EFFECT OF ORAL NIFEDIPINE OR COMBINED WITH SILDENAFIL CITRATE FOR MANAGEMENT OF THREATENED PRETERM LABOUR: RANDOMIZED TRIAL

By

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DR.SHREYA SINGH

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LIST OF ABBREVIATIONS

GLOSSARY	ABBREVIATIONS
FDA	Food and Drug Administration
HELLP	Hemolysis elevated liver enzymes low platelet count
HIV	Human immunodeficiency virus
IM	Intramuscular
IQR	Interquartile range
NICU	Neonatal intensive care unit
PDE-5	Phosphodiesterase type 5 inhibitor
PPROM	Premature rupture of membranes
PTB	Pre- term birth
PTL	Preterm labor
RDS	Respiratory distress syndrome
SC	Sildenafil citrate
TVS	Transvaginal sonography

ABSTRACT

BACKGROUND: In developing countries, preterm birth is a leading cause of neonatal and infant illness and mortality. In southern India, there is an increase in preterm delivery and the prevalence is about 5-8 %. It is related with severe suffering for both women and babies as well as long-term disabilities; hence interventions to prevent preterm birth are critical. The threatened preterm labor can be postponed by using "tocolytic" therapy in order to transfer the patient to a center with a neonatal intensive care unit or administer corticosteroids. It helps in the prevention or treatment of respiratory morbidity.

AIMS: To assess the efficacy of nifedipine combined with sildenafil citrate and nifedipine alone in threatened preterm labor and also to determine the maternal and perinatal outcome.

MATERIALS& METHODS: The final analysis comprised a total of 60 subjects. There were 30 people in Group A (Nifedipine) and 30 people in Group B (Sildenafil +Nifedipine).

RESULTS: The mean age of the participants was identified as 21.07 ± 3.31 years and 22.87 ± 3.15 years in group A and B respectively. The cause of preterm was identified as idiopathic in the majority of the women in group A with 83.33 and in group B with 70% and 16.67%. Maternal side effects in group A were tachycardia, palpitations, nausea, and vomiting with 26.67%, 3.33%, and 16.67%, while in group B, tachycardia, facial flushing, palpitations, and headache were identified with 10%, 6.67%, 10%, 6.67%. Respiratory distress syndrome, Neonatal intensive care unit admission, perinatal death,

alive and healthy neonates were identified with 16.67%, 23.33%, 20%, and 53.33% in group A, whereas it was identified with 23.33%, 36.67%, 3.33%, and 56.67% respectively. The rate of success was higher with group B (93.3%) as compared in group A (50%).

CONCLUSION: The combination of sildenafil citrate and nifedipine is more effective than nifedipine alone in avoiding approaching preterm labor.

INTRODUCTION

INTRODUCTION:

Threatened preterm labor occurs when regular uterine contractions occur at least once every 10 minutes and last for more than 30 minutes before the 37th week of pregnancy has passed without the cervix dilation.[1] Tocolytic has been shown to be effective in extending pregnancy in premature labor with cervical dilation. However, research on the use of tocolytics in impending preterm labor is limited.

Preterm labor is defined as the onset of regular painful uterine contractions with effacement and dilatation of the cervix prior to the completion of 37 weeks of pregnancy, starting on the first day of the last menstrual period and lasting after viability. It causes 75% of neonatal mortality and 50% of long-term morbidities such as respiratory distress and neurodevelopmental impairment.[2]

Premature birth is one of the leading causes of neonatal and newborn mortality in developing countries. To reduce perinatal mortality and morbidity, public health educational initiatives, patient lifestyle modification, obstetric protocols of treatment, and early diagnosis of threatened preterm labor are used as preventative measures.[3]

The main goal of an obstetrician is to delay delivery for at least 24-48 hours in order to give adequate time for corticosteroids to be administered. It aids in lowering the occurrence and severity of newborn complications.

Nifedipine is a calcium channel blocker, and a prototype of dihydropyridine had a rapid onset and short duration of action. It acts by inhibiting the voltage-dependent L-type calcium

channel and thereby decreases the calcium influx into the cells. Smooth muscle relaxation occurs, as well as adverse inotropic and chronotropic effects on the heart. Vasodilation followed by a baroreceptor-mediated increase in sympathetic tone can result in indirect cardio-stimulation. The oral route of administration, availability of immediate and slow-release preparations, mild side effects, and its low costs explain the attraction from the obstetric field and its rapid, widespread distribution.

In a meta-analysis, nifedipine was identified as more effective and safer than other traditional tocolytics agents whereas, another meta-analysis study concluded it as a drug of choice for threatened preterm labor.[4]

Sildenafil can help to prevent the degradation of second messenger cyclic guanosine 3',5'-monophosphate by the enzyme PDE-5. The vasodilator effect of sildenafil citrate manifested on uterine and myometrial vessels can cause an increase in the uterine flow and endometrial thickening and also promote an increase. It has the ability to promote nitric oxide synthesis, as well as vascular system relaxation and vasodilation. in the fetal weight.[5,6,6]

NEED OF THE STUDY:

Tocolytics are used to buy time for steroids provided for fetal lung maturity in preterm labour.[7]

Preterm labor birth having the large burden of disease high cost for medical care, special education and institutionalized care for a disabled infant, the effect of nifedipine have a significant effect in prolongation of pregnancy, therefore, combining with sildenafil will empowered to reduce perinatal outcome.[8]

To date, no additional intervention seen to be advantageous to the children. Only a few studies have found into the tocolytic effect of combining nifedipine and sildenafil citrate in women who are at risk of threatened preterm labour.[9] In southern India, there is an increase in preterm delivery, and the prevalence is about 5-8 %. It's difficult to treat threatened preterm labor, which is defined as consistent uterine contractions without cervical advancement. Preterm delivery is related with severe suffering for both women and babies, as well as negative consequences for women and their families, as well as long-term disabilities; hence interventions to prevent preterm birth are critical.

As per literature, there is a paucity of studies conducted in threatened preterm labor; this randomized controlled study is planned to evaluate the effectiveness assess of the sildenafil in improving neonatal and maternal outcomes.

As a result, the goal of this study is to see if combining nifedipine with sildenafil has a better effect than nifedipine alone in terms of preventing threatening preterm labor and enhancing

perinatal outcomes. In order to prevent threatened preterm labor, close surveillance and a prepared preterm newborn care team are also required.

Threatened preterm labor can be postponed by using “tocolytic” therapy in order to transfer the patient to a center with a neonatal intensive care unit or administer corticosteroids. It helps in the prevention or treatment of respiratory morbidity. The purpose of this study was to see how a combination of nifedipine and sildenafil citrate compared to nifedipine alone in the management of threatened preterm labor.

AIMS & OBJECTIVES

AIMS AND OBJECTIVES:

1. “To assess the efficacy of nifedipine combined with sildenafil citrate in preventing the progress of threatened preterm labor.”
2. “To evaluate the efficacy of nifedipine alone for preventing the progress of uterine contraction in threatened preterm labor.”
3. “To determine the maternal and perinatal outcome among the groups using nifedipine alone and nifedipine combined with sildenafil citrate.”

REVIEW OF LITERATURE

REVIEW OF LITERATURE:

1. Threatened preterm labor

Definition:

The presence of frequent uterine contractions and symptoms of labor (backache, pelvic pressure, or vaginal loss) before 37 weeks of pregnancy without cervical dilation is known as threatened preterm labor.[9]

Clinical presentation:

Cervical shortening is the common sequence preceding preterm birth, followed by decidual membrane activation and then the contractions, which is characterized by cervical effacement/ dilatation, pelvic pressure/ low back pain, lower abdominal cramping, vaginal loss (mucous, blood, or fluid) and regular uterine activity.[9]

2. Preterm labor

Definition, criteria, types:

Preterm labor is defined as the onset of labor with a regular and painful uterine contraction that occur with increasing frequency and intensity with progressive cervical changes of effacement and dilation after 28 weeks of pregnancy and before 37 completed week of gestation.[9]

Based on the gestational age, the preterm is subdivided into the following:[10]

- Extremely preterm (<28 weeks)
- Very preterm (28–<32 weeks)
- Moderate or late preterm (32–<37 completed weeks of gestation).

Epidemiology:

Preterm birth accounts for 70% of fetal death rates and around 50% of neonatal neural deficits.[11,12]

It happens in 5 to 18% of pregnancies and is a common cause of hospital admissions during the antenatal periods.

Etiology:

Chorio-amnionitis, Stress, infection, placental abruption, placenta previa, substance use, history of preterm birth or abortion, inadequate prenatal care, smoking, maternal age <18 or >40, poor nutrition, low body mass index, fetal anomaly, fetal growth restriction, oligohydramnios, polyhydramnios, vaginal bleeding, premature preterm rupture of membranes and environmental factors are the causes of preterm labor.

Risk factors:[13]

- Bacterial vaginosis.
- Black race.
- Cocaine or heroin use.
- History of abdominal surgery.
- History of cervical conization or a loop electrosurgical excision procedure of the cervical transformation zone.
- History of preterm delivery.
- Infections of the urinary and genital tracts.
- Intrauterine infection.
- Low pre-pregnancy body mass index (≤ 19.8 kg per m^2).

