low	Low	Low
Liu et al. 2018	Some concerns	High	Low	High	Low	High
Jamal et al. 2004	Low	Low	Low	Low	Some concerns	Some concerns
Bidgood et al. 1987	Low	High	Low	High	Some concerns	High

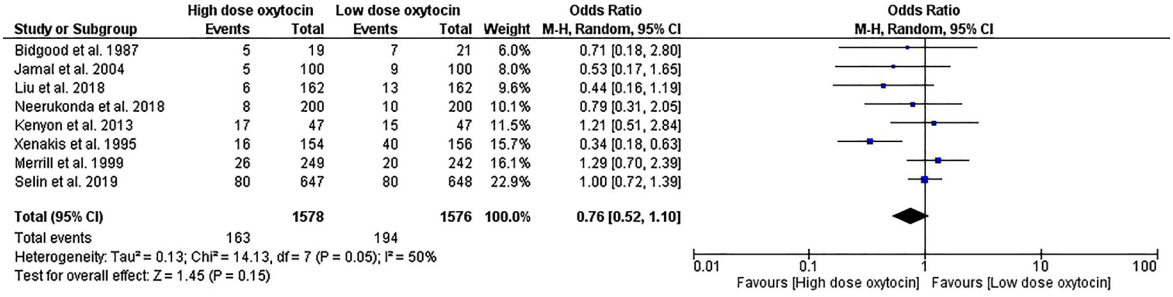

Figure 2: Forest plot for cesarean delivery rate.

neonatal mortality (OR=1.50, 95% CI [0.53, 4.25], p=0.45) as shown in Figure 10. The pooled studies were homogeneous (p=0.27, I^2=23%).

Discussion

Main findings

In the present meta-analysis, the rates of cesarean and instrumental vaginal deliveries were not significantly different between high and low dose oxytocin regimens. After removal of the reported heterogeneity, we found no significant difference between both doses of oxytocin regarding the increase in spontaneous vaginal deliveries. However, high dose oxytocin was associated with a significant increase in the risk of uterine tachysystole and uterine hyperstimulation compared to low dose oxytocin. Labor duration from oxytocin infusion until delivery significantly declined among high dose oxytocin. In addition, there were no significant differences between oxytocin doses regarding neonatal and maternal adverse outcomes including NICU admission, perinatal and neonatal mortality, and postpartum hemorrhage.

Previous studies

Selin et al. [11] compared between high and low dose regimens of oxytocin in 1,295 women for labor augmentation and reported no disparities in the rates of cesarean, vaginal, and instrumental deliveries between both groups. They showed a significant increase in the incidence of uterine tachysystole in high dose oxytocin. However, they found that high dose oxytocin was linked to shorter labor duration in comparison with low dose oxytocin [11]. Furthermore, they reported that there was an association between high dose oxytocin and the increase in the incidence of pathological or suspicious cardiotocography [11].

Neerukonda et al. [22] included 400 women with spontaneous labor onset at term in a district hospital to compare between low dose and high dose oxytocin for labor delay management. They reported no significant differences between both regimens of oxytocin in the

