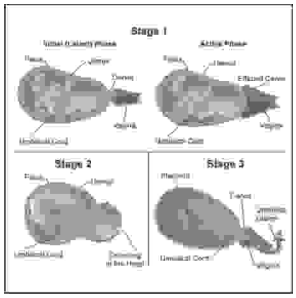
ORIGINAL PROF-1214

MANAGEMENT OF THIRD STAGE OF LABOUR;
USE OF INTRAMUSCULAR SYNTOMETRINE AND INTRAVENOUS OXYTOCIN



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ABSTRACT... Faridi_279@yahoo.com. The routine prophylactic administration of an uterotonic agent is an integral part of active management of the third stage of labor, helping to prevent postpartum haemorrhage (PPH). The two most widely used uterotonic agents are: ergometrine-oxytocin (Syntometrine ®) (a combination of oxytocin, 5 international units (iu) and ergometrine, 0.5 mg) and oxytocin, (Syntocinon ®) 10 international units (iu). **Objective:** To compare the efficacy and safety of intravenous oxytocin, with intramuscularly syntometrine in the management of third stage of labor. **Study design:** Experimental study. **Setting:** Department of obstetrics and gynaecology Combined Military Hospital Peshawar. **Period:** Over one year period from March 2005 to March 2006. **Methods:** A total 200 women having singleton pregnancy and vaginal delivery admitted in maternity ward were divided in two treatment groups by simple random sampling using random number tables, 100 patients received 2 ml Syntometrine, (a combination of oxytocin, 5iu and ergometrine meleate 0.5mg) intramuscularly and 100 patients received 10iu of intravenous syntocinon at the delivery of anterior shoulder of the fetus. **Results:** The use of intravenous oxytocin,, was associated with a reduction in postpartum blood loss (P<0.001) but there was no difference in the risk of post partum hemorrhage, in the need for repeated oxytocin injections and the drop in peripartum hemoglobin level between the two groups, and need for blood transfusion. There was also no difference in the risk of prolonged third stage, or manual removal placenta. The use of syntometrine was associated with a higher risk of hypertension (RR 2.39, 95% CI 1.00-5.70) other side effects were mild in nature with no differences between the two groups. **Conclusions:** There are no important clinical differences in the effectiveness of intramuscular syntometrine and. Intravenous oxytocin for the prevention of post partum blood loss. Intravenous oxytocin is less likely to cause hypertension and other side effect profiles are low

Key words: Oxytocin, Syntometrine, Third stage of labor, Postpartum Haemorrhage.

INTRODUCTION

Pregnancy and childbirth involve significant health risks, even for women with no preexisting health problems. Approximately 40 percent of pregnant women experience pregnancy-related health problems, and 15 percent of all pregnant women suffer long-term or life-threatening complications[1].

The World Health Organization (WHO) estimates that, in 1995, nearly 515,000 women died from complications of pregnancy and childbirth[2]. Most of these deaths occur in developing countries, often because women lack access to life-saving care. A woman living in a developing country is much more likely to receive antenatal care than she is to have skilled care during labor, childbirth, or the postpartum period (Figure 1). Yet more than half of all maternal deaths occur within 24 hours of delivery, mostly from excessive bleeding (Figure 2)[3]. Severe bleeding, or hemorrhage, is the single most important cause of maternal death worldwide. At least one-quarter of all maternal deaths are due to hemorrhage; the proportions range from less than 10 percent to nearly 60 percent in various countries (Table I). Even if a woman survives postpartum hemorrhage causes severe anemia in later live.

Table-I. Mode of admission (n=200)

Admission	No of pts		%age	
	Group A	Group B	Group A	Group B
Emergency	50	48	50%	48%
Out patient Deptt	50	52	50%	52%

A meta-analysis of these studies, available through the Cochrane database and WHO's Reproductive Health Library[15], confirmed that active management was associated with reduced maternal blood loss (including PPH and severe PPH), reduced postpartum anemia, and decreased need for blood transfusion[11]. Active management also was associated with a reduced risk of prolonged third stage labor, and less use of additional therapeutic uterotonic drugs.

