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Comparison of Nifedipine Versus Nitroglycerin Patch in the Management of Preterm Labor: A Prospective Comparative Cohort Study

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Abstract

Background

Preterm labor (PTL) is a major contributor to neonatal morbidity and mortality worldwide, posing a significant global public health concern. The goal of tocolytic therapy is to delay labor sufficiently to allow administration of antenatal corticosteroids and transfer to a facility with neonatal intensive care services. This study evaluated the association of oral nifedipine and transdermal nitroglycerine patch treatment with successful arrest of spontaneous PTL.

Methods

A prospective cohort study with a comparative design was undertaken at Holy Family Hospital, Rawalpindi, Pakistan. A total of 375 women with spontaneous PTL (28-36+6 weeks of gestation) were recruited, with 188 receiving oral nifedipine and 187 receiving a transdermal nitroglycerine patch. The main outcome was successful labor arrest for at least 48 hours. We used logistic regression, adjusting for maternal age, gestational age at admission, and parity, to account for measured baseline factors.

Results

Labor arrest was successful in 142/188 (75.5%) women who received oral nifedipine and in 112/187 (59.9%) who received the transdermal nitroglycerine patch (RR = 1.26, 95% CI: 1.09-1.46; p = 0.001). Treatment with oral nifedipine was associated with higher odds of successful labor arrest after adjustment for maternal age, gestational age at admission, and parity (AOR = 2.13, 95% CI: 1.35-3.36; p = 0.001). Successful treatment was independently associated with increasing gestational age at admission, while increasing maternal age and parity were associated with decreased odds of successful labor arrest.

Conclusion

In this single-center prospective comparative cohort, oral nifedipine was associated with a higher probability of successful short-term labor arrest than transdermal nitroglycerin after adjustment for selected measured covariates. Given the non-randomized design and potential for residual confounding, these findings should not be interpreted as evidence of causal superiority. Randomized controlled trials are needed for definitive comparative assessment.

Categories: Obstetrics/Gynecology, Epidemiology/Public Health
Keywords: cohort study, nifedipine, nitroglycerin, pregnancy outcome, preterm labor, tocolytic agents

Introduction

Preterm labor (PTL), identified by the presence of regular uterine contractions associated with progressive cervical change before 37 completed weeks' gestation, is a major cause of neonatal morbidity and mortality globally [1,2]. Premature birth has been linked to numerous complications, such as respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), neonatal sepsis, and long-term neurodevelopmental impairment [3,4]. If the delivery is delayed for at least 48 hours, a course of antenatal corticosteroids is given and, if needed, the mother is transferred to a tertiary center with NICU services [5].

A wide variety of tocolytic agents have been used to prevent uterine contractions and extend gestation. Oral nifedipine, a calcium channel blocker, is a first-line tocolytic agent, as it is highly effective, easy to give, and has a good safety profile [6,7]. In addition, a nitric oxide donor, transdermal nitroglycerin patch, has been used as an alternative tocolytic, as it stimulates uterine smooth muscle relaxation [8]. Both agents slow preterm delivery, but past research has yielded conflicting results when comparing efficacy and safety [8,9].

Several studies have evaluated the effectiveness of oral nifedipine and a transdermal nitroglycerine patch in women with PTL; however, the current evidence remains limited and is characterized by considerable uncertainty, highlighting the need for further well-designed comparative studies [8,9]. Therefore, this prospective comparative cohort study aimed to evaluate the association between oral nifedipine or a transdermal nitroglycerine patch and successful arrest of spontaneous PTL for 48 hours or more. The results of this study may provide locally relevant observational evidence to inform future research and clinical consideration of tocolytic treatment for women with spontaneous PTL. There is limited comparative evidence in South Asian populations between nifedipine and transdermal nitroglycerine, especially prospective studies. Hence, the present study aims to offer locally relevant evidence from a tertiary care center in Pakistan.

Objective

This study aimed to assess the association of oral nifedipine and transdermal nitroglycerine patch treatment with successful arrest of spontaneous PTL for at least 48 hours.