- Medical disorders such as thyroid disease, diabetes mellitus, or hypertension.
- Mother's work is physically strenuous.
- Multiple gestation pregnancy.
- Polyhydramnios or oligohydramnios.
- Sexual transmitted infections (i.e., Gardnerella-vaginalis and trichomoniasis).
- Tobacco use.
- Uterine anomalies.
- Placental abruption or placenta previa.

Diagnosis:

Clinical assessment of a pregnant women with intact membranes includes:[14]

- Clinical history taking: Estimated date of delivery, ultrasound scans, and antenatal notes.
- Maternal observations: It includes the pain level, pulse, blood pressure, temperature, urinalysis, vaginal loss, contraction length, strength, and frequency.
- Fetal observations: Fetal movement in the last 24 hours, fundal height, lie, presentation, position, and engagement of the presenting part.
- A speculum examination is offered to pregnant women to evaluate if PPROM has occurred. This is carried out by looking for the pooling of amniotic fluid. If the amniotic fluid is not identified, then consider performing vaginal fluid testing for:
- Insulin-like growth factor binding protein-1
- Placental alpha-microglobulin-1
- Digital vaginal examination is offered only if speculum examination cannot identify the extent of cervical dilation.

Complications:[14]

Maternal complications.

Infant Complications:

Premature labor and birth are related with impaired neurodevelopmental outcomes. It consists of impaired cognitive abilities, motor deficits, cerebral palsy, and vision and hearing losses. Risks increases with the decreasing gestational age. It is also associated with behavioral issues like anxiety, depression, autism spectrum disorders.

Neonatal Complications:

Complications associated with the preterm delivery include necrotizing enterocolitis, intraventricular hemorrhage, bronchopulmonary dysplasia, retinopathy of immaturity, and the presence of congenital anomalies.

Management:

The gestational age at which the pregnant woman presents to the hospital determines the course of treatment. If a pregnant woman presents with preterm labor after 34 weeks, she is admitted to the hospital**.**

If she doesn't have any progressive cervical dilation and effacement, as well as foetal well-being on a reactive non-stress test, she will be sent home with instructions to return in 1-2 weeks for a follow-up and if there are any additional signs and symptoms of preterm labor or other pregnancy concerns. Pregnant women who come with signs and symptoms of preterm labor at 34 weeks are admitted to the hospital. Tocolytic are used to stop labor for up to 48 hours in premature labor with intact membranes.[15]

Tocolytics are indeed considered between the weeks of 22 and 34 of pregnancy, and only if there are no contraindications.

The only potential treatment is a single course of corticosteroids, preferred once the preterm labor is confirmed in order to improve the neonatal outcomes, between 24 and 34 weeks of pregnancy, Betamethasone (two 12-mg doses administered intramuscularly 24 hours apart) or dexamethasone (four 6-mg doses given IM every 12 hours) is advised. It can also be considered as early as 23rd weeks of gestation in pregnant women likely to deliver within 7 days regardless of membrane status.

It has been discovered that the use of corticosteroids will decrease neonatal morbidity and mortality. Respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis are less identified in mothers who receive corticosteroids. Administration of magnesium sulphate can decrease the occurrence of cerebral palsy in infants because of its neuroprotective effect. [16–18]

Table 1: Tocolytics for preterm labor.[13]

Medication	Dose	Maternal adverse effects	Fetal adverse effects	Contraindications
Nifedipine (calcium channel blockers)[19]	30-mg loading dose orally then 10 - 20 mg every 4 - 6 hours (maximal dosage: 180 mg per day)	Dizziness, flushing, and hypotension. Suppression of heart rate, contractility, and left ventricular systolic pressure when used with magnesium sulphate, Elevation of hepatic transaminase levels	No known adverse effects	Hypotension and preload-dependent cardiac lesions such as aortic insufficiency
Indomethacin (prostaglandin inhibitor, nonsteroidal anti-inflammatory drug)[15]	50- 100mg loading dose orally or rectally then 25 - 50 mg orally every 4 - 6 hours; therapy is not recommended for > 48 hours because of potential change in amniotic fluid levels and premature closing of fetal ductus arteriosus	Nausea, esophageal reflux, gastritis, emesis	In utero constriction of ductus arteriosus, oligohydramnios, necrotizing enterocolitis in preterm new-borns, patent ductus arteriosus in infants	Platelet dysfunction or bleeding disorder, hepatic dysfunction, gastrointestinal ulcerative disease, renal dysfunction, asthma (in women with hypersensitivity to aspirin)
Terbutaline (beta-adrenergic receptor agonist)	0.25 mg subcutaneously every 20 to 30 minutes for up to four doses or until tocolysis is achieved, then 0.25 mg every 3 to 4 hours until the uterus is quiet for 24 hours Alternate dosage: 2.5 to 5 mcg per	Tachycardia, hypotension, tremor, palpitations, shortness of breath, chest discomfort, pulmonary edema, hypokalemia, and hyperglycemia	Fetal tachycardia	Tachycardia-sensitive cardiac disease and poorly controlled diabetes mellitus

	minute via intravenous infusion, increasing by 2.5 to 5 mcg per minute every 20 to 30 minutes to a maximum of 25 mcg per minute or until the contractions have abated; at this point, the infusion is reduced by decrements of 2.5 to 5 mcg per minute to the lowest dose that maintains uterine quiescence Therapy should not be continued longer than 48 to 72 hours because of serious adverse effects			
Magnesium sulphate	6-g bolus intravenously over 20 minutes, then 2 g per hour as a continuous infusion	Flushing, diaphoresis, nausea, loss of deep tendon reflexes, respiratory depression, and cardiac arrest; suppression of heart rate, contractility, and left ventricular systolic pressure; produce neuromuscular blockade when used with calcium channel blockers	Neonatal depression	Myasthenia gravis

Contraindications of tocolysis: [13]

a) Intrauterine fetal demise.
b) fetal anomaly.
c) Non-reassuring fetal status.
d) Severe preeclampsia or eclampsia.
e) Maternal bleeding with hemodynamic instability.
f) Chorioamnionitis.

THE OUTCOME OF THE MOTHER AND THE FOETUS:

Preterm delivery can be triggered by maternal or foetal indicators, rupture of membranes, or spontaneous preterm labor with intact membranes. Around 32 - 50% of the preterm births occurred due to spontaneous PTL. In a retrospective cohort study, gestational age 34 to 36 weeks, chorioamnionitis, and preterm rupture of membranes were the predictors of delivery during the preterm labor admissions. Delivery occurred between forty-eight hours of hospitalization in 96% ≥34 weeks, while 67% in 31 to 33 weeks and 51.9% in <31 weeks.[20] Neurodevelopmental disability, respiratory illnesses, chronic disease in adulthood were the short- and long-term complications identified in the preterm children.[21]

3. Role of Tocolytics in Threatened preterm labor

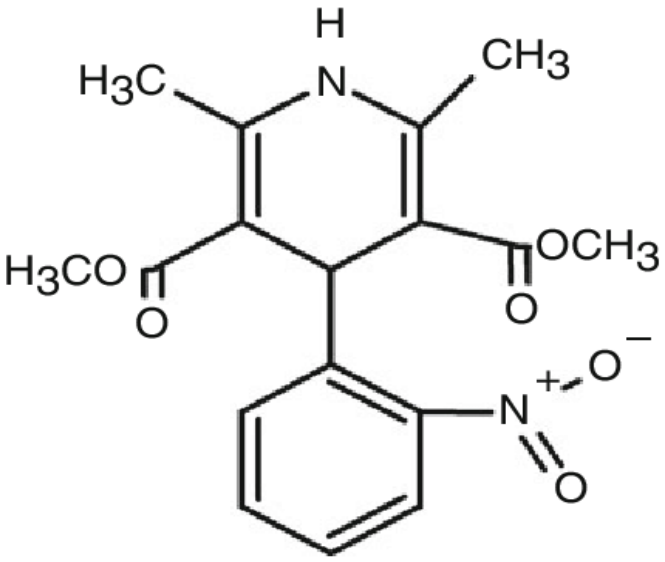
Administration of tocolytic agents must be restricted to pregnant women when there is a benefit from delaying preterm birth. Usually, there is more benefit in delaying birth under 34 weeks of gestation. The approach to tocolysis at 23 - 25+6 weeks must be individualized and will based on the risk to the woman from continuing further pregnancy and treatment for the care of the fetus after birth after the neonatal intensive care team has discussed the various intervention choices, the treatment for the foetus been done.