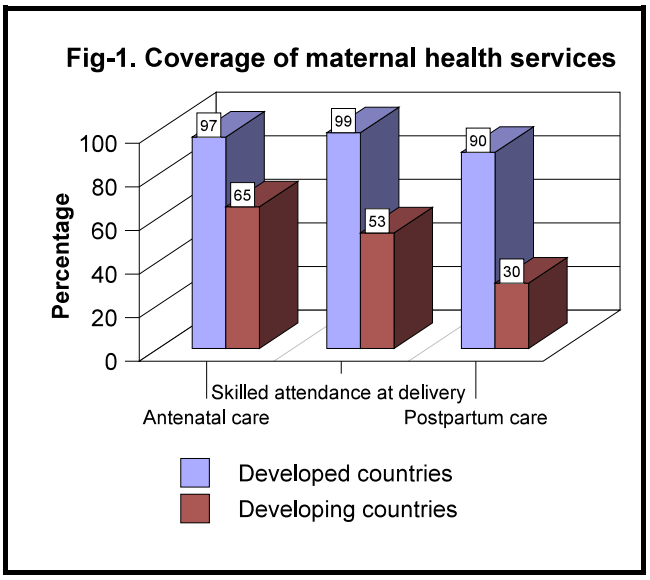
Table-II. Demographic data (n=200)

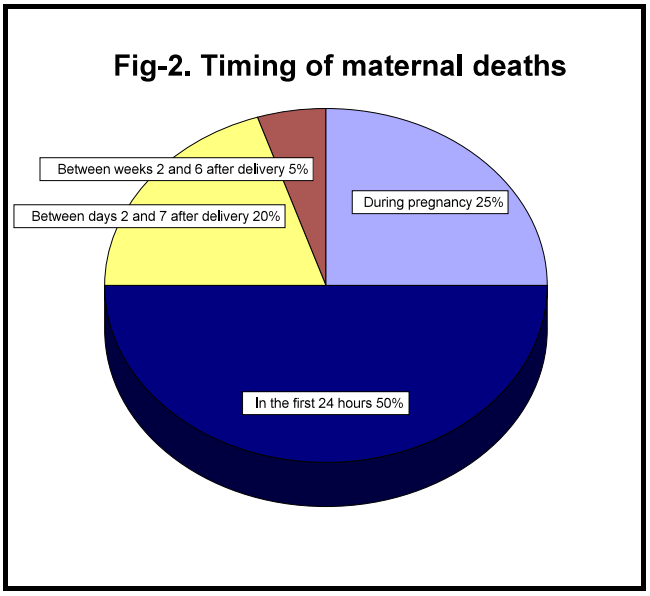
Parity	No of pts		%age	
	Group A	Group B	Group A	Group B
Nulliparous	11	12	11%	12%
Multiparous (2 to 4)	80	78	80%	78%
Grand Multiparous (>5)	9	10	9%	10%

The injection of a uterotonic drug immediately after delivery of the newborn is one of the most important interventions used to prevent PPH. The most commonly used uterotonic drug, oxytocin, has proven to be very effective in reducing the incidence of PPH and prolonged third-stage labor[16,17]. Syntometrine (ergometrine combined with oxytocin) appears to be even more effective than oxytocin alone. Syntometrine is associated with more side effects, such as headache, nausea, vomiting, and increased blood pressure, however[18]. Women with high blood pressure (or pre-eclampsia or eclampsia, which affect approximately[6]. Percent of all women) cannot use ergometrine. Compared with oxytocin, ergometrine is less stable at room temperature and tends to lose its potency[4]. In a prospective, Cohort study[6], oxytocin given intravenously at a dose of 10 iu was found to be as effective as intramuscular Syntometrine in reducing the risk of post partum haemorrhage.

However there has been few randomized trial comparing intramuscular Syntometrine with intravenous oxytocin,

therefore we conducted this trail in our setup to compare the efficacy and safety of intravenous oxytocin with intramuscular Syntometrine in the management of the third stage of labour.





Oxytocin and Syntometrine use is already in our practice, but conducting this trial, in our setup, our confidence enhanced more on the use of these drugs in our day-to-day practice.

