Intravenous versus Intramuscular Oxytocin in the Prevention of Atonic Post-Partum Hemorrhage after Vaginal Delivery

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Taha Mahmoud Abd Elghany Said [1,*] M.B.B.Ch, **Mofeed Fawzy Muhamed** [2] MD and **Muhamed Ahmed Abdelmoaty** [2] MD.

*Corresponding Author:

Taha Mahmoud Abd Elghany Said

taha.mahmoud20794@yahoo.com

[1]*Resident of Obstetrics and Gynecology Department Elmonira General Hospital , Cairo, Egypt.*

[2]*Obstetrics and Gynecology Department, Faculty of Medicine, Al-Azhar University Cairo, Egypt.*

ABSTRACT

Background: Primary postpartum hemorrhage (PPH) is among of the most main sources of mother deaths throughout the world. The changed profile of laboring women, who are now more probable to be aged, overweighted, or have substantial clinical co-morbidities, is leading to an increase in obstetric difficulties.

Aim of the work: To evaluate the effects of a single dose of oxytocin (10 IU per 1 mL) administered either intramuscularly (IM) or intravenously (IV) on PPH, blood transfusions, and adverse effects during a natural birth.

Patients and methods: This randomized controlled experiment was carried out on 200 women who wanted to have a vaginal birth from 1/11/2021 to 1/3/2022. women were divided into two groups; IM Group: got intramuscular (IM) single dose of oxytocin (10 IU per 1 mL) and placebo IV administration (1 mL 0.9 % saline gradually administered). IV Group: got an IV single dose of oxytocin (10 IU per 1 mL administered gradually over 1 min) and placebo IM administration (1 mL of 0.9 percent saline).

Results: severe postpartum hemorrhage and blood transfusion were significantly more frequent in intramuscular group compared to intravenous group.

Conclusion: In comparison to intramuscular oxytocin, intravenous oxytocin causes less severe PPH, blood transfusions, and induction to a critical care unit at the third phase of labor, and has fewer adverse effects.

Keywords: *hemorrhage; maternal mortality; Primary postpartum; Vaginal Delivery.*

INTRODUCTION

Obstetric difficulties are on the rise due to the shifting characteristics of laboring women, who are increasingly more probable to be aged, overweight, or have substantial clinical co-morbidities.[1]

Maternal weariness, lactating problems, anemia, blood transfusions, and the hazards related to obtaining donor blood products are all PPH-related morbidities. It may result in urgent operation, hospitalization to an intensive care unit, or mortality in extreme situations. [2]

According to recent estimates of worldwide maternal deaths, about 300,000 women died each year at gestation and delivery, the majority of whom are from poor nations.[3]

Uterine atony is the greatest prevalent actual reason of PPH.[4]

Over the course of 11 years, a population-based cohort research in Ireland found changes in atonic postpartum bleeding. The total PPH rate among hospital-based births was reported to have grown significantly from 1.5 percent in 1999 to 4.9 percent in 2009. Vaginal and instrumental births, as well as Cesarean section deliveries, all showed an elevation in atonic PPH rates. Importantly, the number of women requiring blood transfusions increased significantly, indicating an increase in more extreme atonic PPH that is improbable to be due to earlier under-reporting. The study's authors suggested that the active treatment of the third phase of labor be evaluated further. [5]

Oxytocin lowers the PPH risk by 60% and the requirement for therapeutic oxytocics by 50%.[6]

The intramuscular (IM) technique has the advantage from being easy to use and needing no prior training. The uterine impact happens 3–7 minutes after the IM administration and lasts 30–60 minutes. The uterine reaction is nearly rapid with IV treatment, within 1 minute or less, compared to IM injection, which has a later beginning of effect but a prolonged lasting impact. [7]

In accordance with RCOG standards, a new strategy was created, proposing the IM administration of 10 IU oxytocin. Established practitioners expressed concerns about an increased risk of bleeding when using the IM route, leading to a shift in practice. This was a great situation for a randomized controlled experiment (RCT). In compliance with worldwide PPH prevention recommendations, we selected to evaluate oxytocin 10 IU delivered by IV versus IM administration. [4]

In a double-blind controlled experiment, to examine the impact of an IM single dose of oxytocin (10 IU per 1 mL) and placebo IV administration (1 mL 0.9 % saline gradually administered) with an IV single dose of oxytocin (10 IU per 1 mL administered gradually over 1 min) and placebo IM administration (1 mL 0.9 % saline) during natural birth.

