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Meta-analysis

Effect of Intra Umbilical Vein (IUV) Injection of Oxytocic Agents on Outcome of the Third Stage of Labor: A Meta-analysis

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ABSTRACT

Background: Active management of the third stage of labor can easily prevent life-threatening complications of the third stage such as retention of the placenta or its parts, prolonged duration, or postpartum hemorrhage due to atonicity of the uterus. Intraumbilical vein (IUV) injection of oxytocic agents is recommended by some guidelines. Unfortunately, intravenous (IV) oxytocin, although common practice, has not been compared with IUV oxytocic agents in reviews and meta-analysis. Therefore, the main objective of this meta-analysis was to compare the effects of IUV oxytocic agents with intramuscular (IM) and Intravenous (IV) oxytocics on outcomes of the third stage. **Materials and Methods:** The authors searched randomized and non-randomized control trials through electronic databases which include PubMed, Cochrane Library, and CINAHL and gray literature. The search terms were "umbilical vein injection," "intraumbilical vein injection," "umbilical vein oxytocin," oxytocin, uterotonic, placenta, "retained placenta," labor, "third stage of labor," and "postpartum hemorrhage." Five hundred and ninety-four articles were identified and nine met the inclusion criteria. Data were analyzed by Review Manager 5.3. **Results:** The pooled results reported that duration of the third stage was 1.23 minutes (95% confidence interval [CI]: 0.41–2.04) shorter, amount of blood loss was 79.09 ml. (95% CI: 46.90–111.28) lesser, and placental separation time was 37.69 seconds (95% CI: 0.58–74.80) shorter in the IUV oxytocin group than the IV oxytocin group. Comparison of IUV oxytocin and IV carbetocin shows no statistically significant differences. In comparison with IM oxytocin, IUV oxytocin also results in 1.13 min (95% CI: 0.28–1.97) shorter duration of the third stage of labor but not shows any significant difference for amount of blood loss. **Conclusion:** IUV oxytocin is more beneficial for reduction of duration of the third stage of labor, amount of blood loss, and placental separation time than the IV and IM oxytocin.

Keywords: Intraumbilical vein, Oxytocin, Postpartum hemorrhage, Retained placenta, Third stage of labor

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Introduction

A period between birth of fetus and delivery of the placenta along with membranes is known as third-stage of labor.[1-3] Many times third stage may cause serious complication for both mother and newborn.[4,5] If duration of the third stage exceeds 30 min, it may result in serious risk of postpartum hemorrhage, puerperal infection, and retained placenta.[2] In developing countries, about 25% of maternal mortality is caused by postpartum hemorrhage.[2,6] Retention of the placenta complicates approximately 0.1–3.3% of cases

globally, and the risk of recurrence may be as high as 16–23%.[5] The most common causes of these complications are uterine atony, retained placental pieces, coagulation disorders, tears of birth canal, multiple pregnancy, large baby, and age of mother <18 or >40 years.[6]

Active management of the third stage of labor (AMTSL) may prevent the said complications, which may include early administration of oxytocic agents,[3] controlled cord traction, and gentle massage over the uterine fundus after the delivery of the placenta and membranes.[7,8] Injecting ecbolic agent like oxytocin (to induce uterine contractions) through umbilical vein after delivery of the fetus is one of the proven interventions with low expenses. Intraumbilical vein (IUV) injection was first discovered in 1826 by "Nardin and Weeks."[9] The effect of umbilical vein oxytocics comparative to intravenous (IV) and intramuscular (IM) oxytocics on outcome of the third stage is controversial.

Results of previous studies about effects of different routes of administration of oxytocic agents on various outcomes of third-stage labor, i.e., overall duration of third-stage labor, time taken for placental separation and expulsion, and amount of blood loss had high confusions. As per the recommendation of NICE guidelines, oxytocin infusion can be given through the umbilical vessels to increase myometrial contraction.[1] However, after the development of this guideline, various randomized controlled trials (RCTs) and reviews reported no significant differences in results of intraumbilical oxytocin and placebo in rates of manual removal of the placenta and other outcomes such as postpartum hemorrhage and infection rate.[9,10] Even the IV infusion of oxytocin is the most common practice and has not been evaluated in reviews and not compared with IUV oxytocic agents.

