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Comparison of intramyometrial and intramuscular 15 methyl $PGF_{2\alpha}$ against traditional prophylactic intramuscular methergin for the active management of third stage of labor

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Abstract

Objective: To compare intramyometrial, intramuscular (I M) 15 methyl $PGF_{2\alpha}$ with IM Methergin on the duration and blood loss of 3rd and 4th stage of labor.

Method: Prospective randomized control study, done from May 2004 to June 2005. Three hundred parturient women were randomly assigned to receive either an intramyometrial or IM 15 methyl $PGF_{2\alpha}$ or IM methergin immediately after delivery of baby. Duration of 3rd stage and blood loss during 3rd and 4th stage of labor was measured. Other parameters measured were – presence of atonic postpartum hemorrhage (PPH), need for MRP, and blood transfusion, any side effects of drugs.

RESULTS: Women who received prophylactic intramyometrial $PGF_{2\alpha}$ had significantly shorter duration of 3rd stage of labor (2.3 + 0.66 mins: p= 0.0000) compared to both IM group (3.04+1.03 mins) and IM methergin group (4.22+ 1.58 mins) and also significantly less blood loss (median- 110ml; P= 0.0002) compare to both IM group (median-145ml) and IM methergin group(medin-197ml).

CONCLUSION: Intramyometrial PGF2α is better than IM $PGF_{2\alpha}$ and methergin in terms of reducing duration of 3rd stage and blood loss. Thus can be prophylactically used especially in those patients where even minimal blood loss will adversely affect the health of mother.

Key words: active management of third stage of labor,$PGF_{2\alpha}$ methergin

Introduction

Of all the experiences of human conditions, childbirth surely represents the most important events. Amidst the complexity & sophistication of modern obstetrics, it is important to remember the simple objective of every pregnancy- delivery of a healthy baby to a healthy mother.

Postpartum hemorrhage is one of the commonest conditions encountered in day-to-day practice & is a nightmare even to the present day obstetrician. Nearly 50,000 to 60,000 women annually (WHO 1990, UNICEF 1996) are still dying in developing countries & a substantial proportion of these deaths are due to PPH. Incidence being 5-10%of total maternal death where 90% is due to atonic PPH.

Maternal mortality rate so far reported in Nepal is 513 per 100,000 live births where postpartum (PPH) remains one of the commonest causes of death at turn of this century. The reason behind this is women out here are unable to cope with a larger amount of blood loss as they are smaller in built & therefore have less blood volume, malnourished & tend to have a lower antenatal hemoglobin level.

Prophylactic use of oxytocic drugs reduces the risk of PPH by approximately 40%. Active management of 3rd stage of labor –is usually implemented as a "package" including early administration of an oxytocic during or immediately after the delivery of the baby, early cord clamping and cutting and controlled cord traction to deliver the placenta.

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Traditionally, oxytocin & ergot preparation have been used as active management of the third stage of labor. 15 methyl $PGF_{2\alpha}$ is one of the first analogues developed for human use. It is potent uterine stimulants, which reduce both the duration of third stage and blood loss. It has the advantage that it can be given by IM route and intramyometrial injection and the action lasts for several hours. Different studies have found that intramyometrial injection of 15 methyl $PGF_{2\alpha}$ is very effective in the management of atonic PPH even when all other oxytocic failed.

Hence, the rational behind this study is to find out whether the prophylactic use of intramyometrial 15 methyl $PGF_{2\alpha}$ can reduce the incidence of PPH and further it can be used prophylactically especially in those patients where even minimal blood loss will adversely affect the health of mother.

Methods

This prospective randomized controlled study was conducted in 300 women in BPKIHS, Department of Obstetrics and Gynecology during the year 2004-2005. Patients who were admitted in labor room were chosen for the study after informed consent and fulfilling the inclusion and exclusion criteria.

Inclusion Criteria

Maternal Age <30 yrs, up to Para 4, estimated birth weight up to<3.5 kg, labor duration in primi - 1st stage up to12 hrs and 2nd stage up to $1^1/_2$ hrs, labor duration in multi - 1st stage up to 6hrs and 2nd stage up to 30 mins.

