Vaginal Micronized Progesterone and Intramuscular 17 α OH Progesterone in Threatened Preterm Labour before 34 Weeks of Gestation

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ABSTRACT

BACKGROUND

Prematurity is a major cause of perinatal mortality and short- and long-term morbidity. Preterm birth before 34 weeks constitutes 40% of total and contributes to majority of mortality and morbidity. Threatened preterm labour (PTL) is diagnosed by painful palpable uterine contraction at least once per 10 minutes and may or may not be associated with cervical changes. Calcium-channel blocker and oxytocin antagonist were shown to delay delivery by 7 days, β_2 - agonist drugs delay by 48 hrs., respectively, but they carry more side effects. Magnesium sulfate has not been proved to have effective tocolytic action. There is insufficient data about the effects on the baby of these tocolytic drugs. Progesterone is essential for the maintenance of pregnancy and acts by establishing uterine quiescence and maintaining cervical length by different mechanisms. Progesterone has been administered as oral capsule, vaginal gel or suppository, or intramuscularly in different trials to show the efficacy and safety of progesterone in prevention of recurrent preterm delivery. Different routes have variable efficacy and different side effect profiles when used in preterm labour. The aim of this study is to assess the efficacy and tolerability of vaginal micronized progesterone compared to intramuscular 17 α OH progesterone caproate in management of threatened preterm labour before 34 weeks of gestation.

METHODS

100 pregnant women with threatened preterm labour before 34 weeks of gestation and fulfilling inclusion and exclusion criteria were randomized into two groups. One group received vaginal micronized progesterone 200 mg twice daily and other group received I/M 17 α OH progesterone caproate 250 mg twice in a week. Cases were followed up till 6 weeks postpartum.

RESULTS

Efficacy and tolerability of progesterone in two different routes for prevention of PTL were compared by statistical analysis of data using chi-square test and student-t test. Efficacy of both routes is similar as determined by primary outcome like gestational age at delivery admission, delivery interval, and birth weight. Vaginal group has significantly lesser side effects in comparison to IM group.

CONCLUSIONS

Vaginal progesterone was as effective as intramuscular progesterone in reducing preterm birth in threatened preterm birth with fewer side effects in vaginal route. Larger studies are required to confirm the findings.

KEY WORDS

Threatened Preterm Labour, Tocolytic, Progesterone, Vaginal, Intramuscular, 17 α OH Progesterone Caproate, Perinatal Outcome

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BACKGROUND

Prematurity is a major cause of perinatal mortality and short and long term complications including disability and impediments in growth and mental development.^{1,2} Rates for preterm birth have been reported between 6% and 12% and 40% of all preterm births occur before 34 weeks and they contribute to majority of morbidity and deaths.^{2,3}

Incidence of preterm labour is high in patients having H/O previous preterm birth, short cervix or threatened preterm labour.² Threatened preterm labour means the presence of uterine activity (contractions) with or without cervical changes after 20 weeks and before 37 weeks gestation.^{2,3,4} In cases of early threatened PTL at <34 weeks gestation, prognosis is often poor.^{3,4}

Wide variety of agents are being advocated for preventing uterine contraction and thus to prevent preterm birth in high risk group.^{5,6,7,8} Calcium-channel blockers, oxytocin antagonist, β_2 agonists, Magnesium sulphate have been tried for decades for prevention of preterm birth in patients at risk of preterm labour.^{5,6,7,8} Same drugs have also been tried for management of threatened PTL.^{5,6,7}

Meta-analysis indicated that Ca-channel blocker and an oxytocin antagonist can delay delivery by 2-7 days, β_2 - agonist drugs delay by 48 hrs., but all these drugs carry more side effects.^{4,5,6,7,8} Magnesium sulfate is a less effective tocolytic agent but has neuro-protective effect.⁸ There are insufficient data about the effects on the baby of these tocolytic drugs. (RCOG Green top guidelines, 2011).⁸

