ORIGINAL ARTICLE

The Effect of Nifedipine used as Tocolytic Agent on Postpartum Blood Loss among Filipino Pregnant Patients in a Tertiary Hospital: a Prospective Cohort Study

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ABSTRACT

Objective. To determine the risk of postpartum hemorrhage among patients who were treated with nifedipine for tocolysis of preterm labor.

Methods. A prospective cohort study was conducted with 66 pregnant women admitted for preterm labor. One group of women was given nifedipine to give time for the administration of corticosteroids for fetal lung maturity and/or control of preterm labor and another group was not given nifedipine as they were admitted in advanced stage of labor (ie, more than or equal to 4 cm cervical dilatation). Independent/paired sample t-test, Mann-Whitney U/Wilcoxon signed rank test, and Fisher's exact test were used to determine the difference of mean, median, and frequency between and within groups, respectively. STATA 12.0 was used for data analysis.

Results. There was more blood loss during delivery, which was statistically significant, among those who received nifedipine compared to those who have not taken the medicine (350 mL versus 250 mL, p = 0.021). Furthermore, the decreases in hemoglobin and hematocrit were also lower among those who did not receive nifedipine compared to those who received nifedipine for tocolysis (8.5 mg/dL versus 16.0 mg/dL, p = 0.014 and 0.03 versus 0.05, p = 0.010), again, statistically significant.

Conclusion. Nifedipine used as tocolytic appear to increase blood loss during delivery, which was statistically significant. Greater amount of blood loss may be anticipated among those with nifedipine intake thus helping the obstetrician in preparing for active management of postpartum hemorrhage and preventing maternal morbidity and mortality.

Key Words: nifedipine, preterm labor, postpartum blood loss

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INTRODUCTION

Postpartum hemorrhage

Postpartum hemorrhage (PPH) is an obstetrical emergency that may happen in vaginal or cesarean delivery. While there is no single, satisfactory definition of postpartum hemorrhage, PPH is best diagnosed clinically as excessive bleeding that makes the patient symptomatic and/or results in signs of hypovolemia. The most common definition is an estimated blood loss ≥ 500 mL after vaginal birth or ≥ 1000 mL after cesarean delivery.[1,2,3] The American College of Obstetrics and Gynecology also advocates the definitions of PPH of either a 10% change in hematocrit between the antenatal and postpartum period or a need for blood transfusion. After delivery associated with an average

blood loss, the hematocrit drops moderately for 3–4 days, followed by an increase. On Day 2 or Day 3 postpartum, the peak drop may be appreciated.[4] The frequency of PPH in vaginal delivery and cesarean delivery is 3.9% and 6.4%, respectively.[1] Major cause of maternal morbidity is linked to postpartum hemorrhage and is one of the top three causes of maternal mortality in both high and low per capita income countries, although the absolute risk of death from PPH is much lower in high income countries (1 in 100,000 deliveries in the United Kingdom versus 1 in 1000 deliveries in the developing world).[1] It accounts for significant maternal mortality, with 28% of maternal deaths in developing countries caused by excessive blood loss after parturition.[5] In an analysis of population-based data from the United States National Inpatient Sample for the years 1994-2006, the discharge diagnosis of PPH increased 26 percent over this period (from 2.3 to 2.9 percent). In the Philippines, 13 mothers die every day from pregnancy-related complications. An estimated 5,000 maternal deaths occur annually – and may be higher due to underreporting. A local study done by Garces in 2008 showed that more than half the deaths (52%) are caused by hemorrhage, while eclampsia accounts for another 27%. Ruptured uterus and other causes account for the remainder.[6] A health survey done in 2011 showed that maternal mortality ratio had increased from 162 per 100,000 live births in 2006 to 221 in 2011. However, as the Millennium Development Goals (MDGs) concluded in 2015, the United Nations reported that maternal mortality ratio dropped by 45% worldwide between 1990 and 2013, from 380 maternal deaths per 100,000 live births to 210. In Southeast Asia, the decline was 64%. This improvement in maternal health still did not meet the Millennium Development Goal 5 target ratio of 52 deaths per 100,000 live births. In fact, it was also reported that globally, there were an estimated 289,000 maternal deaths in 2013, equivalent to about 800 women dying each day. Maternal deaths are concentrated in sub-Saharan Africa and Southern Asia, which together accounted for 86 per cent of such deaths globally in 2013. Hemorrhage still remains the cause of the greatest number of maternal deaths, accounting for more than 27 per cent of maternal deaths in the developing regions and approximately 16 per cent in the developed regions.[7] According to the United Nations, improving maternal health is part of the unfinished agenda for the post-2015 period hence it was still integrated in the Sustainable Development Goals launched last September 25, 2015 at the Sustainable Development Summit. Seventeen new goals, including good health and well-being of women, guarantee to finish the job of MDGs.[8]

