Prevention of postpartum hemorrhage, safety and efficacy

Adnan A. Abu-Omar, *MD, JB(Obs & Gyn).*

ABSTRACT

Objective: This study was carried out to describe the safety and efficacy of intramuscular syntometrine (oxytocin plus ergometrine) compared to intravenous oxytocin for prevention of postpartum hemorrhage, and the difference between administration at the end of the 2nd stage of labor compared with that after delivery of the placenta.

Methods: A prospective study was carried out at Prince Zaid Ben Al–Hussein Hospital, Tafilah, Jordan. Two thousand one hundred and sixty one women delivering singletons during 12 consecutive months were included in our study. Women received either intramuscular syntometrine (oxytocin plus ergometrine) or oxytocin alone. The drugs were used either before or after the 3rd stage of labor, in order to compare their safety and efficacy in prevention of postpartum hemorrhage.

Results: There was no significant difference in the rate of postpartum hemorrhage for syntometrine compared with oxytocin, when used at the end of the 2nd stage of labor (odds ratio 1.08, 95% confidence interval 0.72-1.63) or after the 3rd stage (odds ratio 0.93, 95% confidence interval 0.65-1.34). The patients receiving oxytocics at the end of the 2nd stage of labor had significantly lower rates of postpartum hemorrhage, for both syntometrine (odds ratio 0.86, 95% confidence interval 0.59-0.1.12) and Oxytocin (odds ratio 0.59, 95% confidence interval 0.39-0.88), compared with those treated after the 3rd stage.

Conclusion: Oxytocin alone is as effective as the use of syntometrine (ergometrine plus oxytocin) in the prevention of postpartum hemorrhage, but associated with significantly fewer maternal side effects. Oxytocics administered after the 2nd stage of labor compared with after the 3rd stage of labor (placental expulsion) are associated with a significantly fewer rate of postpartum bleeding.

Keywords: Postpartum hemorrhage, syntometrine, oxytocin, end of 2nd stage of labor, 3rd stage of labor, safety, efficacy.

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The use of oxytocic preparations is an important as part of the active management of the 3rd stage of labor. Routine administration of oxytocic drugs has been found to decrease the rate of postpartum bleeding by 38%.[1] However, there is no agreement regarding the type and route of administration of oxytocic drugs which offers the best efficacy and safety profile. Several controlled trials examining the alternative oxytocic preparations used routinely in the management of the 3rd stage of labor suggested that a mixture of oxytocin and ergometrine (Syntometrine) might be the drug of choice.[2] They commented that the quality of evidence was not satisfactory and thus concluded that there was scope for a controlled comparison of oxytocin plus ergometrine compared with oxytocin alone. This trial would provide important and more precise estimates of the relative effects on postpartum hemorrhage, blood pressure and other maternal side effects.[2] Previous studies[3-5] revealed a small decrease in the rate of postpartum bleeding when syntometrine was used compared with oxytocin.[6] Subsequently, Mitchell et al[7] and MacDonald et al[8] published the results of controlled trials in which they found that

From the Department of Obstetrics and Gynecology, Royal Medical Services, Jordan.

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Address correspondence and reprint request to: Dr. Adnan Abu-Omar, Department of Obstetrics and Gynecology, Royal Medical Services, PO Box 180, Maan, Jordan. Tel. +962 (3) 2131226. E-mail: drabuomarjo@yahoo.com

intramuscular oxytocin was as effective in preventing postpartum hemorrhage as intramuscular syntometrine, but associated with less maternal side effects such as nausea, vomiting, and increase blood pressure. Both trials studied the use of oxytocin used intramuscularly. A more recent trial[9] also used intramuscular administration but, in contrast, found that the syntometrine was significantly more effective than oxytocin, with a low rate of side effects in both groups. Although intramusculare route is primarily used in developing countries, oxytocin is currently mainly given via the intravenous rout in the United States of America and other Western countries. We conducted a prospective study in which women received either intramuscularly syntometrine or intravenous oxytocin. The drugs were used either before or after the 3rd stage of labor, to compare the safety and efficacy in prevention of postpartum bleeding.

