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Original Research

The Relationship between Nifedipine and Postpartum Blood Loss in Patients with Preterm Labor

Huseyin Kiyak[1], Nazli Korkmaz[2,*], Sema Suzen Caypinar[3], Zuat Acar[4], Alev Atis Aydin[5], Batuhan Ustun[6], Zubeyde Aytufan[7], Ali Gedikbasi[8]

[1]Department of Obstetrics and Gynecology, Sarıyer Hamidiye Etfal Education ve Research Hospital, 34453 Istanbul, Turkey
[2]Department of Obstetrics and Gynecology, Demiroglu Bilim University, 34394 Istanbul, Turkey
[3]Department of Maternal Fetal Medicine, Kanuni Sultan Süleyman Education ve Research Hospital, 34303 Istanbul, Turkey
[4]Department of Maternal Fetal Medicine, Istanbul Tema Hospital, 34307 Istanbul, Turkey
[5]Department of Maternal Fetal Medicine, Sarıyer Hamidiye Etfal Education ve Research Hospital, 34453 Istanbul, Turkey
[6]Department of Obstetrics and Gynecology, Namik Kemal University, 59030 Tekirdag, Turkey
[7]Department of Maternal Fetal Medicine, Goztepe Medical Park, 34732 Istanbul, Turkey
[8]Department of Maternal Fetal Medicine, Special Clinic Fulya Terrace, 34365 Istanbul, Turkey
*Correspondence: drnazlikorkmaz@gmail.com (Nazli Korkmaz)

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Abstract

Background: The purpose of the study, to determine whether exposure to nifedipine before delivery is associated with an increased risk of postpartum blood loss in patients with preterm labor. **Methods**: This was a retrospective study screening a total of 486 patients who were admitted due to preterm labor from 2012 to 2019. Patients who were given nifedipine for tocolysis before delivery were considered as the study group (n: 240), and the patients who gave birth without getting tocolysis were considered as the control group (n: 246). The dose of nifedipine used during the last 24 hours, 72 hours and 1 week before delivery, the total dose of nifedipine given and the duration from the last dose to the delivery were recorded separately. Hemoglobin and hematocrit and platelet values measured before and 6 hours after delivery were recorded and postpartum bleeding amount was calculated. **Results**: No significant difference is observed in terms of mean difference between pre/postpartum hemoglobin and hematocrit levels between control group and nifedipine group ($p > 0.05$). But when subgroups that are created according to the time of use of nifedipine before delivery, a positive correlation was observed between difference in hemoglobin and hematocrit levels between prepartum and postpartum and nifedipine dosage for the last 24 hours (r = 0.176, $p = 0.006$), (r = 0.139, $p = 0.030$), but not for 72 hours or one week. **Conclusions**: The use of nifedipine in patients with preterm labor for tocolysis may be associated with increase in postpartum blood loss in the last 24 hours before delivery.

Keywords: nifedipine; postpartum hemorrhage; preterm labor; calcium channel blockers

1. Introduction

Preterm birth is one of the major causes of perinatal morbidity and mortality [1,2]. Despite the improvements in neonatal intensive care, they are at increased risk of long-term neurodevelopmental disabilities and major complications [3]. Because uterine contractions are the most frequently recognized symptoms of preterm labor, inhibition of contractions with tocolytic agents to prolong pregnancy is the main target of the treatment in women with preterm labor.

Common agents that are used for the inhibition of uterine contractility are beta-agonists, prostaglandin synthase inhibitors, magnesium sulfate, oxytocin receptor antagonists and calcium channel blockers. Due to the major side effects of beta-agonists, calcium channel blockers (CCB) have been utilized as effective tocolytic agents owing to their safety profile. Among calcium channel blockers, nifedipine is the most frequently used agent due to the availability of oral formulation, and lower cost in addition to the minimal maternal adverse effects associated with its use [4–6]. A Cochrane review including 12 randomized controlled trials concluded that CCBs, particularly nifedipine, reduce the risk of delivery within 7 days of treatment and delivery before 34 weeks of gestation with reduced fetal complications such as respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis when compared to other tocolytic agents [7,8].

Nifedipine shows its effect by reducing uterine contractility and causing vasodilatation on vascular smooth muscles. From this point of view, we hypothesized that nifedipine might have an adverse effect on the amount of postpartum hemorrhage due to its vasodilatory and contractility properties. The objective of this study is to examine whether or not the exposure to CCBs before delivery is associated with an increased risk of postpartum hemorrhage (PPH) in patients presenting with preterm labor.