Causes of PPH include placenta previa, placenta accreta, lower genital tract laceration, coagulopathy, uterine inversion, ruptured uterus, and uterine atony. Among these causes, *uterine atony* is the most common cause of PPH, seen in about 75-90% of cases.[9] Furthermore, a study by Solanke et al in 2014 showed that among 5,998 women who delivered in a tertiary hospital, 98 ended up with PPH. Atony was found to be the most common cause accounting for 79.17% of all PPH, followed by traumatic cause (16.67%) and retained placenta (4.16%).[10]

Postpartum hemorrhage had more than one predisposing factors including anemia, prolonged labor, multiparity, multifetal gestations, macrosomia, and fibroid uterus.[10] Grand multiparity is defined as five or more live births and stillbirths more than or equal to 20 weeks of gestation. Studies suggested that increasing parity increased the risk of pregnancy complications including hypertension, diabetes mellitus, complications of hemorrhage, and even maternal mortality.[11] A prospective cohort study of 11,323 vaginal deliveries in 2003-2005 showed that multiple pregnancy is a risk factor (20.9%) to postpartum hemorrhage second to retained placenta (33.3%).[12]

Postpartum hemorrhage poses enormous burden to families and to society due to maternal complications that come with it. Various clinical signs and symptoms can be observed in patients suffering from blood loss including hypotension, tachycardia, or even profound shock. Therefore, timely and accurate diagnosis is important to initiate appropriate preventive interventions and management and in turn improve both maternal and fetal outcomes.

Preterm labor

Preterm labor is defined as uterine contractions occurring before 37 weeks age of gestation, resulting into cervical dilatation and progression into preterm birth which is the most common cause of death among infants worldwide. Almost 75% of perinatal deaths occur in infants born before 37 weeks' gestation.[13] Subsequently, preterm birth is associated with a large burden of disease, high costs for medical care, special education, and institutionalized care for disabled infants.[14] About 15 million babies are born preterm each year (5% to 18% of all deliveries). In many countries, rates of premature births have increased between the 1990s and 2010s.[15] In the Philippines, preterm birth is becoming a major health problem being estimated to account for two-thirds of all newborn deaths, and the second major cause of death among children who are less than five years of age.[15]

At the Philippine General Hospital, 5-year statistics from 2010-2014 showed that the prematurity rate has remained to be high, accounting to 24-25% of all deliveries. Therefore, tocolytic use to prevent prematurity and its complications is of prime importance in the management of preterm labor.

Nifedipine as a tocolytic

Tocolytics are used for the prevention of preterm labor. In threatened preterm labor before 34 weeks, delay of delivery for 48 hours allows antenatal corticosteroid treatment to improve fetal maturity and transfer of the pregnant woman to a center with a neonatal intensive care unit. Frequently used drugs include the β2- adrenergic

receptor agonists, calcium-channel blockers, magnesium sulphate, prostaglandin synthetase inhibitors (atosiban). For initial tocolysis, nifedipine is comparable with magnesium sulfate and superior to ritodrine and atosiban.[16]

Nifedipine is an example of a 1,4-dihydropyridine that is prepared using the Hantzsch pyridine synthesis and is the first dihydropyridine isolated, back in 1882. Nifedipine is the most commonly used agent for tocolysis. It is a calcium ion influx inhibitor which inhibits the transmembrane entry of calcium ions into vascular smooth muscle and cardiac muscle. The contractile processes of vascular smooth muscle and cardiac muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Nifedipine selectively inhibits calcium ion influx across the cell membrane of vascular smooth muscle and cardiac muscle without altering serum calcium concentrations. Nifedipine is a peripheral arterial vasodilator which acts directly on vascular smooth muscle. Stores of intracellular calcium in vascular smooth muscle are limited and thus dependent upon the influx of extracellular calcium for contraction to occur. The reduction in calcium influx by nifedipine causes arterial vasodilation and decreased peripheral vascular resistance which results in reduced arterial blood pressure. Furthermore, a Cochrane review concluded that it is comparable with magnesium sulfate and beta-agonists (such as ritrodine) in reducing preterm labor and in improving neonatal outcome with fewer side effects. They should be considered as first-line agents in the management of preterm labor as they also have less side effects.[17]