PATIENTS AND METHODS

This study was Sample size justification done in EL Hosain hospital Al Azhar University for 200 women who wanted to have a vaginal birth from 1/11/2021 to 1/3/2022

Ethical consideration and study approval: The study process was approved by the Research Ethics Committee of Al Azhar University's Faculty of Medicine. All data was kept confidential. All participants had the right to withdraw from the study without affecting their management. Informed written and vocal consents were taken from all the participants before taking any data or doing any investigations.

Inclusion criteria: Age from 18 to 37 years old, singleton pregnancy, full term pregnancy of > 36 weeks, normal body mass index (BMI) (18.5 to 24.9 kg/m2) and no contraindication for vaginal delivery or oxytocin.

Exclusion criteria: If a woman desired physiological control of third phase of labor, she was ruled out. Women having a prior past of postpartum bleeding owing to an atonic uterus, identified fibroids, a past of coagulopathy undergoing anticoagulation treatment, and thrombocytopenia were considered to be at an elevated risk of postpartum bleeding. Women having a history of cardiovascular disorder, as well as those under the age of 18, were excluded.

B. Operative Design:

Randomization: Randomization was performed using an automated web-based randomization system.

Allocation: was divided by parity (nulliparous/multiparous) and blocked utilizing random permuted blocks of varied sizes.

Blinding: The research fellow divided the drug and placebo into two separate sterile 2-mL syringes after randomization and allocation. In accordance with the hospital's procedure of drafting up drugs, the midwife in duty of the female's care in the labor room double-checked this. The syringes were randomly assigned and labeled outside the room. Drug 1-IM or Drug 2-IV injecting syringes were labeled and went back to the midwife in the birthing room. This was done to guarantee that everyone was blinded save the research fellow, who had no involvement in the patient's care.

Intervention: Women were told about the research in outpatient clinics prior to their pregnancy; formal recruiting and written permission were obtained when women presented to the evaluation unit with symptoms and indications of initial labor or were hospitalized for inducement. Following written informed permission, the participant's file was labeled with a trial sticker to notify her care providers, such as midwives and obstetricians, that she was taking part in the research.

Every patient was exposed to: Complete history taking: Personal history, any complaint, obstetric history, past medical and past surgical history and family history, physical examination and general check-up: Vital signs (Temp, Blood Pressure, Heart Rate, and Breathing Rate).

At the same time, a sample was obtained for a complete blood count. When nulliparous women were diagnosed with the second phase of labor, they were randomly allocated.

Following randomization, the lady was given either IM oxytocin 10 IU and a placebo (1 mL 0.9 percent normal saline) IV, or IV oxytocin 10 IU gradual bolus over 1 minute and a placebo (1 mL 0.9 percent normal saline) IM.

Name of the medicinal product: Syntocinon 10 IU/mL infusion or injectable solution.

Name of placebo: Sodium chloride injection, 0.9 percent w/v BP.

The drug and placebo were prepared in two separate sterile 2-mL syringes by the study team. The syringes were randomly assigned and labeled outside the room. Drug 1-IM or Drug 2-IV injection were written on the syringes.

The midwife in duty of the woman's care in the labor unit was handed the syringes with the labels Drug 1-IM and Drug 2-IV. Following the delivery of the infant, the IM syringe was given first, then the IV syringe. The midwife and the laboring lady were both unaware of the treatment assignment.

Experimental arm: IV oxytocin and a placebo uterotonic drug were used in this study. 1 mL 0.9 percent normal saline was IM injected into the thigh muscle immediately after birth, ideally within 1 minute of birth, Then, using a cannula, oxytocin 10 IU was delivered IV gradually over 1 minute.

Standard arm: IM oxytocin and a placebo uterotonic drug were used in this study. oxytocin 10 IU was IM administered into the thigh muscle and 1

mL 0.9 percent normal saline was given by IV via the cannula shortly after the baby was born, ideally within 1 minute. The umbilical cord clamping and delivering placental procedures were identical to those used in the experimental arm. The sole difference between the two therapies was the method of giving oxytocin and the placebo. Direct blood collecting and the gravimetric approach were used to assess blood loss after vaginal births.

The surgical drape containing the blood was weighed. The known dry weight of the swabs and drapes was deducted from the weight of blood-soaked swabs and extra drapes. The estimated blood volume from the surgical drape was added to this amount.

Fig. 1: Postpartum blood collection after the vaginal delivery

Any blood loss that occurred within 24 hours after birth was documented. For women who were transferred to the postnatal ward early or late, there was a variation in blood loss estimations based on various blood loss collection lengths. This possible drawback was addressed by reporting any considerable further blood loss within 24 hours after birth.