Methods. This study was conducted at Prince Zaid Military Hospital in the south of Jordan during a one year period from 1 January 1997. During this period, women delivering singletons by vaginal route were included in our study. Women having any contra-indication for receiving oxytocic drugs such as hypertension, cardiac disease were excluded from our study. Oxytocin infusion, used for augmentation of labor, was stopped before the end of the 2nd stage in all cases. Four treatment protocols were used based on a temporal manner, each given exclusively over a 3-month period. The women were thus assigned to receive either intramuscular syntometrine (oxytocin 5 IU plus ergometrine 0.5 mg) first and 2nd study periods or intravenous oxytocin 10 IU 3rd and 4th study periods. The oxytocics were administered either after the end of the 2nd stage first and 3rd study periods or following 3rd stage of labour a 2nd and 4th study periods. Since all 4 protocols had previously been used in our department, it was thought to be ethically and scientifically justified to carry out this study in order to compare their efficacy and safety. During the study period, the 3rd stage of labor was managed by clamping the cord within 30 seconds after delivery. Traction was applied to the cord only after signs of separation of the placenta. If the placenta was not completely delivered within 60 minutes, manual removal of the placenta was performed by doctor.

Blood collection was carried out by covering the area below the mother's lower body with plastic sheets, which drained into a basin. Blood loss was carefully determined using a measuring receptacle. This method of blood loss determination suffers some degree of underestimation due to blood lost in swabs. Overestimation is also possible as a result of blood being diluted by amniotic fluid. Yet, this inaccuracy should not be influenced by the treatment protocol. Data was prospectively collected using a sheet, which was attached to the patient's obstetric chart and completed by the attending midwife at the delivery room, and the nurse in charge at the maternity ward.

A pilot study was undertaken prior to the actual study, in order to allow the midwives to become accustomed to the blood collecting technique and the use of the patient's data sheet. The statistical significance was determined using one-way ANOVA test (analysis of variance).

Results. A total of 2161 vaginal singletons deliveries took place during the study period 12 months starting from the 1st of January 1997. There were no significant differences between the 4 study groups (maternal age, gestational age and parity) Table 1. Oxytocin augmentation of labour, operative

Table 1 - Maternal and labor management characteristics in the 4 study groups.

	Syntometrine		Oxytocin	
Characteristics	**End of the 2nd stage labor n=630**	**After the 3rd stage of labor n=539**	**End of the 2nd stage of labor n=519**	**After the 3rd stage of labor n=473**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Age (years) mean (SD)	26.3 (7)	28.5 (6.5)	27.8 (6)	25.8 (7)
Gestational age (weeks), mean (SD)	40.2 (1.5)	39.9 (1)	40.3 (1)	40.3 (1)
Instrumental delivery	46 (7)	37 (7)	43 (8)	31 (7)
Oxytocin augmentation	298 (47)	265 (49)	273 (53)	223 (47)
Primipara	82 (13)	69 (13)	69 (13)	66 (14)
Multipara	548 (87)	470 (87)	450 (87)	407 (86)

n=number, SD=standard deviation

Table 2 - The outcome variables after the administration of syntometrine or oxytocin at the end of the 2nd stage of labor.

Variables	Intramuscular Syntometrine n=630 n	%	Intravenous Oxytocin n=519 n	%	Odds ratio (95% CI)
Blood loss >500 ml	64	(10.1)	49	(9.4)	1.08 (0.72-1.63)
Blood transfusion	4	(0.95)	4	(0.7)	0.82 (0.17-3.92)
Nausea & Vomiting	139	(22.1)	35	(6.7)	3.91 (2.60-5.91)
3rd Stage > 30 min	30	(4.7)	25	(4.8)	0.99 (0.56-1.76)
Tachycardia > 100 bpm	16	(2.5)	25	(4.8)	0.51 (0.26-1.01)
Hypertension	45	(7.1)	15	(2.8)	2.58 (1.38-4.91)
Chest pain	26	(4.0)	1	(0.2)	22.30 (3.23-443.34)
Shortness of breath	13	(2.1)	4	(0.7)	2.71 (0.82-9.90)
Excessive sweating	18	(2.8)	0	-	-

n=number, CI=confidence interval, BPM=beats per minute

Table 3 - The outcome variables after administration of syntometrine or oxytocin following the 3rd stage of labor.

Variables	Intramuscular Syntometrine n=539		Intravenous Oxytocin n=473		Odds ratio (95% CI)
Blood loss >500 ml	76	(14.1)	71	(15)	0.93 (0.65-1.34)
Blood transfusion	5	(0.9)	5	(1.0)	0.88 (0.23-3.50)
Nausea & Vomiting	106	(19.6)	15	(3.2)	7.47 (4.51-1.84)
3rd Stage > 30 min	29	(5.3)	28	(5.9)	0.90 (0.51-1.84)
Tachycardia > 100 bpm	11	(2.1)	14	(2.9)	0.68 (0.29-1.62)
Hypertension	29	(5.3)	10	(2.1)	2.63 (1.21-5.84)
Chest pain	19	(3.5)	2	(0.4)	8.06 (1.92-53.73)
Shortness of breath	11	(2.5)	3	(0.6)	3026 (0.84-14.81)
Excessive sweating	9	(1.6)	0	-	-

n=number, CI=confidence interval

vaginal delivery was similar in all study groups Table 1. Administration of either syntometrine or oxytocin at the end of the 2nd stage of labor (Table 2) rather than at the completion of the 3rd stage was significantly more effective in preventing postpartum bleeding. No significant differences were found between the 2 administrations in the incidence of prolonged 3rd stage or maternal side effects (nausea and vomiting, tachycardia, hypertension, chest pain, shortness of breath and excessive sweating) in women who received syntometrine or oxytocin (Tables 2 and 3).

