Archives of Gynecology and Obstetrics (2020) 301:643–653
https://doi.org/10.1007/s00404-020-05467-9

REVIEW

A meta-analysis of the effects of intramuscular and intravenous injection of oxytocin on the third stage of labor

Yu Wu[1] · Huan Wang[2] · Qi-Yan Wu[1] · Xiao-Lei Liang[1] · Jing Wang[1]

Received: 3 December 2019 / Accepted: 13 February 2020 / Published online: 2 March 2020

Abstract

Background Clinical studies and trials have shown that oxytocin can effectively reduce postpartum bleeding, whether by intramuscular (IM) injection or intravenous (IV) injection. These two methods are widely used in the prevention and treatment for the third stage of childbirth. However, it is unclear whether the subtle differences between the mode of these routes have any effect on maternal outcomes.

Objectives To systematically evaluate the efficacy and safety of oxytocin administered intramuscularly or intravenously for prophylactic management of the third stage of labor after vaginal birth.

Methods Computerized retrieval of PubMed, the Cochrane Library, Web of Science, Embase, and ClinicalTrials.gov was conducted to collect randomized controlled trials (RCT) on the effects of IM and IV oxytocin on the third stage of labor. After independent literature screening, data extraction and evaluation of the bias risk of included studies by two evaluators, RevMan 5.3 software was used for a meta-analysis.

Results Six studies with 7734 women were included in this study. Meta-analysis results showed that: the severe postpartum hemorrhage (PPH) rate [risk ratio (RR) 1.54, 95% confidence interval (95% CI) 1.08–2.20, $P=0.02$], PPH rate (RR 1.31, 95% CI 1.11–1.55, $P=0.001$), incidence of blood transfusion (RR 2.30, 95% CI 1.35–3.93, $P=0.002$) and the need of manual removal of placenta (RR 1.44, 95% CI 1.05–1.96, $P=0.02$) for IM group were higher than IV group, but there were no significant differences in the use of additional uterotonics ($P=0.31$) and the incidence of serious maternal morbidity and adverse effects between two groups. None of the included studies reported maternal death.

Conclusion For clinical practice, intravenous injection oxytocin 10 IU may be a good, safe option in the management of the third stage of labor. Medical conditions, available resources, adverse effects, and women' s preferences should also be considered. If an IV line is already in place at delivery, IV administration may be preferable to IM injection.

Keywords Intravenous injection · Intramuscular injection · Oxytocin · The third stage of labor · System evaluation · Meta-analysis

Introduction

Estimates of global maternal mortality suggest that over 300,000 women die each year during pregnancy and childbirth [1]. Most maternal deaths occur within 24 h after delivery and the leading cause is complications during the third stage of labor. Among these complications, postpartum hemorrhage (PPH) is a major cause of maternal death and morbidity worldwide and is most commonly a result of uterine atony [2, 3]. According to the World Health Organization (WHO), PPH is defined as bleeding from the genital tract in excess of 500 mL after the birth of the baby [4]. Active management of the third stage of labor (AMTSL) can help to facilitate uterine contraction and expulsion of the placenta and prevent PPH. AMTSL is a set of interlocking interventions that usually include administration of a prophylactic uterotonic during or immediately after the birth of the baby, cord clamping and cutting, and placental delivery by controlled cord traction [5].

✉ Jing Wang
wy2011nyd@163.com

[1] Department of obstetrics and gynecology, The First Hospital of Lanzhou University, Key Laboratory of Gynecologic Oncology Gansu Province, Lanzhou 730000, Gansu, People's Republic of China

[2] The First Clinical Medical College of Lanzhou University, Lanzhou 730000, Gansu, People's Republic of China

Oxytocin is the gold standard uterotonic drug used in the active management of the third stage of labor [6]. Comparative studies of oxytocin either in combination with other components of active management or alone show that it is safe and effective in reducing PPH [7]. While the value of routine oxytocin in the third stage of labor has been well established, questions remain regarding the optimal route for its administration. Indeed, a comparison of guidelines reveals significant heterogeneity in the recommendations for administering prophylactic oxytocin released by professional associations and leading health authorities [8]. For instance, some guidelines recommend intramuscular (IM) bolus dose of oxytocin 10 IU [9–11], whereas the World Health Organization recommends oxytocin 10 IU intramuscularly or by slow intravenous (IV) injection equally during the third stage of labor [12, 13]. There are some differences between IM injection and IV routes of oxytocin, such as the time taken until oxytocin starts to work and the effects on blood pressure and heart rate. The administration of oxytocin via IM injection has become a more serviceable option as it requires lesser time, relatively fewer skills and equipment to administer than IV administration, particularly in lower levels of care where IV placement may be less feasible [14, 15]. Yet, evidence also supports IV administration, and some researchers report improved clinical outcomes that favor IV routes over IM [16, 17]. Studies also found that IV administration results in a faster uterine response and a higher peak in plasma oxytocin levels [18–20].

A Cochrane review identified a lack of randomized controlled trials that related to comparison of IM and IV injection of prophylactic oxytocin when used for the third stage of labor [14] and another review reported that few studies of prophylactic oxytocin used blind technology [7]. Both studies lack evidence regarding the optimal route of administration of oxytocin [7, 14]. Therefore, this study used a meta-analysis to comprehensively evaluate the efficacy and safety of IM and IV oxytocin injection on the third stage of labor, hoping to provide evidence for clinical medication.

Materials and methods

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [21] were followed. All PRISMA [21] -compliant searches of PubMed, the Cochrane Library, Web of Science, Embase and ClinicalTrials.gov were conducted on studies (dates of inception to Jan 2020) for randomized controlled trials (RCT) assessing the effects of IM and IV oxytocin on the third stage of labor. English search terms include: intravenous injection, intramuscular injection, oxytocin, the third stage of labor, etc. The reference included in the study was traced back to supplement the acquisition of relevant literature. No language restrictions were applied in the search strategy. Table 1 illustrates the sensitive literature search strategy based on the PubMed.

