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A Study Comparing Efficacy of Morning Dosage versus Evening Dosage of Oral Micronised Progesterone Sustained Release SR 300mg in Prevention of Preterm Labour

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Abstract

Objectives: To assess the efficacy of oral micronized progesterone SR 300 in preventing preterm labour after arresting it, with changes in dosage timing. The main purpose of this study is to find out whether there is a clinico pharmacological correlation if same drug is given at different timings

Materials and Methods: Prospective randomized study was done at our institution. Total sample size of 130 women who came in preterm labour and process of preterm labour was arrested with Tocolytics were included in the study group. Sample was divided into 2 groups of 65 womens in each group in view of prevention of preterm labour. One group was given MNP SR 300 at 9am and 2nd group was given MNP SR 300 at 9pm by oral route. They were studied for the difference in maternal outcomes like prolongation of gestational age at delivery and neonatal outcome like birth weight, maturity, morbidity and mortality.

Results: Both the group were comparable with respect to age and parity. Our study showed that there was no statistically significant difference with respect to maternal and fetal outcome with changes in timings to two groups who were given MNP SR 300 orally at 9am and 9pm.

Conclusion: More studies on big samples are recommended to further analyse our results, since this the only study till date.

Keywords: Preterm labour; Prematrity; Micronized Progesterone; Tocolytics; .

Introduction

As per WHO and FIGO spontaneous preterm labour is labour resulting in birth before 37 completed weeks. (259 days of gestation age based on first day of last menstrual period). The prevalence of preterm labour ranges from 5% in developed countries to 25% in 3rd world countries. 28% of total early neonatal death are due to pre term birth. The children who survived, have morbidity associated with physical and psychological issues.[1]

According to WHO statistics number of preterm birth every year is nearly 15 millions out of which one million die due to birth complications.[2] India has got largest number of preterm birth which is 3.5 millions per year leading to financial burden.[3]

The accepted treatment of preterm labour is emergency tocolysis, which may prolong gestation by 2 to 7 days , which is not sufficient to reduce the perinatal morbidityandmortality, only advantage of this is providing time for corticosteroid administration and maternal transport to a tertiary centre.[4,5]

Also these patients subsequently develop premature labour and delivery. So the other supplementary treatment which will avoid side effects of tocolytics and can be given safely for long term was searched for. The progesterone

was given preference for this purpose. The two observations were the basis of progesterone supplementation for prevention of PTB. (A) Functional withdrawl of progesterone activity at uterine level is seen at the onset of labour both at term and preterm.[6] (B) The salivary progesterone has been a biomarker of preterm birth. In women between 24 to 36 wks of gestation it was found in lower concentration in a group having risk factors for preterm labour.[6] Progesterone treatment as adjuvant following successful tocolysis was found to be effective in reducing the prevalence of subsequent preterm delivery by prolonging period of gestation. Progesterone has got multifold action like maintenance of uterine quiescence through out pregnancy by suppressing genes necessary for uterine contractility , up regulating system like nitrous oxide which causes relaxation of muscle and suppress release of cytokines and prostaglandins. it creates estrogen antagonism by inhibiting estrogen receptors in uterine myometrial cells, blocks oxytocin receptors inhibits prostaglandins synthesis and inflammation.[7] Due to safety, satisfactory results and minimum side effects it soon became a popular molecule on which different trials were taken. That's why SFMC recommended progesterone supplementation as a standard care for prevention of preterm birth particularly in associated risk factors.[8] Also FDA has approved and recommended progesterone supplement in such cases in the form of Injectable 17 alpha hydroxyl progesterone and natural micronized progesterone by various routes.[9]

Trials has been taken on different types of progesterone molecules for the prevention of preterm labour, like dydrogesterone, 17 hydroxy progesteronecarporate and MNP. Amongst these MNP was found to be superior to other two.[10]

MNP can be used by two routes that is vaginal and oral. However, Vaginal route causes messy side effects like vaginal discharge, pruritis, irritation and itching which affects the compliance . that's why we have opted for MNP by oral route, to avoid side effects of vaginal route.[11,12] Also we got good number of studies with maintenance of Tocolysis with oral micronized progesterone for prevention of preterm labour with satisfactory results.[11,13] Surveillance done by piyush et all has recommended the use of NMP SR strongly.[14]

Recently MNP is available in SR (sustain release) form which has got the benefits due to the special manufacturing technology. The benefits of oral administration the sustain release tablet formulation currently marketed contains progesterone in methyl cellulose base which hydrates in GI tract providing slow release matrix for gradual release of progesterone . this achieves a constant release pattern over 24 hours while demonstrating long elimination half life of 18 hours with high protein binding capacity leading to once a dose convenience . This also avoids dose dumping event and minimizes side effect.[15] It has got better compliance and convenience of patients.