OBJECTIVES

1. To compare the efficacy of intramuscular syntometrine and intravenous oxytocin in the management of third stage of labor by measuring the pre-delivery haemoglobin and 24 hrs post delivery haemoglobin, use of blood transfusion to estimate the blood loss and duration of third stage of labor in singleton pregnancies who delivered vaginally in our set up

2. To determine the safety of the two drugs in these women by comparing the side effects e.g. nausea, vomiting, headache, chest pain, & blood pressure immediately after delivery, 30 minute after delivery and 60 minute after delivery.

MATERIAL AND METHODS

The data was collected during one year period from March 2005 March 2006 in the Department of obstetrics and gynaecology Combined Military Hospital Peshawar. Hundred patients were studied in each group under trial.

Sampling technique

Two groups were assigned to the two treatment groups by simple random sampling using random number tables.

Sample selection

Inclusion criteria

All patients delivered vaginally.

Exclusion criteria

Patients refused to be included in study groups.

Data collection procedure

The patients admitted through the emergency and out patient department in maternity ward combined military hospital Peshawar. All patients in labour were undergone complete history and physical examination. Consent of patient was taken. Prior to entry in trial group. Blood was also taken to estimate haemoglobin before and 24 hours after delivery. Patients were divided into two groups, A

and B, by simple random sampling.

Group A: injection Syntometrine {ergometrine meleate 0.5 mg+ oxytocin 5iu} intramuscular was given at the delivery of anterior shoulder of baby. The vital signs of patients were monitored before delivery, immediately after delivery, thirty minutes after delivery and one hour after delivery.

Group B: Injection oxytocin (10 IU) intravenous was given at the delivery of anterior shoulder of baby and vital signs before, immediately after delivery, thirty minutes after delivery and one hour after delivery were monitored and necessary entries done in proforma.

In case of excessive blood loss, the blood transfusion made or not was entered in the proforma and the duration of third stage was also measured. The side effects of active management of third stage with Syntometrine and Oxytocin were also checked e.g. Nausea, vomiting, headache and chest pain. At the end the women perception regarding the management of third stage, drug and side effects also taken into consideration for future compliance.

RESULTS

Total of 200 patients were studied in Combined Military Hospital Peshawar from March 2005 to March 2006. All had singleton vaginal deliveries there were no differences in demographic characteristics between the two groups. The use of intravenous oxytocin was associated with a reduction in postpartum blood loss. There was no difference in the incidence of postpartum haemorrhage (t - 1.087, p 0.279), The need for repeat oxytocic injection (RR 1.47. 95% CI 0.94-2.29) or the incidence of delayed haemorrhage in both groups. There

was no significant difference in the incidence of prolonged third stage of labour, the need for manual removal of placenta, the change in heamoglobin levels 24 hours after delivery or the need for blood transfusion. Syntometrine was associated with a higher risk of hypertension (defined as blood pressure > 140/90 mm of Hg after delivery) than intravenous oxytocin. In our study the change in haemoglobin in both groups was not significant (p .279, t - 1.087) there was no difference in the mean change in Hb in both groups , duration of third stage of labor in both groups[t .ooo, p 1.000] was not significant by comparing the results. Blood Pressure change immediately after delivery was significant in 18 patients in group A and 10 patients in group B. but blood pressure after 60 minutes of delivery was normal in both groups. The incidence of vomiting was similar in both groups (x^2 =2.044) and other side effects occurred with similar incidence in both groups and were mild. There were 07 blood transfusions in both groups because their initial Hb was low. The duration of third stage was short in Syntometrine group comparing to oxytocin group. There were need for manual removal of placenta in our study group and more than average blood loss. The women perception was quite good in group B patients.

Table-III. Change in hemoglobin in both groups (t-test)

	Mean	N	Std. Devoation	Z/T	P value
Change in Hb of group A	.7320	100	.2616	-1.103	0.279
Change in HB of Group B	.7800	100	.3476		

Note: We use Z test in place of T test as the no of patients are more than.