In this context, the main goal of this meta-analysis is to evaluate the available evidence about the effect of various routes (IUV, IV, and IM) of oxytocic agent administration on outcomes of the third stage of labor, which will contribute to develop or revise existing guidelines for oxytocic agent administration for better outcome.

Objectives

The objective of this meta-analysis is to determine the effect of various routes (IUV, IV, and IM) of oxytocic administration in AMTSL.

Materials and Methods

Criteria for considering studies for this review

Types of studies

This meta-analysis included randomized or non-randomized control trials which compared umbilical vein injection of oxytocic agents with IV or IM oxytocic agents for the management of the third stage of labor.

Participants

All pregnant women undergoing vaginal delivery (with or without episiotomy) or cesarean delivery were included.

Types of interventions

1. IV oxytocin versus IUV oxytocin
2. IV carbetocin versus IUV oxytocin
3. IM oxytocin versus IUV oxytocin.

Outcome measures

We evaluated the following outcomes. We choose two primary outcomes and six secondary outcomes.

Primary outcomes

1. Duration of the third stage of labor
2. Amount of blood loss.

Secondary outcomes

1. Placental separation time
2. Placenta expelled spontaneously
3. Necessity of manual removal of the placenta
4. Time needed for placental expulsion
5. Requirement for additional uterotonics
6. Need for blood transfusion.

Search methods for identification of studies

In this review, the following databases were searched: PubMed, Cochrane Library, and CINAHL. In addition to this, we searched a list of references of identified studies, peer-reviewed articles, research gate, and Google Scholar to boost database searches. The review authors also searched various national and international journals and gray literature for unpublished studies. For identification of relevant articles, Rayyan QCRI was used to screen the duplicate articles and to segregate the included and excluded studies. After that, two authors independently assessed and reviewed each study to decide the suitability for final inclusion.

Information sources and search strategy

Studies were identified by searching the following keywords: "Umbilical vein injection," "intraumbilical vein injection," "umbilical vein oxytocin," oxytocin, uterotonic, placenta, "retained placenta," labor, "third stage of labor," "postpartum hemorrhage," and "postnatal hemorrhage." These keywords were combined by using Boolean operators "AND" and "OR" to narrow the search. The search of databases was done by two of the reviewers who had enough experience in search (Bishnoi and Devi).

Table 1: Inclusion and exclusion criteria for selection of studies

Inclusion criteria	Exclusion criteria
PICO Population: Pregnant women undergoing normal vaginal delivery (with or without episiotomy) and cesarean delivery Interventions: Umbilical vein injection of oxytocics Comparison: Traditional route of oxytocic administration (intravenous and intramuscular) Outcomes: Outcomes of the third stage of labor such as duration of the third stage of labor, amount of blood loss, and placenta expulsion time. Others Randomized and non-randomized clinical trials	Articles published in non-English languages Pilot study articles Specific kind of articles (conference presentations, case reports, and qualitative and observational studies)

Inclusion and excluded criteria

The eligibility criteria for inclusion or exclusion of articles are summarized in Table 1.

Assessment of risk of bias

The risk of bias of selected studies was evaluated with the guidelines given in the Cochrane Handbook. These criteria included six dimensions of risk of bias: Sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. The result of risk of bias assessment with this tool included low risk of bias, high risk of bias, and unclear or unknown bias.

Study selection and data extraction

Selection of studies

All the potential studies were independently assessed by two review authors (Bishnoi and Devi) for inclusion, which were retrieved by a planned search strategy. Any disagreement was resolved through discussion or, if required, by consulting a third reviewer (Desai).