Inclusion and exclusion criteria

Research types All randomized controlled trials (RCTs) related to comparison of IM and IV injection of oxytocin when used for intervention of the third stage of labor in English. Non-randomized trials (e.g., descriptive study, clinical control study and semi-randomized controlled trials) were excluded.

Participant Women to give birth vaginally, regardless of other aspects of third stage of labor management.

Intervention Intramuscular (IM) injection bolus of oxytocin given as prophylaxis for the third stage of labor.

Comparison Intravenous (IV) injection of oxytocin (used alone by bolus infusion or combined with saline by slow intravenous injection) as prophylaxis for the third stage of labor, at any dose and timing of administration.

Outcome We included studies if they reported one or more than one of the following outcomes: primary outcome: (1)

Table 1 Search terms used in the PubMed

Database	Search items
PubMed	(intravenous injection [mh] OR intravenous administration [mh] OR mainline [mh] OR intravenous [mh] OR injection [mh] OR intravenous injection [tiab] OR intravenous administration [tiab] OR mainlin [tiab] OR intravenous [tiab] OR injection [tiab] OR vein injection [tiab] OR venous injection [tiab]) AND (intramuscular injection [mh] OR muscle injection [mh] OR muscular injection [tiab] OR intramuscular injection [tiab] OR muscle injection [tiab] OR intramuscularly injected [tiab] OR muscle injected [tiab] OR treated with intramuscular injection [tiab] OR intramuscular administration [tiab]) AND (oxytocin [mh] OR pitocin [mh] OR utedrin [mh] OR alpha hypophamine [mh] OR oxytocin [tiab] OR pitocin [tiab] OR utedrin [tiab] OR alpha hypophamine [tiab]) AND (the third stage of labor [mh] OR third stage [mh] OR third stage labour [mh] OR the third stage of labor [tiab] OR third stage [tiab] OR third stage labour [tiab])

severe PPH (blood loss of 1000 mL or more), (2) serious maternal morbidity (e.g., organ failure, coma, intensive care unit (ICU) admission and hysterectomy); secondary outcomes: (1) PPH (blood loss of 500 mL or more), (2) use of additional uterotonics, (3) blood transfusion, (4) retained placenta or manual removal of placenta, (5) maternal death, (6) adverse effects: including minor adverse effects (e.g., headache, nausea or vomiting) and major adverse effects (e.g., maternal hypotension or any adverse effect requiring treatment) between delivery of baby and discharge from the labor ward.

Study selection

Two review authors independently screened the title and abstract. Then, the full text should be further read to determine the final inclusion after excluding the obviously irrelevant literature.

In case of differences, they consulted a third party to assist in the judgment, and tried to contact the author to supplement the lacking data.

Data extraction

Two evaluators independently extracted the following data using a pre-standardized form and cross-checked them. The content of data extraction mainly includes: (1) basic information of the included study, including authors, publication year, sample size, gestational age, specific details of the intervention measures (the usage and dosage of oxytocin), etc.; (2) results measurement indicators, including primary outcomes, secondary outcomes, and adverse effects, etc. The extracted data were rechecked by a third author.

Risk assessment of bias included in the study

The risk of bias in the included studies was assessed by two reviewers using the Cochrane manual tool [22] for risk of bias in RCT.

Assessment of reporting biases

If there are ten or more studies available in analysis of an outcome parameter, we will use funnel plots to investigate reporting biases (such as publication bias). We will assess their symmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Statistical analysis

RevMan 5.3 software was used for this meta-analysis. The relative risk (RR) was used as the effect index for the dichotomous data, and the Std. mean difference (SMD) was used as the effect index for the measurement data. The point estimates and 95% CI of each effect quantity were given. Heterogeneity among the included studies was evaluated by chi-square test (alpha = 0.1), and the heterogeneity was evaluated quantitatively. If there was no statistical heterogeneity among the results, a fixed effect model was used for meta-analysis. If there was statistical heterogeneity among the results, the sources of heterogeneity were further analyzed. After excluding the effect of obvious clinical heterogeneity, a random effect model was used for meta-analysis. Significant clinical heterogeneity was treated by sensitivity analysis, or descriptive analysis.

Results

Literature retrieval results

The electronic searches identified 154 potentially eligible studies. 130 studies were excluded by title and abstract screening. The remaining 14 full-text articles were assessed for eligibility. Ultimately, six studies [23–28] satisfied the eligibility criteria. Figure 1 presents a flow diagram outlining how the final papers were selected.

The basic characteristics of studies included in the analysis

As shown in Table 2, finally, six studies [23–28] including seven RCTs [a three-arm study [25] has three groups and two comparisons: IM injection (2104 women) vs IV infusion (2108 women) and IM injection vs IV bolus (701 women)] with 7734 women met the inclusion criteria and contribute data to the review. Six studies were carried out in hospital settings in Turkey [23, 27], Ireland [24], Egypt [25], Thailand [26] and Argentina [28] respectively, and one of them selected pregnant women in two hospitals [25]. All women were 18 years or older and underwent vaginal deliveries. The doses of oxytocin were 10 IU with two administration routes in six studies: intramuscular injection or intravenous injection (used oxytocin alone or oxytocin diluted in normal saline solution). In addition, the measurements of blood loss were all described as 'objective measurement and specific description'. The time of postpartum blood loss measured and side effects observed varied in six studies. There were no differences between the two groups in terms of demographic and clinical characteristics in six studies.