Materials And Methods

Research design and setting

It was a prospective comparative cohort study carried out in the Department of Gynaecology Unit-I, Holy Family Hospital, Rawalpindi, Pakistan, for nine months (January 2025 to September 2025) after approval from the Institutional Ethical Review Committee. Treatment allocation was not randomized. The choice of tocolytic agent was based on the treating obstetrician's routine clinical practice and drug availability, without a standardized treatment-selection protocol. The resulting group sizes (188 women receiving oral nifedipine and 187 receiving transdermal nitroglycerine) reflected the treatment decisions made in routine clinical practice during the consecutive recruitment period and were not determined by a prespecified allocation ratio or target. No randomization, alternation, block allocation, quota scheme, or other prespecified treatment-allocation procedure was used. Patients did not select their treatment regimen; treatment was determined by the treating obstetrician according to routine clinical practice and drug availability. No additional formal criteria guiding treatment selection were prospectively recorded. The available baseline variables for adjustment were maternal age, gestational age at admission, and parity. The study evaluated the association between treatment with oral nifedipine or transdermal nitroglycerine and successful arrest of spontaneous PTL.

Sample size and participant selection

The minimum sample size was initially estimated using a comparison of two independent proportions. Based on anticipated successful labor-arrest proportions of 68.3% in the nifedipine group and 86.7% in the transdermal nitroglycerine-patch group, as reported by Kashanian et al. [10], with 80% power and a one-sided significance level of 5%, the required sample size was approximately 63 participants per group. This was conservatively rounded to 65 participants per group, giving a minimum total sample size of 130 participants. Subsequently, the sample size was recalculated using the same anticipated proportions, 80% power, and a two-sided significance level of 5%, yielding a minimum required sample size of approximately 80 participants per group. The final study sample of 375 participants (188 in the nifedipine group and 187 in the transdermal nitroglycerine-patch group) therefore exceeded the minimum required sample size. The sample size was estimated using the standard formula for comparison of two independent proportions, with reference to the WHO manual for sample size determination in health studies [11]. All eligible women who met the inclusion and exclusion criteria were recruited consecutively over nine months. This resulted in an analytical sample of 375 women, 188 receiving oral nifedipine and 187 receiving a transdermal nitroglycerine patch.

The required sample size was calculated using the following formula:

$$n = \frac{\left[Z_\alpha \sqrt{2\bar{p}(1-\bar{p})} + Z_\beta \sqrt{p_1(1-p_1)+p_2(1-p_2)}\right]^2}{(p_1-p_2)^2}, \quad \bar{p} = \frac{p_1+p_2}{2}$$, where n is the required sample size per group, p_1 and p_2 are the anticipated proportions of successful labor arrest in the nifedipine and transdermal nitroglycerine groups, respectively, $\bar{p} = \frac{p_1+p_2}{2}$, Zα corresponds to the specified significance level (one-sided 5% for the initial calculation and two-sided 5% for the subsequent recalculation), and Zβ corresponds to 80% power.

Inclusion criteria

Women were included if they had a singleton pregnancy at 28+0 to 36+6 weeks' gestation and were aged 18-35 years. Participants were enrolled once spontaneous PTL was confirmed based on the clinical definition used at the study site. The presence of regular uterine contractions with at least two contractions in 10 minutes, cervical dilatation of 2-4 cm, and effacement of the cervix was considered to be spontaneous PTL. Women who met all the predefined eligibility criteria were deemed eligible for enrollment.

Exclusion criteria

Women who had conditions that could be treated as the primary gestation problem or would affect the management of preterm delivery were also excluded. These were polyhydramnios, antepartum haemorrhage, intrauterine fetal death, pregnancy-induced hypertension, multiple gestation, and preterm premature rupture of membranes (PPROM). These criteria were applied prior to enrolment to ensure the study population of women with spontaneous PTL was suitable for conservative tocolytic management.