The recommended dosage for calcium-channel blockers is 20 mg four-hourly, with half-life of 2-7 hours. Side effects include hypotension (which may reduce placental perfusion), headaches and flushing, conduction abnormalities (which may be more profound with a volatile anaesthetic), and difficulties in managing postpartum hemorrhage using oxytocin and prostaglandins as they all work in relation to the calcium receptors.[12] An experimental study done by Tobin et al in 2011 showed that release of oxytocin and vasopressin in somato-dendritic cells can be regulated both by activity-dependent Ca^{2+} influx and by mobilization of intracellular Ca^{2+}. Like the release of conventional neurotransmitters, oxytocin and vasopressin secretion from axon terminals in the neurohypophysis depends on depolarisation-evoked Ca^{2+} entry through high voltage-activated Ca^{2+} channels.[18]

In our hospital and in most Philippine Obstetrics and Gynecology Society (POGS)-accredited training hospitals in our country, nifedipine is used as the first line drug for tocolysis, to be able to prolong the age of gestation for at least 48 hours, enough time to administer steroids to improve fetal lung maturity.

Nifedipine and postpartum blood loss

A cohort study done by Bateman et al, showed that there was no meaningful association between calcium channel blocker exposure used for the treatment of hypertension and postpartum hemorrhage (odds ratio 0.77, 95% CI 0.50–1.18).[19] On the other hand, a study by Yang X and Liu Y in 2003, which aimed to determine the efficacy of nifedipine on postpartum blood loss in patients with pregnancy-induced hypertension (PIH), showed that the amount of postpartum hemorrhage in the study group was significantly higher than that of control group. The postpartum hemorrhage rate in study and control group was 43.75% and 18.75%, respectively, which was statistically significant ($p < 0.05$). The study therefore concluded that during labor, using nifedipine for PIH cases can increase the amount of postpartum blood loss and rate of postpartum hemorrhage.[20]

The effect of nifedipine on postpartum blood loss has not been widely studied internationally. Hence, little is known regarding its actual effect on postpartum blood loss. Furthermore, to date, there has been no documented study in the Philippines that tackles the effect of nifedipine, used as tocolytic among women in preterm labor, to postpartum hemorrhage.

General objective

To determine the risk of postpartum hemorrhage among patients who were treated with nifedipine for tocolysis of preterm labor.

Specific objectives

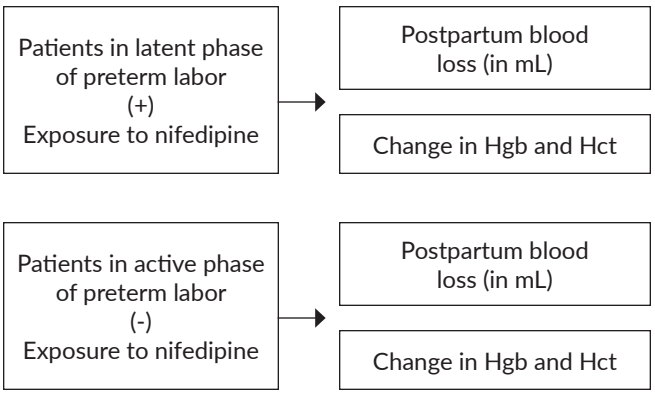
1. To quantify maternal blood loss incurred during normal spontaneous delivery or cesarean section delivery.
2. To measure the change in hemoglobin and hematocrit levels of patients, before and after delivery.
3. To compare the postpartum blood loss of patients who were given nifedipine and those who were not given.

METHODS

Research design

This is a prospective cohort study that determined the risk of postpartum hemorrhage among patients who had intake of nifedipine used for tocolysis.

Conceptual framework



Study population

The study population consisted of Filipino women who were admitted for preterm labor and delivered at the Obstetrics Admitting Section of the Philippine General Hospital between the period of April 2016 to August 2016.

Inclusion criteria for the study were the following:

- Patients 19-35 years old
- Singleton pregnancy
- No known comorbidities (eg, hypertension, diabetes mellitus, blood dyscrasia)
- At most parity 3 (ie, with 3 term babies delivered vaginally)
- In preterm labor (ie, less than 37 weeks age of gestation with cervical dilatation of 1 cm and above)
- With and without use of nifedipine as tocolytic

Exclusion criteria were the following:

- Patients who were not in preterm labor
- Patients taking aspirin, warfarin, or heparin for any medical condition
- Patients with coagulation disorder (eg, low platelet count, deranged coagulation factors such as PT, PTT)
- Patients who would require operative vaginal delivery
- Patients who were in preterm labor but were given other tocolytics aside from nifedipine
- Those who would refuse/withdraw consent
- Those allergic to nifedipine

Withdrawal criteria

Patients who were evaluated to have any of the exclusion criteria and who withdrew their consent were excluded in the study.