The primary aim for the use of tocolytics is to 48-hour postponement of premature birth. It provides time for the administration of maternal corticosteroid therapy, which promotes fetal lung maturation, maternal transfer for higher-level care, and for the administration of magnesium sulphate for fetal neuroprotection if indicated. Maternal corticosteroids and birth at an appropriate facility can significantly improve neonatal outcomes.[22]

A calcium channel blocker that relaxes smooth muscle is considered first-line therapy if tocolysis is recommended in the treatment of threatened preterm labor. The used drug is nifedipine. It is associated with fewer side effects and improved neonatal outcomes as compared to beta-agonists.[9]

Nifedipine (oral):

Figure 1: Molecular structure.[23]



Nifedipine is a calcium channel blocker and a prototype of dihydropyridine. It has a quick onset of action and a brief duration of activity. It acts by inhibiting the voltage-dependent L-type calcium channel and thereby decreases the calcium influx into the cells. It causes negative inotropic and chronotropic effects on the heart. Vasodilation followed by a

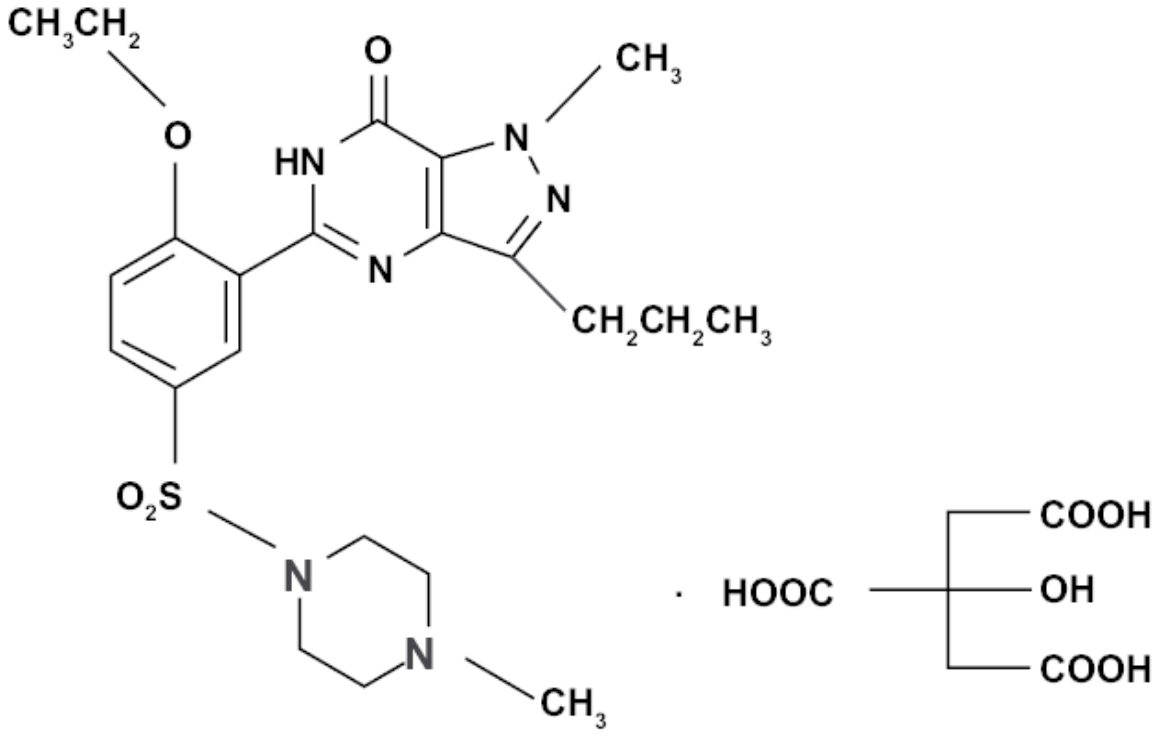
baroreceptor-mediated increase in sympathetic tone can result in indirect cardio-stimulation. FDA-approved indications for nifedipine include chronic stable angina, vasospastic angina - and hypertension. Whereas off-label uses are the Raynaud phenomenon, severe hypertension during pregnancy and post-partum hypertension, high altitude pulmonary edema, pulmonary arterial hypertension, achalasia, distal ureteric calculi, and tocolysis.[24]

Contraindications of nifedipine:[9]

- Known sensitivity to nifedipine.
- In-utero fetal death/ lethal fetal abnormalities/ suspected fetal compromise.
- Severe maternal cardiac disease.
- Maternal condition is compromised, such as bleeding with hemodynamic instability, placental abruption, severe pre-eclampsia, and chorioamnionitis.

Sildenafil citrate:

Figure 2: Molecular structure of sildenafil citrate.[25]



Sildenafil can help to prevent the degradation of second messenger cyclic guanosine 3',5'-monophosphate by the enzyme PDE-5. It has the ability to promote nitric oxide synthesis, as well as vascular smooth muscle relaxation and vasodilation. The vasodilator effect of sildenafil citrate manifested on uterine and myometrial vessels can cause an increase in the uterine flow and endometrial thickening and also encourage growth in the fetal weight.[5 6] In a meta-analysis study, a significant increase of 222.58 grams was identified in the fetal weight at birth of women taking sildenafil.[26]

4. Oral nifedipine combined sildenafil citrate versus "nifedipine alone."

The majority of participants of the combined group in a randomized control trial remained un-delivered as compared to the nifedipine alone group. There was an association identified between additional sildenafil citrate, fewer deliveries within 7 days of admission, prolonged latency, fewer admissions to neonatal intensive care units, fewer very preterm deliveries, and increased neonatal birth weight in a prospective study.[27] Ayub S et al.[28] study concluded that nifedipine is more effective in prolonging pregnancy for more than 48 hours.

In a randomized study.[29] Within 72 hours of intervention, pregnant women who got the combination medication had a decreased risk of preterm delivery. The rate of delivery during the first 7 days after discharge in the nifedipine plus sildenafil group was less as compared to the nifedipine alone group.

Maher M et al.[27] conducted a prospective randomized study. The study's goal was to determine the tocolytic effect of nifedipine in combination with sildenafil citrate. According to the findings, nifedipine combined with sildenafil citrate was associated with more women going into labor while in the hospital. Additional Sildenafil Citrate was related to fewer

delivery within seven days of admission, longer latency, fewer admissions to neonatal intensive care units, fewer very preterm births, and higher neonatal birth weight. The vaginal SC in combination with nifedipine was more effective tocolytic therapy during threatening PTL in this investigation.

Ayub S et al.[28] conducted a study on to compare the efficacy of Nifedipine and also salbutamol in the treatment of preterm labor. The study results revealed that 28.53 ± 5.84 as the mean age of the women on nifedipine whereas 28.26 ± 5.47 on the salbutamol group. When compared to salbutamol, nifedipine was found to be more successful in extending pregnancy for more than 48 hours. Nifedipine is more successful than salbutamol in the treatment of premature labor.

Mohammadi E et al.[29] performed a randomized double-blinded clinical trial. To determine the effect of nifedipine combination with sildenafil on preterm delivery compared with nifedipine alone. Pregnant women who conventional the combination therapy experienced lower preterm delivery within 72 hours of intervention with 4.5% as compared to nifedipine alone with 27.3%. The rate of delivery during the first 7 days after discharge in the nifedipine plus sildenafil group was identified as 7.6%, whereas 31.8% in the nifedipine alone group. The average birth weight was more in the nifedipine group alone. This study concluded that the use of sildenafil in addition to nifedipine can cause more delay in delivery in cases of preterm labor.

Karya U et al.[30] performed a prospective randomized study on 80 women to determine the tocolytic effect of sildenafil citrate and nifedipine versus nifedipine alone for the treatment of preterm labor. The study results revealed 28.23±18.3 as the mean latency in sildenafil and nifedipine combination while 12.98±13.35 days for nifedipine alone. Fewer days of

hospitalization, fewer deliveries during hospitalization or within 7 days after discharge, decreased NICU admission, improvement in birth weight, and fewer neonatal complications were identified in the combination regimen. Facial flushing, headache, dyspepsia, nasal congestion, palpitation, hypotension, constipation, nausea, and dizziness were the minor side effects identified in both groups. This study concluded that the combination of sildenafil citrate with nifedipine is a superior and successful regimen as a tocolytic therapy.

Abdelhamid A. et al.[31] conducted a study on 200 pregnant women to compare the efficacy of Sildenafil citrate along with Dydrogesterone in the prevention of premature labor in pregnant women with a short cervix. The study results revealed 9.37% and 14.28% as the incidence of preterm labor. There was a highly difference identified between the groups in drug side effects and birth weight. This study concluded that Sildenafil is most effective for preventing preterm labor in women who are at risk of giving birth prematurely.

Abd El-Aziz RH et al.[32] performed an interventional study in 96 pregnant women nifedipine, and sildenafil citrate was as tocolytics. There was a statistically significant difference in maternal heart rate and mean blood pressure before and after treatment in the combo group. In terms of delivery 24, 48, and 72 hours after admission, there was a substantial difference between the two analyzed groups, with the combination group having fewer early deliveries. The combination of vaginal sildenafil citrate and nifedipine, according to the findings of this study, is an effective tocolytic treatment for threatened preterm labor.

Shoukat F, et al.[3] To compare the tocolytic effects of nifedipine with sildenafil citrate vs. nifedipine alone in preventing impending preterm labor. This study results revealed that 82.9% in the combination group and 70.5% in the nifedipine alone group were remained un-

delivered. Differences identified with respect to delivery at one week for both treatment groups. This study concluded that oral SC combined with nifedipine is an effective choice for tocolytic therapy for threatened PTL.

ElSayed Y et al.[33] conducted a study in 192 women to determine the risk of adding sildenafil citrate to nifedipine for tocolysis on the maternal outcomes with threatened preterm labor. There were major changes identified between the studied groups with respect to neonatal birth weight. The neonatal respiratory distress was higher in the combined group. The combination group showed a better fetal outcome on neonatal birth weight while a poor outcome on neonatal respiratory distress.

Habib S et al.[34] Performed a study to determine the effectiveness of nifedipine in inhibiting preterm labor. The study results revealed effective tocolysis in 73.33% of patients, while tocolysis was not achieved in 27.7% of patients. This study concluded that nifedipine can successfully inhibit uterine contractions and prolong the labor by> 48 hours.