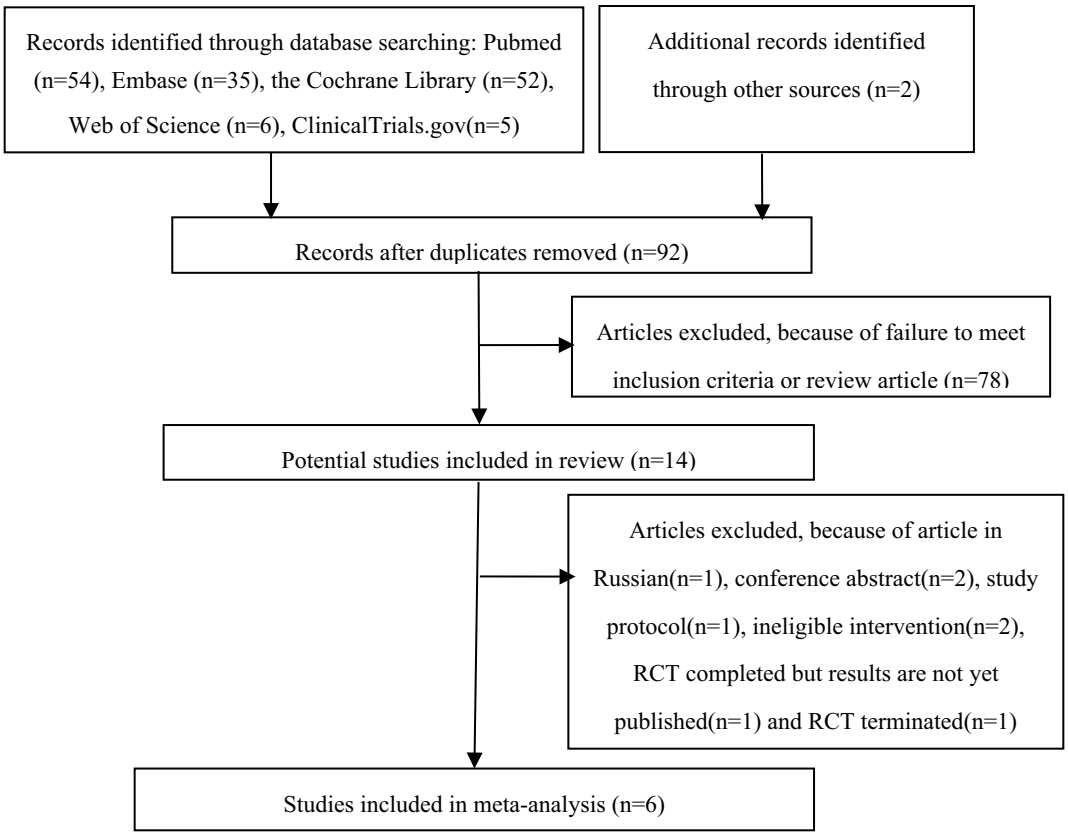

Fig. 1 The study selection and inclusion process

Meta-analysis results

Primary outcomes1: severe PPH (blood loss 1000 mL or more)

Four studies [23–25, 28] reported severe PPH as an outcome. The pooled analysis of 6681 pregnant women demonstrated that the IM group was associated with significantly more severe PPH compared to IV group (2.61% vs 1.27%, RR 1.54, 95% CI 1.08–2.20, $P=0.02$; Fig. 2). Heterogeneity among the studies was low ($I^2=11\%$, $P=0.34$).

Primary outcomes2: serious maternal morbidity

Three studies [24, 27, 28] reported serious maternal morbidity as an outcome. One study [24] reported that fewer women were admitted to a high dependency unit in the IV group compared with the IM group (1.7% vs 3.7%, adjusted odds ratio 0.44, 95% CI 0.20–0.98, $P=0.04$, 1,035 women). One study [28] reported that only one woman in IM group needed hysterectomy or other surgery (IV vs IM group: 0% vs 0.4%, RR and 95% CI cannot estimate, $P=1.00$,480 women). And one study [27] reported that none of the study participants required any further intervention, such as laparotomy or postpartum hysterectomy.

Secondary outcomes1: PPH (blood loss 500 mL or more)

All studies reported PPH as an outcome. PPH occurred in 253 (7.20%) and 201 (4.77%) pregnant women in the IM group and the IV group, respectively. The pooled analysis of 7731 pregnant women demonstrated that the incidence of PPH was higher in IM group (RR 1.31, 95% CI 1.11–1.55, $P=0.001$; Fig. 3). No heterogeneity existed among the included studies ($I^2=0\%$, $P=0.60$).

Assessment of reporting biases The likelihood of publication bias was moderate (Fig. 4). However, there may still have some reporting biases due to lack of rigor, clinical heterogeneity, and methodological heterogeneity, et al.

Secondary outcomes2: use of additional uterotonics

A total of 384 pregnant women who needed additional uterotonics were reported by five studies [23–25, 27, 28] (7284 pregnant women), 205 (6.23%) in the IM group and 179 (4.48%) in the IV group. No significant difference was found in the use of additional uterotonics between the two