Progesterone is essential for maintenance of pregnancy and helps in prolongation of pregnancy.⁹ It acts primarily through establishing uterine quiescence and maintains cervical length by a) It has immunosuppressive activity against the activation of T-lymphocytes & blocks effects of oxytocin on myometrium, b) It is a potent inhibitor of formation of gap junctions between myometrial cells, c) Local changes in progesterone or Oestrogen/Progesterone ratio suppresses calcium-calmodulin-myosin light chain kinase system, reducing calcium influx and preventing alteration of the resting potential of smooth muscle.⁹ Progesterone has been administered as oral capsule, vaginal gel or suppository, or intramuscularly in different trials to show the efficacy and safety of progesterone in prevention of recurrent preterm delivery.^{10,11,12,13,14,15,16} Oral administration has better patient compliance but there is variability in the plasma concentrations of the drug due to personal variation in gastric filling and entero-hepatic circulation, also this route might be associated with side effects such as nausea, headache, sleepiness, etc.^{10,11,13} The vaginal route results in higher local concentrations in uterus but its blood levels are low and side effects are minor like vaginal discharge, itching, irritation, yeast infection, rarely breast engorgement,^{10,11,13} while progesterone administered intramuscularly results in optimal blood levels and side effects are restricted to injection site, like pain, swelling, itching, bruising and systemic side effects like nausea, vomiting, pain abdomen, diarrhoea.^{10,12,14} Screening for high risk factors for PTL is not always possible in our set up. As a result many cases are admitted with threatened preterm labour with associated risk factors like UTI, past H/O-PTL. Progesterone is the physiological agent which can prevent preterm labour evidenced by different meta-

analysis.¹⁰⁻¹⁶ So this study was conducted to assess the efficacy and tolerability of vaginal micronized progesterone compared to intramuscular 17 α OH progesterone caproate in management of threatened preterm labour before 34 weeks' gestation.

METHODS

It is a randomized control study. Sample size was 100 with 50 in each group was taken depending on availability of cases during three years period and calculating number needed to treat. Pregnant women attending Obstetric emergency of NRS Medical College with threatened preterm labour before 34 weeks of gestation satisfying exclusion criteria, were enrolled for the study from 2012 to 2014. Threatened Preterm labour among attending patients was diagnosed by painful palpable uterine contraction with a frequency of at least once for every 10 minutes and with or without any cervical changes (position, consistency, length and dilatation). Detailed history was taken to find out risk factors for preterm labour. Multiple gestations, dribbling, evidence of chorio-amnionitis, cervical dilatation >4 cm, diabetes, foetal anomaly, IUGR, hypertension, active liver-disease, active thrombo-embolism were excluded from the study. Gestational age was confirmed clinically and by USG of early weeks of gestation. Per abdominal examination regarding uterine activity, tone and tenderness, liquor volume, fundal height and presentation, FHS were noted. Per speculum examination were done to exclude any dribbling or bleeding P/V, and to see the position and length of cervix. Per vaginal examination were done to detect position, consistency, length, dilatation of cervix, head station, presentation of fetus, membrane status. Patients were screened for exclusion criteria by clinical examination. Those cases fulfilling the inclusion criteria were counselled regarding the study and written consent were taken and each case was randomly allocated in one of the two groups. 100 pieces of similar folded papers, fifty having A and fifty having B written within were taken and each patient was asked to lift one out of those. Those receiving A were allocated to vaginal progesterone and those having B to IM progesterone. One group received vaginal micronized progesterone 200 mg daily and another group receiving 17 α OH progesterone caproate 250 mg I.M. in a week. Progesterone was continued up to 37 weeks or till active labour started which ever was earlier. Then the cases were followed up through labour, delivery and postnatal period

Statistical Analysis

Antepartum, intrapartum and perinatal outcomes were compared between two groups by statistical analysis of data using chi-squares test and student-t test, and Fischer's exact test.