Faisal J et al.[35] conducted a randomized control trial. The purpose of the study was to evaluate the efficacy of Magnesium sulphate and Nifedipine in preterm labor management. In the nifedipine group, the average time gained in delaying delivery was 6.2 days, while in the magnesium sulphate group, it was 5.8 days. Burning at the injection site, dry mouth, headache, flushing, dizziness, sweating, and nausea were identified in the magnesium sulphate group with 60%, 56.6%, 53.3%, 80%, 30%, 20%, and 16.6%, respectively. While, headache, tachycardia, hypotension, flushing, dizziness, and nausea were identified with 60%, 40%, 26.6%, 3.3%, 3.3%, and 6.6% in Nifedipine, respectively. This study concluded that nifedipine is better in efficacy and safety as compared to magnesium sulphate.

Aggarwal A et al.[36] conducted a study in 50 women. The aim of the research was to see how maintenance tocolysis with nifedipine affected established preterm labor. The mean gestation at admission, cervical dilatation, and effacement was identified as similar in the case and control group. The median number of days of neonatal hospital stay was identified as decreased with tocolysis. This study concluded that the maintenance of tocolysis cannot prolong the pregnancy or decrease the neonatal hospital stay.

Naz S et al.[37] conducted a study in 85 pregnant women to determine the role of nifedipine in preterm labor. The study results revealed that 74.1% of the participants achieved successful tocolysis. The contractions before the tocolysis were 3/10 mins in 30.58%, 2/10 mins in 52.94%, and 1/10 mins in 14.11% of women, while after the nifedipine management, uterine contractions were identified 0/10 in 74.1%, 2/10 mins in 11.76%, and 3/10 mins in 14.11% of women. The administration of nifedipine delayed for 2 days in 26 cases while 3 days in 37 cases. This study concluded that Nifedipine can effectively suppress preterm labor.

Alkady MA et al.[38] conducted a prospective study to determine the efficacy of sildenafil for stopping the labor for 48 hours compared to nifedipine in preterm labor. The study results revealed 26.55 years and 26.75 years of age in the sildenafil citrate group and nifedipine group. Mean Gestational age at admission was 27.1 weeks and 28.16 years in the sildenafil and nifedipine groups. This study concluded that the administration of sildenafil in pregnant women with preterm labor pain can be a promising future therapy of preterm labor.

El-Sayed M et al.[39] conducted a prospective randomized observational comparative clinical study to compare the safety, nifedipine versus combined use of vaginal progesterone and nifedipine. The study results revealed that the time interval between the last epilate capsules to

tocolytic effect in minutes was less in group B. This study showed that the combination of oral nifedipine and vaginal progesterone can provide a more rapid response for threatened preterm labor.

TA N et al.[40] conducted a study. To determine the effect of prolonged tocolysis with nifedipine versus placebo in women. The median gestational age was 29.9 weeks and 27.0 weeks in the nifedipine and placebo groups. The adverse perinatal outcome was identified in 33.3% of the nifedipine group while 32.1% in the placebo. The nifedipine group was identified with 2 perinatal deaths. Bronchopulmonary dysplasia was less common in the nifedipine group. This study did not show a beneficial effect of prolonged tocolysis on neonatal outcomes in women with PPROM.

C R et al.[41] conducted a study in 406 women to evaluate whether maintenance tocolysis with nifedipine will reduce adverse perinatal outcomes. The study results revealed 29.2 (1.7) weeks as cases and control. The adverse perinatal outcome was identified with 11.9% in the nifedipine group while 13.7% in the control group. This study concluded that in patients with threatened preterm labor, nifedipine-maintained tocolysis did not result in the reduction of adverse perinatal outcomes.

CONDE-AGUDELO A et al.[22] conducted a systematic review and meta-analysis to evaluate the role of nifedipine as a tocolytic agent in women with preterm labor; there was a definitive link between nifedipine and a lower risk of respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, neonatal jaundice, and before 34 weeks of pregnancy, as well as respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, neonatal jaundice, and admission to the neonatal intensive care unit. The risk of

maternal adverse events was lower with nifedipine. This study concluded that nifedipine is superior to β_2-adrenergic-receptor agonists.

Ashraf B. et al.[42] performed a study in 276 pregnant women to determine the efficacy and safety of nifedipine alone and nifedipine with vaginal progesterone in threatened PTL. The study results revealed that 86.23% of patients achieved successful tocolysis with nifedipine. Mean pregnancy prolongation in groups A and B were identified as 11.13 ± 5.08 days and 29.73 ± 3.10 days, respectively. This study found that nifedipine-based acute tocolytic therapy is effective for threatened preterm labor.

LACUNAE OF LITERATURE:

There are limited studies which have explored the tocolytic effect of sildenafil and the use of sildenafil citrate in pregnant women. Few research has focused into the exact factors that cause threatened preterm labor and delivery. Investigated the tocolytic effect of a combination of nifedipine and sildenafil citrate in threatened preterm labor.

MATERIAL & METHODS

MATERIALS AND METHODS:

Study site: Department of Obstetrics & Gynecology RL JALAPPA and Research Center attached to Sri Devaraj Urs Medical College, affiliated to Sri Devaraj Urs Academy of higher Education and Research Tamaka, Kolar- 563101.

Study population: All the eligible patient's pregnant women admitted to the labor room with threatened preterm labor at R.L JALAPPA Hospital attached to Sri Devaraj Urs Medical College were considered as the study population.

Study design: Randomized Trial

group A: Nifedipine

group B: Sildenafil +Nifedipine

Sample size: (Formula to compare two independent means)

The sample size was calculated assuming the expected mean and standard deviation of the birthweight of group A as 1500 and in group B as 1900 grams with standard deviations of 400 and 600 as per the previous study by MA Maher et al.[27] The other parameters considered for sample size calculation included were 80% power of study and 5% two-sided alpha error. The required sample size was calculated using the following formula as proposed by Kirkwood BR et al.[43]

Formula used for sample size calculation:

$$N = \frac{(u + v)^2(\sigma_1^2 + \sigma_0^2)}{(\mu_1 - \mu_0)^2}$$

N = Sample size

μ_1 , μ_0 =Difference between the means (μ_1=1500 and μ_0=1900)

σ_1, σ_0 =Standard deviations (σ_1=400 and σ_0 =600)

u =two-sided percentage point of the normal distribution corresponding to 100 % - the power = 80%, u =0.84

v =Percentage point of the normal distribution corresponding to the (two sided) significance level for significance level = 5%, *v* = 1.960

The required sample size as per the above-mentioned calculation was 26 in each group. To account for a non-participation rate/ loss to follow up rate of a about 11%, another 4 subjects will be added to the sample size. Hence the final required sample size would be 30 subjects in each group.

Sampling method: All the eligible subjects were recruited into the study consecutively by convenient sampling till the sample size is reached.

Study duration: The data collection was done between January 2020 to June 2021 for a period of 1 year 5 months.

Inclusion Criteria:

- Age: 18 to 35 years & gestational age 28 to 37 weeks.
- Singleton pregnancy.
- No vaginal discharge.

Exclusion criteria:

- Cervical dilatation
- On Transvaginal Sonography (TVS), the cervical length >15mm

- Chorioamnionitis (unexplained fetal tachycardia or maternal temperature)
- Maternal medical complications like eclampsia, HELLP (Hemolysis Elevated Liver enzymes Low Platelet count) syndrome
- Bronchial asthma, cardiac disorder, thyroid disorder.

Ethical considerations: The approval was obtained by the Institutional ethics committee . Informed written consent for all the study participants and only those participants given consent were included in the study. The risks and benefits involved in the study and the voluntary nature of participation were explained to the participants before obtaining consent. The confidentiality of the study participants was maintained.

Data collection tools: All the relevant parameters were documented in a structured study proforma.

Methodology:

Pregnant women hospitalized to the labor room were recruited for the study

General examination includes

- Maternal pulse rate.
- Blood pressure.
- Uterine contraction.
- Fetal heart rate.

Routine examination

- Complete blood count.
- Serology: HIV and Hepatitis B.

- Bleeding time.
- Clotting time.
- Random blood sugar.
- Transvaginal ultrasound- cervical length was more than 15 mm, diagnostic for preterm labor.

Transvaginal Ultrasound examination is done prior to randomization by chit system. Chit system was,

- The first group had received nifedipine alone and
- "Second group had received nifedipine along with sildenafil citrate per vaginal. Nifedipine 20 mg orally a stat dose followed by 10 mg orally every 6-8 hours at the same time as vaginal administration of sildenafil citrate 25 mg at 8^{th} hourly interval every 6-8 hrs .
- Each woman was followed up until delivery, and the outcome was recorded.
- The success of tocolysis was considered at the end of 48 hours, after the onset of tocolysis
- Tocolysis was considered as failed if uterine quiescence was not stopped, despite a maximum dose of delivery or when the patient delivered within 48 hours of initiation of therapy.