2. Materials and Methods

Study Design and Patients

This single-center retrospective case-control study was conducted at the Department of Maternal-Fetal Medicine, Kanuni Sultan Süleyman Education and Research Hospital from 2012 to 2019. The review board and the Ethics Committee of the hospital approved the study. All pregnant women between 24–34 weeks of gestation, who were admitted to the emergency department of our hospital with the diagnosis of threatened premature labor were included in the study. Inclusion criteria for the study were: singleton pregnancy, no known comorbidities (e.g., hypertension, blood dyscrasia), in preterm labor (i.e., less than 37 weeks age of gestation with cervical dilatation <4 cm). Exclusion criteria were the following: Patients with coagulation disorder (e.g., low platelet count, deranged coagulation factors such as prothrombin time, partial thromboplastin time), patients taking aspirin, warfarin, or heparin for any medical condition, patients given other tocolytics aside from nifedipine, patients who refuse/withdraw consent and those allergic to nifedipine. Women with chorioamnionitis, oligohydramnios, polyhydramnios, grand multiparity, multiple gestations, macrosomia, fetal growth restriction, coagulopathy disorders, uterine anomalies, placenta localization anomalies, maternal hypertension ($\geq$140/90 mmHg) or hypotension ($<$90/60 mmHg) were excluded from the study since they could influence the amount of bleeding. Suspected intrauterine infection cases were assumed as chorioamnionitis and were excluded as additional potential confounders for PPH.

Subjects were divided into two groups according to the administration of the nifedipine. The group of patients who were admitted to the clinic for preterm labor and were appropriate candidates for tocolysis was considered as the study group (n = 240). Tocolysis was carried out to prevent preterm delivery and to prolong pregnancy only in subjects with cervical dilatation $\leq$4 cm, and with a risk of delivery within 7 days. The standard protocol for the management of preterm labor, premature prelabour rupture of membranes (PPROM) and related treatment with nifedipine, antibiotics and antenatal corticosteroids was performed in accordance with the recommendations stated by the American College of Obstetricians and Gynecologists (ACOG) practice bulletins [9–11]. A pregnancy-week matched group of patients who were not appropriate candidates for tocolysis and underwent delivery without tocolysis (cervical dilatation $>$4 cm, cervical effacement $>$80%) were selected as the control group.

Potential complications, including postpartum atony, and chorioamnionitis associated with PPROM or nifedipine use, and laboratory measurements of hemoglobin and hematocrit levels at pre- and postpartum 6th hour were recorded. Subjects with chorioamnionitis were monitored using C-reactive protein and leukocyte count in addition to the clinical findings such as tachycardia, fever and fundal tenderness. Chorioamnionitis was established clinically in subjects with fever ($\geq$38 °C orally), vaginal discharge, maternal tachycardia ($>$100 beats per minute), fetal tachycardia ($>$160 beats per minute), abdominal pain, uterine tenderness, and leukocytosis. Non-reassuring fetal status, clinical chorioamnionitis, and persistent uterine contraction leading to cervical dilatation $>$4 cm were accepted as the indications for delivery.

In addition to the total dose of nifedipine given and the duration from the last dose to the delivery, the dose of nifedipine used during the last 24 hours, 72 hours and 1 week before delivery were recorded separately for all patients. Hemoglobin and hematocrit values measured before and 6 hours after delivery were recorded. Pre/postpartum hemogram and hematocrit, platelet changes were compared in control and nifedipine groups taking into account the total duration of use of the drug, the dose and the time of use before delivery.

Number Cruncher Statistical System (NCSS) 2007 Statistical Software (NCSS LLC, Kaysville, UT, USA) was used for statistical analysis. Shapiro-Wilk test was used to determine whether variables were distributed normally or not. The homogeneity of variances was assessed with the Levene test. Data are presented as mean $\pm$ standard deviation or median (minimum–maximum) for continuous variables regarding the distribution and as frequency (percentage) for categorical variables. Paired samples *t*-test was used in comparison of the change in the variables from pre- to postpartum period. Independent samples *t*-test and Mann Whitney U tests were used for group comparisons. Categorical variables were compared using the Pearson chi-square test. Correlation analysis was performed to identify the association between the nifedipine duration or dose and the change in hemoglobin and hematocrit levels. The $p < 0.05$ values were accepted as statistically significant.

