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Is Vaginal Progesterone More Effective to Treat Threatened Preterm Labour than Oral Nifedipine?

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Author`s Contribution

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ABSTRACT

Objective: To compare the effectiveness of vaginal progesterone versus oral nifedipine in the treatment of threatened preterm labor (TPL).

Methodology: This randomized control trial was carried out at Gynae and OBS department of Ibn-E-Siena Hospital, Multan, during a period of six months from December 2020 to June 2021. Participants were randomly allocated to either the vaginal progesterone group or the oral nifedipine group. In Group A, participants received oral nifedipine at a dose of 20mg every 30 minutes for three initial doses, followed by long-acting nifedipine SR 20mg every 12 hours until reaching 37 weeks of gestational age or until cervical dilation exceeded 4cm. In Group B, participants were instructed to use vaginal micronized progesterone tablets at a dosage of 200mg once daily until reaching 37 weeks of gestational age or until cervical dilation exceeded 4cm. Effectiveness, refers to the ability of each treatment option to successfully prolong pregnancy duration in cases of threatened preterm labor.

Results: The mean age of the subjects was 29.6 years, with a standard deviation of 5.44 years. Mean gestational age was 33.32 weeks. In Group A, oral nifedipine showed effectiveness in (73.0%) of the cases. Conversely, Group B, which received vaginal progesterone, exhibited significantly higher efficacy rates, among 57 (90.5%) of the patients (p-value of 0.011). Effectiveness among two treatment modalities was found to be statistically insignificant according to age and parity of the women (p=>0.05).

Conclusion: Study revealed a significant difference in efficacy between the two treatment modalities. Specifically, vaginal progesterone demonstrates superior efficacy compared to oral nifedipine, which underscores the potential advantages of vaginal progesterone in managing threatened preterm labor.

Key Words: Tocolytic therapy, Nifedipine, Progesterone, Preterm labour.

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Introduction

Preterm birth continues to be the most substantial clinical and public health challenge.[1] It is characterized by delivery before 37 weeks of gestation or fewer than 259 days from the onset of a woman's last normal menstrual period. The method of delivery is a crucial consideration in the management of preterm labor. Preterm birth affects 5% to 10% of pregnancies and represents the leading cause of maternal and fetal morbidity and mortality globally.[2] Providing adequate care for premature infants born at or just after the threshold of viability poses significant challenges. Enhancing our understanding of the circumstances or factors contributing to preterm deliveries could enhance neonatal outcomes for infants born prematurely.[3] Preterm infants belong to diverse categories with a range of potential outcomes.[1,4] The incidence of adverse neonatal outcomes is significantly higher in developing regions. In low and middle-income countries, viability, defined as a fifty percent chance of survival with

or without medical intervention, typically occurs around 34 weeks of gestational age.[1,5] Pregnancy outcomes in Pakistani settings are significantly inferior compared to those observed in other global network sites.[6] This discrepancy in outcomes is likely attributed to several factors, including the predominantly low level of education, anemia among reproductive-aged women, undernourishment and a high incidence of preterm and low-birthweight births.[6] Additionally, these outcomes are exacerbated by the often inadequate maternal and newborn care available in these settings.[6] In Pakistan, the perinatal mortality rate stands at 96 per 1000 total births, with prematurity accounting for 8.81% of perinatal deaths.[7,8]

However, there is widespread recognition that preventing or effectively managing preterm labor has the potential to improve neonatal outcomes and reduce healthcare costs.[9] Tocolytic therapy plays a clearly defined role in managing preterm labor, achieving the following goals: facilitating the transfer of the pregnant woman to a tertiary care center, extending pregnancy for at least 48 hours to maximize the beneficial effects of steroids on fetal lung maturity, and prolonging pregnancy in an effort to enhance perinatal outcomes.[9]

Maintenance tocolysis refers to the continuation of tocolytic therapy following the cessation of preterm labor to prevent its recurrence.[10] Among the various tocolytic agents available, including beta-agonists, magnesium sulfate, and calcium channel blockers, oral nifedipine and vaginal progesterone have emerged as prominent options for TPL management. These agents offer distinct mechanisms of action and routes of administration, influencing their efficacy and tolerability profiles. The oral administration route, known for its cost-effectiveness, may be effective in reducing neonatal morbidity, making calcium channel blockers preferable. Nifedipine is considered a safe and effective drug for acute tocolysis, with minimal adverse effects. However, its use for maintenance tocolysis has yielded conflicting results.[10,11]

On the other hand, progesterone plays a vital role in maintaining uterine quiescence and is increasingly utilized in women at high risk for preterm labor, as well as for maintenance tocolysis.[10,12] Nonetheless, the effectiveness of maintenance tocolytic therapy following successful arrest of preterm labor remains a topic of debate. As according to some studies, the efficacy of vaginal progesterone in extending the duration of pregnancy in cases of preterm labor was superior to that of oral nifedipine.[12,13] On the other hand, few studies observed that the in most of the patients, acute tocolytic treatment with nifedipine proved effective.[14] Moreover, incorporating daily vaginal progesterone suppositories led to a notable extension of pregnancy duration, along with a decrease in the incidence of low birth weight and neonatal ICU admissions.[14] However taking above controversial effectiveness this study has been done to observe the effectiveness of vaginal progesterone versus oral nifedipine in the treatment of threatened preterm labor (TPL).