Table 2 Characteristics of studies included in the meta-analysis

Study	Type	Country	IM group or/and IV group				Intramuscular injection of oxytocin	Intravenous injection of oxytocin	Measure of blood loss
			Sample size (*n*)	Age (years)	Pregnancy term(week)	Clinical characteristics			
Dagdeviren et al. [23]	RCT	Turkey	128/128	18–45	37–42	Similar	IM oxytocin 10 IU after delivery of the anterior shoulder	IV oxytocin 10 IU in 1000 mL saline at 1 mL/min after delivery of the anterior shoulder	Objective, specific
Adnan et al. [24]	RCT	Ireland	518/517	≥ 18	≥ 37	Similar	IM group received 10 IU IM oxytocin in 1 ml in the thigh within 1 min and a placebo intravenous injection (1 ml 0.9% saline)	IV group received 10 IU IV oxytocin in 1 ml over 1 min and a placebo intramuscular injection (1 ml 0.9% saline)	Objective, specific
Charles et al. [25]	RCT	USA	2104/2108	27/27 (mean)	Unclear	Similar	10 IU oxytocin administered in the thigh	IV infusion: 10 IU oxytocin was given in 500 ml of fluid	Objective, specific
	RCT	USA	2104/701	27/26 (mean)	Unclear	Similar	10 IU oxytocin administered in the thigh	IV bolus: 10 IU oxytocin pushed into the IV port over 1 min	
Sangkomkamhang et al. [26]	RCT	Thailand	225/225	24.2/24.4 (mean)	38.4/38.6 (mean)	Similar	10 IU oxytocin by IM injection after delivery of the anterior shoulder	10 IU of oxytocin in 10 mL normal saline administered over 2 min after delivery of the anterior shoulder	Objective, specific

Table 2 (continued)

Study	Type	Country	IM group or/and IV group				Intramuscular injection of oxytocin	Intravenous injection of oxytocin	Measure of blood loss
			Sample size (*n*)	Age (years)	Pregnancy term(week)	Clinical characteristics			
Oguz Orhan et al. [27]	RCT	Turkey	300/300	21–31	> 37	Similar	2 IM groups (150 women in each) received 10 IU IM oxytocin, in group IM (A) this was given after delivery of the baby and cord clamping, in group IM (B) oxytocin was given at the point of delivery of the anterior shoulder. Total number randomised = 300 in IM group	2 IV groups (150 women in each) received 10 IU IV oxytocin at 1 mL/min, in group IV (A) this was given after delivery of the baby and cord clamping, in group IV (B) oxytocin was given at the point of delivery of the anterior shoulder. Total number randomised = 300 in IV group. NOTE: in the data and analysis we combined the 2 IM and IV groups to form a single	Objective, specific
Durocher et al. [28]	RCT	USA	241/239	24.3/24.1 (mean)	38.9/38.6 (mean)	Similar	IM group received IM administration of 10 IU oxytocin ampoule in the thigh and IV infusion of a matching placebo ampoule(500 ml saline for 40 min)	IV group received IV infusion of 10 IU oxytocin ampoule in 500 ml saline for 40 min and IM administration a matching placebo ampoule in the thigh	Objective, specific

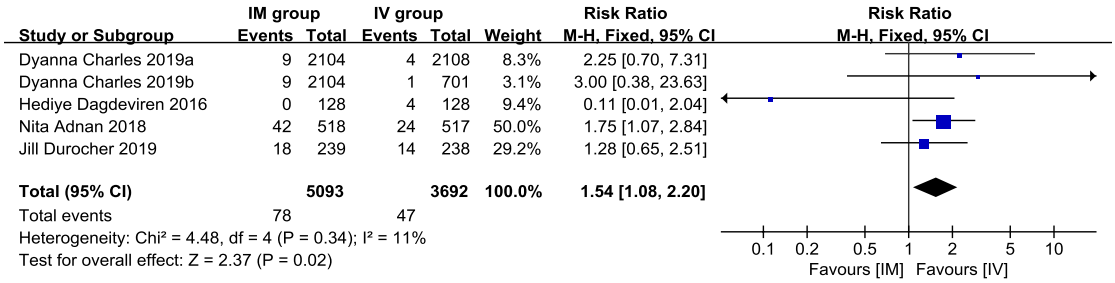

Fig. 2 IM vs IV injection of oxytocin in the 3rd stage of labor, Outcome: severe PPH (≥ 1000 mL)

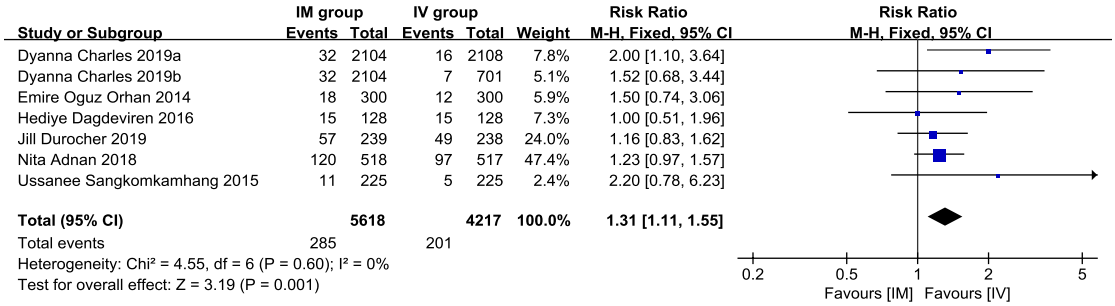

Fig. 3 IM vs IV injection of oxytocin in the 3rd stage of labor, outcome: PPH (≥ 500 mL)

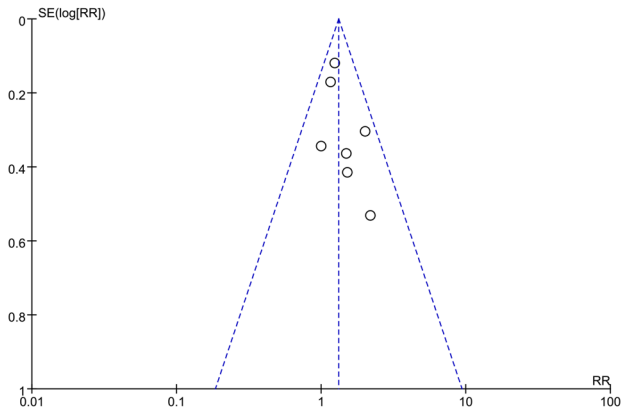

Fig. 4 Funnel plots of comparison of outcome: PPH (≥ 500 mL)

groups (RR 1.25, 95% CI 0.82–1.91, $P = 0.31$, Fig. 5). There was moderate heterogeneity among the included studies ($I^2 = 60\%$, $P = 0.03$).