After birth and before transfer to the postnatal unit, the mother's vital signs were recorded. Side effects were seen and reported. A record of deviations from the usual process was kept. In the event that the uterus remained atonic despite the trial intervention, the obstetrician/midwife/anesthetist utilized any further uterotonic medication as directed by the hospital postpartum bleeding strategy.

Follow-up: On the first day (24 hours) following birth, a thorough blood count was conducted to determine hemoglobin and hematocrit levels. The mother's clinical follow-up was completed prior to her release from the hospital.

Outcomes

Primary outcomes: PPH (measured blood loss > 500 mL) is the main endpoint. A clinically relevant result of ≥ 500 mL was selected to facilitate direct comparisons with other trials. It was commonly acknowledged that doctors underestimate rather than exaggerate blood loss, thus instead of relying on subjective estimations, we officially quantified blood loss for this investigation.

Secondary outcomes: Secondary findings included the frequency of negative consequences after oxytocin administering, median estimated blood loss, main obstetric bleeding (evaluated loss ≥1000 mL), change in hemoglobin and hematocrit, considerable anemia (Hb fall ≥20%) 24 hours after delivering, need for blood transfusion, duration of post birth hospitalization, and the require for an extra uterotonic agent. Hypotension was described as a reduction in blood pressure of more than 30% below pre-delivery values, as well as the use of ephedrine, and tachycardia as a heart rate of more than 100 beats per minute.

Statistical Analysis: The trial statistician and researcher were blinded to the group status and performed data evaluation and report according to CONSORT criteria for RCTs. SPSS software was utilized for data input and analysis (SPSS 20.0 Version). The average, proportion, and percentage will all be computed. The Chi square test was performed to determine whether or not there was a link.

RESULTS

	Intravenous (n=100)	Intramuscular (n=100)	t	P
Age (years) Mean ± SD	28.39 ± 3.16	28.65 ± 2.87	.609	.543
BMI (kg/m^2) Mean ± SD	26.84 ± 3.1	27.35 ± 2.31	1.32	.189
Parity Mean ± SD	2.15 ± 1.1	2.06 ± 1.24	MU .295	.628
GA (weeks) Mean ± SD	38.59 ± 1.52	38.73 ± 1.48	.569	.510

Table 1: Demographic and clinical features of the examined groups
There are no substantial differences between groups in terms of mother age, BMI, parity, and GA. Table (1)

	Intravenous (n=100)	Intramuscular (n=100)	t	P
Hemoglobin (g/dl) Mean ± SD				
Pre labor	10.78 ± 1.42	10.91 ± 1.37	.659	.511
Post labor	9.61 ± 0.952	9.27 ± 0.949	**2.53**	**.012**
P	**<0.001**	**<0.001**		
HCT (%) Mean ± SD				
Pre labor	31.78 ± 2.16	31.62 ± 2.23	.515	.607
Post labor	29.71 ± 1.57	29.34 ± 1.62	1.64	.103
P	**<0.001**	**<0.001**		

Table 2: Hemoglobin and HCT levels pre and post labor between the studied groups.

There is a substantial variation between the groups regarding post labor hemoglobin only. Moreover, there is a substantial reduce in hemoglobin and HCT post labor in both groups. Table (2)

	Intravenous (n=100)	Intramuscular (n=100)	χ^2	P
Postpartum hemorrhage	20 (20%)	25 (25%)	.717	.397
Severe Postpartum hemorrhage	3 (3%)	10 (10%)	4.03	.045
Blood loss (mL) Mean ± SD	392.4 ± 298.7	454.2 ± 409.5	MU 497	.037
Blood transfusion	3 (3%)	12 (12%)	5.84	.016

Table 3: Outcome between the two studied groups

Severe postpartum hemorrhage and blood transfusion were substantially more frequent in intramuscular group compared to intravenous group. Moreover, blood loss was substantially greater in intramuscular group compared to intravenous group. Table (3)

		Intravenous (n=100)	Intramuscular (n=100)	t/ χ^2	P
Birth weight (kg) Mean ± SD		3.12 ± 0.563	3.06 ± 0.709	.663	.508
Mode of delivery	Male	54 (54%)	51 (51%)	.181	.671
	Female	46 (46%)	49 (49%)		
Apgar at 1 min Mean ± SD		7.23 ± 1.27	7.18 ± 1.16	.291	.772
Apgar at 5 min Mean ± SD		9.7 ± 1.09	9.81 ± 1.13	.701	.484