RESULTS

Efficacy and tolerability of progesterone in two different routes for prevention of threatened preterm labour were compared Antepartum, intrapartum and perinatal outcomes were compared between two groups by statistical analysis of data using chi-squares test and student-t test.

	Group Receiving Vaginal Progesterone (n=50)	Group Receiving IM Progesterone (n=50)	Chi Square	p
Age of mother (average in years)	23.72±5.5219	23.36 ±5.32518	0.179	=0.9143
Parity	Primi-30, multi-20	Primi-28, multi-22	Chi-squared test, X2=0.0411	p value-0.8394
Below poverty line	26	28	X2=0.0403	p value-0.8410
H/O spontaneous preterm birth	10	12	X2 =0.583	p Value -0.8092,
Chorioamnionitis	1	0		, p value-1.00
Mean gestational age ± SD	230.4 days ± 8.005927	228.96 days ±9.930288	Student t test, 95% CI -5.0286 to 2.1486	p value=0.4278

Table 1. Comparison between the Two Groups Regarding Epidemiology and Risk Factors

There was no significant difference in age distribution (p Value=0.9143), distribution of parity between two study groups. Study group receiving vaginal progesterone have 60% primigravida and 40% multigravida mother, study group receiving IM progesterone have 56% primigravida. (Chi-squared test X2=0.0411, p value-0.8394).

There was no statistically significant difference between two groups as far as socioeconomic status is concerned (X2=0.490; p value-0.4839). H/O of previous preterm labour was present in 10 cases of vaginal progesterone group and 12 cases of I/M progesterone group (X2 =0.583 P Value -0.8092). One case of Chorio-amnionitis were present in vaginal progesterone group. 84% of vaginal progesterone receiving group and 80% of IM progesterone receiving group were admitted at 32 to 34 weeks of gestation. Student t test is applied which shows there is no statistically significant difference between two study groups regarding mean gestational age at admission.

	Group Receiving Vaginal Progesterone (n=50)	Group Receiving IM Progesterone (n=50)	Statistical Analysis
Gestational Age at Delivery Mean Gestational Age ± SD	236.82 days± 8.589719	235.82 days ± 10.45826	Student t test 95% CI -4.7981 to 2.7981 DF 98 p value=0.6025
Delay of Delivery (Days)Mean Latency(days)± SD	7.02±3.755214	6.9±4.087063	Student t test 95% CI -1.67766 to 1.43766 p value=0.8788

Table 2. Relation of Gestational Age at Delivery and Delay of Delivery between the Two Groups

The mean gestational age at delivery for each group was first calculated and then T test was applied to calculate the p value. Result shows there is no statistically significant difference regarding gestational age at delivery between two different routes of administration of progesterone. Mean latency period for each group was calculated first and then Student t test was applied to calculate the p value. Result shows no statistically significant difference between two study groups.

Birth Weight	Group Receiving Vaginal Progesterone (n=50)	Group Receiving IM Progesterone (n=50)	Statistical Analysis
<1.5 KG	2	4	
≥1.5- <2 KG	14	15	
≥2-<2.5 KG	32	29	
≥2.5 KG	2	2	
Mean(Kg)±SD	2.094±0.299258	2.048±0.335176	p value=0.4709 DF=98 95% CI=-0.1721 to 0.801

Table 3. Relation of Birth Weight in Both the Study Groups

Mean birth weight for each group was calculated first and then student t test was applied to calculate the p value. Comparison of two means and standard deviations by student t test shows there was no statistically significant difference in birth weight of babies in two different routes(p value-0.4709)

Mode of Delivery	Group Receiving Vaginal Progesterone (n=50)	Group Receiving IM Progesterone (n=50)	Statistical Analysis
ND	32	30	Chi-square test X ² =0.489 p value-0.7832
Instrumental	6	5	
LSCS	12	15	

Table 4. Relation of Mode of Delivery between the Two Study Groups

There is no statistically significant difference of mode of delivery between two groups. (p value-0.7832)