Sampling design

All patients who delivered at the institution were included in the study unless they had one or more of the criteria for being excluded in the study. This was done to reduce the selection and sampling bias due to the variety of women delivering at the hospital. Patient selection was done by the principal investigator after the patient was referred by the OB Admitting Section Senior Resident and the research assistant. Patients who were included in the study were assigned into two groups, the nifedipine group and the control group. One group consisted of pregnant patients in preterm labor, admitted for tocolysis using nifedipine, however, preterm labor was not controlled by the said drug and eventually delivered. Another group consisted of patients in advanced stage of preterm labor (> 3 cm cervical dilatation), who were therefore not given nifedipine. All patients included in the study were given the same quality of care during their labor regardless if they were in the control group or nifedipine group or did not consent to be included in the study.

Sample size

A total of 106 subjects or 53 per group were required for this study based on a level of significance of 5%, a power of 80%, and reference values as noted from the reference article by Yang et al.[7] In this study, however, there were only 24 patients who were given nifedipine and 42 patients who had no nifedipine intake. Sample size calculation is shown below.

Description of the study procedure

Procedure on the conduct of the study was explicitly explained to the patients who were included in the study. Verbal and written consents were secured by one of the following: the principal investigator, the research assistant,

Sample size formula[1]:

$$P = [p_1 \times q_1] + [p_2 \times q_2]$$

$$N \geq \frac{\left[Z_\alpha \sqrt{P \times (1-P) \times \left(\frac{1}{q_1} + \frac{1}{q_2} \right)} + Z_\beta \sqrt{\frac{P_1 \times (1-P_1)}{q_1} + \frac{P_2 \times (1-P_2)}{q_2}} \right]^2}{(P_1 - P_2)^2}$$

$$n \geq \frac{\left[1.96 \sqrt{0.3125 \times (1-0.3125) \times \left(\frac{1}{0.5} + \frac{1}{0.5} \right)} + 0.842 \sqrt{\frac{0.4375 \times (1-0.4375)}{0.5} + \frac{0.1875 \times (1-0.1875)}{0.5}} \right]^2}{(0.4375 - 0.1875)^2}$$

$$n \geq 106$$

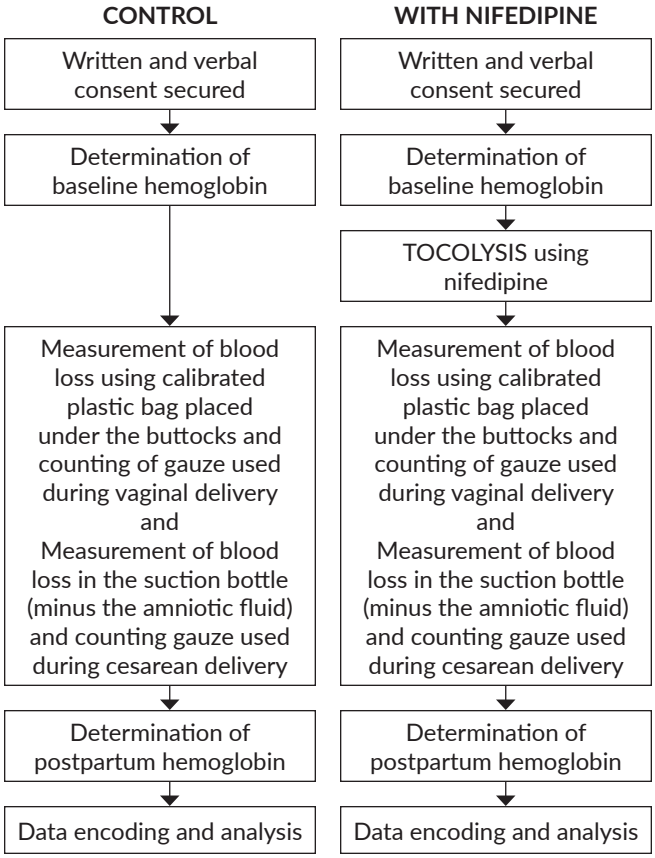
Legend:

n = Minimum sample size per group
P = Effect size = (0.4375*0.5) + (0.1875*0.5) = 0.3125
P_1 = Postpartum hemorrhage rate in study group = 43.75%
P_2 = Postpartum hemorrhage rate in control group = 18.75%
q_1 = Proportion of subjects in study group = 50%
q_2 = Proportion of subjects in control group = 50%
Z_α = 1.96
Z_β = 0.842

Reference:

[1] Hulley SB, Cummings SR, Browner WS, Grady D, Newman TB. Designing clinical research: an epidemiologic approach. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013. Appendix 6B, page 78.