Table 4: Neonatal characteristics between the two studied groups

There is no substantial variation between the groups regarding neonatal characteristics. Table (4)

	Intravenous (n=100)	Intramuscular (n=100)	χ^2	P
Side effects	6 (6%)	8 (8%)	.307	.597
Need for additional uterotonic agent	24 (24%)	28 (28%)	.416	.519
Need for additional surgical procedure	3 (3%)	6 (6%)	1.05	.308
Admission to ICU	2 (2%)	6 (6%)	2.08	.149
Prolonged hospital stay > 3 days	10 (10%)	12 (12%)	.204	.651
Hemoglobin decrease > 20% 24-hours after delivery	18 (18%)	20 (20%)	.130	.719

Table 5: Complications between the two studied groups

Complications were comparable in both groups without statistically substantial variation. Table (5)

	Intravenous (n=100)	Intramuscular (n=100)	χ^2	P
No side effects	94 (94%)	92 (92%)	.307	.579
Nausea & vomiting	1 (1%)	2 (2%)	.338	.561
Hypotension	3 (3%)	5 (5%)	.521	.471
Tachycardia	2 (1%)	4 (4%)	.687	.407
Headache	1 (1%)	2 (2%)	.338	.561
Shivering	1 (1%)	3 (3%)	1.02	.315

Table 6: Side effects distribution between the two studied groups

The side effects were comparable in both groups without statistically substantial variation. Table (6)

DISCUSSION

The intravenous route's fast action may reduce the incidence of PPH, but it has been linked to cardiovascular adverse impacts such tachycardia and hypotension. prophylaxis oxytocin, efficient at any dosage range from 3 IU to 10 IU, reduces the incidence of PPH by 50-60% when compared to placebo, according to Cochrane systematic studies. After birth, the Royal College of Obstetricians and Gynaecologists (RCOG) advises IM bolus dosage of oxytocin 10 IU, whereas the World Health Organization suggests oxytocin 10 IU IM or by gradual IV administration. [8]

in a double-blind controlled experiment, to examine the impact of an IM single dose of oxytocin (10 IU per 1 mL) and placebo IV administration (1 mL 0.9 % saline gradually administered) with an IV single dose of oxytocin (10 IU per 1 mL administered gradually over 1 min) and placebo IM administration (1 mL 0.9 % saline) during natural birth.

In terms of maternal age, BMI, parity, and GA, there is no substantial variation in the groups. regarding history and clinical features, there is no substantial variation between the groups.

Our results were in agreement with study of Adnan et al., [9] as they reported a sum of 11 ladies (8 in the IV group and 3 in the IM group). About 30% of the women were 35 or older, 12% were obese, and about half were nulliparous. In terms of mother age, BMI, and parity, there was no considerable distinction between the groups. regarding history and clinical features, there was no considerable distinction between the groups.

Similarly, Dagdeviren et al., [10] revealed that They gathered a total of 256 volunteers, with 128 receiving IM oxytocin and 128 receiving IV oxytocin. Sixty-

four of these instances were removed because they did not fulfil the criteria for inclusion. The ladies who took part in this research varied in age from 18 to 43 years old, with an average age of 25.7 years. The patients' parity varied from one to six. The gestational age was determined from the first day of the previous menstrual cycle and varied from 37 to 41 weeks.

In terms of maternal age, BMI, parity, and GA, there was no substantial variation between the groups.

Our findings revealed no substantial differences between the groups in terms of pulse, SBP, or DBP.

Our results were supported by study of Dagdeviren et al., [10] as they reported that the antepartum and postpartum blood pressures groups were not statistically different.

The current study showed that only in terms of post-labor hemoglobin, there is a substantial variation between the groups. Furthermore, both groups had a considerable reduction in hemoglobin and HCT after childbirth.

However, in the study of Dagdeviren et al., [10] regarding prepartum Hb levels (p = 0.349) or postpartum Hb drop (p = 0.941; p > 0.05), there were no statistically substantial variations between the two groups. This conclusion is consistent with Davies et al. [11] findings.

In the study of Adnan et al., [9] In each group, the prevalence of severe anemia (a ≥20% reduction in hemoglobin concentration) was comparable with the documented prevalence of PPH. Hematological indicators before and after delivery showed small non-significant changes across the groups, which might represent the intramuscular group's increased rate of blood transfusion.