Other Outcome Measures	Group Receiving Vaginal Progesterone (n=50)	Group Receiving IM Progesterone (n=50)	p
Prolonged Labour	1	2	0.9580
Fetal Distress	15	18	0.6706
NICU admission	16	17	1.0
Apgar Score<7	12	14	0.8197
Neonatal Sepsis	5	3	0.7124
Baby with RDS	7	8	1.00
Need for Mechanical ventilation of baby	8	9	1.00
Convulsion	3	1	0.6098
Neonatal Death	5	3	0.7124

Table 5. Comparison between the Two Groups Regarding Other Outcome Measures

Table shows 6% of vaginal progesterone receiving mothers have complained various side effects such as vaginal irritation, itching, white discharge, whereas 22% of mother receiving IM progesterone have complained pain at injection site, redness, itching, bruises, breast engorgement etc. Fisher's exact test shows IM progesterone group have more side effect than vaginal group which is statistically significant (p value=0.0407).

DISCUSSION

In the present study there is no significant difference between vaginal and IM progesterone groups regarding baseline characteristics like maternal age, parity, gestational age at admission, risk factors. Efficacy of both routes are similar as determined by primary outcome like gestational age at delivery (p value=0.6025), admission delivery interval (p value=0.8788) and birth weight (p value=0.4709). In the study of Borna and Sahabi¹⁶, Bomba opon DA,¹⁷ Arikan et al¹⁸ progesterone vaginal suppository was compared with placebo after initial tocolysis in PTL and there was significant longer latency period in vaginal progesterone group. Mohan and Regmi et al¹⁹ Compared the effect of I/M progesterone with placebo after treatment with tocolytic and they also found longer latency period in progesterone group.

The admission – deliver interval of these studies were significantly large than our study because majority of them used acute tocolysis before use of progesterone. There is also no significant difference in duration of labour (p value-0.9580), foetal distress (p value-0.6706), mode of delivery (p value-0.7832), NICU admission (p value-1.00), Apgar score <7 at 1 min (p value-0.8197), occurrence of neonatal sepsis(p value-0.7124), RDS (p value-1.00), need for mechanical ventilation(p value-1.00), convulsion (p value-0.6098), neonatal death (p value-7967) in two groups. Mohamed Ahmed Hussein et al⁴¹ also founds similar outcome between two groups regarding foetomaternal adverse outcome.

Azza A and ABD El Hameed,²⁰ found in their study that vaginally administered progesterone was nearly as equally effective as intramuscular progesterone in the prevention of PTL. Gharib MN and others⁽²¹⁾ drew a comparison between the vaginal and intramuscular groups to prevent preterm labour in women with single fetus at risk of premature birth and found less cases of preterm delivery in the vaginal group. More side effects were seen in the intramuscular group. In contrary, the OPPTIMUM Study⁽²²⁾ a multi-center, randomized, double blind trial and largest study on vaginal progesterone in PTL found no effect of progesterone. In the updated meta-analysis, by Stephen Wood et al⁽²³⁾ progesterone treatment did reduce delivery <37 weeks' gestation and increase latency to delivery, but they found that, this treatment effect was not evident in the high-quality trials. Ahmed N. Askalani,⁽²⁴⁾ et al found vaginally administered progesterone was nearly as equally effective as intramuscular progesterone in the prevention of PTL in women at risk, with superior effect with vaginal route. In the present study, 6% of vaginal and 22% of IM progesterone receiving mothers have complained of various side effects i.e vaginal group has significantly lesser side effects in comparison to IM group. (p value=0.0407) Study by Mohamed Ahmed Maher Hussain et al 2011¹⁵ reported side effects in 19.1% in intramuscular group but only in 7.6% in vaginal group. M. N. EL-Gharib & T. M. EL- found less undesirable effect with vaginal route.²¹

CONCLUSIONS

Vaginal progesterone was as effective as intramuscular progesterone in reducing preterm birth with fewer side effects. Future studies should identify the most appropriate route in women at risk.

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