Sensitivity analysis There was a moderate statistical heterogeneity in this outcome ($I^2 = 60\%$, $P = 0.03$). Thus, we carried out a sensitivity analysis to find the potential heterogeneity sources. The method is to remove the included studies sequentially to evaluate whether there is an impact on the outcomes. When the study (Hediye Dagdeviren 2016) was removed, the heterogeneity I^2 value reduced from 60 to 38%. The RR was 1.39 (95% CI 1.00–1.94), and there was still no significant difference between the two groups ($P = 0.05$). After reading this article, there was no obvious mistake or error.

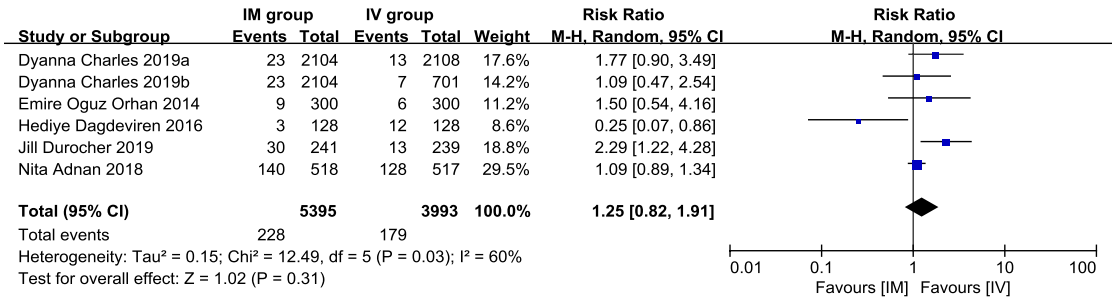

Fig. 5 IM vs IV injection of oxytocin in the 3rd stage of labor, outcome: use of additional uterotonics

Secondary outcomes3: blood transfusion

Four studies [23–25, 28] reported blood transfusion as an outcome. Blood transfusion occurred in 40 (1.34%) and 19 (0.51%) patients in the IM and the IV groups, respectively. The pooled analysis of 6684 pregnant women demonstrated that the incidence of blood transfusion was higher in IM group (RR 2.30, 95% CI 1.35–3.93, $P=0.002$; Fig. 6). No heterogeneity existed among the included studies ($I^2=0\%$, $P=0.86$).

Secondary outcomes4: retained placenta or manual removal of placenta

Four studies [23, 25, 27, 28] reported manual removal of placenta as an outcome. The pooled analysis, which included 6249 pregnant women, demonstrated that the IM group was associated with significantly high retained placenta compared to the IV group (2.42% vs 1.81%, RR 1.44, 95% CI 1.05–1.96, $P=0.02$, Fig. 7). No heterogeneity among the included studies was detected ($I^2=0\%$, $P=0.44$).

Secondary outcomes5: maternal death

None of the included studies reported maternal death.

Secondary outcomes6: adverse effects

All studies reported adverse effects as outcomes. We conducted a descriptive analysis because of the lack of relevant data. Hediye Dagdeviren 2016 reported that there were no statistically significant differences between IM and IV groups for adverse effects of oxytocin, which included shivering, nausea and/or vomiting, pyrexia and tachycardia. Nita Adnan 2018 showed the incidence of nausea (0.2% in both groups), vomiting (0% in both groups), headache (0.8% vs 0.6%), shivering (1.0% vs 0.4%), tachycardia (2.7% vs 1.9%) and hypotension (2.9% vs 2.3%) in IM and IV groups respectively. Ussanee Sangkomkamhang 2015 also reported that there was no significant difference in the incidence of hypotension. Emire Oguz Orhan 2014 reported that only one woman in IM group developed uvular edema. Dyanna Charles 2019 and Jill Durocher 2019 showed that there were no reports of any adverse effects associated with oxytocin administration in either study group.

Risk of bias in included studies

See Figs. 8 and 9 for a summary of our 'Risk of bias' assessments. In the risk bias analysis, the study by Sangkomkamhang [26] did not describe their method for generating the randomization sequence (unclear risk of bias). 66.67% studies had unclear risk of selection bias

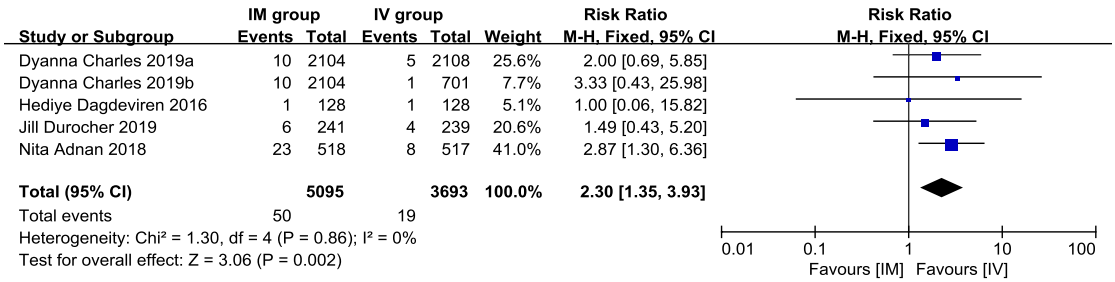

Fig. 6 IM vs IV injection of oxytocin in the 3rd stage of labor, outcome: blood transfusion