Exclusion Criteria

Previous cesarean section or any other laparotomy scar, multiple pregnancies, intrauterine fetal death, polyhydroamnios, chorioamnionitis,, III ^{o} perineal tear, systemic illness (cardiac disease, D.M, asthma), coagulopathy, grand multi, macrosomic baby, prolonged labor, Rh negative blood group, hypertensive disorder, obese patients (fundus of the uterus is not easily accessible) and hypersensitivity to prostaglandin and methergin.

Once the women were in 2nd stage of labor, she was randomly grouped (computerized generator randomization) to one of the three groups to receive prophylactic oxytocic. Group A received intramyometrial 15-methyl $PGF_{2\alpha}$, Group B received IM 15-methyl $PGF_{2\alpha}$ and Group C received IM methergin 0.2 mg immediately after delivery of fetus. For intramyometrial administration, patient was catheterized, abdomen prepared with betadine and draped in second stage of labor. Five cc syringe with 21 G needle was used. 250 mcg $PGF_{2\alpha}$ was injected transabdominally. While injecting resistance of myometrium was felt, plunger was slightly withdrawn and checked to rule out possibility of intravascular injection of drug.

Immediately following birth of the baby, a sterilized kidney tray was placed in close approximation to the vulva to collect the blood. Episiotomy site was covered with sterile gauze pieces and was discarded. After noting the signs of separation of the placenta, it was delivered by Brandt Andrew's method.

Time required for 3rd stage of labor was noted in all groups. Blood loss in 3rd & 4th stage of labor was estimated by blood & blood clots collected in kidney tray. The other variables measured were need for manual removal of placenta (MRP), requirement of use if additional dose or any other oxytocics, presence of atonic PPH , any side effects of drugs. The data were analyzed with Epi- Info and STATA statistical software. Quantitative variables were summarized by means and S.D variables, following non- normal distribution were summarized by median and range. Median values were compared using Kruskal –Wallis values test followed by wilcoxon ranson test as post – Hoc ANOVA if required was used. Categorical variables were summarized by frequencies (%) & were compared using Pearson chi- Sq. test or fisher exact test.

Results

There were 300 normal parturient – low risk cases of vaginal deliveries, recruited for the study. Majority i.e. 68% of women was between 21-30yrs of age. There were 62.3% (187) primigravidas & 37.7% multigravidas. Mean gestational age was 40 weeks (280.87 days±12.1) and range was from 259 days to 375 days.

Most of the women studied were admitted in spontaneous labor, others were induced either with misoprostol or cerviprime gel. Average hemoglobin (Hb) level before delivery was 11.31 gm% (range- 6.8gm% to 15.1gm%). All 3 groups were well matched in terms of age, gravidiy, parity, gestational age & Hb level (Table 1).

Average birth weight of newborn baby (kg) was 2.93± 0.382 (range: 1.8-3.5). The median duration of active 1st stage of labor was 149 mins (range: 45-480), 2nd stage of labor was 11 mins (range: 2-60) & ruptured membrane was 152min (range: 3-720). However, the differences among different oxytocic groups were not statistically significant. (Table II).

Table I. Comparison of the groups in terms of general characteristics:

	Gr I Intramyometrial $PGF_{2\alpha}$ (n=100)	**Gr II** IM $PGF_{2\alpha}$ (n=100)	**Gr III** IM Methergin (n=100)	P-value
Mean Age (years)	22.9± 4.1	24.04± 4.2	23.3± 3.9	0.152
Primi	64	62	61	
Multi	36	38	39	0.9054
Gest Age (weeks) 37-40>40	4159	5545	5149	0.12
Mean Hb level (gm%)	11.3±1.5	11.21±1.67	11.28±1.34	0.922