STATISTICAL METHODS:

Maternal side effects and neonatal outcomes were considered as primary outcome variable variables. The study group (Group A Vs. Group B) was considered as the primary explanatory variable. Skewed distributed quantitative variables were summarized by the median and interquartile range (IQR). Data was also represented using appropriate diagrams like Error bar diagram, Stacked bar diagram, and cluster bar diagram. All Quantitative variables were checked for normal distribution. For normally distributed Quantitative parameters, the mean values were compared between study groups using an independent sample t-test (2 groups). For non-normally-distributed Quantitative parameters, Medians and Interquartile range (IQR) were compared between study groups using Mann Whitney u test (2 groups). Categorical outcomes were compared between study groups using the Chi-square test /Fisher's Exact test (If the overall sample size was < 20 or if the expected number in any one of the cells is <5, Fisher's exact test was used.). P-value <0.05 was considered statistically significant. Data were analyzed by using coGuide software, V.1.03.[44]

RESULTS

RESULTS:

The final analysis comprised a total of 60 subjects. Group A (Nifedipine) were 30 participants, and Group B (Sildenafil +Nifedipine) were 30 participants.

Table 2: Comparison of mean of age between study group (N=60)

Parameter	Study group (Mean± SD)		P-value
	Group A (N=30)	Group B (N=30)	
Age (in years)	21.07 ± 3.31	22.87 ± 3.15	0.035

The average age of the participants in study group A was 21.07 ± 3.31 years, and group B was 22.87 ± 3.15 years. There was a statistically significant difference between mean age between study groups (P-Value 0.035). (Table 2 & Figure 3)

Figure 3: Error bar chart of comparison of age between study group (N=60)

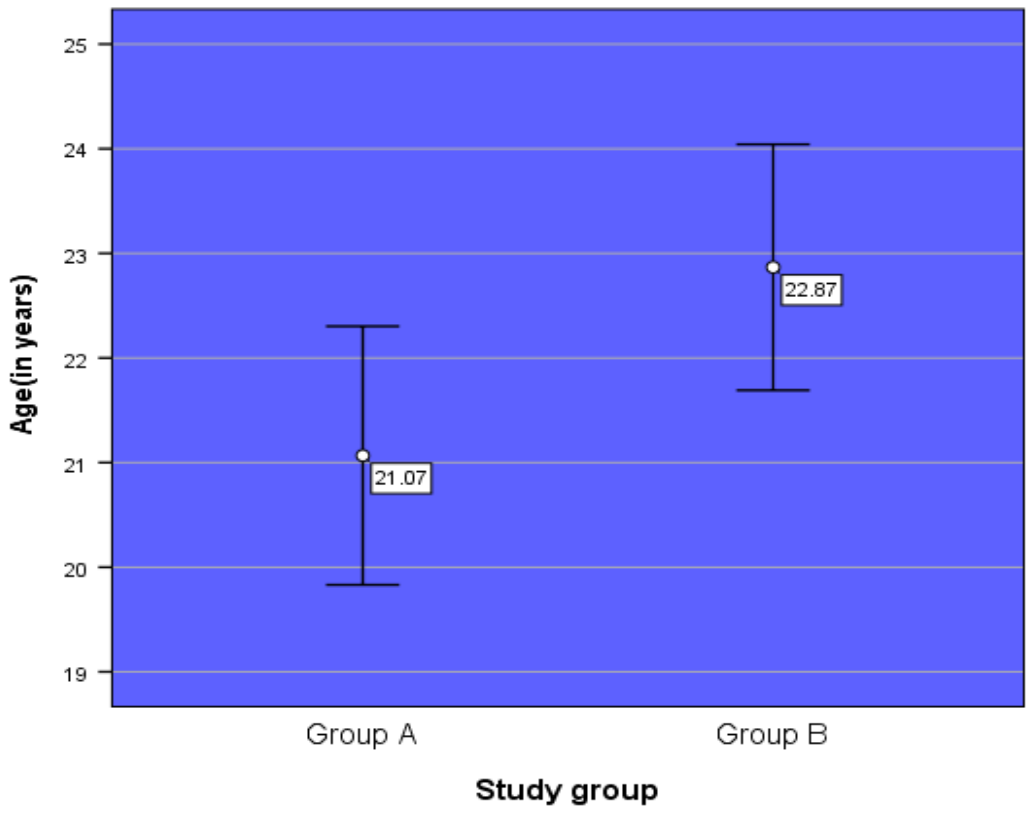


Table 3: Comparison of age group (in years) between study groups (N=60)

Age group (in years)	Study Group		Chi-square	P-value
	Group A (N=30)	Group B (N=30)		
18 to 20 years	14 (46.67%)	8 (26.67%)	2.608	0.271
21 to 25 years	12 (40%)	16 (53.33%)		
26 years and above	4 (13.33%)	6 (20%)		

Among the study population in group A, 14 (46.67%) participants were age group between 18 to 20 years, 12 (40%) participants between 21 to 25 years and 4 (13.33%) participants belonged to age group above or equal to 26 years. Among the study population in group B, 8 (26.67%) participants belonged to the age group up to 20 years, 16 (53.33%) participants between 21 to 25 years, and 6 (20%) participants belonged to age group above or equal to 26 years. There was not any statistically significant difference in the age group between the study group (P-Value 0.271). (Table 3 & Figure 4)

Figure 4: Stacked bar chart of comparison of age group (in years) between study group (N=60)

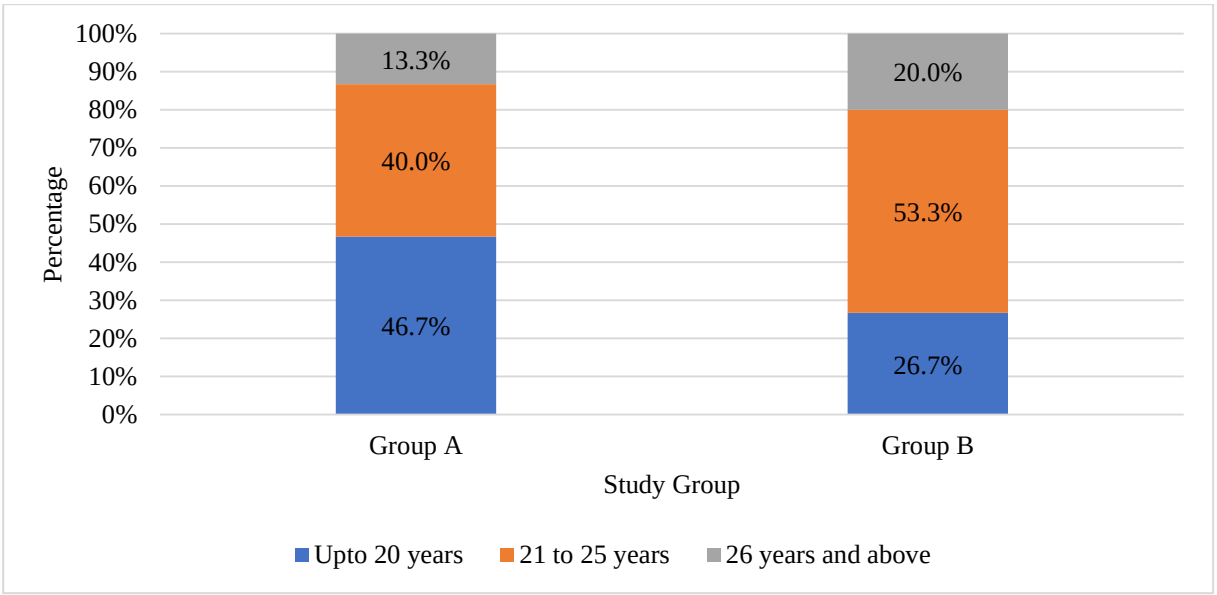


Table 4: Comparison of booked /un booked between study group (N=60)

Booked/un booked	Study Group		Chi-square	P-value
	Group A (N=30)	Group B (N=30)		
Booked	8 (26.67%)	15 (50%)	3.455	0.063
Un booked	22 (73.33%)	15 (50%)		

Among the study population, there were 8 (26.67%) booked and 22 (73.33%) un booked pregnancies in group A, and there were 15 (50%) booked and 15 (50%) un booked pregnancies in group B. No statistically significant difference between the two groups booked/un booked (P-value 0.063). (Table 4 & Figure 5)

Figure 5: Stacked bar chart of comparison of u/b between study group (N=60)

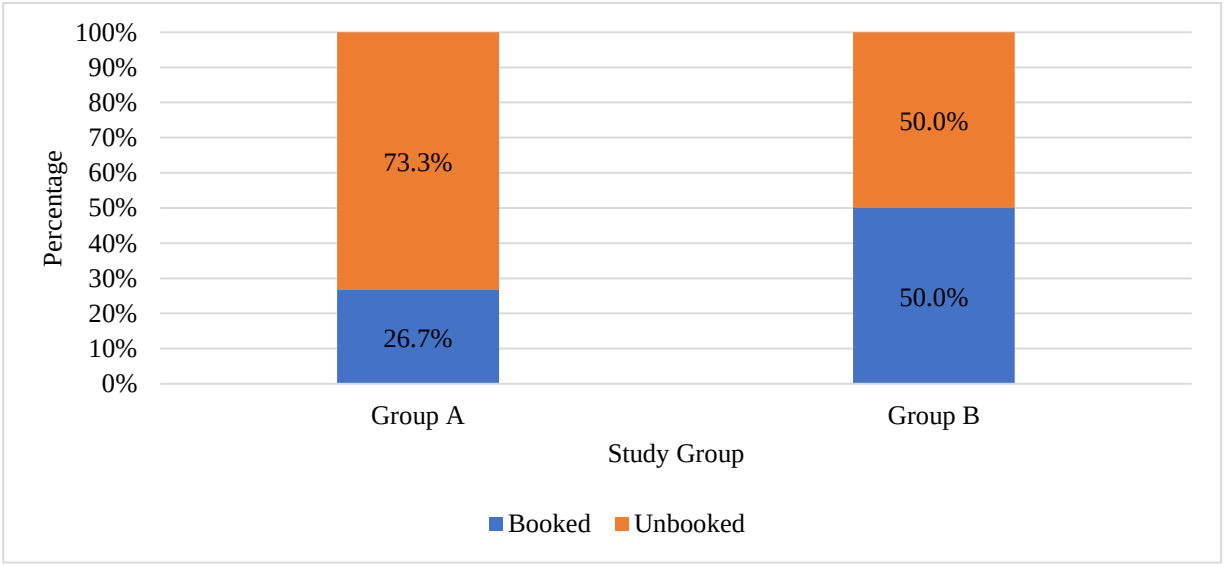


Table 5: Comparison of gravida between study group (N=60)