Also, Dagdeviren et al., [10] revealed that in the intramuscular group, episiotomy was done in 46 women (35.9%), whereas in the intravenous group, it was conducted in 53 women (41.4%). In each group, there was a third/fourth degree perineal tear. In the early phase of birth, oxytocin was administered intramuscularly to 18 patients and intravenously to 28 patients in the IM and IV groups, respectively. In the IV group, the requirement for further uterotonic treatments to avoid PPH was considerably greater than in the IM group (p = 0.033; p <0.05). Furthermore, no statistically substantial differences were seen in the two groups in terms of labor length, third-phase labor duration, excision of the placenta by hand, or the necessity for instrumental delivery.

In comparison to the intravenous group, serious postpartum bleeding and blood transfusion were substantially more prevalent in the intramuscular group. Furthermore, blood loss in the intramuscular group was much greater than in the IV group.

In the study of Adnan et al., [9] PPH was shown to be less common in the IV group than in the IM group (18.8% vs. 23.2%), although the variation was not statistically substantial (exact variance 4.4 percent, modified odds ratio 0.75, 95 percent confidence interval 0.55 to 1.03). The risk of extreme PPH was substantially smaller in the IV group than

in the IM group: 4.6 percent vs. 8.1 percent (modified odds ratio 0.54, 95 percent confidence interval 0.32 to 0.91), as was the necessity for blood transfusion (1.5 percent v 4.4 percent, 0.31, 0.13 to 0.70). The number of people who needed to be treated to avoid one serious case of PPH was 29 (95 percent confidence range 16 to 201), and the number of people who needed to be treated to avoid one blood transfusion was 35. (20 to 121).

In the study of Begley et al., [12] They comprised seven trials that compared active managing of the third phase of labor versus physiological managing employing a variety of uterotonic medication like ergometrine, symmetrize, IM oxytocin, and IV oxytocin. Regardless of the drug employed, active treatment was linked to a decreased prevalence of PPH, however none of the trials had a better-quality rating.

According to a study by Westhoff et al., [8] prophylactic oxytocin at any dosage reduced PPH more than 500 mL in 20 trials comparing it to placebo or other treatments. The authors suggested using the IV route, which had the most support, with the IM route as a backup, and noted that further high-quality research was needed.

Oladapo et al. [13] presented a Cochrane review that found no randomized controlled studies that explicitly compared IM oxytocin with IV oxytocin for the avoidance of PPH during natural birth (published or unpublished).

Oguz Orhan et al., [14] reported that an IV oxytocin infusion of 10 IU in 1 L normal saline given at a ratio of 1 mL/min was comparable to IM oxytocin 10 IU in a trial of 256 women. The doctors, patients, and investigators were not blinded, and no change in estimated blood loss or PPH was identified.

The present investigation discovered that there is no substantial variation in newborn features across the groups.

In accordance with our results study of Adnan et al., [9] as they reported that In terms of newborn sex and high birthweight infants, there was no substantial variation between their study groups (≥4000 g).

Similarly, Dagdeviren et al., [10] demonstrated that There was no substantial variation between their study groups when it came to fetus weight at birth, which varied from 1905 to 4360 g.

Our results showed that complications were equivalent in both groups without a statistically substantial variation, according to our findings. There was no substantial distinction in adverse effects between the two groups.

Our results were supported by study of Adnan et al., [9] as they reported that The frequency of oxytocin adverse reactions was not higher in the intravenous group (4.1 percent v 5.2 percent, modified odds ratio 0.75, 95 percent confidence interval 0.42 to 1.35) than in the intramuscular group (table 3). Hypotension and tachycardia were the most common side effects, as predicted with oxytocin, and no major medication responses occurred.

Similarly, Dagdeviren et al., [10] stated that There was no statistically substantial variation in both groups for the adverse consequences of oxytocin, which includes shivering, nausea and/or vomiting, pyrexia, and tachycardia, within the first 24 hours postpartum.

Chest discomfort, temporary severe tachycardia, hypotension, and ECG abnormalities indicative of myocardial ischemia have all been reported after receiving oxytocin intravenously. Furthermore, there is a scarcity of data on the adverse consequences of injectable oxytocin, owing to the fact that there are rarely clinically significant side effects. When safety protocols are not followed, however, the standard adverse consequences of any IM administration, such as discomfort at the administration site and abscesses at the injections site, are to be anticipated. [15]

CONCLUSION

Oxytocin is the gold standard uterotonic drug, and numerous clinical trials have suggested it as the first-line preventive treatment against PPH. In comparison to intramuscular oxytocin, intravenous route causes less severe PPH, blood transfusions, and admittance to a high-dependency unit during the third phase of labor and has fewer adverse effects. These results should be utilized to help decision-making when counseling women on third-stage pregnancy managing alternatives.

Conflict of interest : none

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