Table 2. About labor and delivery outcome

	Gr I Intramyometrial $PGF_{2\alpha}$ (n=100)	**Gr II** IM $PGF_{2\alpha}$ (n=100)	**Gr III** IM Methergin (n=100)	P-value
Median duration of 1st stage (mins)	135 (45-480)	145 (60-360)	150 (45-360)	0.92
Median duration of 2nd stage (mins)	10.5 (2-60)	11 (2-60)	11.5 (3-5)	0.4703
Median duration of ruptured membrane (mins)	150 (5-720)	147.5 (3-720)	155 (3-720)	0.8551

Average duration of third stage of labor was 3.21 ± 0.07 mins & range from 1- 15 mins. Table III shows that those women who received prophylactic intramyometrial $PGF2_{2\alpha}$ had statistically significant shorter duration of third stage of labor compare to both and also those who received IM $PGF_{2\alpha}$ had significant shorter duration of third stage when compared with methergin.

Median total blood loss in 300 parturient was145ml (range: 35- 950). Cases in $PGF_{2\alpha}$ was found to have significantly less amount of blood loss compared to methergin group. With in $PGF_{2\alpha}$ group also, those receiving intramyometrial were found to have significantly less amount of blood loss.

A stratified analysis was done for primary outcome i.e., mean blood loss and subgroups of age, gravidity, parity, gestational age, birth weight of newborn, duration of labor and ruptured membrane in parturient. Except by the weight of newborn all other factors did not appear to influence the amount of blood loss. Higher weight of the babies had found to be statistically significant influenced on the amount of blood loss in all three groups.

Table 3. Duration of third stage of labor

Durations (mins) \ Groups	Intramyometrial $PG_{2\alpha}$ (n=100)	IM $PGF_{2\alpha}$ (n=100)	IM methergin (n=100)
<3	89	62	23
3.1-6	11	36	73
> 6	0	2	4
	Chi square test	χ^2 =90.6155 ;	P-value= 0.0001
Mean (SD)	2.3±0.66	3.04±1.03	4.22±1.58
Range	1-5.4	1-7	2-15
F = 64.35; p-value=0.0001(one way ANOVA to compare mean value)			

Table 4. Amount of blood loss:

Blood loss	**Gr I** Intramyometrial $PGF_{2\alpha}$ (n=100)	**Gr II** IM $PGF_{2\alpha}$ (n=100)	**Gr III** IM Methergin (n=100)	P-value
Median(ml)	110 (35-270)	145 (40-560)	197 (35-950)	0.001

Table 5. Amount of blood loss (ml) in relation to birth weight

Groups / Birth Weight (Kg)	**Gr I** Intramyometrial $PGF_{2\alpha}$ (n=100) Median(range)	**GrII** IM $PGF_{2\alpha}$ (n=100) Median(range)	**Gr III** IM Methergin (n=100) Median(range)	P-value Between groups
1.8-2.5(n=50)	75 (35-150)	125 (50-200)	135 (35-500)	k-wH=11.09 p=.0039
2.6-3(n=138)	110 (45-270)	130 (40-560)	200 (45-950)	k-wH=22.79 p=0.000
3.1-3.5(n=112)	127.5 (65-260)	170 (60-540)	225 (110-540)	k-wH=26.52 p=0.000
Between birth weight p value	k-wH=15.54 p=0.004	k-wH=5.99 p=0.05	k-wH=8.43 p=0.0147	

Incidence of PPH (>500ml) was 3.3%. The proportion of women noted to have PPH were highest (6%) in methergin group; 4% in IM $PGF_{2\alpha}$ and none in intramyometrial group. The additional dose of the drug was required in one case in IM $PGF_{2\alpha}$ group and three in methergin group. However both were not statistically significant. There was no cases of retained placenta in any of the groups. Diarrhea was the most common side effects observed (63 out o 300 i.e. 21%). Almost all of them are from $PGF_2\alpha$ group but that was transient only. IM group had significantly higher proportion than intramyometrial group (48% Vs 15%). Headache, nausea, vomiting was other side effects noted and were seen in only few women and were mild, transient and the problem required no active intervention.