Diagrammatic flow chart of the conduct of study



or the senior resident on duty. Once consent was secured, maternal factors such as age, gravidity, parity, weight, height, presence of co-morbidities, history of premature labor, and history of nifedipine use were obtained and recorded in a data collection form by the principal investigator or the research assistant.

Baseline hemoglobin and hematocrit were measured. The blood sample for the baseline was extracted by the medical student (intern or clerk) or first year resident assigned at the OB admitting section. Samples were sent to the laboratory and the cost was shouldered by the patient as this was part of the routine laboratory examinations done to patients in the admitting section. The total blood loss that was incurred during vaginal delivery was measured using a calibrated plastic bag placed under each patient's buttocks while lying in a lithotomy position waiting for the baby to be delivered. This plastic bag was directly placed in a pail to prevent spillage of the blood. Sterile operating sponges that were soaked by blood were also measured and the equivalent blood loss was added to collected amount of blood in the plastic bag (ie, 1 fully soaked 4 x 4 cm sterile gauze was equivalent to 30 mL). On the other hand, the total blood loss during cesarean delivery was measured from the suction bottle minus the estimated amount of amniotic fluid and fluid wash. Same as in vaginal delivery, the amount of blood measured from the number of sterile operating sponges that were soaked by blood was added. Data collection and recording was done mainly by the principal investigator. Data collected by the research assistant were evaluated and analyzed by the principal investigator. Blood samples 2 days post-delivery were extracted by the principal investigator or the first year resident student and was sent for examination. The cost for the postpartum hemoglobin and hematocrit determination of those who underwent vaginal delivery was shouldered by the principal investigator as this was not part of the routine laboratory examination. Quantity of blood loss and change in hemoglobin and hematocrit from all the subjects were compared and analyzed. Possible errors during the conduct of the study including inaccurate collection of blood loss was minimized by conducting proper orientation by the principal investigator on the labor room resident on duty and by using calibrated plastic bag to determine the blood loss.

Description of analysis

All the information was checked by the primary investigator to ensure completeness and correctness of data. Data were then manually entered into a Microsoft Excel file. Descriptive statistics was used to summarize the clinical characteristics of the patients. Frequency and proportion were used for nominal variables, median and Interquartile Range (IQR) for ordinal variables, and mean and SD for interval/ratio variables. Independent/Paired Sample T-test, Mann-Whitney U/Wilcoxon Signed rank test and Fisher's Exact test were used to determine the difference of mean, median, and frequency between and within groups, respectively. All valid data were included in the analysis. Missing variables were neither replaced nor estimated. Null hypothesis was rejected at 0.05 α-level of significance. STATA 12.0 was used for data analysis.

Ethical considerations

This research protocol was submitted to the University of the Philippines Manila Research Ethics Board (UPMREB) PGH Review Panel, and the commencement of the data collection was started after approval by the board.

Informed consent was secured. The process of obtaining informed consent was as follows:

i. The research objectives, information about the study including risks, benefits, and possible discomforts that can be experienced by the patient during the course of the study were thoroughly explained by the investigators to the subjects and their attending physicians.
ii. The person who conducted the orientation was the one to secure consent from the patient. Consent was read and explained to the patient.
iii. A patient was given the recourse to consult or confer with their doctors, partner/spouse or family members prior to affording their consent.
iv. Should the patient decide not to continue with the participation, she was allowed to do so with the same quality of care given to her during the course of labor.

Disclosure of conflict of interest

The investigators are not affiliated with organizations or committees that could affect the results and conclusions of the study. They also have no competing financial interests that could reasonably be viewed as a conflict of interest.

Recruitment and obtaining of informed consent were done by the principal investigator, research assistant, and senior resident-on-duty. The measurement of the blood loss during deliveries was obtained by the delivery room resident on-duty and the resident-in-charge.