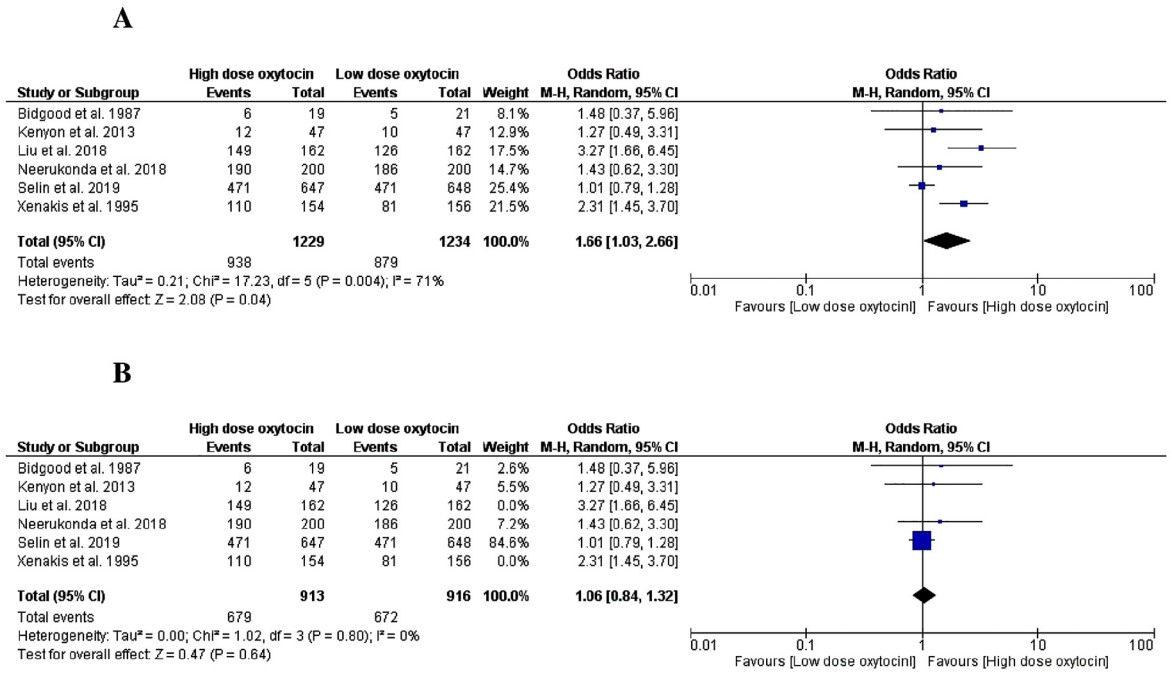

Figure 3: Forest plot for spontaneous vaginal delivery rate.

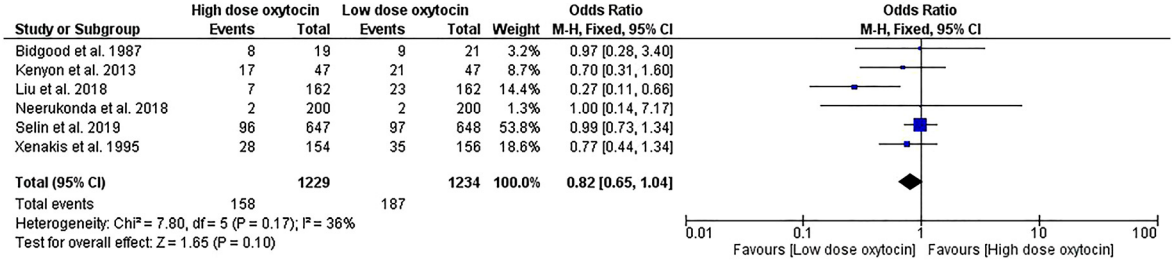

Figure 4: Forest plot for instrumental delivery rate.

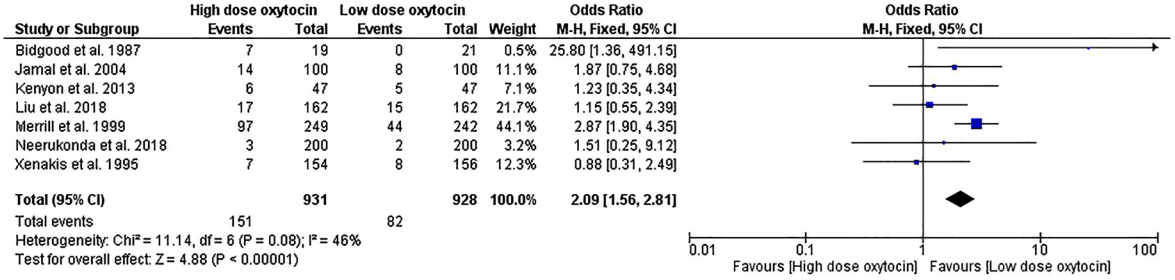

Figure 5: Forest plot for uterine hyperstimulation.

incidence of cesarean, vaginal, and instrumental deliveries. They also realized a significant decline in duration from oxytocin infusion to delivery in high dose oxytocin group compared to low dose oxytocin with more decline in delivery interval found in nulliparous in comparison with multiparous women [22]. They uncovered that high dose oxytocin was linked to an increase in the number of neonates admitted to the NICU [22].

Conversely, an RCT that was conducted in China by Liu et al. [23] in women suffering from abnormal delay in delivery demonstrated a significant reduction in the risk of cesarean and instrumental deliveries with significant increase in spontaneous vaginal deliveries in high dose oxytocin group. Moreover, they did not find any significant difference between both oxytocin regimens in labor duration and uterine hyperstimulation risk [23].