Table-IV. Duration of 3rd stage of labour in both groups

Duration of third stage of labor	No of Pts	Mean±SD	Std Deviation	T	P
Group A	100	5.29±0.53	.73	.000	1.00
Group B	100	5.29±0.49	.49		

Table-V. Side effects of group A & B (n=200)

Side effects	No of patients		Total
	Group A	Group B	
Nausea	16	9	25
Vomiting	5	-	5
Headache	23	9	32
Chest pain	5	2	7
Total	49	20	69
Chi Square Test: X^2=2.044			

By comparing the side effects of both drugs, it is observed that there is no significant difference between the side effects of both the drugs.

Table-VI. Comparative chart of systolic blood pressure between groups, at different time interval

Systolic BP after delivery	Group A(n=100)	Group B (n=100)	P-value
Immediately	131.80±10.29	129.40±9.73	0.108
30 min	128.20±11.32	126 ±10.35	0.137
60 min	123.4±8.19	122.1±7.01	0.239
Group-A=Syntometrine group		*Group- B=Syntocinon group*	

Table-VII. Comparison of distolic blood pressure between groups at different time interval (Mean ±SD) n=200

Distolic BP after delivery	Group A(n=100)	Group B (n=100)	P-value
Immediately	85.4±6.9	84.3±7.3	0.256
30 min	79.3±5.17	79.2±4.64	0.88
60 min	77.45±5.66	76.85±5.49	0.425

Table-VIII. Comparison of systolic blood pressure immediately, 30 minutes and 60 minutes after delivery in group A&B (Paired Samples Statistics)

		Mean	N	Std. Deviation	Std error mean
Pair 1	Systolic BP immediately after the Delivery A	131.80	100	10.29	1.03
	Systolic BP immediately after the Delivery B	129.4	100	9.73	0.97
Pair 2	Systolic BP 30 min after Delivery A	128.20	100	11.32	1.13
	Systolic BP 30 min after Delivery B	126.00	100	10.35	1.03
Pair 3	Systolic BP 60 min after Delivery A	123.40	100	8.19	0.82
	Systolic BP 60 min after Delivery B	122.10	100	7.01	0.70
Group A = Syntometrine		*Group B = syntocinon*			

Table-IX. Comparison of diastolic blood pressure immediately, 30 minutes and 60 minutes after delivery in group A&B (Paired Samples Statistics)

		Mean	N	Std. Deviation	Std error mean
Pair 1	Diastolic BP immediately after Delivery A	85.40	100	6.88	0.69
	Diastolic BP immediately after Delivery B	84.30	100	7.28	0.73
Pair 2	Diastolic BP 30 min after Delivery A	79.30	100	5.17	0.52
	Diastolic BP 30 min after Delivery B	79.20	100	4.64	0.46
Pair 3	Diastolic BP 60 min after Delivery A	77.45	100	5.66	0.57
	Diastolic BP 60 min after Delivery B	76.85	100	5.49	0.55

Paired statistics shows that no significant difference between syntometrine and syntocinon group except mild rise of blood pressure in syntometrine group.

DISCUSSION

In most of the early studies comparing oxytocin with Syntometrine in the prevention of postpartum haemorrhage oxytocin was given intra muscularly at a dose of 5 units[7-9] in the study published by Dumoulin in 1981,[5] it was clearly stated that the dose of intramuscular oxytocin had to be changed from 5 units to 10 units during the course of trials because of the high incidence of postpartum haemorrhage associated with the lower dose 12.4% versus 8.6%.[5] The author subsequently studied a series of 402 patient using 5iu oxytocin intravenously and concluded that oxytocin was associated with a lower primary postpartum haemorrhage rate in the absence of statistical significance. In a series of 1378 subjects, Nieminen and Jarvinen[7] reported no difference in the postpartum haemorrhage rate between the two drugs when given intramuscularly with an odds ratio of 0.56 (95% CI 0.20-1.61).