Treatment and follow-up

Women who met the eligibility criteria received oral nifedipine or transdermal nitroglycerine according to the institutional treatment protocol. Oral nifedipine was administered as 20 mg orally at 30-minute intervals, up to a maximum cumulative dose of 80 mg. In the transdermal nitroglycerine group, a 5-mg transdermal nitroglycerine patch was applied over the uterine fundus and replaced every 24 hours when continued tocolytic treatment was clinically indicated. No prespecified criteria for repeat dosing, treatment discontinuation, crossover, or rescue tocolysis were recorded beyond the treating obstetrician's clinical assessment according to routine institutional practice. Treatment allocation was not randomized and was determined by the treating obstetrician’s usual clinical practice and drug availability; patients could not select their treatment regimen. Because treatment was non-randomized, clinical characteristics or treatment-selection factors not captured in the study dataset may have influenced treatment allocation. During the observation period, all participants were managed according to the hospital obstetric protocol. No standardized crossover or rescue-tocolysis protocol was specified beyond routine clinical management.

Demographic and obstetric data were collected after obtaining written informed consent. Participants were followed up prospectively throughout their hospital stay after tocolytic therapy. All uterine contractions, clinical status of the mother, patient's response to therapy, and the course of labor were observed as per hospital protocol. The primary outcome was successful arrest of PTL, defined as cessation of clinically significant uterine contractions for at least 48 hours after initiation of tocolysis. Labor arrest was assessed clinically during the observation period according to the institutional obstetric protocol. Baseline cervical dilatation and effacement were assessed clinically as part of the routine eligibility assessment; however, the individual measurements were not recorded in the study dataset. Therefore, treatment-group-specific baseline values could not be reconstructed, and these variables could not be included in the adjusted regression model. Maternal adverse effects and neonatal outcomes were not prespecified or systematically collected in the study dataset and therefore were not included in the comparative analysis. Accordingly, the present study was limited to evaluating the association between treatment and 48-hour labor arrest and does not permit conclusions regarding comparative maternal safety, neonatal outcomes, or overall clinical preference between the two treatments.

Data collection

After obtaining informed written consent, baseline demographic and obstetric data, including maternal age, gestational age at admission, and parity, were collected using a predesigned structured proforma. Parity was recorded as the number of previous births and did not include the current pregnancy. This study was not based on a validated questionnaire, score, or clinical scale.

Data analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 26.0 (Released 2018; IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to assess the distribution of continuous variables, which are presented as mean ± SD or median (IQR), as appropriate. Frequencies and percentages are used for categorical variables. Comparisons between groups were made using an independent-samples t-test or Mann-Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables. The primary outcome was analysed by chi-square test, and treatment effects were reported as relative risk (RR) and 95% confidence intervals (CIs). To investigate the association between treatment group and successful labor arrest, we ran a multivariable binary logistic regression model. Treatment group, maternal age, parity, and gestational age at admission were entered simultaneously into the model as measured covariates available in the study dataset. Because treatment allocation was not randomized, the adjusted estimates were interpreted as associations rather than causal treatment effects. Because treatment allocation was non-randomized, the possibility of residual confounding could not be excluded. Variables such as cervical measurements, previous preterm birth, BMI, and maternal comorbidities were not available in the dataset and therefore could not be included in the adjusted model.

Ethical considerations

The institutional Ethical Review Committee of Rawalpindi Medical College (Holy Family Hospital), Rawalpindi, cleared all ethical issues before the initiation of the study. Before participation, all eligible women provided written informed consent. All participants were free to attend, and their personal and clinical data were kept confidential. All procedures were done in compliance with institutional ethical rules and the Declaration of Helsinki.

Results

Descriptive statistics and normality testing results of the continuous study variables for 375 participants are shown in Table 1. The mean maternal age was 26.89 ± 4.03 years, and the mean gestational age at admission was 32.83 ± 1.88 weeks. Maternal age showed a mild deviation from normality (W = 0.984, p < 0.001), whereas gestational age was approximately normally distributed (W = 0.993, p = 0.064). The mean parity was 2.78 ± 1.33, with a median of 3.00 (IQR: 2.00-4.00), and exhibited a non-normal distribution (W = 0.909, p < 0.001), consistent with its discrete count nature.

Variable	Range	Mean ± SD	Median (IQR)	Shapiro-Wilk W	p	Distribution decision
Maternal age, years	18-35	26.89 ± 4.03	27.00 (24.00-30.00)	0.984	<0.001	Mild departure from normality; parametric analysis acceptable
Gestational age at admission, weeks	28.00-36.86	32.83 ± 1.88	32.71 (31.57-34.22)	0.993	0.064	Approximately normally distributed
Parity	1-6	2.78 ± 1.33	3.00 (2.00-4.00)	0.909	<0.001	Non-normal discrete count variable

TABLE 1: Descriptive Statistics and Tests of Normality for Continuous Study Variables (N = 375)

Note: N = 375; Shapiro-Wilk tests were conducted using the complete sample.