In clinical practice it is important to consider circadian rhythm in pharmacokinetics and cell response to therapy in order to design proper protocol for drug administration. Drug pharmaco kinetics can be modified according to the timings of drug absorption. some drug has better absorption and results in taken in morning than evening and vise versa . guideline protocol regarding timing of particular drug administration is based on this principal.[16] So considering the importance of timing factor we decided to give MNP SR 300 preparation at different timings and comparing the efficacy and outcome results of both groups.

Materials and Methods

A prospective randomized controlled study was conducted in department of Obstetrics and Gynaecology, D. Y. Patil Medical college, Pimpri, Pune 18.

Period of study: June 2017 to May 2019.

The ethical committee permission was obtained from the Institution.

The pregnant women with period of gestation between 26 wks to 34 wks who were admitted for threatened preterm labour received IV fluids for hydration, betamethasone 12mg IM followed by another dose of 12 mg after 24 hours and tocolysis with nifedipine as per recommendation by RCOG and AICOG. In our research the choice of tocolytic has been nifedipine, it is a calcium channel blocker and reduces Intracellular calcium leading to relaxation of muscle. It is commonly used due to ease of oral administration, low cost and is recommended by RCOG and ACOG due to lower side effect profile.[17]

With the initial dose of 20mg oraly followed by 20mg after 30mins and 20mg every 3 to 8 hourly for 48 to 72 hrs according to response with maximum dose not exceeding 160mg in 24 hrs.[5] The detail evaluation of each case was done by a thorough history, general, physical and obstetrical examination with routine antenatal investigations and ultrasonography.

After confirmation of threatened preterm labour all patients initially were managed with tocolytics, steroids and antibiotic prophylaxis. After complete arrest of labour that is a 12 hours of uterine contraction free period, these patients were enrolled in our study by applying inclusive and exclusive criteria. Informed consent was taken after counseling.

Inclusion criteria were singleton normal pregnancy with vertex presentation intact fetal membrane with absence of labour signs and symptoms.

Exclusion criteria were multiple pregnancy, placenta previa, Premature rupture of membranes, fetal growth restriction, fetal congenital anomaly, fetal distress, hypertensive disorders, all medical disorders in pregnancy vizheart disease, liver disorders, Gestational Diabetes Mellitus, Thromboembolic disorders etc.

Sample size formula: Assuming a difference of 1 week or more in the period of gestation to be significant and taking 5% level of significance, the required sample size was found out to be 46 patients in each group the power of such a procedure was 91%. In our study we have sample size of 65 patients in each group.[18]

Patients were randomly divided into 2 groups having 65 women in each group . After patients were completely stabilized they were discharged and monitored on outdoor basis. In this period regular antenatal check up and necessary investigations if required were done. Patient were given MNP-SR 300mg orally in the morning at 9 am (group 1) and at night 9 pm (group 2) upto 37 weeks or upto the delivery of fetus if earlier. This dose has been shown to deliver high concentration of progesterone with least side effects.[19]

The basic outcome of the study was to know prolongation of pregnancy in terms of days gained until delivery. Secondary outcome was to note number of preterm birth weight, geatational age of delivery , neonatal condition at birth and admission, need for NICU admission, neonatal morbidity and mortality.

Statistical analysis was performed using chi square test, Fisher exact for qualitative variables and unpaired Student t test for quantitative variable. We used Winpepi software for this purpose. P value of 0.05 was considered to be statistically significant.

Observation and Results

After collection of data we have presented it in 4 tables for comparing the difference between two groups.

Table number 1 shows the comparibility of both groups to know wheather they are comparible or not regarding Age, Parity, Risk factors for preterm labour, Gestational age at the time of admission and status regarding labour.

Table 1: Baseline characters in 2 groups. n=130.