RESULTS

A total of 66 patients were included in the study, 24 were given nifedipine while 42 were not. The mean age of patients with nifedipine versus without nifedipine was similar (24.5 versus 22, p = 0.384). The median age of gestation between patients who received nifedipine (32 4/7 AOG) and who did not receive nifedipine (34 3/7 AOG) was significantly different (p=0.023). Most of the patients delivered via spontaneous vaginal delivery both for the control group and study group. The mean number of hours of labor was 9.5 hours for the control group and 7 hours for the study group which was not statistically significant. Table 1 shows the demographic profile of the patients.

Table 2 shows the summary of the baseline and postpartum hemoglobin and hematocrit of patients enrolled in the study. In both groups, the postpartum hemoglobin and hematocrit were significantly lower compared to baseline. Across the two groups, the decrease from baseline hemoglobin was lower among those who did not take nifedipine compared to those who took nifedipine (8.5 mg/dL versus 16 mg/dL), which was statistically significant (p=0.014). Furthermore, there was a significant decrease in hematocrit from baseline to postpartum hematocrit for both groups. Comparing the two groups, the decrease in hematocrit among those who were not given nifedipine was lower compared to those who took nifedipine (0.03 versus 0.05), which was statistically significant (p=0.010).

Table 3 shows the summary of the postpartum blood loss of patients enrolled in the study. Majority of the patients had spontaneous vaginal delivery (n = 58). Among the patients who had spontaneous vaginal delivery, the control group showed lower amount of blood loss compared to the study group (250 mL versus 350 mL) which was statistically significant (p=0.021).

Table 1. Demographic profile of 66 patients with and without previous tocolysis using nifedipine at the Philippine General Hospital

	With nifedipine (n=24)	Without nifedipine (n=42)	p-value
	Frequency (%); Mean + SD; Median (Range)		
Age	24.5 (19 to 34)	22 (19 to 34)	0.384ǂ
Age of gestation	32 4/7 (29 4/7 to 35 2/7)	34 3/7 (25 4/7 to 36)	**0.023ǂ**
Gravidity			0.745ł
Primigravid	11 (45.83)	21 (50)	
Multigravid	13 (54.17)	21 (50)	
Parity			0.838§
Nullipari	12 (50)	22 (52.38)	
Primipari	8 (33.33)	11 (26.19)	
Multipari	4 (16.67)	9 (21.43)	
Manner of delivery			**0.023§**
SVD	18 (75)	40 (95.24)	
CS	6 (25)	2 (4.76)	
No. of hours of labor	7 (1 to 26)	9.5 (2 to 36)	0.123ǂ
Birthweight (in grams)	1882 + 380	2101 + 508	0.070*

*Statistical test used: * – Independent Sample T-test; ǂ– Mann-Whitney U Test; ł– Chi-square test; §– Fisher's Exact test*

Table 2. Baseline and postpartum hemoglobin and hematocrit of 66 patients who were admitted for preterm labor at the OB admitting section of the Philippine General Hospital

	With nifedipine (n=24)	Without nifedipine (n=42)	p-value
	Mean + SD; Median (Range)		
Hemoglobin			
Baseline	123.63 + 14.47	117.55 + 15.96	0.129*
Postpartum	106.21 + 13.21	106.71 + 17.51	0.903*
p-value§	**0.000**	**0.000**	
Hgb difference	16 (1 to 46)	8.5 (1 to 31)	**0.014ǂ**
Hematocrit			
Baseline	0.37 + 0.04	0.36 + 0.05	0.527*
Postpartum	0.31 + 0.04	0.33 + 0.05	0.237*
P-value§	**0.000**	**0.000**	
Hct difference	0.05 (0 to 0.16)	0.03 (0 to 0.11)	**0.010ǂ**

*Statistical test used: * – Independent Sample T-test; ǂ– Mann-Whitney U Test; §– Paired T-test*

Table 3. Postpartum blood loss of 66 patients with and without intake of nifedipine for preterm labor at the Philippine General Hospital

	With nifedipine (n=24)	Without nifedipine (n=42)	p-value
	Frequency (%); Median (Range)		
SVD (n=58)			0.706§
< 500mL	16 (88.89)	**33 (82.50)**	
> 500mL	2 (11.11)	**7 (17.50)**	
Cesarean delivery (n=8)			-
< 1500mL	6 (100)	2 (100)	
> 1500mL	0	0	
Blood loss (mL)	350 (60 to 800)	250 (50 to 850)	**0.021‡**

Statistical test used: ‡– Mann-Whitney U Test; §– Fisher's Exact test

Table 4. Drug profile of the patients given nifedipine for tocolysis (n=24)

	Frequency (%); Median (Range)
Initial dose of nifedipine	
30mg	24 (100)
Succeeding dose of nifedipine	
No succeeding doses	9 (37.5)
10 mg	10 (41.67)
20 mg	5 (20.83)
Frequency given of succeeding dose (hours)	4 (0 to 6)
Number of days	2 (0 to 6)
Number of hrs from last intake (hours)	4 (2 to 72)

Table 4 shows the amount, frequency, and duration of nifedipine intake by patients who were included in the study group. Furthermore, the table shows the number of hours from the delivery to the last intake of nifedipine.