Uterotonic action of 15-methyl $PGF_{2\alpha}$ has been well established. Cochrane Database has done systemic reviewed of seventeen misoprostol and eight intramuscular prostaglandin trial on 2002 and concluded that injectable prostaglandins are associated with reduced blood loss in the third stage of labor. (Weighted mean difference: 70mls. 95% CI: -73 –67mls) when compared to conventional uterotonic but have more side effects.

Different literature have shown that intramyometrial $PGF_{2\alpha}$ is very effective in treating atonic PPH even when all other measures failed and thus avoid surgical intervention, which is last resort. There are only few studies done with intramyometrial $PGF_{2\alpha}$ as prophylactic 3rd stage management, which shows

Table 6. Prophylactic oxytocics –Side effects

Side Effects	Intramyometrial $PG_{2\alpha}$ (n=100)	IM $PG_{2\alpha}$ (n=100)	IM methergin (n=100)	Statistical significance-χ^2	p-value
Diarrhea (n=63)	15	48	0	72.69	0.000
Headache (n=7)	6	1	0	9.068	0.0107
Vomiting (n=3)	1	2	0	2.02	0.364
Nausea (n=1)	1	0	0	2.006	0.366
Nil (n=226)	77	49	100	-	-

Discussion

Prostaglandins are 20- carbon atom “fatty acids” with a 5- member (cyclopentane) ring and two-side chain and the term were named by Von Euler (1935). Prostaglandins are named A to I depends upon the structure of the carbon ring. 15- methyl $PGF_{2\alpha}$ is a synthetic compound that structurally resembles the naturally occurring prostaglandins and is one of the 1st analogues to be developed for human use.

significant less blood loss compared to conventional uterotonics. Thus present study was carried out especially to see the efficacy of $PGF_{2\alpha}$ by intramyometrial or IM route, in reducing blood loss.

Three hundred low risk normal vaginal parturient were assigned to this study. We did not take high-risk cases for PPH as it may cause bias in the study. In the present study the average amount of blood lost at/ after delivery of placenta in one hour of observation by using

prophylactic intramyometrial $PGF_{2\alpha}$, which was 119.8ml compared to intramuscular $PGF_{2\alpha}$, which was 172.65ml, and intramuscular methergin, 225.8ml. This was comparable to the other studies[2,3,4,5,6,7], since there are not many studies on blood loss during vaginal deliveries using intramyometrial $PGF_{2\alpha}$, we compared to the blood loss during cesarean section.

Even mean duration of 3rd stage of labor (mins) is comparable with other studies. [2,4,5,6,7,8]

Thus it could be proposed that, $PGF_{2\alpha}$ causes the process of placental separation faster and shorter the duration & decrease blood loss.

In present study those parturient, who received prophylactic intramyometrial $PGF_2\alpha$ had no PPH, not required additional dose and not required any other form of other oxytocics. This might be explained by a sustained contraction of the uterus and subsequent reduction of blood loss. This could also be attributed to the fact that only low risk cases were taken in this study. Side effects like headache, vomiting, nausea were seen more common with $PGF_{2\alpha}$ but incidence was too low to allow for a meaningful analysis. Cochrane Database Systemic Review 2004 showed other side effects like abdominal pain, shivering and pyrexia (> 38^o c) in some studies with $PGF_{2\alpha}$. In this study, we did not follow up these women in long term basis. But since none of the women came back with postpartum endometritis and secondary PPH, we assume that prophylactic use of intramyometrial $PGF_{2\alpha}$, does not increase risk of endometritis.

Conclusion

Routine "active management" of 3rd stage of labor with $PGF_{2\alpha}$ is superior to methergin in terms of blood loss & PPH. Moreover intramyometrial administration of $PGF_{2\alpha}$ is better than IM. Routine clinical application of direct intramyometrial injection of 15 – methyl $PGF_{2\alpha}$ is recommended in view of its easy performance, excellent hemostasis, minimal side effects and good prognosis especially in domiciliary or rural settings and especially in those patients where even minimal blood loss will adversely affect the health of mother.

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