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# A COMPARATIVE STUDY OF VARIOUS UTEROTONICS IN ACTIVE MANAGEMENT OF THIRD STAGE OF LABOUR

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**ABSTRACT**

Post partum hemorrhage is the second most common cause of maternal mortality. Routine active management of third stage of labor has definitive role in reducing maternal mortality and morbidity due to PPH. It includes administration of uterotonics, uterine massage and controlled cord traction in third stage of labour. Various uterotonics used are oxytocin, methyl ergometrine, 15 methyl prostaglandin F2 and misoprostol. Objective of our study was to know the efficacy and side effects of these agents in active management of third stage of labour. Material and methods - A total of 300 patients more than 37 weeks of gestation in active labour were enrolled after informed consent and clearance from ethical committee. They were divided into three groups Group O(N=100) received intramuscular oxytocin (10IU) Group M(N=100) received I ml intramuscular 0.2 mg methyl ergometrine, and Group P(N=100) received 1 ml intramuscular 250 mcg 15- methyl prostaglandin F2 alpha at the time of delivery of anterior shoulder of baby. Observation & Results : Intramuscular oxytocin is safest and most effective prophylactic uterotonic agent. It is associated with significantly lesser third stage blood loss, shorter duration of third stage, no significant fall in postpartum haemoglobin and minimum adverse effects, as compared to methylergometine and prostaglandins. There is no evidence to support for the use of ergot alkaloids in active management of third stage of labour. Prostaglandins has the disadvantage of significant increase in side effects.

## I. Introduction

The third stage of labour begins with expulsion of baby and ends with expulsion of placenta and membranes. It is the most crucial stage of labour, as sometimes in this stage an uncomplicated pregnancy may turn into a castrotrophic condition within no time. Postpartum hemorrhage (PPH) is one of the dreaded complications of third stage of labor. It is defined as excessive bleeding after delivery leading to deterioration of the condition of parturient woman which may lead to maternal mortality and morbidity.

The maternal mortality in India is 178 per 100,000 live birth and PPH is the second most common cause of maternal mortality[1,2]. Routine active management of third stage of labor is an important part of modern obstetrics rather is a rule which had definitive role in reducing maternal mortality and morbidity due to PPH[3]. It includes administration of uterotonics, uterine massage and control cord traction in third stage of labour[4].

Systematic reviews and Meta analysis have concluded that active management of third stage of labour, particularly the use of uterotonic agents can significantly decrease the incidence of postpartum haemorrhage byabout40% compared with that of expectant management[5,6,7].Drugs routinely used for prophylaxis against PPH are oxytocin, methyl ergometrine, 15 methyl PGF2 (carboprost),misoprostol(PGE1) and syntometrine (combination of ergometrine and oxytocin). There are still variations in the use of uterotonics in management of third stage of labour[8,9].

Injectable oxytocin (Syntocinon), a synthetic nonapeptide has been recommended for routine use in the active management of the third stage of labour. The uterine contractions are similar to physiological pattern i.e. causing fundal contraction with relaxation of cervix. Oxytocin is a first-line agent because it is effective in 2-3 minutes after injection and, as it has minimal secondary effects it can be used in all women. A disadvantage of oxytocin is its short half-life thus it doesn't have well sustained effect. There are no absolute contraindications to oxytocin; however, an antidiuretic effect with volume overload may develop with high cumulative doses during intravenous infusion[10,11].

Methlylergometrine (Methergine) is an ergot alkaloid available as oral (0.125 mg) and injectable (0.2 mg) preparations. The parenteral route is preferable in active management of third stage of labour for faster absorption. It has a generalized vasoconstrictive action on the myometrium, causing powerful and prolonged spasms. Hypertension is a contraindication to this class of agent, due to potential for severe hypertension and tissue (myocardial) ischemia, thus some authors have questioned the continued role of ergometrine in modem obstetrics[12].

Oxymetrine (also available as Syntometrine) is a mixture of oxytocin and ergometrine, and 1 ml of oxymetrine contains 5 I.U. oxytocin and 0.5 mg ergometrine. This mixture combines the rapid onset of action of oxytocin and sustained uterotonic effect of ergometrine and is one of the most popular uterotonic agents used in the third stage of labour[13].

15-methyl derivative of prostaglandin F2 alpha was approved in mid 1980s by FDA for treatment of uterine atony and is very effective in controlling uterine bleeding refractory to oxytocin and methylergometrine. It has got powerful oxytocic effect, with predominant action on myometrium and is extensively used as Carboprost 250 mcg/ml, 125 mcg/ml intramuscular injections. A major contraindication to its use is asthma, which may be exacerbated due to its broncho-constrictive properties[14].