DISCUSSION

The results obtained in our study showed that there was more blood loss during delivery among those who received nifedipine compared to those who did not receive the medicine, which was statistically significant (p=0.021). Furthermore, the decrease in hemoglobin and hematocrit were also lower among those who did not receive nifedipine compared to those who received nifedipine for tocolysis (8.5 mg/dL versus 16.0 mg/dL, p=0.014 and 0.03 versus 0.05, p=0.010), which were statistically significant.

Predisposing factors that may contribute to the increase in blood loss across each group (including prolonged labor, grand multiparity, multiple gestations, and macrosomia) were controlled since we were strict in the inclusion and exclusion criteria. Although the difference was not statistically significant, it is prudent to note that the mean birth weights of babies of those who took nifedipine was smaller compared to babies of those who did not take nifedipine (1,882 +/- 380 grams versus 2,101 +/- 508 grams, p = 0.070).

This is a pilot study since there has been no documented data in the Philippines or even internationally tackling the effect of nifedipine on the postpartum blood loss obtained among women in preterm labor. However, one cohort study showed that there was no meaningful association between calcium channel blocker exposure in the treatment of hypertension and postpartum hemorrhage.[19] Conversely, one study in 2003, which aimed to determine the effect of nifedipine on postpartum blood loss in patients with pregnancy-induced hypertension (PIH), showed that the amount of postpartum hemorrhage in the study group was significantly higher (43.75%) than that of control group (18.75%). The difference was statistically significant ($p < 0.05$) and therefore concluded that during labor, using nifedipine for PIH cases can increase the amount of postpartum blood loss and rate of postpartum hemorrhage.[20] The results of this study and our pilot study seem to agree with the finding that nifedipine causes increased blood loss during delivery.

Several drugs including COX inhibitors (eg, indomethacin), calcium channel blockers (eg, nifedipine), and oxytocin antagonists (eg, atosiban) have been investigated for their tocolytic property, but to date, no study has shown that tocolysis reduces the rates of preterm delivery or improves the neonatal outcome. Despite the lack of evidence showing reduction in rates of preterm delivery and continuing gestation to term, pregnancy can be prolonged for up to 48 hours in 80% of preterm labor cases, enough time for the administration of corticosteroids for fetal lung maturity.

Nifedipine is cheap and can be given orally. This is one of the advantages of using the drug as a tocolytic over atosiban and ritodrine. Despite the lack of standard protocol for the administration of nifedipine, in most studies, it has been given as 10 mg sublingually every 15 minutes for an hour or until contractions stop, followed by 60-160 mg slow release nifedipine daily, in four divided doses.[21] In our study, nifedipine was given as an initial dose of 30 mg orally with succeeding doses of either 10 mg or 20 mg every 4 to 6 hours with an average duration of 2 days (Table 4). The average time from last intake of nifedipine to delivery of the baby was 4 hours, which is within the half-life of nifedipine which is 2-7 hours. This means that the effect of nifedipine on inhibiting calcium ion influx across the cell membrane of vascular smooth muscles including the myometrium, and therefore affecting muscle contractility, is present during the time of delivery of the babies. Furthermore, a study in 2011 showed that the release of oxytocin and vasopressin in somato-dendritic cells can be regulated both by activity-dependent Ca^{2+} influx and by mobilization of intracellular

Ca^{2+}. Like the release of conventional neurotransmitters, oxytocin and vasopressin secretion from axon terminals in the neurohypophysis depends on depolarization-evoked Ca^{2+} entry through high voltage-activated Ca^{2+} channels.[18] With nifedipine and oxytocin both acting on the calcium receptors, contractility of muscle fibers is affected thus contributing to the blood loss during delivery. Nifedipine used as tocolysis increases the blood loss during vaginal and cesarean delivery hence it is important for clinicians especially obstetricians to anticipate possible complications (ie, postpartum hemorrhage) if they use nifedipine in their practice.