3. Results

There were 246 patients in the control group and 240 patients in the study group. Demographic variables are shown in Table 1. No significant difference was observed in terms of age, BMI (body mass index), gravidity, parity, live birth numbers, weeks of gestation and previous delivery methods between the control group and nifedipine group. However, the presence of PPROM in the nifedipine group was significantly lower than that of the control group ($p <$ 0.001). Related to PPROM, we had a chorioamnionitis incidence of 11.2% (n = 31) in the control group and 10.8% (n = 29) in the nifedipine group (p = 0.888). There were no significant differences between the groups in terms of cesarean section indications, labor durations and mean newborn weight. Besides, we had in both groups statistically insignificant 2 cases complicated with atony, which were managed medically or with Bakri balloon insertion.

Both pre- and postpartum hemoglobin and hematocrit levels were similar in the two groups. However, both

Table 1. Maternal baseline characteristics of patients with preterm birth with related demographics, delivery and neonatal outcome.

Variables		Control group (n = 246)		Nifedipine group (n = 240)		*p*
Maternal characteristics						
Age (years)		28.82 ± 6.28		29.09 ± 6.6		0.644*
Height (cm)		161.5 ± 4.67		161.57 ± 5.26		0.924*
Weight (kg)		75.86 ± 14.26		76.97 ± 17.85		0.628*
BMI (kg/m^2)		29.09 ± 4.98		29.21 ± 5.53		0.874*
Gravidity (n, %)		2 (1–3)		2 (1–3.5)		0.411‡
Parity (n, %)		1 (0–2)		1 (0–2)		0.128‡
Live births (n, %)		1 (0–2)		1 (0–2)		0.076‡
Delivery and maternal outcome						
Weeks of gestation at birth		30.49 ± 3.33		30.46 ± 3.53		0.911*
Previous delivery methods (n, %)	none	83	36.89%	105	42.86%	0.288+
	NSVD	75	33.33%	65	26.53%	
	C-section	56	24.89%	58	23.67%	
	NSVD + C-section	11	4.89%	17	6.94%	
PPROM (n, %)	no	10	4.42%	57	23.36%	<0.001+
	yes	216	95.58%	187	76.64%	
Delivery type (n, %)	NSVD	83	33.74%	81	33.06%	0.873+
	C-section	163	66.26%	164	66.94%	
C-section indication (n, %)	Previous C-section	66	40.24%	69	40.12%	0.792+
	Fetal distress	32	19.51%	27	15.70%	
	Failed induction of labor	4	2.44%	4	2.33%	
	CPD	0	0.00%	2	1.16%	
	Breech position	15	9.15%	15	8.72%	
	Other maternal factors	46	28.05%	53	30.81%	
	Other fetal factors	1	0.61%	2	1.16%	
Anesthesia type (n, %)	General	163	100.00%	158	93.49%	0.001+
	Regional	0	0.00%	11	6.51%	
Time from inclusion to delivery (days)		4 (3–6)		4 (2–7)		0.882‡
Atony (n)		2		2		0.980
Neonatal outcome						
Weight of newborn (g)		1657.08 ± 695.1		1608.89 ± 1029.01		0.544*
NICU (n)		71 (30%)		83 (34%)		0.331
Fetal mortality (n)		10 (4%)		10 (4%)		0.826

*Unpaired *t* test; ‡Mann Whitney U test; + Chi Square Test.

BMI, body mass index; PPROM, premature rupture of membranes; NICU, neonatal intensive care unit; NSVD, normal spontaneous vaginal delivery; CPD, cephalopelvic disproportion; C-section, cesarean section.

hemoglobin level and hematocrit decreased significantly in the two groups from the pre- to postpartum period (Table 2). Postpartum platelet count was significantly lower than the prepartum platelet count in the nifedipine group, but was still in normal range.

The nifedipine dose administered at the last 24 hours of the treatment was significantly correlated with the change in the hemoglobin (r = 0.176, $p = 0.006$) and hematocrit levels (r = 0.139, $p = 0.030$) form the pre- to the postpartum period (Table 3, Fig. 1).