Misoprostol (Cytotec), a prostaglandin E 1 analogue, is more stable than oxytocin and has been administered by oral, sublingual, and rectal routes; however there are concerns that misuse of misoprostol can lead to significant maternal morbidity and even death[15].

The high cost of prostaglandins, their rapid rate of metabolism and local inflammatory effects have precluded the routine use of prophylactic prostaglandins in the active management of third stage of labour and are not widely used for the prevention of PPH. A recent Cochrane review (2007) concluded that neither intramuscular prostaglandins nor misoprostol is preferable to

conventional uterotonicsas a part of the management of the third stage of labour especially for low risk women[16].

The present study was undertaken to evaluate the scope of using intramuscular 0.2 mg methylergometrine and intramuscular 250 meg 15-methyl prostaglandin F2 alpha and their efficacy in terms of blood loss, duration of third stage of labour, side effects in comparison with oxytocin (10 I.U.) in active management of third stage of labour.

## II. Materials and Methods

This prospective double-blinded randomized study was conducted for a period of one year in Dr BSA hospital in the department of Obstetrics & Gynaecology New Delhi. A total of 300 patients of age 18 -35 years, more than 37 weeks of gestation with single live fetus in active labour were enrolled. Patients with multiple pregnancy, malpresentations, anaemia, scarred uterus, antepartum haemorrage and preeclampsia were excluded. All enrolled patients were randomly divided into three groups by using computer generated numbers group O(N=100) received intramuscular oxytocin (10 IU) group M(N=100) received 1 ml intramuscular 0.2 mg methyl ergometrine, and group P(N=100) received 1 ml intramuscular 250 mcg 15- methyl prostaglandin F2 alpha at the time of delivery of anterior shoulder of baby. The patients and attending doctors were blinded regarding the groups till the completion of the study.

A blood sample for pre-delivery haemoglobin measurement was taken during first stage of labour and measured using automated analyser. All the deliveries were conducted by similarly qualified doctors. The third stage of labour was managed actively by giving uterotonic agent, clamping and cutting of umbilical cord, delivering the placenta by controlled cord traction and uterine massage. Simultaneously blood collection in the kidney tray kept beneath the patient's buttocks was done till 30 minutes after delivery of the baby. The vitals of the parturient & duration of third stage of the labour recorded, blood loss measured quantatively, perineal trauma (episiotomy/ perinea] tear) was noted & sutured if present. Side effects were observed up to 24 hours of delivery.

Blood loss was measured immediately after cutting the cord till 30 minutes after delivery of the baby. A kidney tray was used to collect all blood, clots, and swabs soaked with blood. Total amount of blood loss was carefully calculated by volumetric method i.e. measuring the actual volume of blood using a calibrated measuring jug, plus the amount determined by the weighing of blood-stained under sheets (disposable or linen) and sanitary pads and subtracting their known dry weight. Maternal blood pressure, pulse rate was checked every 5 minutes for 30 minutes till delivery. Any apparent side effects like vomiting,diarrea headache, fever, shivering, was noted and asked from the patient.

The primary outcome variable of this study was the total amount of blood loss measured quantitatively, drop in haemoglobin level documented by comparing the maternal haemoglobin on admission to labour ward with that measured 24 ± 4 hours after delivery.Secondary outcome variables assessed included the duration of third stage, incidence of postpartum haemorrhage, use of additional therapeutic uterotonic and blood transfusion. The incidences of prolonged third stage (duration longer than 30 minutes) and the need for manual removal of placenta were recorded.

### Statistical Analysis:

All statistical analysis was performed using Statistical Package for Social Science, version 15. Fischer's- exact / Chi-square test was applied and p value of less than 0.05 ($p<0.05$) was considered as statistically significant.

## III. Observations and Results

Out of 300 patients maximum number of patients were in age group 20-25 years. Mean age in O, M and P groups was 25.5, 25.2 and 24 years respectively. Socioeconomic status was comparable in all three groups. Median parity in all groups was one. Overall descriptive statistics highlights that the sample was equally distributed in all three groups. This reduces the chances of confounding cause due to variability in covariants in the analysis.

The mean pre-delivery haemoglobin ± SD was 10.3±1.08, 10.3±1.17 and 10.6±1.17 respectively in three study group which was comparable (p=0.08). 28%, 29% and 36% patients had episiotomy in groups O, M and P respectively while 9% ,9% and 11% had perineal tears which was comparable with no significant difference between the groups (p=0.64).