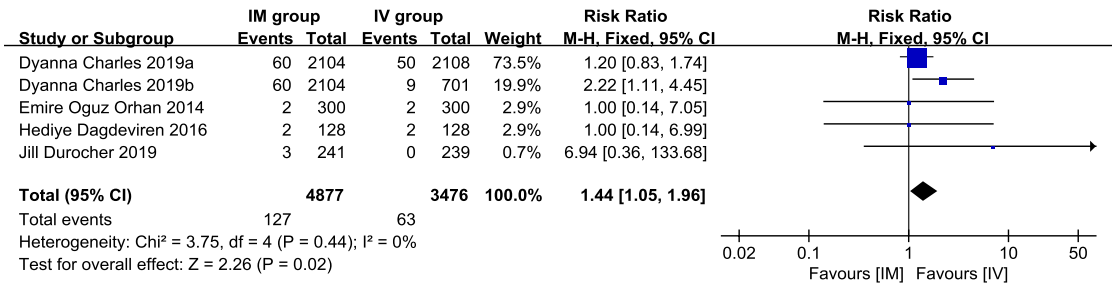

Fig. 7 IM vs IV injection of oxytocin in the 3rd stage of labor, outcome: retained placenta or manual removal of placenta

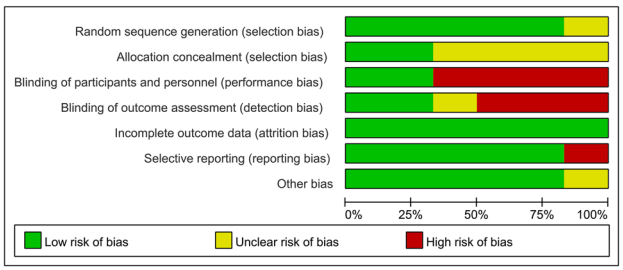

Fig. 8 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

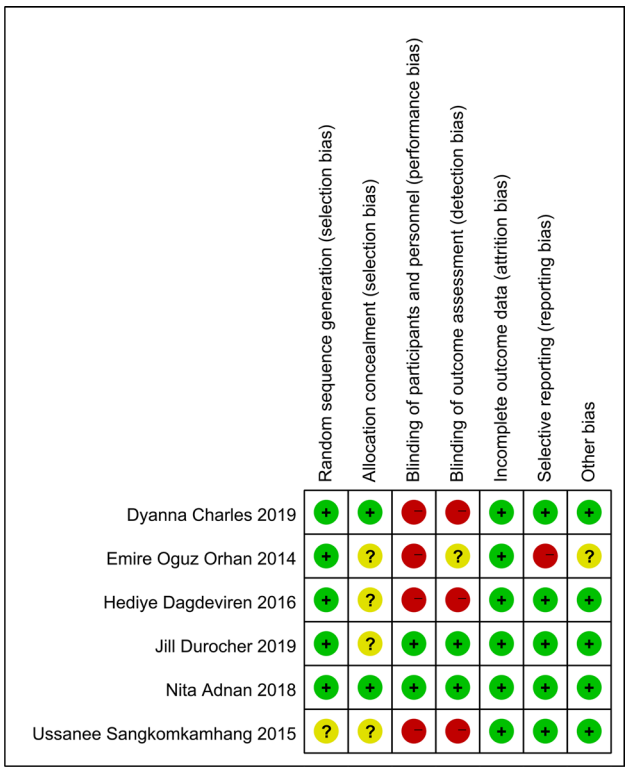

Fig. 9 Risk of bias summary: review authors' judgements about each risk of bias item for each included study

of allocation concealment [23, 26–28], whereas other two studies [24, 25] were low in risk of adopting opaque and sealed envelopes and using random permuted blocks of varying size. Only two studies [24, 28] were rated low in risk of performance bias and detection bias with two-blind technology used, whereas other four studies [23, 25–27] did not mention performance bias and detection bias, so lack of blinding may have had an impact on outcomes such as blood loss estimation. Only one study [27] may had reporting bias and other bias. All studies were low in risk of attrition bias.

Discussion

Overall completeness and applicability of evidence

In this analysis, the incidence of severe PPH, PPH, blood transfusion and manual removal of placenta were lower in IV group compared with IM group, while there were no significant differences in the use of additional uterotonics and the incidence of serious maternal morbidity between two groups. And none of the included studies reported maternal death. These results substantiate earlier findings [16, 18, 20] that both IV infusion and IV bolus administration of 10 IU of oxytocin were associated with significantly less average postpartum blood loss when compared to IM injection. Although IV administration have beneficial effects, but it requires sterile conditions, accurate dosing and protection from light which limit its use in poorly equipped areas [29]. When deciding which route to use, some other factors should be considered, including provider skill levels, available resources, and women' s preferences. For instance, if an IV line is already in place at delivery, IV infusion or IV bolus administration of oxytocin may be preferable to IM injection and may reduce the subsequent need for additional uterotonics. Conversely, if there is no IV line established, IM administration is likely the most efficient way to administer oxytocin safely after delivery of the baby. The short half-life and adverse effects of oxytocin affect the choice of route of administration. This trend is further supported by results from studies of prophylactic oxytocin showing that the most efficient route of oxytocin administration is slow intravenous infusion [4] or bolus infusion given in 1–2 min [30]. Because rapid injection of oxytocin has been reported to have some adverse effects (such as adverse cardiovascular effects, nausea, vomiting, chest pain, headache, etc.). In addition, the incidence of severe PPH and PPH depend upon the accurate measure of the amount of blood loss, but variable measurements and the time of collecting the amount of blood loss still remain among researches affecting this outcome [31]. Thus, the future studies should identify these problems. And it is necessary to publish more well-designed, high quality studies to further accurately evaluate the postpartum hemorrhage complications of intramuscular and intravenous injection of oxytocin on the third stage of labor.