SD: standard deviation; IQR: interquartile range

Table 2 shows the base demographic and obstetric data for the oral nifedipine group (n = 188) and the nitroglycerine patch group (n = 187). There was no significant difference found between the groups in maternal age (Mann-Whitney U = 16,982.00, p = 0.569). Likewise, the difference between the two groups in gestational age at admission was not significant (t(373) = -0.65, p = 0.516), and parity was not significantly different between the two groups (Mann-Whitney U = 17,326.00, p = 0.805). No significant differences were observed in age group ($\chi^2(1) = 0.13$, p = 0.721), gestational-age group ($\chi^2(1) = 0.97$, p = 0.324), or parity group ($\chi^2(1) = 0.19$, p = 0.663)

Characteristic	Oral nifedipine (N = 188)	Nitroglycerine patch (N = 187)	Test statistic	p
Continuous Variables				
Maternal age, years, Mdn (IQR)	27.00 (24.00-30.00)	27.00 (24.00-30.00)	U = 16,982.00	0.569
Gestational age at admission, weeks, Mean ± SD	32.89 ± 1.94	32.77 ± 1.81	t(373) = -0.65	0.516
Parity, Mdn (IQR)	3.00 (2.00-4.00)	3.00 (2.00-4.00)	U = 17,326.00	0.805
Categorical Variables				
Age group, n (%)			$\chi^2(1) = 0.13$	0.721
18-30 years	148 (78.7)	150 (80.2)	-	-
31-35 years	40 (21.3)	37 (19.8)	-	-
Gestational-age group, n (%)			$\chi^2(1) = 0.97$	0.324
28+0-32+6 weeks	95 (50.5)	104 (55.6)	-	-
33+0-36+6 weeks	93 (49.5)	83 (44.4)	-	-
Parity group, n (%)			$\chi^2(1) = 0.19$	0.663
1-3	136 (72.3)	139 (74.3)	-	-
>3	52 (27.7)	48 (25.7)	-	-

TABLE 2: Baseline Demographic and Obstetric Characteristics of Participants by Treatment Group (N = 375)

Note: Values are presented as mean ± SD, median (IQR), or n (%), as appropriate. Maternal age and parity were analyzed using the Mann-Whitney U test, gestational age at admission with the independent-samples t-test, and categorical variables with Pearson's chi-square test. All tests were two-tailed, and $p < 0.05$ was considered statistically significant.

N: total participants; IQR: interquartile range; SD: standard deviation

Table *3* presents the comparison of successful arrest of labor for at least 48 hours between the two treatment groups. In the oral nifedipine group, successful labor arrest was obtained in 142/188 (75.5%) women compared to 112/187 (59.9%) women in the nitroglycerine patch group. The oral nifedipine group had a significantly higher proportion that was successful in labor arrest ($\chi^2(1) = 10.49$, $p = 0.001$) with an RR of 1.26 (95% CI: 1.09-1.46). The observed absolute risk difference was 15.6 percentage points, corresponding to an observational NNT estimate of 6.39. Because treatment allocation was non-randomized, this NNT is derived from the observed unadjusted difference and should not be interpreted as the causal number of patients who would need to receive nifedipine instead of nitroglycerine to produce one additional successful labor-arrest outcome.

Primary outcome	Oral nifedipine, n (%)	Nitroglycerine patch, n (%)	RR	95% CI	Absolute risk difference	NNT	$\chi^2(1)$	p
Successful arrest, yes	142 (75.5)	112 (59.9)	-	-	-	-	-	-
Successful arrest, no	46 (24.5)	75 (40.1)	-	-	-	-	-	-
Total	188 (50.1)	187 (49.9)	1.26	1.09-1.46	15.6%	6.39	10.49	0.001***

TABLE 3: Comparison of Successful Arrest of Labor for at Least 48 Hours Between the Treatment Groups (N = 375)

Note: Values are presented as frequency and percentage within each treatment group. The relative risk compares the probability of successful arrest of labor for at least 48 hours in the oral-nifedipine group with that in the transdermal-nitroglycerin-patch group. The absolute risk difference was calculated as 75.5% - 59.9% = 15.6 percentage points. The NNT was calculated as the reciprocal of the exact absolute risk difference, 1/0.1564 = 6.39. Pearson's chi-square test was used because no expected cell count was less than 5; all tests were two-tailed, and p < 0.01*** was considered statistically significant.