**Table 1** Measured blood loss till 30 minutes after delivery

| Study groups | Range of blood loss(ml) | Median blood loss(ml) | |
|---|---|---|---|
| Group O (n=100) | 25-500 | 80 | P= 0.01 |
| Group M (n=100) | 30 – 660 | 110 | |
| Group P (n=100) | 30- 800 | 90 | |

Above table shows the measured blood loss till 30minutes of delivery. The median blood loss in group O, M, and P was 80ml, 110ml, and 90ml respectively. It was found that total blood loss was significantly higher both in group M and group P as compared to group O.

**TABLE 2** Change in haemoglobin from predelivery to postpartum day 2 values

| Study groups | Pre-delivery Hb.(gm/dl) Mean ± SD | Postpartum day 2 Hb.(gm/dl) mean± SD | p value |
|---|---|---|---|
| Group O | 10.3 ± 1.08 | 10.2 ± 1.06 | 0.001 |
| Group M | 10.3 ± 1.17 | 10 ± 1.2 | 0.001 |
| Group P | 10.6 ± 1.17 | 10.4 ± 1.15 | 0.001 |

Above table shows change in haemoglobin from pre-delivery to postpartum Day 2 values in the study. In all the three groups the change in haemoglobin was found to be statistically significant (p=0.001) although the change is clinically insignificant.

**TABLE 3** Change in haemoglobin (postpartum day 2- predelivery)

| Study groups | Group O | Group M | Group P | p value |
|---|---|---|---|---|
| PredeliveryHb.(gm/dl) Mean ± SD | 10.3 ± 1.08 | 10.3 ±1.17 | 10.6± 1.17 | p=0.08 |
| Postpartum day 2 Hb.(gm/dl) mean ± SD | 10.2 ± 1.06 | 10 ± 1.23 | 10.42 ± 1.15 | p=0.058 |
| Change in haemoglobin (postpartum day 2 - pre delivery) gm/dl | -0.5 to 1 | - 0.3 to 1 | - 0.5 to 1.6 | |
| Median value of change in haemoglobin(gm/dl) | 0.1 | 0.19 | 0.19 | p=0.002 |

Above table shows change in haemoglobin from pre-delivery to postpartum day 2 was statistically significant . There was statistically significant difference between the median value of change in haemoglobin between group O and group M, and between group 0and group P. i.e. fall in postpartum haemoglobin was more in group M(0.19) and group P(0.19) as compared to group O(0.1) although change in haemoglobin was not clinically significant.

**TABLE 4** Duration of third stage of labour

| Study groups | Range of duration (min.) | Duration of third stage(min.) (Mean ± SD) | |
|---|---|---|---|
| Group O | 1 – 10 | 3.7± 1.57 | p=0.0095 |
| Group M | 1 – 12 | 3.9± 2.02 | |
| Group P | 2-25 | 4.6± 2.81 | |

The above table shows duration of third stage (minutes) in study

groups. The mean duration ± SD in group O, M and P was3.7±1.57 3.9± 2.02 and 4.6± 2.81 respectively. The duration of third stage was comparable between group O and group M as well as between group M and group P and the difference was insignificant but the duration of third stage was found significantly higher in group P (4.6±2.81) in comparison to group O (3.9±2.02).

**TABLE 5** Side Effects

| Study Group | No Side Effects | Side Effects | | | |
|---|---|---|---|---|---|
| | | Vomiting | Diarrhoea | Hypertension | *Fever* |
| Group O (n=100) | 99% | 1% | - | - | - |
| Group M (n=100) | 98% | - | - | 2% | - |
| *Group P* (n=100) | 77% | 13% | 9% | - | 1% |

The incidence of side-effects was significantly lower in group O and group M. Group P had significantly maximum side- effects (23%) i.e. vomiting (13%), diarrhoea (9%), fever (1%) in comparison to group O (1%) and group M (2%) (p=0.001). In group O only 1 subject had vomiting, in group M only 2 subjects had hypertension (blood pressure >140/90 mmHg) at 30 minutes after delivery. There was no significant difference with respect to side effects between group O and group M.