No significant correlations were observed between the duration of the labor and medication for 72 hours, medication for 1-week, total nifedipine dosage, nifedipine dosage for the last 24 hours, total nifedipine use in days and time between nifedipine stop to birth ($p > 0.05$) (Table 4). The only statistic that is different in Table 4 is the p value = 0.028.

As shown in Table 5, we conducted subgroup analyses for various aspects of nifedipine medications, including the sum of nifedipine medications taken over 72 hours, the sum of medications taken over 1 week, the overall total nifedipine dose, and the total nifedipine dose for the last 24 hours before delivery.

Table 5 provides a comprehensive overview of the measures of nifedipine use, including median values, interquartile ranges (IQRs) and minimum–maximum ranges

Table 2. Laboratory variables.

		Control group (n = 246)	Nifedipine group (n = 240)	*p*
Hemoglobin (g/dL)	Prepartum	11.44 ± 1.43	11.54 ± 1.45	0.433*
	Postpartum	10.61 ± 1.5	10.76 ± 1.56	0.279*
	*p*ǂ	0.0001	0.0001	
	Difference between pre- and postpartum	0.8 (0.2–1.3)	0.7 (0–1.55)	0.510‡
Hematocrit (%)	Prepartum	33.14 ± 3.62	35.15 ± 4.10	0.0001*
	Postpartum	30.5 ± 3.91	32.70 ± 4.38	0.0001*
	*p*ǂ	0.0001	0.0001	
	Difference between pre- and postpartum	2.6 (1–4.2)	2.2 (0–4.9)	0.411‡
Platelets (mcl)	Prepartum	247.59 ± 86.44	228.82 ± 63.08	0.006*
	Postpartum	230.55 ± 76.37	221.73 ± 80.27	0.213*
	*p*ǂ	0.0001	0.131	
	Difference between pre- and postpartum	17 (−2–39)	12 (−13.5–37.5)	0.123‡

*Unpaired *t* test; ‡Mann Whitney U test; ǂPaired *t* test.

Table 3. Differences in laboratory values according to medication duration.

		Difference between pre- and postpartum Hgb	Difference between pre- and postpartum Htc	Difference between pre- and postpartum PLT
Medication for 72 hours	r	0.078	0.011	0.047
	p	0.226	0.863	0.465
Medication for 1-week	r	0.029	0.015	0.043
	p	0.655	0.813	0.506
Total nifedipine dosage	r	0.119	0.091	0.022
	p	0.064	0.154	0.728
Nifedipine dosage for the last 24 hours	r	0.176	0.139	−0.055
	p	0.006	0.030	0.387
Total nifedipine use in days	r	0.087	0.099	0.052
	p	0.174	0.122	0.421
Time between nifedipine stop and birth	r	−0.119	−0.078	0.016
	p	0.064	0.223	0.807

Pearson correlation test; Hgb, hemoglobin; Htc, hematocrit; PLT, platelet.

Table 4. Correlation analysis.

		Duration of labor
Medication for 72 hours	r	−0.029
	p	0.81
Medication for 1-week	r	0.129
	p	0.286
Total nifedipine dosage	r	0.138
	p	0.253
Nifedipine dosage for the last 24 hours	r	0.127
	p	0.296
Total nifedipine use in days	r	0.111
	p	0.361
Time between nifedipine stop and birth	r	−0.042
	p	0.028

for values for which min–max values were not available for some values within the nifedipine group.

4. Discussion

Postpartum hemorrhage is one of the major causes of maternal morbidity and mortality worldwide. That's why modern medicine tries to find out possible agents for the treatment of postpartum hemorrhage to diminish the blood loss used in the course of labor. Calcium channel blockers are one of these agents frequently used during pregnancy for tocolysis during preterm labor course, in addition to its antihypertensive properties [12–16].