			Group 1 (n=65)	Group 2 (n=65)	P value
1	Age (years)		25.12 +/–2.76	24.28+/2.36	0.064
2	parity	0	24	34	0.061
		1	33	9	
		2	08	02	
3	h/o previous Preterm birth		09	03	0.127
4	presence of Risk factor		22	24	0.715
5	Gestational age In wks		31.87+/–2.07	32.33+/–1.92	0.22
6	cervical dilatation In cms		1.72+/–0.38	1.66+/–0.35	0.351
7	Cervical Effacement		41.20+/–9.98	41.5+/–7.11	0.844

As seen from above table and statistical P value of each character shows that both the groups are comparible with each other.

Table number 2 shows the result and outcome of our treatment regarding effect on gestational age at delivery and prolongation of pregnancy in days.

Table 2: Outcome and Result of treatment.

	Outcome parameters	group 1 (n=65)	group 2 (n=65)	P value
1	Gestational age at delivery (wks.)	35.90+/–2.14	36.12+/–1.92	0.538
2	preterm birth	25	23	0.713
3	prolongation of pregnancy in days	33.71+/–15.81	34.84+/–16.13	0.687

As seen in table number 2 there seems to be no statistically significant difference between the two groups.

Table 3 shows neonatal outcome in which we have considered birth weight, Apgar score, Morbidity like RDS, Sepsis, NICU admission status including duration and Neonatal Mortality.

Table 3 shows there is no statistical significant difference regarding different factors for considering neonatal outcome in both groups.

Table 4 shows distribution of cases in terms of neonatal birth weight in both groups.

Table 3: Neonatal Outcome.

	Parameters	Grp 1	Grp 2	P value
1	Birth weight (grams)	2.36+/–0.54	2.42+/–0.58	0.224
2	Apgar score at birth 1min <7	2	6	0.137
3	Apgar score after 5 mins< 7	1	2	1.0
4	Low birth weight in grams	25	23	0.717
5	Respiratory distress syndrome	11	9	0.672
6	Sepsis	4	3	1.0
7	Hyper bilirubinema	1	2	1.0
8	Others	3	2	1.0
9	NICU admissions	12	13	0.824
10	Duration of admission	4.25+/–3.25	4.30+/–3.61	0.912
11	Neonatal Mortality	2	1	1.0

Table 4: Birth weight wise neonatal outcome (Grams).

	Group 1	Group 2	
1000 to 1500	2	1	0.9
>1500 to 2000	10	11	
>2000 to 2500	11	13	
>2500	42	40	

As seen from P value regarding 3 groups there is no statistical significant difference in both groups.

It is clear from the conclusion of these 4 tables that the outcome do not differ with change of timming of drug delivery MNP 300SR which are given at two different timings that is morning and evening.

As our study is first and unique study of its type we could not get any previous statistic for comparison of out results of MNP 300SR given at different timings, that is morning and evening.

As mentioned above, sample were divided into 2 groups, first group of 65 patients was advised to take MNP-SR300mg at 9am and second group of 65 patients was advised to take the same at 9pm. Both the groups were comparable with respect to age ,parity and presence of risk factor for preterm birth. All clinical characteristics were noted between 2 groups for analysis. Mean gestation age at recruitment was 31.87 wks in first group and 32.33 in second group. The mean period of prolongation was 33.71 days in first group and 34.84 days in second group which was not found to be statistically significant . Similarly gestation age at delivery was 33.71 in first group and 34.84 in second group, which was not showing any statistically significant difference.

Both the groups tolerated MNP SR 300 orally well without any significant side effects which is advantage of sustained release preparations.[19]

Mean birth weight in first group was 2.36 as opposed to 2.42 in second group which was also found to be of no statistical significance. The number of preterm birth was 25 in first group and 23 in second group showing no statistically significant difference.

There was also no significant difference in Apgar score at birth and after 5 minsin both the groups. The number of low birth weight babies in first group was 25 and second was 23 which showed no statistic difference. Similarly the rate of different complications like RDS, sepsis, Hyperbilirubinemia and others were not showing statistical significant difference in 2 groups. There was no statistical significance with respect to duration of admission, NICU admission and neonatal mortality in both groups.