**TABLE 6** Use of additional uterotonic blood loss >500ml, need for blood transfusion

| Study groups | Use of additional uterotonic (%) | Blood loss >500 ml (%) | Need for blood transfusion |
|---|---|---|---|
| Group O (n=100) | 1 | 1 | 0 |
| Group M (n=100) | 6 | 5 | 0 |
| Group P (n= 100) | 10 | 6 | 0 |

Above table shows additional therapeutic uterotonic drug was required in 1 patient in group O, 6 patients in group M, 10 patients in group P. The difference was statistically insignificant (p >0.05). Blood loss >500ml occurred in one patient in group O, 5 patients in group M, 6 patients in group P. There was no need for blood transfusion in any of the study groups.

## IV. Discussion

Patients in all the three groups were comparable with regards to their age, socioeconomic status & parity. And they were comparable as regards episiotomy and perineal tears.

The incidence of postpartum haemorrhage (blood loss > 500 ml) in our study was 1% in group O, 5% in group M, and 6% in group P. This is comparable to incidence of PPH during active management of third stage in previous studies (6.8 %) and is much less than the incidence of PPH that can be expected with conservative management of third stage of labour (16.5%)[17].

The mean duration (standard deviation) of third stage of labour in group O, M and P was 3.7±1.57 3.9± 2.02 and 4.6± 2.81 minutes respectively. The duration of third stage was comparable between group O and group M as well as between group M and group P and the difference was insignificant but the duration of third stage was found significantly higher in group P (4.6±2.81) in comparison to group0(3.7± 1.57 ). whereas in the study by KS Sunil et al duration of third stage of labour was significantly less in prostaglandin group as compared to oxytocin18.In study done by Gohil et al mean duration of third stage of labour in oxytocin group was 8.94 ± 4.18 minutes which is much higher than 3.7±1.57 minutes in our study19 But our study was comparable with Modi V et al in which duration of third stage was 4.72minutes in oxytocin group, 3.84 minutes in methyergometrine group and 5.04 minutes in prostaglandin group[20].

In our study the median value of blood loss in-group O, group M, group P was 80 ml, 110 ml and 90 ml respectively. There was statistically significant less blood loss in-group O as compared to group M and group P (p = 0.001). Our results were comparable with study done by Modi V et al[20].

Additional therapeutic uterotonic drug was required in 1 patient in group O, 6 patients in group M, 10 patients in group P. The difference was statistically insignificant (p >0.05). Blood loss >500ml occurred in one patient in group O, 5 patients in group M, 6 patients in group P. There was no need for blood transfusion in any of the study groups this is in contradiction with study done by Modi V et al in whom two patients in prostaglandin group had PPH requiring blood transfusion20.

There was no significant difference (p = 0.08) observed in pre delivery haemoglobin level between the three groups, when blood was drawn in the first stage of labour. Median value of change in haemoglobin concentration (pre delivery haemoglobin value subtracted from 24 ± 4 hours post delivery haemoglobin value) in group O, group M, and group P was 0.1, 0.19, 0.19respectively. there was statistically significant difference between the median value of change in haemoglobin between group O and group M, and between group O and group P. i.e. fall in postpartum haemoglobin was more in group M(0.19) and group P(0.19) as compared to group O(0.1). Although change in haemoglobin was not clinically significant. Our study was consistent with Modi V and Gohil et al regarding drop in haemoglobin level in prostaglandin group only but they had not found significant fall in haemoglobin in oxytocin and metylergometrine group[19,20].

In our study group P had maximum incidence of side effects (23%) in comparison to group 0 (1%) and group M (2%). This difference was found to be statistically significant (p = 0.001).In group O only one woman (1%) experienced vomiting as a side effect, this is consistent with study of Gohil et al. In group M two women (2%) developed hypertension as the only side-effect whereas in study of Modi V et al hypertension was observed in 12% of patients . In group P thirteen women (13%) developed vomiting, 9% had watery diarrhea and 1% developed fever and shivering. The significantly increased association of side-effects in group P is comparable to other studies on intramuscular prostaglandin[19,20].

## V. Conclusions

The present study concludes that intramuscular oxytocin is safest and most effective prophylactic uterotonic agent amongst the three uterotonics used in study in prevention of postpartum haemorrhage. It is associated with significantly lesser third stage blood loss, shorter duration of third stage, no significant fall in postpartum haemoglobin and minimum adverse effects. There is no evidence to support the use of ergot alkaloids in active management of third stage of labour. Prophylactic intramuscular prostaglandin offers no advantage over prophylactic intramuscular oxytocin. Moreover use of prostaglandins has the disadvantage of higher cost as well as significant increase in the incidence of profuse diarrhea and vomiting. However it can be used as additional drug in uncontrolled PPH.

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