In our study, there was no significant difference in the incidence of adverse effects between the two groups. But the risk of cardiovascular adverse events related to IV injection of oxytocin needs to be valued [32, 33]. Two studies have demonstrated that intravenously injected oxytocin can induce transient profound tachycardia, hypotension, chest pain and electrocardiogram changes

of myocardial ischemia [34, 35]. A report also showed the death of two women associated with cardiovascular instability was related to cardiac arrest after intravenous injection of 10 IU oxytocin [32]. However, a study about the Elective caesarean Section Syntocinon Infusion Trial indicated that circulatory disturbances occurred in otherwise healthy women due to regional anesthesia and not in response to intravenous bolus of oxytocin [36]. These results remind us of using oxytocin in women with unstable cardiovascular conditions (such as hypovolemia, shock, or cardiac disease) with caution. However, there is a paucity of data regarding the side effects of intramuscular oxytocin, probably because the usual adverse effects of intramuscular injection of oxytocin, including pain and abscess at the injection site, always occur in unsafe procedures and have few clinical importance.

Quality of the evidence

The studies contributing data to this analysis were at moderate risk of bias: four studies did not provide clear information about how allocation was concealed at the point of randomization, and three studies were at high risk of performance bias and detection bias. Because the use of blinding of participants and researchers is difficult. Two groups would have needed to receive a placebo injection, and the use of such placebos would cause additional discomfort for participants and may be unethical. The limitations of study design may induce the imprecision of outcomes. The future studies should give importance to study design (especially allocation concealment and blinding of outcome assessment) to improve the quality of the research evidence available.

Advantages and disadvantages of this study

As the interest in women-centered care is growing rapidly, we used a meta-analysis to comprehensively evaluate the efficacy and safety of intramuscular and intravenous injection of oxytocin in the third stage of labor. The advantages in this study include the use of a comprehensive search strategy, independent literature screening and data extraction. We also pay attention to adverse effects beyond effectiveness alone. However, there are following disadvantages: (1) there was a high risk of selection bias and detection bias due to not all studies reported allocation concealment and blinding of outcome assessment; (2) the inconsistence and inaccuracy in the measurements and observation time may affect the results of the study; (3) the intravenous injection of oxytocin was implemented inconsistently, such as different timing and form of administration.

Conclusion

For clinical practice, intravenous injection oxytocin 10 IU may be a good, safe option in the management of the third stage of labor, resulting in less frequent severe PPH, PPH, need for blood transfusion, and incidence of retained placenta, and without excess side effects. Moreover, recommendations on routes of administrating oxytocin should consider other factors, including medical conditions, available resources, adverse effects and women's preferences. If an IV line is already in place at delivery, IV administration of oxytocin may be preferable to IM injection in the third stage of labor. In addition, it is necessary to publish more researches to confirm this conclusion. It is worth noting that these findings should inform decision making when advising women on management options for the third stage of labor.

Acknowledgements The authors would like to thank the editors and reviewers for their suggestions.

Author contribution YW: literature searching, data collection and manuscript writing. HW: manuscript writing, data management, data analysis. QYW: data collection, data interpretation. XLL: literature searching. JW: conception, design and revise the manuscript.

Funding This study was supported by the National Natural Science Foundation of China (no. 81960278 and 81601351), and the Natural Science Foundation of the First Hospital of Lanzhou University (no. ldyyyn2018-52).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Bongaarts J (2016) WHO, UNICEF, UNFPA, World Bank Group, and United Nations Population Division Trends in Maternal Mortality: 1990 to 2015 Geneva: World Health Organization, 2015. Popul Dev Rev 42(4):726–726
2. Say L, Chou D, Gemmill A, Tunçalp O, Moller AB, Daniels J et al (2014) Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health 2:e323–e333
3. Bateman BT, Berman MF, Riley LE, Leffert LR (2010) The epidemiology of postpartum hemorrhage in a large, nationwide sample of deliveries. Anesth Analg 110:1368–1373
4. Department of Reproductive Health and Research WHO (2012) WHO Recommendations for the prevention and treatment of postpartum haemorrhage. World Health Organization, Geneva
5. World Health Organization (WHO) (2017) Managing complications in pregnancy and childbirth: a guide for midwives and doctors, 2nd edn. World Health Organization, Geneva
6. World Health Organization (2005) The World health report: 2005: make every mother and child count. http://www.who.int/whr/2005/whr2005_en.pdf. Accessed 24 Mar 2014