Discussion

Whenever any drug trials are taken pharmacologist take into consideration different aspects of the drugs like drug absorption, diurnal variation, half life of the drug etc which can affect the efficacy and safety of the drug and results for the disease cure. About diurnal variation of progesterone there has been conflicting reports. We have also mentioned about the significance about the drug timings. Satyanarayanet also insist about significance of timing of drugs to have satisfactory results and safety.[20]

Basically we decided to do study on this subject to know about any difference in prevention of preterm birth with MNP SR 300 if it is given at different times of the day because we could not get any article on this type of study after extensive review of literature. Our study focuses on the clinico pharma cological correlation of the action of progesterone depending upon timing of dose.

We were inspired to select this topic after going through the article by Bolk et all. In their studies they have changed their regime of L Thyroxine the standard does of which is recommended by drug information resources to be taken 30 minutes before breakfast on empty stomach. Contrary to this Bolket all noted that results were better after changing the administrative time to evening instead of routine timing of morning. They concluded that L thyroxin taken according to change in timing by patients of primary hypothyroidism is associated with higher

thyroid hormone concentration and lower TSH concentration without disturbing circadian rhythm compared to routine regime of L thyroxin in early morning.[21] This was supported by many other trails.[22]

The title of our manuscript topic is comparison of MNP SR 300 in two groups regarding change in the timing of ingestion, that is between morning and evening dose with respect to efficacy.

It has been observed that the trials taken on this subject has used progesterone supplementation in a fixed dose at bed time. In clinical practice it is important to consider circadian rhythms in pharmacokinetics and cell response to therapy in order to design a proper protocol for drug administration. A drug pharmacokinetics can be modified according to the time of drug absorption. Some drug have better action and results if taken in morning time than evening . The base of the guideline protocol for any drug is the chronobiology that is way in which biological processes are expressed throughout 24 hrs . This is relatively new thinking which pays attention to the importance of not only the quantity of the drug that is administered but also when it is administered.–eg- Acetaminophen or theophylline shows different pharmacokinetics in the morning time as compared to evening.[20]

While going through the literature related to MNP SR 300 in preterm labour we have not seen a single article where there is comparison of the results after change in the dose timing. Our results showed that there was no statistically significant difference with respect to maternal and fetal outcome in two groups who are given progesterone supplement at 9 am and 9 pm and we recommend further more studies on large samples.

In present era more focusing on administration of drugs with respect to the timings is advised. According to chronopharmacology the drug administration should be done at appropriate time at which it shows maximum therapeutic effect and minimum adverse effects.[23]

Conclusion

Our study conclude that the results of maternal and fetal outcome are similar irrespective of drug timing in both the groups so patient can be advised to take her drug as per her convenience at fixed time. This might be due to absence of diurnal variations in progesterone and the action of sustained release MNP SR 300 which lasts for 24 hours irrespective of time, only thing required is to keep fixed timing of medication daily.

We recommend that more studies on large samples should be done to further analyse the results if there is a change in timing of MNP SR 300. As there was no study found in literature we could not compare our results with it.

Abrevation

MNP SR 300: Micronisednatural progesterone sustained release 300 mg.

PTL : Preterm labour.

PTB: Preterm birth.

SFMC: Society for maternal-fetal medicine.

References

1. Dr Seemapandey, Chapter 1 Epidiomology of preterm labour, in labour in FOGSI focus book on prevention of preterm labour published by FOGSI 2016, edited by Jaideep Malhotra and Narendra Malhotra.
2. WHO preterm birth facts sheets, number 363 updated in November 15, 2015.
3. Blencore H, Cousens S, Ostergaard M, Chout D et all, National regional and world wide estimate of PTB. the lancet 2012, 379(9832), 2162–2172.
4. Manju Chaudhary, Amita Suneja, Neelam B Vaid, kiran Guleria, MMA Faridi. maintenance tocolysis with oral micronised progesterone for prevention of preterm birth after arrested preterm labour. International journal of gynaecology and obstetrics. vol 126 issue 1, july 2014, page 60 to 63.
5. Neema Acharya, chapter 4.2, tocolytics evidence based update, FOGSI focus prevention of preterm labour edited by Jaydeep and NarendraMalhotra 2016. (2 to 7 days).
6. A: Dr AnuradhaKhar, Chapter number 4.1, can we prevent preterm labour.page 28. and B:Raju Sahetya chapter 3.1, page 19, Predictors of preterm birth in FOGSI FOCUS book on prevention of preterm labour, edited by Jaydeep and Narendra Malhotra, june 2016.
7. Suk-Joe-Choi, supplement therapy for prevention of Preterm birth, Review of literature. obstgyaecol science 2017 September 60(5) 405 to 420.
8. Berghella V, Society for maternal-fetal medicine publication committee, progesterone and preterm birth translating clinical trial into clinical practice AMJ.obstandgynecol 2012, 206, 376–86.
9. Ajay mane and Rajendrasinhpardeshi, progesterone in RPL chapter in FOGSI FOCUS, progesterone the feel good hormone . FOGSI publication book 2014, edited by Ashwathkumar R and Nileshbalkawade page 53.