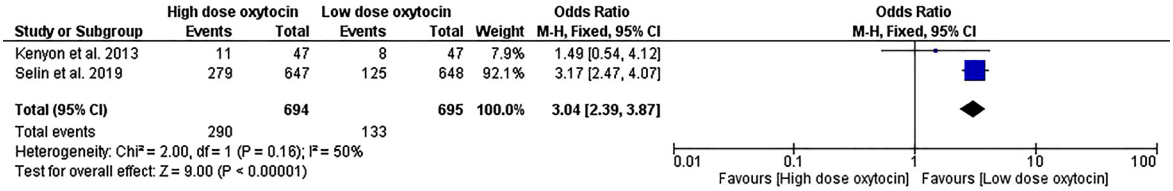

Figure 6: Forest plot for uterine tachysystole.

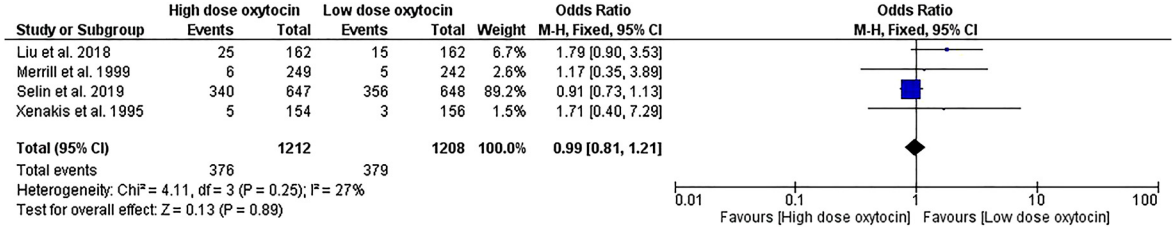

Figure 7: Forest plot for postpartum hemorrhage.

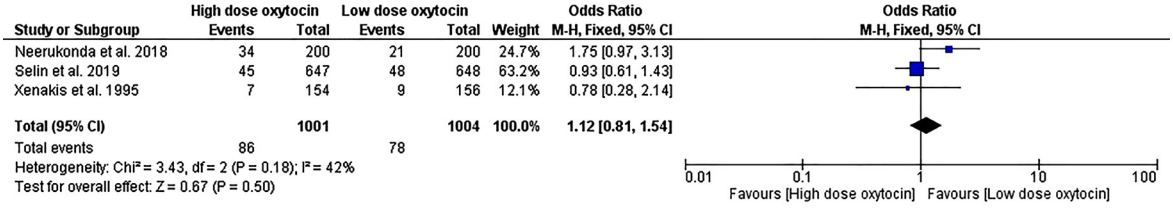

Figure 8: Forest plot for neonatal intensive care unit (NICU) admission.

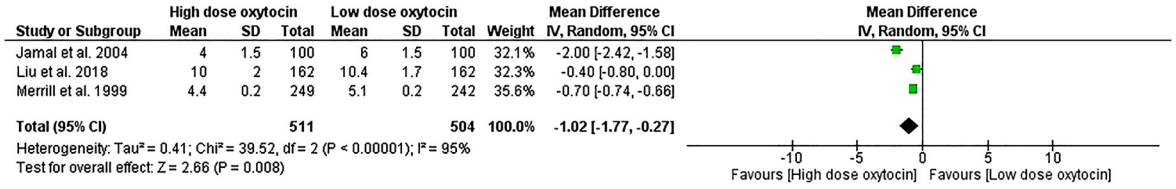

Figure 9: Forest plot for duration from infusion till delivery.

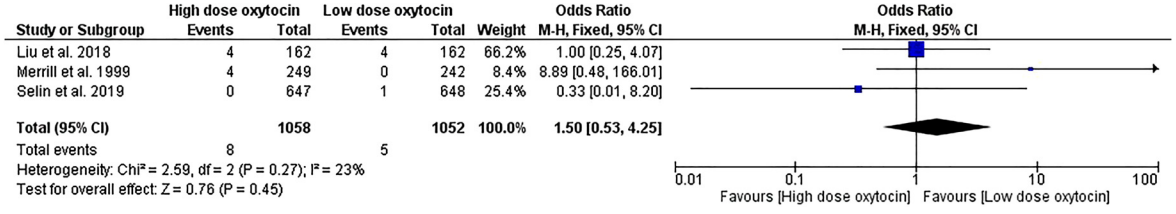

Figure 10: Forest plot for perinatal and neonatal mortality.

No significant differences were found between high dose and low dose oxytocin regarding the rates of cesarean and vaginal deliveries as stated by Bidgood et al. [26]. In addition, they showed a significant shortening in labor duration with high dose oxytocin. They found seven women experienced uterine hyperstimulation in high dose oxytocin with no cases found in low dose oxytocin; however, they showed no differences in different neonatal outcomes between both oxytocin regimens [26]. Another RCT reported no significant differences between high and low dose oxytocin in the incidence of cesarean, vaginal, and instrumental deliveries and the risk of uterine tachysystole [27].