Gravida	Study Group		Chi-square	P-value
	Group A (N=30)	Group B (N=30)		
Primigravida	26 (86.67%)	22 (73.33%)	1.667	0.197
Multigravida	4 (13.33%)	8 (26.67%)		

Among the study population, Primigravida for 26 (86.67%) participants and Multigravida for 4 (13.33%) participants in group A the gravida was primi for 22 (73.33%) participants and multi for 8 (26.67%) participants in group B. There was not any statistically significant difference in gravida between study group (P-Value 0.197). (Table 5 & Figure 6)

Figure 6: Stacked bar chart of comparison of gravida between study group (N=60)

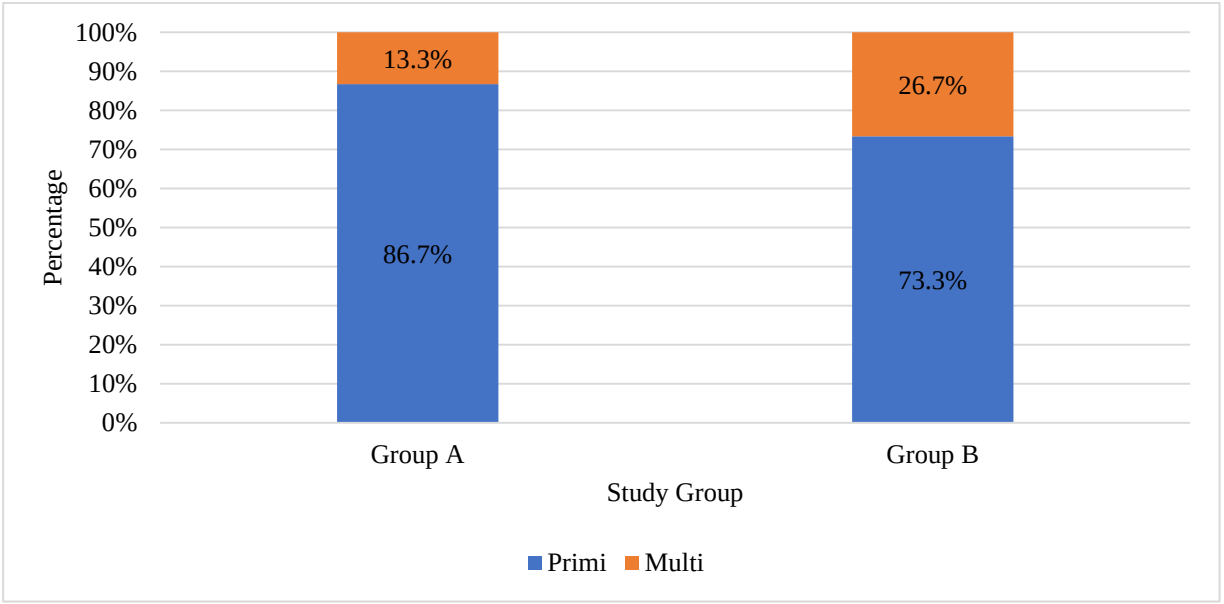


Table 6: Comparison of the previous history of PTB between study group (N=13)

Previous History of PTB	Study Group		Fisher exact P-value
	Group A (N=5)	Group B (N=8)	
Yes	2 (40%)	6 (75%)	0.293
No	3 (60%)	2 (25%)	

Among the study population, 2 (40%) participants in group A and 6 (75%) participants in group B had a previous history of PTB. There was not any statistically significant difference in the previous history of PTB between the study group (P-Value 0.293). (Table 6 & Figure 7)

Figure 7: Stacked bar chart of comparison of the previous history of PTB between study group (N=13)

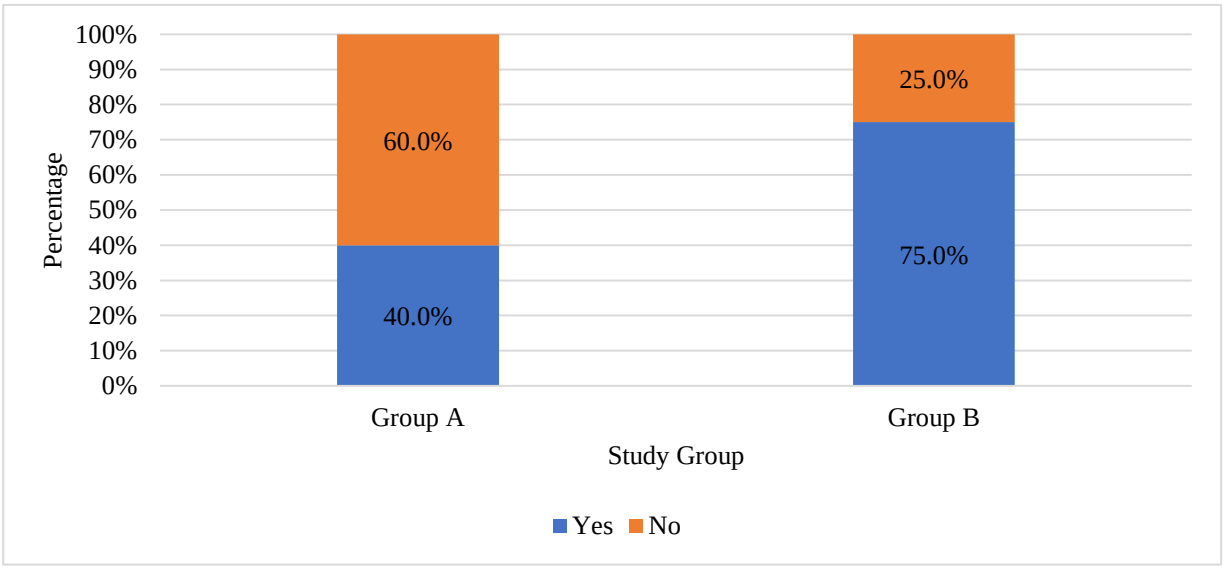


Table 7: Comparison of periods of gestation between study group (N=60)

Periods of gestation (in weeks)	Study Group		Mann Whitney U test (P-value)
	Group A Median (IQR)	Group B Median (IQR)	
Median	32.50 (30,34)	34 (31,34.25)	0.208
Minimum	24	29	
Maximum	35	35	

In group A, the median period of gestation was 32.50 (30,34) weeks, ranging from 24 weeks to 35 weeks. In group B, the median period of gestation was 34 (31,34.25) weeks, ranging from 29 weeks to 35weeks. No statistically significant difference was observed in the median period of gestation between the study group (P-Value 0.208). (Table 7)

Table 8: Comparison of gestational age (in weeks) between study group (N=60)

Gestational age (in weeks)	Study Group		Chi-square	P-value
	Group A (N=30)	Group B (N=30)		
24 to 30 weeks	9 (30%)	6 (20%)	1.161	0.559
31 to 32 weeks	6 (20%)	5 (16.67%)		
33 to 35 weeks	15 (50%)	19 (63.33%)		

Among the study population, the gestational age was 24 to 30 weeks for 9 (30%) participants in group A and 6 (20%) participants in group B; the gestational age was 31 to 32 weeks for 6 6 (20%) participants in group A and 5 (16.67%) participants in group B, the gestational age was 33 to 35 weeks for 15 (50%) participants in group A and 19 (63.33%) participants in group B. There was not any statistically significant difference in gestational age between study group (P-Value 0.559). (Table 8 & Figure 8)

Figure 8: Stacked bar chart of comparison of gestational age (in weeks) between study group (N=60)