Methodology

This was a randomized Controlled Trial study was conducted at Gynae and OBS department of Ibn-E-Siena Hospital, Multan. Study duration was six months from December 2020 to June 2021. Non probability consecutive sampling technique was used. All the females aged more than 17 years old, singleton pregnancy with gestational age of 24 weeks to 36 weeks with presentation of the threatened preterm labor, defined as uterine contractions occurring before 37 weeks of gestation without cervical dilation of either parity were included. Pregnant women with presentation cervical dilation (>3 cm), patients with known contraindications to receiving either vaginal progesterone or oral nifedipine, including allergic reactions and history, administration of vaginal progesterone or oral nifedipine for the current pregnancy, patients with severe comorbidities and those who did not give consent to participate in the study were excluded. The study was conducted following approval from the institutional ethical committee. Informed consent was obtained from all participants or their caregivers after thorough counseling regarding the treatment options.

Participants were randomly allocated to either the vaginal progesterone group or the oral nifedipine group using computer-generated randomization. In Group A, participants received oral nifedipine at a dose of 20mg every 30 minutes for three doses initially, followed by long-acting nifedipine SR 20mg every 12 hours until reaching 37 weeks of gestational age or until cervical dilation exceeded 4cm (for a duration of 48 hours). In Group B, participants were instructed to use vaginal micronized progesterone tablets at a dosage of 200mg once daily or until reaching 37 weeks of gestational age or until cervical dilation exceeded 4cm (for a duration of 48 hours). Effectiveness, in the context of the study "Is vaginal progesterone more effective to treat threatened preterm labor than oral nifedipine," refers to the ability of each treatment option (vaginal progesterone and oral nifedipine) to successfully prolong pregnancy duration in

cases of threatened preterm labor. This includes the treatment's capacity to delay delivery beyond 48 hours from the initiation of therapy, as well as its impact on reducing the incidence of preterm birth and improving neonatal outcomes. All the information was collected via study proforma and SPSS version 16 was utilized for the data analysis.

Results

The mean age of the subjects is 29.6 years, with a standard deviation of 5.44 years. Mean gestational age was 33.32 weeks, with a standard deviation of 1.58 weeks. Mean parity was 2.21, with a standard deviation of 1.33. The mean BMI (Body Mass Index) of the subjects was 25.34 ±2.55 kg/m^2. Regarding socioeconomic status, 31.7% cases were classified as poor, 49.2% fell into the middle socioeconomic status category and 19.0% were categorized as having upper socioeconomic status. (Table I)

In Group A, oral nifedipine demonstrated effectiveness in 46 individuals (73.0%), while it was not found effective in 17 individuals (27.0%). Conversely, Group B, which received vaginal progesterone, exhibited higher efficacy rates, with 57 cases (90.5%) showing positive response and only 6 cases (9.5%) responding negatively. The significant difference in efficacy between the two groups is indicated by a p-value of 0.011. (Figure 1)

Effectiveness among both groups was found to be statistically insignificant according to age and parity of the women (p=>0.05). Table II & III

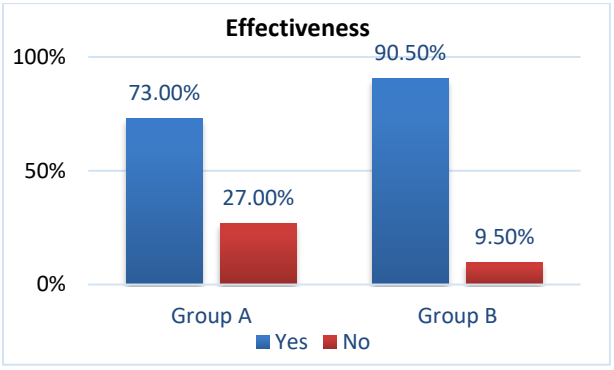

Figure 1. Comparison of efficacy between the groups. n=126. (P- value= 0.011)

Table I: Demographic characteristics of the study subjects. (n=126)

Variables		Statistics
Age (Mean± Standard deviation)		29.6±5.44 years
Gestational age (Mean± Standard deviation)		33.32+1.58 weeks
Parity (Mean± Standard deviation)		2.21+1.33
BMI (Mean± Standard deviation)		25.34±2.55 Kg/m^2
Socioeconomic status	Poor	40(31.7%)
	Middle	62(49.2%)
	Upper	24(19.0%)