Double blind randomised controlled trial involving 461 patients, Mitchell et al.[9] reported a significant reduction in postpartum haemorrhage rate in the sytometrine group with an odds ratio of 0.37 (95% CI.16-0.85). Combining these studies, intramuscularly syntometrine was associated with a significantly lower rate of postpartum haemorrhage than 5 units of oxytocin alone with an overall summary odds ratio of 0.36 (95% CI 0.23-0.55)[2].

In the literature there were four randomised studies comparing higher dosage of intramuscular oxytocin (10 units) with intramuscular syntometrine[8-11]. Docherty and Hooper[8] reported that oxytocin was associated with a 40% increase in mean blood loss, but the absolute rate of postpartum haemorrhage was not stated.

McDonald et al[10] haemorrhage rate with an odds ration of 0.90 (95% CI 0.75-1.07) and 0.89 (95% CI 0.53-1.51), respectively. However, the use of syntometrine was associated with an increase in the incidence of nausea, vomiting, headache and hypertension. On the contrary, Yuen et al.[11] reported a 40% reduction of the risk of postpartum haemorrhage (OR 0.60, 95% CI 0.21-0.88) and the need for repeated oxytocic injections (OR 0.63, 95% CI 0.44-0.89) in the syntometrine group compared with oxytocin and side effects were uncommon in both groups. The overall comparison of 10 units of intramuscular oxytocin anagement of with syntometrine still favours syntometrine (OR 0.81, 95% CI 0.70-0.94)[2].

We believe that this is the tip of ice burg among randomized controlled trials comparing intravenous oxytocin (10 units) with intramuscular syntometrine in the management of third stage of labour. In a Medline literature review, we could only identify few prospective cohort studies[6] that reported intravenous oxytocin being as effective as intramuscular syntometrine in the prevention of postpartum haemorrhage, but was associated with a significantly higher rate of unpleasant maternal side effects. Our results confirmed the efficacy of intravenous oxytocin in preventing postpartum haemorrhage with a lower risk of hypertension. The superior prophylactic effect of intravenous over intramuscular oxytocin is likely to be related to the early onset of action of the intravenous administration. As suggested by Soriano et al[6]. early delivery of the uterotonics drug is associated with a lower risk of postpartum haemorrhage.

Ergometrine-oxytocin (Syntometrine®) is more effective than oxytocin (Syntocinon®) in reducing blood loss during the delivery of the placenta, but has more side-effects.

Active management of the third stage of labour, when delivery of the placenta occurs, involves the clinician giving a drug as the baby's shoulder is born, clamping the umbilical cord immediately after birth and putting traction on the cord to speed delivery. This process is widely used to reduce the risk of excessive blood loss. The review of trials found ergometrine-oxytocin appears to be associated with less blood loss than oxytocin when a 'moderate' blood loss definition is taken rather than a 'severe' blood loss definition. However, ergometrine-oxytocin was associated with more side-effects of vomiting, nausea and high blood pressure. The use of

ergometrine-oxytocin as part of the routine active management of the third stage of labour appears to be associated with a small but statistically significant reduction in the risk of PPH when compared to oxytocin for blood loss of 500 ml or more. No statistically significant difference was observed between the groups for blood loss of 1000 ml or more. A statistically significant difference was observed in the presence of maternal side-effects, including elevation of diastolic blood pressure, vomiting and nausea, associated with ergometrine-oxytocin use compared to oxytocin use. Thus, the advantage of a reduction in the risk of PPH, between 500 and 1000 ml blood loss, needs to be weighed against the adverse side-effects associated with the use of ergometrine-oxytocin(cochrane data review)[8].

A potential complication of using oxytocics in the third stage of labour is retained placenta. When ergometrine is compared with oxytocin, the risk of retained placenta was significantly increased[12,13]. Yuen et al[7] reported a higher incidence of retained placenta associated with the use of syntometrine compared with intramuscular oxytocin, but a similar finding was not observed in our current study. This might be related to the different way of delivering the placenta. In that trial, the placenta was not delivered until signs of placental separation appeared, in contrast to the early clamping of the umbilical cord and immediate controlled cord traction in our current study. Such early intervention allows the placenta to be delivered before the occurrence of uterine spasm, thereby reducing the risk of retained placenta.