RR: relative risk; CI: confidence interval; NNT: number needed to treat

Table 4 presents the crude and adjusted binary logistic regression analyses of factors associated with successful arrest of labor for at least 48 hours. Compared with the nitroglycerine patch group, women who received oral nifedipine had higher odds of successful labor arrest in both crude (OR = 2.07, 95% CI: 1.33-3.22, p = 0.001) and adjusted analyses (AOR = 2.13, 95% CI: 1.35-3.36, p = 0.001). Increasing gestational age at admission was independently associated with higher odds of successful labor arrest (AOR = 1.22, 95% CI: 1.08-1.39, p = 0.002), whereas increasing maternal age (AOR = 0.94, 95% CI: 0.89-1.00, p = 0.043) and parity (AOR = 0.80, 95% CI: 0.67-0.95, p = 0.012) were associated with lower odds of successful labor arrest (Table 4).

Predictor	Category	Crude OR	95% CI	Crude p	Adjusted OR	95% CI	Adjusted p	Tolerance	VIF
Treatment group	Oral nifedipine vs. nitroglycerin patch	2.07	1.33-3.22	0.001***	2.13	1.35-3.36	0.001***	0.997	1.00
Maternal age	Per 1-year increase	0.93	0.88-0.98	0.009**	0.94	0.89-1.00	0.043*	0.916	1.09
Gestational age at admission	Per 1-week increase	1.18	1.05-1.33	0.006**	1.22	1.08-1.39	0.002**	0.986	1.01
Parity	Per 1-unit increase	0.80	0.68-0.94	0.008**	0.80	0.67-0.95	0.012*	0.909	1.10

TABLE 4: Crude and Adjusted Binary Logistic Regression Analyses of Predictors of Successful Arrest of Labor for at Least 48 Hours (N = 375)

Note: The model had a -2 log-likelihood of 439.51, a Cox and Snell R^2 of 0.082, a Nagelkerke R^2 of 0.115, and a C-statistic (area under the ROC curve) of 0.672, 95% CI (0.613, 0.730), p < 0.001. The modeled event was successful arrest of labor for at least 48 hours, coded as 1 = yes and 0 = no. The nitroglycerine-patch group was the reference treatment category. Crude ORs were obtained from separate univariable binary logistic regression models. Adjusted ORs were obtained from a multivariable model containing treatment group, maternal age, gestational age at admission, and parity simultaneously. Because treatment allocation was non-randomized, adjusted odds ratios represent associations conditional on the measured covariates and should not be interpreted as causal treatment effects.

All tests were two-tailed, and p < 0.05 was considered statistically significant. For table presentation, *, **, and *** denote p < 0.05, p < 0.01, and p < 0.001, respectively.

OR: odds ratio; CI: confidence interval; VIF: variance inflation factor; AUC: area under the receiver operating characteristic curve

Discussion

The present prospective comparative cohort study found that treatment with oral nifedipine was associated with higher odds of successful labor arrest for at least 48 hours compared with transdermal nitroglycerin. Approximately three-quarters of women receiving nifedipine achieved successful labor arrest compared with approximately three-fifths of those receiving the nitroglycerin patch. After adjustment for maternal age, gestational age at admission, and parity, the association remained statistically significant. However, because treatment allocation was not randomized and important clinical factors were not available for adjustment, these findings should be interpreted as an observational association rather than evidence that nifedipine causally improves labor arrest.