Kenyon et al. [14] published a systematic review in 2013 to compare high dose vs. low dose oxytocin for delayed labor augmentation where they included only four RCTs with 644 women in their study. They recommended high dose oxytocin administration over low dose oxytocin for labor augmentation as it was linked to a significant decline in labor duration and cesarean section incidence with increase in spontaneous vaginal deliveries rates [14]. They found no significant differences between high and low dose oxytocin in uterine hyperactivity incidence, FHR changes, and the risk of admission to the NICU. However, they suggested that this was an insufficient evidence for recommending high dose oxytocin regimen in delayed labor management [14]. Our findings are in contrast to this review may be due to our inclusion of eight trials in our study double the studies included in the review.

Wei et al. [28] conducted another systematic review where they included 10 RCTs with 5,423 women in their study to estimate the safety and efficacy of high dose over low dose oxytocin for labor augmentation with different inclusion criteria compared to our study. They established that high dose oxytocin was associated with a slight increase in spontaneous vaginal delivery, a slight decrease in cesarean section risk, and a decline in labor duration [28]. High dose oxytocin regimen was linked to a significant increase in uterine hyperstimulation with no increase in neonatal or maternal morbidity in comparison with low dose oxytocin regimen [28].

Liu et al. [23] assessed the costs of delivery in both regimens of oxytocin for labor augmentation. They reported that low dose oxytocin (2 mU/min following 1 mU/min) was linked to more cost-effectiveness regarding delivery compared to high dose oxytocin (8 mU/min following 4 mU/min). In contrary, Merrill et al. [24] conducted a cost-effectiveness analysis to compare between high and low dose oxytocin during labor augmentation. They supposed the cost of administration of oxytocin per hour to be $140, and with shortening of labor duration by 1.5 h with high dose oxytocin, the reduction in the cost of labor and delivery would be nearly $210/patient in high dose oxytocin group. These savings were due to shortening in labor duration rather than decline in rates of cesarean deliveries in this study [24].

Strengths and limitations

The main strengths of the present meta-analysis are its high quality as it is based on RCTs, well-defined search methods and eligibility criteria, and a large sample size of participants included. Finally, we followed the steps of the Cochrane handbook of systematic review for interventions in preparing this review.

Our main limitation is the reported heterogeneity in some of the outcomes which has several reasons including great disparities in inclusion criteria between the included studies, differences in the timing of the initial administration of oxytocin, and variation in the doses of oxytocin administered either the initial doses or increments between the included studies. Limited number of included studies and changes in terms of the definitions of delayed or slow labor over the years and across the countries where these studies were conducted add further limitations to our study.

Furthermore, we did not perform any subgroup analysis between nulliparous and multiparous women due to great differences in the inclusion criteria realized between the included studies. The differences in aspects of oxytocin administration, low quality of most of the included studies as reported during risk of bias assessment, and the variability in the definitions in high dose and low dose oxytocin across the studies are considered further limitations in this study which may decline the evidence reported in our study.

Implications for practice

Low dose oxytocin can be used instead of high dose oxytocin regimen for labor augmentation as low dose oxytocin is as effective as high dose oxytocin in reducing the rates of cesarean and instrumental deliveries and in increasing the rates of spontaneous vaginal deliveries. In addition, low dose oxytocin appears to be safer as it reduces the risk of uterine hyperstimulation and tachysystole that may be associated with serious effects on the fetal heart rate patterns and their oxygen status. However, there is not enough evidence due to the limited number of included RCTs regarding this topic.

Implications for research

More high quality RCTs are needed to confirm our findings with the inclusion of a large sample size. The coming trials should assess the neonatal effects and women's birth experience in high dose and low dose oxytocin regimens during their administration for augmentation of labor. The

future RCTs should evaluate the influence of oxytocin doses for labor augmentation in relation to the body mass index (BMI). They should assess the benefits of both regimens of oxytocin in nulliparous and multiparous women separately for labor augmentation. More cost-effectiveness analysis studies should be performed between high dose and low dose oxytocin administrated for labor augmentation.

Conclusions

There are no differences between high dose and low dose oxytocin regarding the rates of cesarean, vaginal, and instrumental deliveries. High dose oxytocin is associated with increased risk for uterine hyperstimulation and tachysystole with shorter labor duration.

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