CONCLUSION

There are no important clinical differences in the effectiveness of intramuscular Syntometrine and intravenous oxytocin for the prevention of postpartum blood loss. Intravenous oxytocin in particularly beneficial in patient with hypertensive disorder and it is less likely to cause hypertension. Both drugs are time tested and easily available with good compliance in all patients.

REFERENCES

1. Prendiville W, Elbourne D, Chalmers I. **The effects of routine oxytocic administration in the management of the third stage of labour:** an overview of the evidence from controlled trials. Br J Obstet Gynaecol 1988; 95:3-16.

2. McDonald S, Prendiville WJ, Elbourne D. **Prophylactic syntometrine versus oxytocin for delivery of placenta**. The Cochrane Database of Systemic Reviews Volume 1, 2001.

3. Du Vigneaud V, Ressler C, Tipp et S. **The sequence of amino acids in oxytocin. with a proposal for structure of oxytocin**, J Biol Chem 1953;73:757-60.

4. McDonald S, Abbott JM, Higgins SP. **Prophylactic ergometrine-oxytocin versus oxytocin for the third stage of labour** (Cochrane Review) 23 September,2003.

5. Dumoulin JG. **A reappraisal of the use of ergometrine**. Br J Obstet Gynaecol 1981; 1:178- 819.

6. Soriano D, Dultzki M, Schiff E, Barkai G, Mashiach S, Seidman DS. **A prospective cohort study of oxytocin plus ergometrine compared with oxytocin alone for prevention of postpartum haemorrhage**. Br J Obstet Gyneacol 1996; 103:1068- 73.

7. Nieminen U, Jarvinene PA. **A comparative stuffy of different medical treatment of the third stage of labour**. Ann Chir Gynaecol Fenn 1963;53:424- 9.

8. Docherty PW, Hooper M. **Choice of an Oxytocic agent for routine use at delivery**. J Obstet Gynaecol 1981;2:60.

9. Mitchell G, Elbourne DE, Ashurst HA, **The Salford third stage trial: oxytocin plus ergometrine versus oxytocin alone in active management of the third stage of labour**. Online J Curr Clin Trials 1993;Doc.No 83.

10. McDonalds SJ, Prendville WJ, Blair E. **Randomised control trial of Oxytocin alone versus oxytocin and ergometrine in active management of the third stage of labour**. BMJ 1993;307:1167-

11. Yuen PM, Chan NST, Yim SF, Chang AMZ. **A randomized double blind comparison of syntometrine and Syntocinon in the management of the third stage of labour**. Br J Obslet Gynaecol 1995; 102:377- 80.

12. Sorbe B. **Active pharmacological management of the third stage of labour: a comparison of oxytocin and ergometrine**. Obstet gynecol 1978;52:647-94.

13. Hammar M. Bostrom K. Borgvall B. **Comparison between the influence of methylergometrine and oxytocin on the incidence of retained placenta in the third stage of**

labour. Gynecol Obstet Inves 1990;30:91- 3.

14. Ng PS, Chan ASM, Sin WK, Tang LCH, Cheung KB, Yuen PM. **A multicentre randomized controlled trial of oral misoprostol and im syntometrine in the management of the third stage of labour**. Hum Reprod 2001; 16:31-5.

15. Duthie SJ, Ven D, Yung GL, et al. **Discrepancy between laboratory determination and visual estimation of blood loss during normal delivery**. Eur J Obstet Gynecol Reprod Biol 1991; 38:119- 24.

16. Razvi K, Chua S, Arulkumaran S, et al. **A comparison between visual estimation and randomisedatory determination of blood loss during the third stage of labour**. Aust NZ J Obstet Gyneacol 1996;36:152-7.

17. American college of Obstetricians and Gynecologists. **Quality Assurance in Obstetrics and Gynecology,** 1989. Washington, DC: American college of Obstetricians and Gynaecologist.

18. N.J.A de Groot A, van Dongen P.W.J, Vree T.B, Hekster Y-A. **Ergot Alkaloids: current status and Review of clinical pharmacology and therapeutic use compared with other oxytocics in obstetrics and gynecology;** 1998;56:523