Data extraction and management

A data extraction form was designed using Microsoft excel. The following data were extracted by two review authors (Bishnoi and Devi) from included studies: The authors, year of publication, study setting, study design, sample size, and inclusion criteria. The study identification and extraction of data were done from May 15, 2019, to June 20, 2019. Discrepancies were resolved by consulting a third person (Desai). We checked the data for accuracy and entered into RevMan 5.3. For unclear information, we tried to contact authors to get required details.

Data analysis

The retrieved data were analyzed by RevMan 5.3. The authors used risk ratio (RR) for dichotomous data and mean difference (MD) for continuous data with 95% confidence intervals (CI). We used Chi-square test to verify the presence of heterogeneity and inconsistency index (I^2) to describe the percentage of variation across studies. The I^2 explains the variability due to heterogeneity rather than the sampling error or chance difference. A substantial heterogeneity indicated if the value of I^2 is 50% or more and an I^2 value of 0% means no observed heterogeneity between the studies. For overall summary, a random-effects meta-analysis was used.

Results

Characteristics of included studies

Overall 449 studies were recovered after removal of duplicate articles, of which 43 studies were selected as being potentially eligible for final inclusion. All in all nine studies involving 1382 participants were incorporated in the meta-analysis [Figure 1]. All included studies were hospital-based and conducted in labor room and labor operation theater. The studies included pregnant women undergoing normal vaginal delivery or cesarean delivery and with a sample size ranging from 78[11] to 400.[4] Among the articles included in the analysis, four studies compared IUV oxytocin with IV oxytocin,[6,12-14] which favored IUV oxytocin administration for comparatively short length of the third stage of labor, less amount of blood loss, and less time needed for placental expulsion. Two studies compared IUV oxytocin with IV carbetocin,[5,11] and these studies have not reported statistically significant differences for outcomes of the third stage of labor. Three studies compared IUV oxytocin with IM oxytocin,[4,7,15] of which two studies[4,15] favor IUV oxytocin comparative to IM oxytocin for less time of the third stage of labor and less blood loss in the third stage of labor, but result of one study[7] shows contradictory results for these two outcomes. No study has reported the potential side effects of the drugs and route of administration. The studies were conducted in India,[4,6] Pakistan,[13] Nepal,[7] Iran,[12] Russia,[15] Saudi Arabia,[11] Egypt,[5]and Sri Lanka.[14]

Effects of interventions

Comparison 1: IV oxytocin versus IUV oxytocin

The comparison between IV oxytocin and intraumbilical oxytocin included four studies (489 samples) and three