Discussion

Threatened preterm labor (TPL) represents a significant challenge in obstetric care, accounting for a substantial portion of hospital admissions during pregnancy. To address TPL and its associated complications, tocolytic agents are widely employed as the primary therapeutic strategy.[15] This study was conducted to compare the effectiveness of vaginal progesterone versus oral nifedipine in the treatment of threatened preterm labor. The subjects had an overall mean age of 29.6 years, with a standard deviation of 5.44 years. The mean gestational age was 33.32 weeks, with a standard deviation of 1.58 weeks. Additionally, the mean Body Mass Index (BMI) of the subjects was 25.34 +2.55 kg/m^2. In the comparison of this study Yoneyama K et al[16] reported that mean age of the patients with threatened preterm labor was 30.5 years and their average gestational age was 30.0 weeks. Luechathananon S et al[17] also found mean age 29.1±6.1

Table II: Comparative effectiveness between the groups according to age. (n=126)

STUDY GROUPS			AGE GROUP		
			18-28 years	29-35 years	p-value
Group A (oral nifedipine)	**Efficacy**	**Yes**	22	24	**0.957**
			73.3%	72.7%	
		No	8	9	
			26.7%	27.3%	
	Total		30	33	
			100.0%	100.0%	
Group B (vaginal progesterone)	**Efficacy**	**Yes**	32	26	**0.514**
			94.1%	89.7%	
		No	2	3	
			5.9%	10.3%	
	Total		34	29	
			100.0%	100.0%	

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Table III: Comparative effectiveness between the groups according to parity. (n=126)

STUDY GROUPS			AGE GROUP		p-value
			18-28 years	29-35 years	
Group A (oral nifedipine)	**Efficacy**	**Yes**	23	23	**0.534**
			76.7%	69.7%	
		No	7	10	
			23.3%	30.3%	
	Total		30	33	
			100.0%	100.0%	
Group B (vaginal progesterone)	**Efficacy**	**Yes**	27	31	**0.022**
			84.4%	100.0%	
		No	5	0	
			15.6%	0.0%	
	Total		32	31	
			100.0%	100.0%	

years of the patients with threatened preterm labor. Consistently Ducarme G et al[18] also conducted study on patients with threatened preterm labor and they reported that the mean age of the patients was 27.3 ± 4.8 years and their average gestational age at presentation was 31.7 weeks.

In this study, socioeconomic status was analyzed, revealing that 31.7% of cases were classified as poor, 49.2% fell into the middle socioeconomic status category, and 19.0% were categorized as having upper socioeconomic status. These findings align with the research conducted by Ullah NA et al,[19] as they reported that the majority of our study cases, specifically 105 (62.9%), had poor socioeconomic status, while 62 (37.1%) belonged to the middle class, with none falling into the wealthy category. TPL poses significant risks to both maternal and fetal health, including the potential for preterm birth, which is associated with increased morbidity and mortality rates for infants. Identifying and addressing risk factors associated with TPL, including socioeconomic status, are essential for implementing targeted interventions and optimizing maternal and neonatal outcomes. Socioeconomic status can influence access to healthcare resources, nutritional status, stress levels, and overall health, all of which may impact the risk of preterm labor.

In this study, Group B, which received vaginal progesterone, exhibited significantly higher efficacy rates (90.5%) compared to Group A, which received oral nifedipine (73.0%), with a p-value of 0.011. Mohamed MO et al. consistently observed that progesterone demonstrated a more effective tocolytic effect compared to nifedipine, resulting in longer pregnancy duration, reduced NICU admissions, shorter NICU stays, and higher gestational age. However, Chawanpaiboon S et al. found inconsistency in their findings, stating that while nifedipine, proluton depot, and bed rest were effective in suppressing contractions in cases of threatened preterm labor, nifedipine achieved the fastest inhibition of uterine contractions among these options.[20] Alloush MK et al. noted little association between nifedipine and vaginal progesterone, with vaginal progesterone being associated with fewer adverse effects, making it a safer choice.[12] However, Haghighi L et al. reported that the effectiveness of progesterone and nifedipine in treating threatened preterm labor (TPL) was observed to be 83% and 82.7%, respectively, with no notable distinction between the two treatments concerning gestational age at delivery, mode of delivery, time interval until delivery, birth weight, rate of admission to the Neonatal Intensive Care Unit (NICU), or length of hospital stay.[14] However, administration of progesterone was associated with a shorter duration of NICU stay compared to nifedipine. Despite these findings, controversies persist, and many studies are conducted with combined treatment modalities. However, this study also poses several limitations, specifically a limited study sample size and the lack of observation of the side effects of the treatment modalities. Further large-scale studies are recommended to observe the separate effectiveness and safety of the drugs independently.

Conclusion

In conclusion, the study underscores the substantial therapeutic effectiveness of vaginal progesterone in managing threatened preterm labor. With its demonstrated superior efficacy compared to oral nifedipine, vaginal progesterone emerges as a promising option for mitigating the risks associated with preterm birth and enhancing outcomes for both mothers and infants. However, it's important to note that findings cannot be conclusively implemented due to several study limitations. However continued exploration of the efficacy and safety of various

interventions will contribute to refining clinical guidelines and advancing evidence-based care for individuals at risk of preterm birth.

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