These findings are consistent with the comparative study by Kaur et al., who observed that oral nifedipine had a higher success rate than transdermal nitroglycerine, with increased gestational prolongation and improved neonatal outcomes [12]. Similarly, Zamani et al. conducted a systematic review and meta-analysis of 40 studies that demonstrated that nifedipine was more effective than nitroglycerine in prolonging pregnancy during the first 48 hours [7]. Another randomized controlled trial reported similar effectiveness between oral nifedipine and transdermal nitroglycerine for delaying delivery beyond 48 hours, with fewer maternal adverse events reported with nifedipine therapy [13]. More recently, a 2025 systematic review and meta-analysis of randomized controlled trials found no statistically significant difference between transdermal nitroglycerine and oral nifedipine for pregnancy prolongation beyond 48 hours (RR = 0.93, 95% CI: 0.81-1.07; p = 0.30) [8]. The present study therefore differs from the available randomized evidence, which does not establish a clear comparative advantage of either treatment. The discrepancy may reflect differences in study populations, eligibility criteria, treatment protocols, outcome definitions, and study design. Importantly, treatment allocation in the present study was not randomized and may have been influenced by clinical factors that were not captured in the dataset. Consequently, the higher observed success rate with nifedipine should not be interpreted as evidence of pharmacological superiority, and the findings should be considered hypothesis-generating in the context of existing randomized evidence. The findings are consistent with the established use of nifedipine as a short-term tocolytic intended to delay delivery sufficiently to allow completion of antenatal corticosteroid therapy [14]. The treatment groups did not differ significantly in maternal age, gestational age at admission, or parity. Although these measured baseline characteristics were comparable between groups, residual confounding cannot be excluded because treatment allocation was not randomized and other potentially important clinical factors were not available for adjustment.

The observed association between oral nifedipine treatment and successful labor arrest is biologically plausible. Nifedipine inhibits calcium influx into uterine smooth muscle cells, which decreases the contractility of myometrium cells and diminishes uterine contractions [15]. Nitroglycerin, by contrast, is a nitric oxide donor that relaxes smooth muscle via nitric oxide pathways. Available evidence does not recommend its routine use as a first-line tocolytic due to its frequent adverse effects of vasodilation, such as headache [9]. The observed association favoring nifedipine is biologically plausible given its mechanism of action; however, pharmacological plausibility does not establish a causal treatment effect in a nonrandomized study. These results, however, should be interpreted in light of the observational design. In this study, treatment allocation depended on routine clinical practice, and treatment selection may have been affected by clinical factors not captured in the data, unlike in randomized trials. Other potentially important clinical factors were not available to be included in the multivariable model. However, measured confounding factors such as maternal age, gestational age at admission, and parity were included. Thus, this association of nifedipine treatment with labor arrest should not be taken as compelling evidence that nifedipine causes labor arrest.

A notable finding of this study was that gestational age at admission was an independent risk factor for successful labor arrest, with women presenting at more advanced gestational ages showing significantly higher odds of successful labor arrest. In contrast, a retrospective observational study evaluating atosiban as a tocolytic reported that gestational age at diagnosis did not significantly influence the success of pregnancy prolongation [16]. Differences between these studies may reflect variations in study design, sample size, the tocolytic agent studied, and statistical methods, since the former included only 84 women who received atosiban. In contrast, the current study used multivariable logistic regression to control for potential confounding factors when evaluating nifedipine and transdermal nitroglycerine. The finding may also be clinically relevant because the likelihood of successful short-term labor arrest may differ according to the gestational stage at presentation. The association is, however, to be treated with some degree of caution as it may also represent differences in underlying clinical characteristics and severity of PTL. Future prospective studies with more detailed obstetric data would help further elucidate this relationship.

On the other hand, greater maternal age and parity were independently associated with decreased likelihood of successful labor arrest. Another recent study by Kim et al. found that maternal age ⩾33 years was an independent factor in the failure of tocolytic therapy, which indicates that maternal age may be associated with the likelihood of successful labor arrest [17]. Higher parity was also independently correlated with unsuccessful labor arrest in the current study; however, there is limited evidence on the effect of parity on tocolytic responsiveness. This result could be due to population-specific differences or to remnants of biological differences and should be replicated in larger, prospective studies. These findings should be considered hypothesis-generating, and their clinical relevance should be evaluated in future studies incorporating more comprehensive obstetric and clinical characteristics.