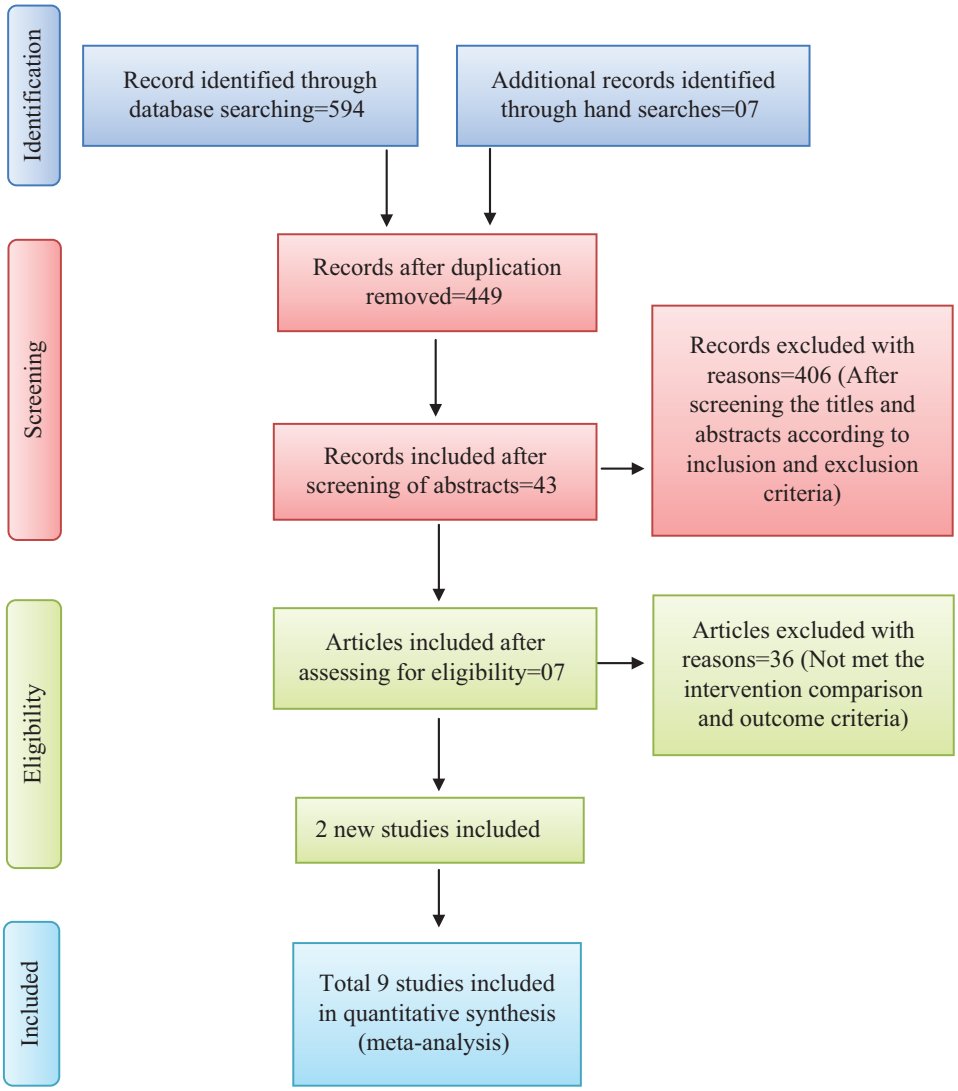

Figure 1: PRISMA flow diagram that depicts the phases of study selection

outcomes, of which outcome 1.1 (duration of the third stage of labor) was reported in two studies, outcome 1.2 (amount of blood loss) was reported in two studies, and outcome 1.3 (placental separation time) was reported in only one study.

IUV oxytocin was associated with a statistically significant reduction in duration of the third stage of labor (MD: 1.23 min, 95% CI: 0.41–2.04; 02 trials, 302 samples) [Figure 2] from the random-effects model with a substantial heterogeneity across the studies (χ^2 = 12.01; P = 0.0005; I^2 = 92%). This means that duration of the third stage was 1.23 min shorter in the IUV oxytocin intervention group than the IV oxytocin intervention group.

In this meta-analysis, IUV oxytocin was also found beneficial for reduction of amount of blood loss in the third stage of labor. The overall pooled MD for amount of blood loss from the random-effects model revealed 79.09 ml (95% CI: 46.90–111.28; 02 trials, 300 samples) [Figure 3] with a wide heterogeneity across the studies (χ^2 = 5.71; P = 0.02; I^2 = 82%). This indicates that women in the IUV oxytocin intervention group lost 79.09 ml less amount of blood than the IV oxytocin intervention group. Only study reported mean and standard deviation values for placental separation time, which shows that the IUV oxytocin intervention group was associated with 37.69 s less time for placental separation (95% CI: 0.58–74.80; 01 trial, 87 samples) [Figure 4] than the IV oxytocin intervention group.

Comparison 2: IV carbetocin versus IUV oxytocin

The comparison between IV carbetocin and intraumbilical oxytocin included two studies (268 samples) and five outcomes – 2.1: Placenta expelled spontaneously, 2.2: Need for manual removal of placenta, 2.3: Time needed for placental expulsion, 2.4: Need for additional uterotonics, and 2.5: Need for blood transfusion.