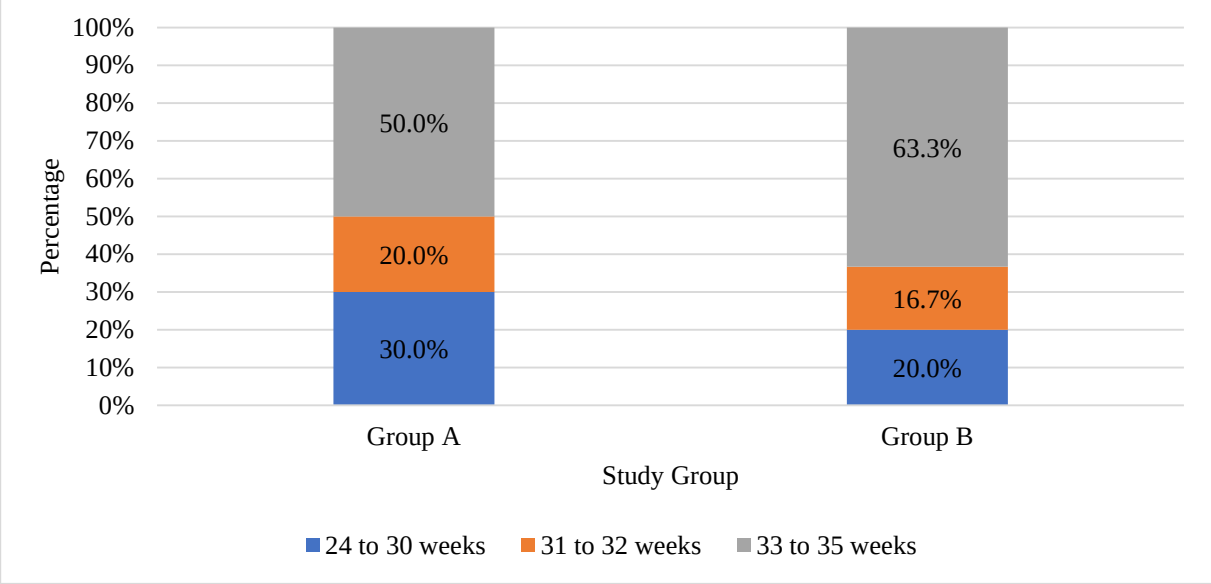


Table 9: Comparison of prolongation of pregnancy(IN DAYS) between study group (N=60)

Parameter	Study Group		Mann Whitney U test (P-value)
	Group A Median (IQR)	Group B Median (IQR)	
Prolongation of pregnancy (in days)	2 (2,5)	7 (2.75,20)	<0.001
Minimum	1	1	
Maximum	15	28	

In group A, the median prolongation of pregnancy was 2 (2,5) days, ranging from 1 day to 15 days. In group B, the median prolongation of pregnancy was 7 (2.75, 20) days, ranging from 1 day to 28 days. A statistically significant difference was observed in median prolongation of pregnancy between the study group (P-Value <0.001). (Table 9 & Figure 9)

Figure 9: Box plot for comparison of prolongation of pregnancy between study group (N=60)

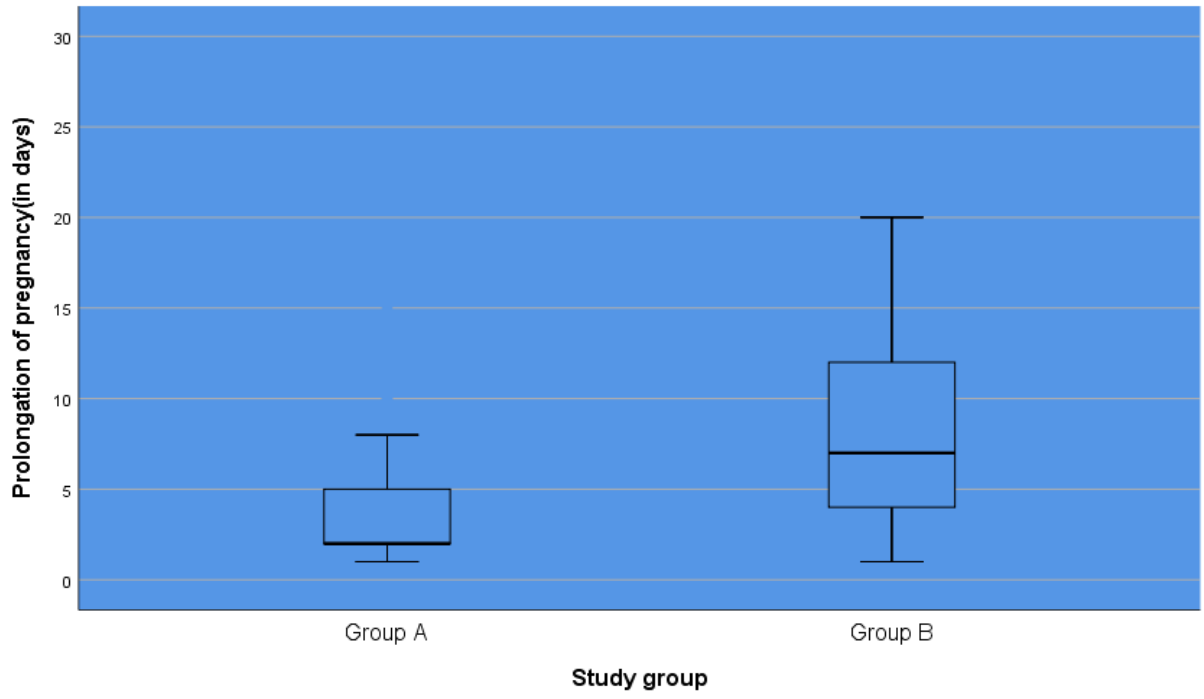


Table 10: Comparison of the causes of preterm between study group (N=60)

Cause of preterm	Study Group	
	Group A (N=30)	Group B (N=30)
Cervical Incompetence	1 (3.33%)	2 (6.67%)
Idiopathic	25 (83.33%)	21 (70%)
Lower Genital Tract Infection	4 (13.33%)	5 (16.67%)
Urinary Tract Infection	0 (0%)	2 (6.67%)

*No statistical test was applied- due to 0 subjects in the cells

Among the study population, the cause of preterm was Cervical incompetence for 1 (3.33%) participant in group A and 2 (6.67%) participants in group B, Idiopathic for 25 (83.33%) participants in group A and 21 (70%) participants in group B, Lower Genital Tract Infection for 4 (13.33%) participants in group A and 5 (16.67%) participants in group B and Urinary Tract Infection for no participant in group A and 2 (6.67%) participants in group B. (Table 10 & Figure 10)

Figure 10: Cluster bar chart of comparison of the cause of preterm between study group (N=60)

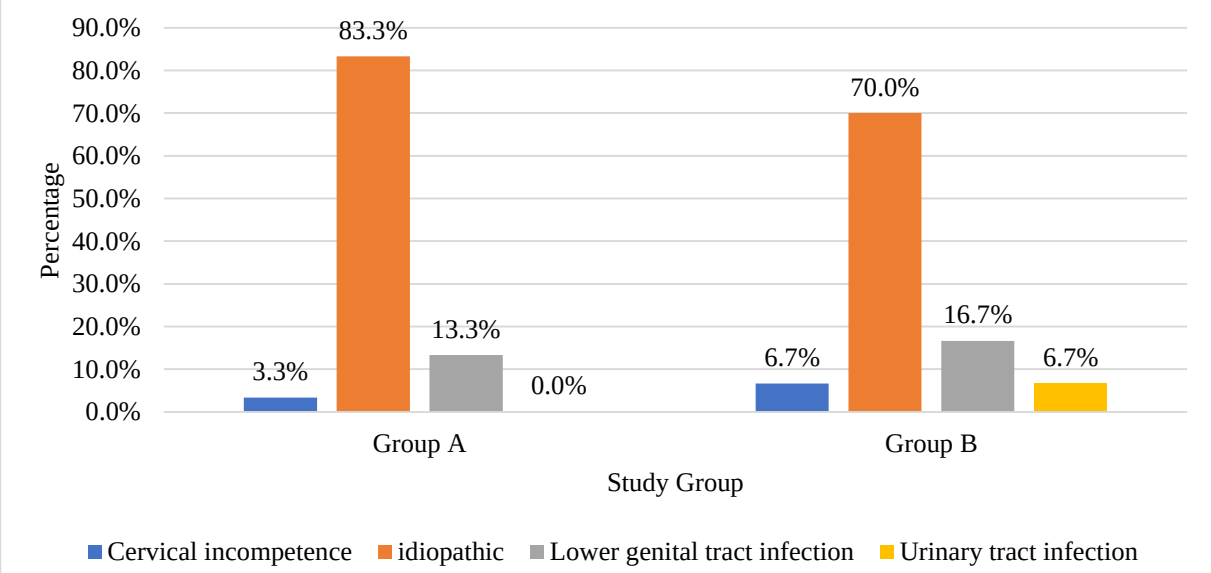


Table 11: Comparison of maternal side effects between study group (N=60)

Maternal side effect	Study Group		Chi-square	P-value
	Group A (N=30)	Group B (N=30)		
Tachycardia	8 (26.67%)	3 (10%)	2.783	0.095
Facial Flushing	0 (0%)	2 (6.67%)	*	*
Palpitations	1 (3.33%)	3 (10%)	†	0.612
Headache	0 (0%)	2 (6.67%)	*	*
Nausea and vomiting	5 (16.67%)	0 (0%)	*	*

*No statistical test was applied- due to 0 subjects in the cells† Fishers exact test was used

Among the study population, the maternal side effect was tachycardia for 8 (26.67%) participants in group A and 3 (10%) participants in group B, Facial Flushing for no participants in group A and 2 (6.67%) participants in group B, Palpitations for 1 (3.33%) participant in group A and 3 (10%) participants in group B, headache for no participants in group A and 2 (6.67%) participants in group B and nausea and vomiting for 5 (16.67%) participants in group A and no participant in group B. No statistically significant difference was observed in tachycardia and palpitations between the study group (P-Value >0.05). (Table 11)