CONCLUSION

In conclusion, this study showed that nifedipine used as a tocolytic increased blood loss during delivery among those women in preterm labor compared to those who did not take nifedipine; the difference was statistically significant. This is reflected in the greater decrease in hemoglobin and hematocrit from baseline compared to two days post-delivery among those who took nifedipine, which was also significantly different. From these findings, we therefore recommend that obstetricians should anticipate greater blood loss in women given nifedipine for tocolysis and be more prepared to initiate preventive and active management of postpartum hemorrhage which in turn could prevent maternal morbidity and even mortality.

Limitations of the study

The sample size may be too small to see a significant effect in terms of sputum conversion. Moreover, the differences in the dosing of the interventions in each study may account for differences in their results.

Statement of Authorship

All authors have approved the final version submitted.

Author Disclosure

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REFERENCES

1. Belfort MA, Bertner EW. Overview of Postpartum Hemorrhage. 2010; 20(8):235-24.
2. Cunningham GF, Leveno KJ, Bloom SL, et al. Obstetrical Hemorrhage. In: Cunningham GF, Leveno KJ, Bloom, SL, eds. Williams Obstetrics, 24th ed. USA: McGraw Hill Education; 2014. p.781.
3. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists Number 76, October 2006: postpartum hemorrhage. Obstet Gynecol. 2006; 108(4):1039-48.
4. Maruta S. The observation of the maternal haemodynamics during labour and caesarean section. Nihon Sanka Fujinka Gakkai Zasshi. 1982; 34(6):776–84.
5. Briggs GG, Wan SR. Drug therapy during labor and delivery. Am J Health Syst Pharm. 2006; 63(12):1131-9.
6. Garces RG, Feliciano J, Pabellon J, Lopez, J, Tayag E. Reproductive Age Mortality Studies (RAMOS): Analysis on the Risk Factors of Maternal Death, Bukidnon [Online]. 2008 [cited 2013 Nov]. Available from https://www.pop.org/why-do-filipino-women-die-in-childbirth/
7. United Nations Millennium Development Goal Task Force. The Millennium Development Goal Report 2015. pp.38-39.
8. Philippine Council for Health Research and Development. MDG to Sustainable Development Goals: is there enough emphasis on health? [Online] [cited 2016 Aug]. Available from http://www.pchrd.dost.gov.ph/index.php/news/4945-mdg-to-sustainable-development-goals-is-there-enough-emphasis-on-health.
9. World Health Organization. The prevention and management of postpartum haemorrhage. Report of a Technical Working Group, Geneva, 3-6 July, 1989. WHO/ MCH/90.7. Geneva: World Health Organization; 1990. Unpublished.
10. Solanke P, Patil S, Patil P. Study of Postpartum Hemorrhage in Tertiary Care Centre. International Journal of Scientific and Research Publications. 2014; 4(10):1-3.
11. National Institute for Health and Care Excellence. Parity and postpartum haemorrhage (query bank) [Online]. 2012 [cited 2016 Aug]. Available from https://www.rcog.org.uk/en/guidelines-research services/guidelines/parity-and-postpartum-haemorrhage---query-bank/
12. Sosa CG, Althabe F, Belizan JM, Buekens P. Risk factors for postpartum hemorrhage in vaginal deliveries in a Latin-American population. Obstet Gynecol. 2009; 113(6):1315-9.
13. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008; 371(9606):75-84.
14. Petrou S, Eddama O, Mangham L. A structured review of the recent literature on the economic consequences of preterm birth. Arch Dis Child Fetal Neonatal Ed. 2011; 96(3):F225-F232.
15. Villaverde M, Beltran M, David L. National Objectives for Health Philippines, 2005-2010. Department of Health. Manila: Department of Health; 2005.
16. Madima NR. Anesthetics Supplement: Obstetrics drugs. South African Family Practice. 2013; 55(3):S8-12.
17. RxList. Nifedipine (Adalat CC) [Online]. 2016 [cited 2016 Aug]. Available from http://www.rxlist.com/adalat-drug/clinical-pharmacology.htm
18. Tobin VA, Douglas AJ, Leng G, Ludwig M. The involvement of voltage-operated calcium channels in somato-dendritic oxytocin release. PLoS One. 2011; 6(10): e25366. doi:10.1371/journal.pone.0025366.
19. Bateman BT, Hernandez-Diaz S, Huybrechts KF, et al. Outpatient calcium-channel blockers and the risk of postpartum haemorrhage: a cohort study. BJOG. 2013; 120(13):1668-76.
20. 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(3):151-2.
21. Hamilton SA, Tower CL. Management of preterm labor. Obstetrics, Gynaecology and Reproductive Medicine. 2010; 20(8):235-40.