We found no overall statistically significant difference in number of spontaneous expulsion of placenta in the

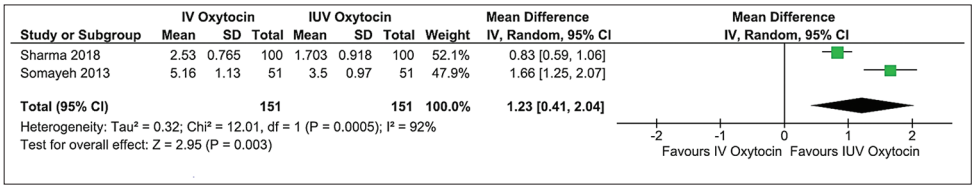

Figure 2: Duration of the third stage of labor

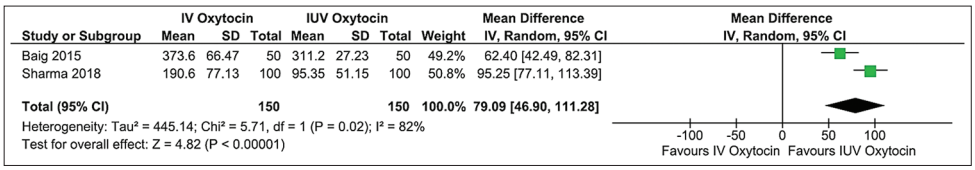

Figure 3: Amount of blood loss

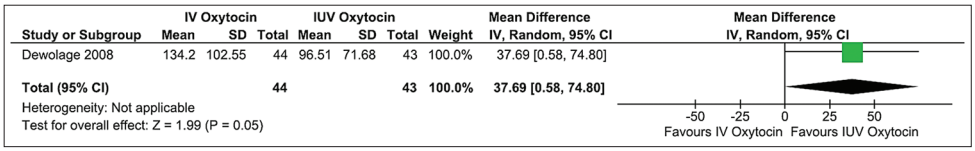

Figure 4: Placental separation time

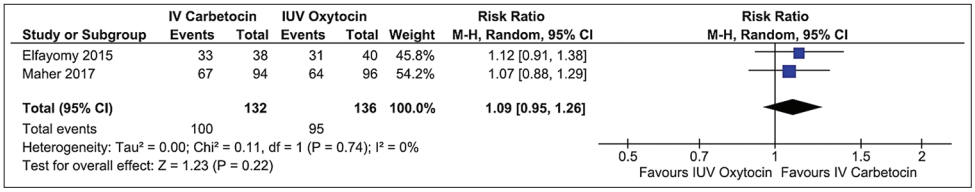

Figure 5: Placenta expelled spontaneously

IUV oxytocin and IV carbetocin groups (69.85% vs. 75.75%, RR: 1.09, 95% CI: 0.95–1.26; $I^2 = 0\%$, two trials) [Figure 5] from the random-effects model. Difference in need for manual removal of the placenta was also not found statistically significant from the random-effects model in the IUV oxytocin and IV carbetocin groups (27.20% vs. 22.72%; RR: 0.84, 95% CI: 0.56–1.26; $I^2 = 0\%$, two trails) [Figure 6].

We found no overall difference in time needed for placental expulsion in both the groups from the random-effects model (MD: 4.10; 95% CI: −1.93–10.14) [Figure 7] with substantial heterogeneity among studies ($\chi^2 = 4.11$; $P = 0.04$; $I^2 = 76\%$). Similarly, there was no statistically significant difference in additional requirements of uterotonics in the IUV oxytocin intervention and IV carbetocin intervention groups (11% vs. 5.30%; RR: 0.50; 95% CI: 0.21–1.20; $I^2 = 0\%$; two trials) [Figure 8] from the random-effects model, and we also not found any statistically significant difference in number of samples needed blood transfusion in the IUV oxytocin and IV carbetocin groups from the random-effects model (8.08% vs. 5.30%; RR: 0.67; 95% CI: 0.28–1.65; $I^2 = 0\%$) [Figure 9].

Comparison 3: IM oxytocin versus IUV oxytocin

This comparison included three studies (625 samples) and two outcomes: Duration of the third stage of labor and blood loss in the third stage of labor.