Calcium channel blockers show their effects by inhibiting the influx of calcium into peripheral arterial smooth muscle cells and uterine smooth muscle cells, which further leads to vasodilatation and relaxation in myometrium [12]. While this effect is beneficial in the management of preterm labor or gestational hypertension; however, following delivery, this effect becomes dangerous as effective uterine contractions are required to compress the uterine vasculature [13]. In the absence of effective contractions, the uterus becomes relaxed and excessive bleeding resulting in post-

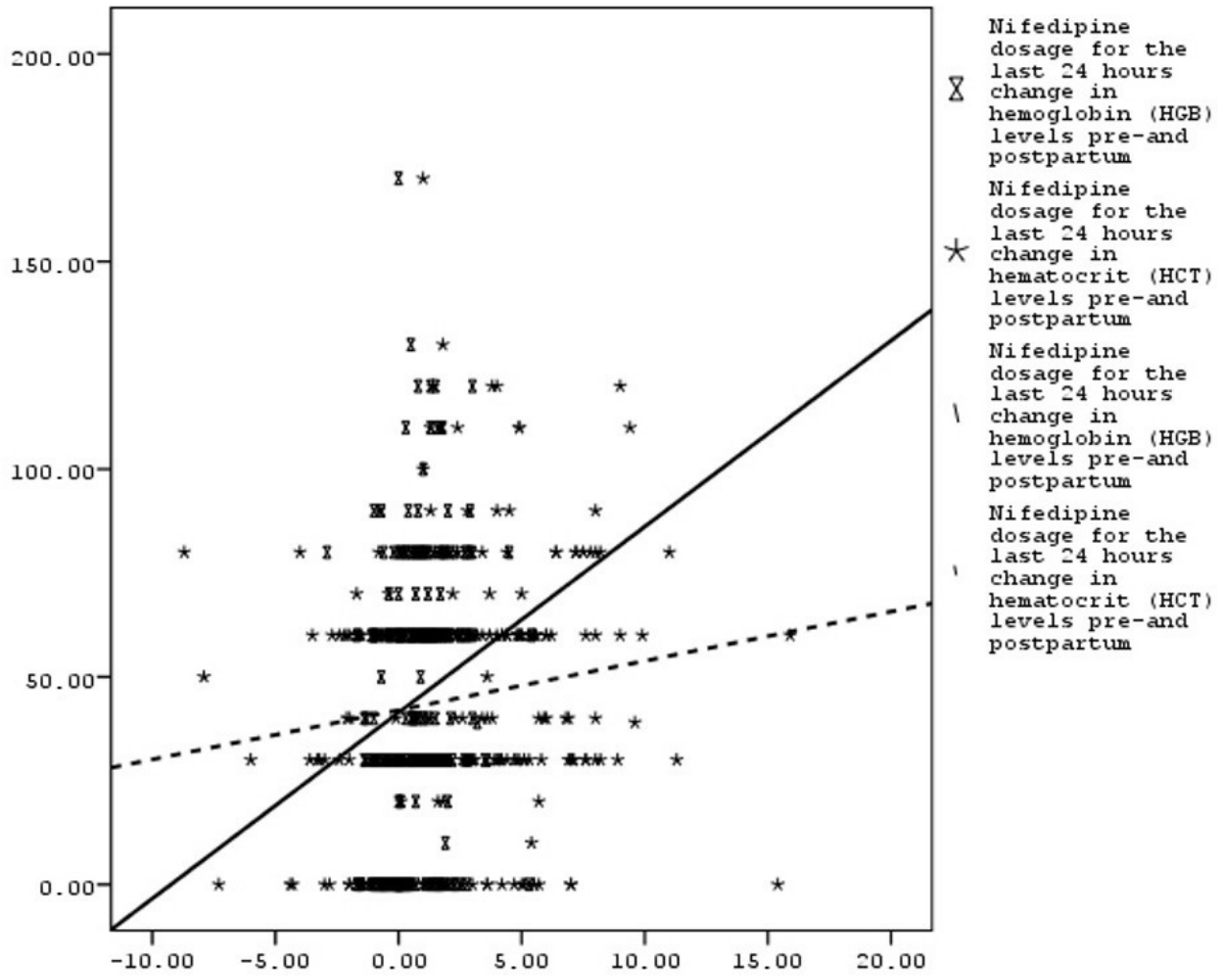

Fig. 1. Correlation graphic for related nifedipin use 24 hours before delivery.

partum hemorrhage and maternal mortality may occur. Because of the relaxation effect on smooth muscles and uterine muscles, several authors have suggested that exposure to CCBs before delivery may increase the risk of uterine atony and PPH [17,18].