The baseline demographic and obstetric characteristics were similar between the treatment groups, with no statistically significant differences in maternal age, gestational age at admission, or parity. This comparability reduces the likelihood that differences in these measured characteristics alone explain the observed difference in labor-arrest rates. Nevertheless, statistical similarity in measured baseline variables does not eliminate the possibility of residual confounding. Important clinical characteristics, including cervical measurements, previous preterm birth, BMI, and maternal comorbidities, were not available for adjustment. Therefore, the adjusted association between nifedipine treatment and successful labor arrest should be interpreted cautiously.

From a clinical perspective, delaying delivery by at least 48 hours remains one of the most important objectives in the management of spontaneous PTL because it provides sufficient time for administration of antenatal corticosteroids and referral to tertiary care centers equipped with neonatal intensive care facilities. Thus, successful 48-hour labor arrest may provide an opportunity for timely administration of antenatal corticosteroids and referral to appropriate neonatal care; however, this potential benefit was not directly evaluated in the present study.

Clinical implications

The findings of this study may have practical implications for the short-term management of spontaneous PTL. In this observational cohort, oral nifedipine was associated with a higher rate of successful 48-hour labor arrest. However, this finding should not be interpreted as evidence of treatment superiority because treatment allocation was nonrandomized and residual confounding and selection bias cannot be excluded. Treatment choice should therefore remain based on the individual clinical circumstances of the mother and fetus and the treating obstetrician's clinical judgment. Because this study is a nonrandomized comparative cohort study, any differences observed should be interpreted as associations rather than evidence of treatment superiority.

Limitations and future directions

There are multiple limitations to this study. First, the study was carried out in one tertiary care center, which may constrain the generalizability of the results. Second, treatment was not randomly assigned and was chosen according to routine clinical practice and drug availability. Consequently, selection bias and confounding by indication cannot be excluded. Although the analysis adjusted for maternal age, gestational age at admission, and parity, other potentially important determinants of treatment selection and labor progression were not available. Although cervical dilatation and effacement were assessed clinically as part of the eligibility assessment, individual baseline measurements were not recorded in the study dataset. Consequently, treatment-group-specific cervical measurements could not be compared, and these variables could not be included in the multivariable model, representing a potential source of residual confounding. Previous preterm birth, BMI, and maternal comorbidities were also unavailable and could not be incorporated into the model. Third, maternal adverse effects and neonatal outcomes were not systematically collected and therefore could not be compared between treatment groups. Specifically, data on maternal headache, hypotension, flushing, tachycardia, and dizziness, as well as neonatal birth weight, Apgar scores, RDS, NICU admission, and neonatal mortality, were unavailable. Consequently, this study cannot assess the comparative safety of the two tocolytic strategies or determine whether successful 48-hour labor arrest translated into improved neonatal outcomes. Finally, because this was a nonrandomized observational study, the observed association between treatment and successful 48-hour labor arrest should not be interpreted as evidence of comparative treatment efficacy or superiority. Future comparative studies should incorporate prespecified maternal and neonatal safety and outcome measures and use randomized designs to better establish comparative effectiveness.

Conclusions

In this single-center prospective comparative cohort, oral nifedipine was associated with a higher rate of successful short-term arrest of spontaneous PTL than transdermal nitroglycerin. The association remained statistically significant after adjustment for maternal age, gestational age at admission, and parity. However, treatment was not randomized, important potential confounders were unavailable, and maternal and neonatal safety outcomes were not systematically collected. Accordingly, the findings should be interpreted as observational evidence rather than evidence of causal treatment superiority. Multicenter randomized controlled trials incorporating maternal adverse effects and neonatal outcomes are warranted to establish the comparative effectiveness and safety of these two tocolytic strategies.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Saadia Hassan, Hafiza Ateeqa Mubarak

Acquisition, analysis, or interpretation of data: Saadia Hassan, Khadija Khan, Hafiza Ateeqa Mubarak

Critical review of the manuscript for important intellectual content: Saadia Hassan, Khadija Khan

Drafting of the manuscript: Khadija Khan, Hafiza Ateeqa Mubarak

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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Saadia Hassan and Khadija Khan contributed equally and should be considered co-first authors.

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