The pooled mean duration of the third stage of labor is presented in a forest plot [Figure 10]. The reported MD in duration of the third stage of labor is 1.13 min, (95% CI: 0.28–1.97) from the random-effects model with a substantial heterogeneity across studies ($\chi^2 = 30.72$; $P = <0.00001$; $I^2 = 93\%$). This indicated that duration of the third stage of labor was 1.13 min shorter in the IUV oxytocin group than the IM oxytocin group [Figure 10].

We found no overall difference in amount of blood loss in the third stage of labor in both the groups from the random-effects model (MD: 17.03; 95% CI: −8.50–42.55) [Figure 11] with substantial heterogeneity among studies ($\chi^2 = 13.57$; $P = 0.001$; $I^2 = 85\%$).

Discussion

Various clinical trials, systematic reviews, and meta-analysis of trials comparing IUV oxytocin (with or without

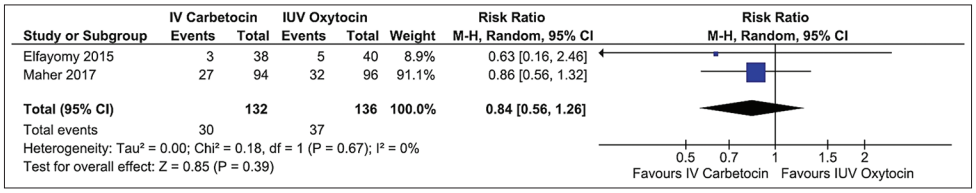

Figure 6: Need for manual removal of the placenta

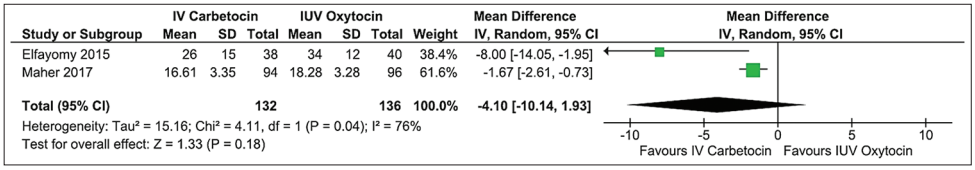

Figure 7: Time needed for placental expulsion

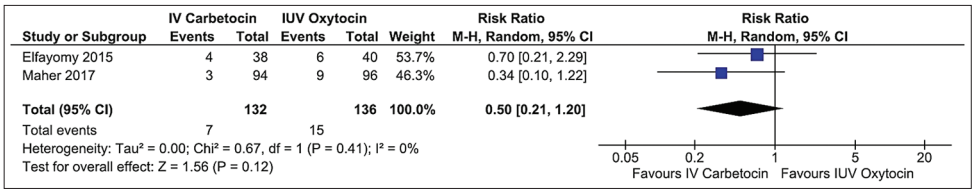

Figure 8: Need for additional uterotonics

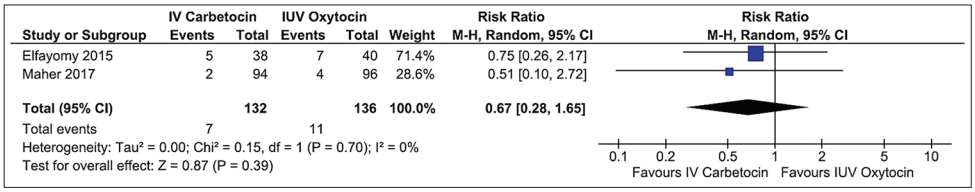

Figure 9: Need for blood transfusion

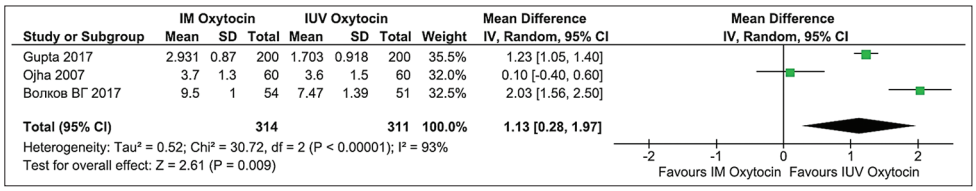

Figure 10: Duration of the third stage

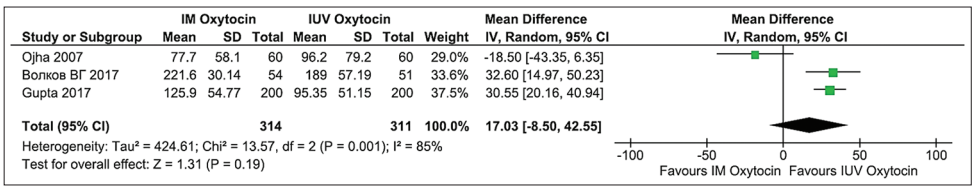

Figure 11: Blood loss in the third stage of labor

saline solution) with other drugs (prostaglandins, plasma expander, and saline solution) injected through IUV found compelling controversial evidences about IUV oxytocin improving outcomes of the third stage of labor such as blood loss, duration of the third stage of labor, placental separation and expulsion time, need for blood transfusion, need for manual removal of the placenta, and spontaneous expulsion of the placenta.[1,9,16,17] In this meta-analysis, we included nine trials to compare IUV injection route with conventional IM and IV routes for administration of oxytocic agents. Of which, four trials compared IUV versus IV oxytocin,[6,12-14] two trials compared IUV oxytocin with

IV carbetocin,[5,11] and three trials compared IUV versus IM oxytocin.[4,7,15]

The trials comparing IUV oxytocin with IV oxytocin found compelling evidence that IUV oxytocin is associated with a statistically significant reduction in duration of the third stage of labor, reduction in amount of blood loss in the third stage of labor, and low placental separation time. Trials comparing IUV oxytocin with IV carbetocin found no significant difference in both the intervention groups in pooled data for spontaneous expulsion of the placenta, manual removal of the placenta, time for placental expulsion, need for additional uterotonics, and need for blood transfusion, but at study level, both included studies significantly favor IV carbetocin over IUV oxytocin for less time needed for placental expulsion.