The use of CCB prior to delivery may theoretically increase the risk of PPH by causing uterine relaxation has not been studied thoroughly. The study by Yang *et al*. [19] which investigated the amount of blood loss during labor in hypertensive patients taking CCBs found a significant increase in postpartum hemorrhage in patients receiving CCB's during the active stages of labor compared to subjects in whom CCBs were stopped before the labor. In accordance with Yang's study, we found a positive correlation between the PPH and the nifedipine dosage received 24 hours before the labor, although there were no significant correlations between the PPH and the nifedipine dosage received 72 hours before the labor. In this cohort study, we did not observe a significant difference in terms of pre- and postpartum hemoglobin and hematocrit levels between control and nifedipine groups; however, when we analyzed the PPH risk according to the time of CCB use in subgroups, usage before the last 24 hours of delivery is likely related to an increase in PPH. A positive correlation is observed between difference in hemoglobin and hematocrit levels from the pre- to the postpartum period and nifedipine dosage for the last 24 hours but not for 72 hours or the dosage received for the last 1 week.

A possible explanation for this might be that CCBs have short half-life and the drug may have been cleared from the blood quickly until delivery, so that their effect easily dissolves in myometrium. However, when nifedipine is received close to the labor, there is not enough time for the drug to be cleared off. The risk of PPH associated with CCBs may results from the direct action on the myometrium. It appears that subjects are vulnerable to PPH promoted by the nifedipine immediately before the delivery. Another large scaled study, which was conducted by Bateman *et al*. [20] confirms our results. They compared the risk of postpartum hemorrhage in hypertensive patients receiving CCBs and other antihypertensive drugs (methyldopa or labetalol). They found no differences in the risk

Table 5. Nifedipine sum of the taken medication.

	Nifedipine group	Median (IQR)	Min–Max
Total medication for 72 hours (mg) (n = 230)	114.13 ± 65.48	90 (60–162.5)	20–380
Total medication for 1-week (mg) (n = 89)	186.85 ± 141.23	120 (85–260)	10–630
Total nifedipine dosage (mg)	221.51 ± 134.11	120 (60–210)	20–3330
Total nifedipine dosage for the last 24 hours (mg)	54.99 ± 25.50	60 (30–60)	10–170
Total nifedipine use in days	3.71 ± 4.64		
Time between nifedipine stop and delivery in days	13.31 ± 23.76		

IQR, interquartile range.

of PPH between two groups. The possible explanation for the lack of a difference in the PPH rate between the subjects receiving CCBs and other antihypertensive drugs is that Bateman and colleagues included outpatient subjects, and CCBs were probably stopped long before the delivery so that the unfavorable effects of the CCBs on the PPH was not observed in that study.

The main difference of our study from the previous studies is that the study population included in our study was consisting of subjects with preterm labor in contrast to the previous studies conducted on subjects with gestational hypertension. To the best of our knowledge, this is the first study investigating the obstetric adverse effects of (i.e., bleeding effect) CCBs when used for the management of preterm delivery. According to preterm delivery protocols, after loading dose, CCB's may be given up to 8 times a day in the first 24 hours, and then the dosage is decreased gradually until corticosteroid medication is completed. Because the doses are higher than used in hypertensive states (4 or 6 times a day), the uterine relaxation may be exaggerated because of higher plasma levels soon before delivery.

The lack of direct measurement of the bleeding during and after the labor would provide more accurate information regarding the impact of nifedipine on postpartum hemorrhage. However, data concerning the blood loss was not available in many of the patients. Therefore, we had to use the pre-and postpartum hemoglobin and hematocrit levels to estimate the amount of the postpartum blood loss in the two groups. These results therefore need to be interpreted with caution.

5. Conclusions

In conclusion, our study showed that nifedipine use for tocolytic purpose may increase hempglobin/hematocrit levels and platelate counts during delivery among women with preterm labor, but this was in an acceptable amount and statistically insignificant. However, other studies may have totally different results, which shows us that this topic needs further investigation. Although not to conclude with our study, obstetricians should be aware with the use of nifedipin and be prepared for greater blood loss and postpartum hemorrhage to prevent maternal morbidity and even mortality [21].

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

HK and AG designed the research study. HK and NK performed the research. SSC, ZAcar, AAA and BU provided help and advice on topic and methods. NK, ZAyt and AG analyzed the data. NK and AG wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Kanuni Sultan Süleyman Training and Research Hospital review board, ethics committee or ethical review board approved the study on 19/07/2016 with the number 26817412. All human subjects provided written informed consent with guarantees of confidentiality.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Heron M, Sutton PD, Xu J, Ventura SJ, Strobino DM, Guyer B. Annual summary of vital statistics: 2007. Pediatrics. 2010; 125: 4–15.