10. Pustonia O, effectiveness of dydrogesterone 17OH progesterone and MNP in prevention of preterm birth in women with short cervix, Journal of maternal fetal and neonatal medicine, july 2017, vol 31,(14) page 1830 – 38.

11. Sherif Ashoush, Osomael. Kady, Gehonai-Hawary, Ahmad Othaman. The value of oral micronized progesterone in prevention of recurrence spontaneous preterm birth randomized controlled trial. Actaobstetrcianetgynacologicascendinvica. vol 96, issue 12, september 2017, page 1460–66.

12. Tomic V, Tomic J, Klaic D Dz, Kasum M, Kunak, Oral dydrogesterone Vs vaginal progesterone gel in the lutueal phase support, randomized controlled trial. Eur.j.obst.gynecol. reproductive biology 2015: 186: 49 – 53.

13. Ruspa C, Boelig MD, Vincenzo Berghellia. Oral progeserone for the prevention of recurrent premature birth systemic review and metaanalysis. American Journal of obstetrics and gynaecology [mfm, vol1, issue 1, march 2014, pages 50 to 62.

14. Piyush Prabhat, Krishnaprasad korukonda. A drug utilization surveillance study to assess the clinical utility of oral natural MNP-SR in high risk pregnancy.NAP-delay study.journal of clinical and diagnostic research . Oct 2018, vol 2(10), page oc 04 to oc 06.

15. Sonia Malik, Korukonda Krishnaprasad. natural MNP-SR and luteal phase: Role redefined. Jornal of clinical and diagnosticRresearch: jcdr. 2016 feb;10(2): qe01–qe04.

16. Nevin FW, Maha Yousif Ahmed S, Batia et all. Chronotherapeutics: Recognising the importance of timing factor in the treatment of disease. Clinical neuropharmcology 42(3) july 2019.

17. Clinical practice guideline tocolytic treatment in pregnancy, Institute of obgyn Royal college of physician Ireland, version 1, guideline number 22, published in april 2013 and revised in april 2015.

18. Prinka Bajaj, Sandhya Jain, Seema Pundir, Ritu Khatuja. The role of micronized progesterone in preterm labour.Indian Journal of obstetrics and gynaecology research . April june 2018;5(2): 253–258.

19. Neetha George, Elavarasi Elamaran, Chapter 4 progesterone for safe motherhood in FOGSI FOCUS, progesterone the feel good hormone, page 27–34, edited by Aswath Kumar, Nilesh Balkawade, published in 2014 by FOGSI.

20. Satyanarayan V, Pavithra Krishnan- Review article chronoparmacology : Tailoring therapy to endogenious rhythms, Journal of international medicine and dentistry. 2015; 2(1): 3–16.

21. Bolk N, Visser TJ, RolsBeek B, Van Domburg RT and Berghout A, effects of evening versus morning thyroxine ingestion on serum hormone thyroid profiles in hypothyroid patients. Clinical endocrinal (oxf) 2007;66;43–48.

22. Shahram Ala, Ozra Akha, Zahra Kashi, Hussain Asagari Adelech Bahar, Neda Sasanpour, Caspian j of internal medicine 2015, summer, 6(3)page 134–340.

23. Dharani DR, Shashirekha CH, Shruthi SL, the study of Chronopharmacology relevance of antihypertensive drugs at a tertiary hospital a prospective observation study, Research article in national journal of physiology, pharmacy and pharmacology. 2018, vol 8, issue 3, page 446–452.