Further, in this meta-analysis, three trials included for comparison between IUV oxytocin and IM oxytocin. The overall pooled result of these studies favors IUV oxytocin over IM oxytocin for significant reduction in duration of the third stage of labor, whereas one trial[7] reported no significant difference in both interventions. These three studies do not show any statistically significant difference in amount of blood loss in the third stage of labor at pooled data level in forest plot, but at study level, two studies[4,15] significantly favor IUV oxytocin for reduction of blood loss in the third stage of labor, whereas one study[7]reported no significant difference in both interventions.

Limitation

This meta-analysis included only nine studies, so reviewers are no table to determine an effect size on all outcomes. We included randomized and non-randomized trials. In addition, these studies were based only on published peer-reviewed studies, and important data might be missed from unpublished studies.

Conclusion

This meta-analysis favors IUV oxytocin over IV oxytocin and IM oxytocin for reduction of duration of the third stage of labor, amount of blood loss, and placental separation time, but while compared to IV carbetocin, IUV oxytocin shows no significant difference for need for additional uterotonics, blood transfusion, time needed for placental expulsion, spontaneous expulsion of the placenta, and manual removal of the placenta.

Recommendations

Oxytocin is the most commonly used drug for the management of labor in all stages from augmentation of labor to prevention of postpartum hemorrhage. Therefore, health facilities may implement IUV oxytocin to their routine practice. Further some good quality large RCTs should be conducted to strengthen the evidence for optimization of routes of oxytocin administration for their beneficial effects and potential side effects. Well-designed economic evaluations are also needed to assess the cost-effectiveness of various routes of oxytocin administration.

Conflict of Interest

The authors declared that they have no conflict of interest.

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