[2] Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. The Lancet. 2008; 371: 75–84.

[3] Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. The Lancet. 2008; 371: 261–269.

[4] Bussey HI, Talbert RL. Promising Uses of Calcium-Channel

Blocking Agents. Pharmacotherapy: the Journal of Human Pharmacology and Drug Therapy. 1984; 4: 137–143.
[5] Kaul AF, Osathanondh R, Safon LE, Frigoletto FD Jr, Friedman PA. The management of preterm labor with the calcium channel-blocking agent nifedipine combined with the β-mimetic terbutaline. Drug Intelligence & Clinical Pharmacy. 1985; 19: 369–371.
[6] Ulmsten U, Andersson KE, Wingerup L. Treatment of premature labor with the calcium antagonist nifedipine. Archives of Gynecology. 1980; 229: 1–5.
[7] King JF, Flenady VJ, Papatsonis DN, Dekker GA, Carbonne B. Calcium channel blockers for inhibiting preterm labour. Cochrane Database of Systematic Reviews. 2003; CD002255.
[8] van Geijn HP, Lenglet JE, Bolte AC. Nifedipine trials: effectiveness and safety aspects. BJOG: an International Journal of Obstetrics and Gynaecology. 2005; 112: 79–83.
[9] Kuba K, Bernstein PS. ACOG Practice Bulletin no. 188: Prelabor Rupture of Membranes. Obstetrics and Gynecology. 2018; 131: 1163–1164.
[10] American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. Practice Bulletin No. 171: Management of Preterm Labor. Obstetrics and Gynecology. 2016; 128: e155–e164.
[11] Hemorrhage P. Practice bulletin no. 183: Postpartum hemorrhage: Postpartum hemorrhage. Obstetrics and Gynecology. 2017; 130: e168–e181.
[12] Oyelese Y, Ananth CV. Postpartum Hemorrhage: Epidemiology, Risk Factors, and Causes. Clinical Obstetrics and Gynecology. 2010; 53: 147–156.
[13] King JF, Flenady V, Papatsonis D, Dekker G, Carbonne B. Calcium channel blockers for inhibiting preterm labour; a systematic review of the evidence and a protocol for administration of nifedipine. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2003; 43: 192–198.
[14] Nassar A, Aoun J, Usta I. Calcium Channel Blockers for the Management of Preterm Birth: a Review. American Journal of Perinatology. 2011; 28: 57–66.
[15] Yamasato K, Burlingame J, Kaneshiro B. Hemodynamic effects of nifedipine tocolysis. Journal of Obstetrics and Gynaecology Research. 2015; 41: 17–22.
[16] Inan C, Sayin C, Dolgun N, Uzun I, Erzincan SG, Sutcu H, *et al*. Comparison of the efficacy of the immediate-release and osmotic push–pull system formulations of nifedipine for tocolysis. Journal of Obstetrics and Gynaecology Research. 2019; 45: 2351–2357.
[17] Papatsonis DNM, Lok CAR, Bos JM, Geijn HPV, Dekker GA. Calcium channel blockers in the management of preterm labor and hypertension in pregnancy. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2001; 97: 122–140.
[18] Breathnach F, Geary M. Uterine Atony: Definition, Prevention, Nonsurgical Management, and Uterine Tamponade. Seminars in Perinatology. 2009; 33: 82–87.
[19] Yang X, Liu Y. The effect of Nifedipine on postpartum blood loss in patients with pregnancy induced hypertension. Zhonghua Fu Chan Ke Za Zhi. 2000; 35: 151–152. (In Chinese)
[20] Bateman B, Hernandez-Diaz S, Huybrechts K, Palmsten K, Mogun H, Ecker J, *et al*. Outpatient calcium-channel blockers and the risk of postpartum haemorrhage: a cohort study. BJOG: an International Journal of Obstetrics and Gynaecology. 2013; 120: 1668–1677.
[21] de Jesus MSR, Zalameda-Castro CR. The Effect of Nifedipine used as Tocolytic Agent on Postpartum Blood Loss among Filipino Pregnant Patients in a Tertiary Hospital: a Prospective Cohort Study. Acta Medica Philippina. 2018; 52: 32–39.