Comparison of intramuscular syntometrine to intravenous oxytocin, administered either at the end of the 2nd stage of labor (Table 2), or after complete expulsion of the placenta (Table 3), revealed a similar outcome in terms of the risk for postpartum bleeding, prolonged 3rd stage and retained placenta. However, side effects such as elevated blood pressure, nausea and vomiting, chest pain, and excessive sweating, were all more common in women who received syntometrine compared with those who received oxytocin, regardless of timing of administration (Tables 2 and 3).

Discussion. No significant difference was found in the effectiveness of intramuscular syntometrine compared with intravenous oxytocin in reducing the risk of postpartum bleeding. However, the administration of either syntometrine or oxytocin at the end of the 2nd stage of labor was significantly more effective in preventing postpartum bleeding, compared with administration after the placenta was expelled. The demonstration of a significant influence of the timing of oxytocic administration is important, as little data is available regarding this issue. Only one earlier study examined the intramuscualr administration of syntometrine, in respect to whether it was given at the end of the 2nd stage of labour compared with the end of the 3rd stage, and found no significant difference.[10] Yeun et al[9] recently compared the intramuscular administration of syntometrine with oxytocin at the time of delivery of the anterior shoulder. They found a high rate of manual removal of the placenta among women who received syntometrine, and attributed this finding to spasm of the lower uterine segment induced by the drug. They speculated this effect might result in a longer 3rd stage and an increase in the risk of placental retention.[9] We found no evidence that administration of syntometrine increased the risk for prolonged 3rd stage or retained placentas. Another concern raised regarding the use of oxytocics before delivery of the placenta is that an undiagnosed, undelivered 2nd twin may become entrapped.[11] In our country, where prenatal care is available to all, and highly used, the later danger seems very low. Nevertheless, this potential complication should always be considered, especially in the obese grand multipara. The magnitude of the reduction in postpartum bleeding revealed in our trial does suggest that the administration of oxytocic drugs at the end of the 2nd rather than 3rd stage may be advocated for most parturient.

The use of syntometrine (oxytocin plus ergometrine) was associated with a significant increase in blood pressure and a high rate of maternal

side effects, including nausea and vomiting. The high rate of side effects associated with the use of Syntometrine as observed in our study has been well recognized elsewhere.[3-5,7,8] Other maternal side effects include chest pain, shortness of breath, excessive sweating and bradycardia. It has been suggested that in developing countries, where postpartum hemorrhage remains an important cause of morbidity and mortality, the use of the apparently more effective intramuscular agent, the oxytocin-ergometrine preparation, should be preferred despite the high rate of maternal side effects.[7,12,13] Our study contributes to this debate only as far as showing that when oxytocin can be safely administered intravenously, it is probably the drug of choice.

In our study the parameters of the objective outcomes, such as blood pressure, pulse rate and duration of the 3rd stage are apt to be influenced by rounding up or down of numbers, but are relatively easy to determine precisely. Subjective complaints of the women were recorded prospectively. The major problem was in accurately determining the most important outcome variable: postpartum blood loss. The difficulty is apparent from the enormous differences in the rate of postpartum hemorrhage (> 500 ml) reported. An incidence of 1%,[3] 5%,[7] 7%,[8] was found in previous studies that compared the use of syntometrine with oxytocin. It is very difficult to attribute these differences simply to variation in patient population. It seems much more plausible that these differences reflect the various methods used for determining the degree of blood loss.

Great efforts were taken to carefully instruct all the participating midwives regarding the precise technique of collecting and measuring postpartum blood loss. The principal investigators undertook constant monitoring of the adequacy of their performance. We found a relatively high rate of postpartum hemorrhage, similar to that reported by McDonald et al.[8] We agree with their suggestion that this may be explained in part by the increased awareness to blood loss due to the implementation of the study, which demanded careful measurements. The limited reliability of clinical assessment of blood loss has long been recognized.[10] We believe that possible inaccuracies, due to inclusion fluid or loss of blood on swabs, most likely affected the results similarly during the various study periods.

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