7. Westhoff G, Cotter AM, Tolosa JE (2013) Prophylactic oxytocin for the third stage of labour to prevent postpartum haemorrhage. Cochrane Database Syst Rev 10:CD001808
8. Sentilhes L, Goffinet F, Vayssiere C, Deneux-Tharaux C (2017) Comparison of postpartum haemorrhage guidelines: discrepancies underline our lack of knowledge. BJOG 124:718–722
9. FIGO Safe Motherhood and Newborn Health Committee (2012) Prevention and treatment of postpartum hemorrhage in low-resource settings. Int J Gynecol Obstet 117:108–118
10. RCOG (2017) Prevention and management of postpartum haemorrhage: green-top guideline No. 52. BJOG 124:e106–e149
11. ACOG (2017) Practice Bulletin No. 183: postpartum hemorrhage. Obstet Gynecol 130:e168–e186
12. World Health Organization (2018) WHO recommendations: uterotonics for the prevention of postpartum haemorrhage. World Health Organization, Geneva. Licence: CC BY-NC-SA 3.0 IGO.
13. Shields L, Lagrew D, Lyndon A (2015) Uterotonic medications for prevention and treatment of postpartum hemorrhage. 2015. CMQCC Obstetric Hemorrhage Toolkit, Version 2.0.
14. Oladapo OT, Okusanya BO, Abalos E (2018) Intramuscular versus intravenous prophylactic oxytocin for the third stage of labour. Cochrane Database Syst Rev 9(CD009332):1–42
15. Rashid M, Clark A, Rashid MH (2009) A randomised controlled trial comparing the efficacy of intramuscular Syntometrine and intravenous Syntocinon, in preventing postpartum haemorrhage. J Obstet Gynaecol 29(5):396–401
16. Sheldon WR, Durocher J, Winikoff B, Blum J, Trussell J (2013) How effective are the components of active management of the third stage of labor? BMC Pregnancy Childbirth 13:46
17. Dzuba I, Durocher J, Dilbaz B, Gelisen O, Ngoc NTN, Montesinos R et al (2012) Route of administration of oxytocin in prevention of postpartum hemorrhage. Int J Gynecol Obstet 119:S333
18. Prendiville WOCM (2006) Active management of the third stage of labor. In: Karoshi CB-LLGKABLM (ed) A textbook of postpartum hemorrhage, 1st edn. Sapiens Publishing, Duncow, p 462
19. Breathnach F, Geary M (2006) Standard medical therapy. In: Lynch CB, Keith LG, Lalonde AB, Karoshi M (eds) A textbook of postpartum hemorrhage: a comprehensive guide to evaluation, management and surgical intervention, 1st edn. Sapiens Publishing, Duncow, pp 256–262
20. Gibbens D, Boyd NR, Crocker S, Baumber S, Chard T (1972) The circulating levels of oxytocin following intravenous and intramuscular administration of Syntometrine. J Obstet Gynaecol Br Commonw 79:644–646
21. Moher D, Liberati A, Tetzlaff J, Altman DG (2010) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 8:336–341
22. Higgins JPT, Altman DG, Sterne JAC (ed) (2017) Chapter 8: assessing risk of bias in included studies. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (eds) Cochrane handbook for systematic reviews of interventions version 5.2.0 (updated June 2017), Cochrane
23. Dagdeviren H, Cengiz H, Heydarova U et al (2016) Intramuscular versus intravenous prophylactic oxytocin for postpartum hemorrhage after vaginal delivery: a randomized controlled study. Arch Gynecol Obstet 294(5):911–916
24. Nita A, Rebecca CT, Ciara MC et al (2018) Intramuscular versus intravenous oxytocin to prevent postpartum haemorrhage at vaginal delivery: randomised controlled trial. BMJ 362:k3546
25. Charles D, Anger H, Dabash R et al (2019) Intramuscular injection, intravenous infusion, and intravenous bolus of oxytocin in the third stage of labor for prevention of postpartum hemorrhage: a three-arm randomized control trial. BMC Pregnancy Childbirth 19(1):19–38
26. Sangkomkamhang U, Kruangpatee A (2015) A randomized controlled trial of intravenous versus intramuscular oxytocin in the prevention of postpartum hemorrhage during the third stage of labor. J Health Sci. 24(2):354–359
27. Oguz Orhan E, Dilbaz B, Aksakal SE, Altinbas S, Erkaya S (2014) Prospective randomized trial of oxytocin administration for active management of the third stage of labor. Int J Gynecol Obstet 127(2):175–179
28. Durocher J, Dzuba IG, Carroli G, Morales EM, Aguirre JD, Martin R et al (2019) Does route matter? Impact of route of oxytocin administration on postpartum bleeding: a double-blind, randomized controlled trial. PLoS ONE 14(10):e0222981
29. Miller S, Lester F, Hensleigh P (2004) Prevention and treatment of postpartum hemorrhage: new advances for low-resource settings. J Midwifery Womens Health 49:283–292
30. Davies GA, Tessier JL, Woodman MC, Lipson A, Hahn PM (2005) Maternal hemodynamics after oxytocin bolus compared with infusion in the third stage of labor: a randomized controlled trial. Obstet Gynecol 105(2):294–299
31. Tan J, Cao Q, He G-L et al (2016) Misoprostol versus ergometrine-oxytocin for preventing postpartum haemorrhage: a systematic review and meta-analysis of randomized controlled trials. J Evidence-Based Med. 9(4):194–204
32. Lewis G, Drife J (eds) Why mothers die 1997–1999. The fifth report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. RCOG
33. Thomas JS, Koh SH, Cooper GM (2007) Haemodynamic effects of oxytocin given as i.v. bolus or infusion on women undergoing Caesarean section. Br J Anaesth 98:116–119. https://doi.org/10.1093/bja/ael302
34. Charbit B, Funck-Brentano C, Samain E, Jannier-Guillou V, Albaladejo P, Marty J (2007) QT interval prolongation after oxytocin bolus during surgical induced abortion. Clin Pharmacol Ther 76:359–364
35. Svanström MC, Biber B, Hanes M, Johansson G, Näslund U, Bålfors EM (2008) Signs of myocardial ischaemia after injection of oxytocin: a randomized double-blind comparison of oxytocin and methylergometrine during caesarean section. Br J Anaesth 100:683–689
36. McLeod G, Munishankar B, MacGregor H, Murphy DJ (2010) Maternal haemodynamics at elective caesarean section: a randomised comparison of oxytocin 5-unit bolus and placebo infusion with oxytocin 5-unit bolus and 30-unit infusion. Int J Obstet Anesth 19:155–160. https://doi.org/10.1016/j.ijoa.2009.08.005