Table 12: Comparison of mean of birth weight (in grams) between study group(N=60)

Parameter	Study group (Mean± SD)		P value
	Group A (N=30)	Group B (N=30)	
Birth weight (in grams)	2090 ± 372.64	2381.67 ± 492.44	0.012
Minimum	1200	1600	
Maximum	3200	3400	

In group A, the mean birth weight was 2090 ± 372.64 grams, ranging from 1200 grams to 3200 grams. In group B, the mean birth weight was 2381.67 ± 492.44 grams, ranging from 1600 grams to 3400 grams. A statistically significant difference was observed in mean birth weight between the study group (P Value 0.012). (Table 12 & figure 11)

Figure 11: Error bar chart of comparison of birth wight (in grams) between study group (N=60)

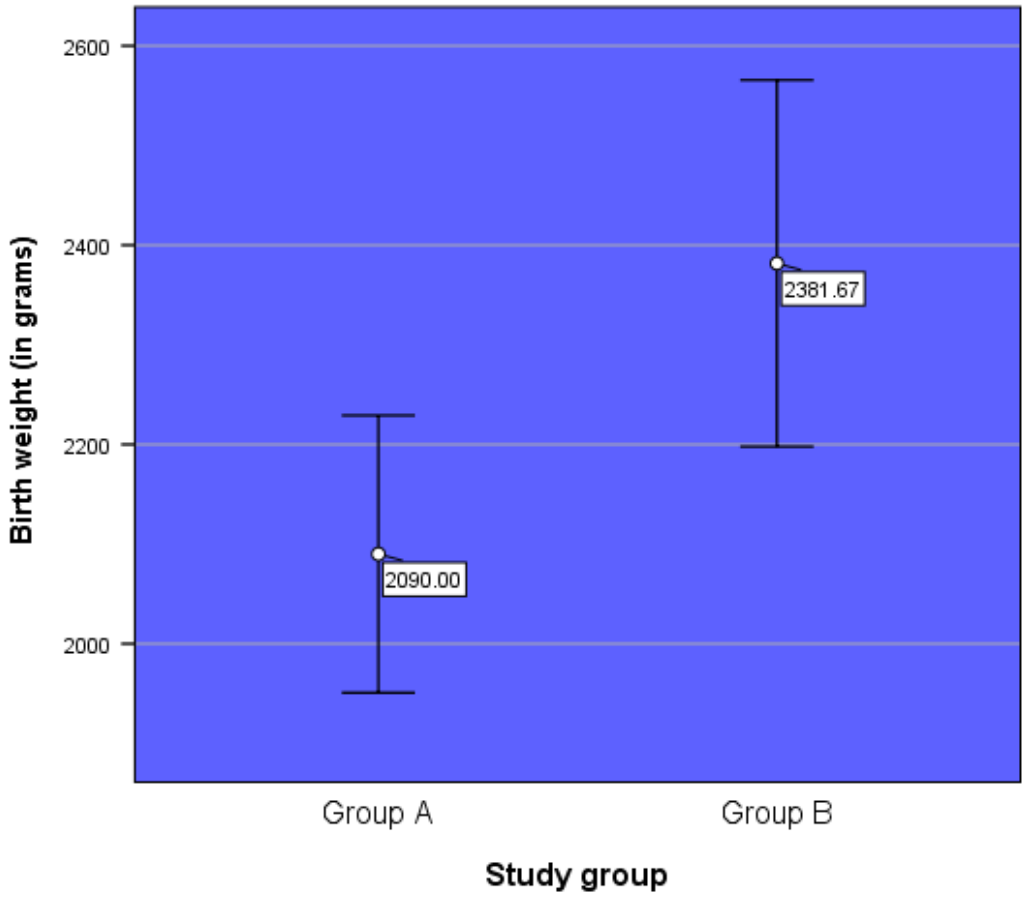


Table 13: Comparison of neonatal complication between study group (N=60)

Neonatal complication	Study Group		Chi-square	P-value
	Group A (N=30)	Group B (N=30)		
RDS	5 (16.67%)	7 (23.33%)	0.417	0.519
NICU	7 (23.33%)	11 (36.67%)	1.270	0.260
Alive and healthy	16 (53.33%)	17 (56.67%)	0.067	0.795
Perinatal death	6 (20%)	1 (3.33%)	*	0.103

* Fisher's exact test was used

Among the study population, the neonatal complications were respiratory distress syndrome for 5 (16.67%) participants in group A and 7 (23.33%) participants in group B. The neonatal

complication was NICU admission for 7 (23.33%) participants in group A and 11 (36.67%) participants in group B. The neonatal complication was alive and healthy for 16 (53.33%) participants in group A and 17 (56.67%) participants in group B. The perinatal death for 6 (20%) participants in group A and 1 (3.33%) participant in group B. No Significant difference was observed in any of the neonatal complications between the study group (P Value>0.05). (Table 13)

Table 14: Comparison of betnesol between study group (N=60)

Betnesol	Study Group		Fisher exact P-value
	Group A (N=30)	Group B (N=30)	
Yes	25 (83.33%)	29 (96.67%)	0.195
No	5 (16.67%)	1 (3.33%)	

Among the study population, the Betnesol was given to 25 (83.33%) participants in group A and 29 (96.67%) participants in group B. No statistically significant difference was observed in betnesol between the study group (P-Value 0.195). (Table 14 & Figure 12)

Figure 12: Stacked bar chart of comparison of betnesol between study group (N=60)

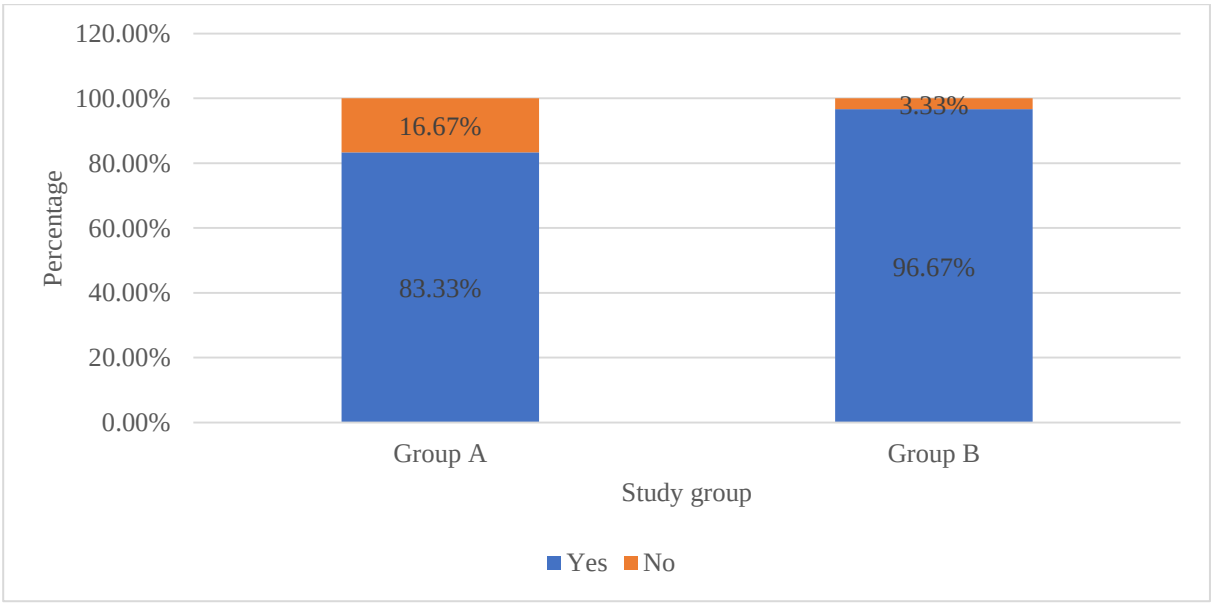


Table 15: Comparison of cervical length between study group (N=60)

Parameter	Study Group		Mann Whitney U test (P-value)
	Group A Median (IQR)	Group B Median (IQR)	
Cervical length	32 (31,33)	32 (31.75,34)	0.368
Minimum	21	21	
Maximum	35	36	

In group A, cervical length was 32 (31,33) units, ranging from 21 to 35. In group B, cervical length was between 32 (31.75,34) units, ranging from 21 to 36. No statistically significant difference was observed in median cervical length between the study group (P-Value 0.368). (Table 15)

Table 16: Comparison of cervical score between study group (N=60)

Cervical score	Study Group	
	Group A (N=30)	Group B (N=30)
21 to 25	1 (3.33%)	2 (6.67%)
26 to 30	2 (6.67%)	0 (0%)
31 to 36	27 (90%)	28 (93.33%)

*No statistical test was applied- due to 0 subjects in the cells

Among the study population, the cervical score was 21 to 25 for 1 (3.33%) participant in group A and 2 (6.67%) participants in group B, 26 to 30 for 2 (6.67%) participants in group A and no participant in group B and 31 to 36 for 27 (90%) participants in group A and 28 (93.33%) participants in group B. (Table 16 & Figure 13)

Figure 13: Cluster bar chart of comparison of cervical score between study group (N=60)

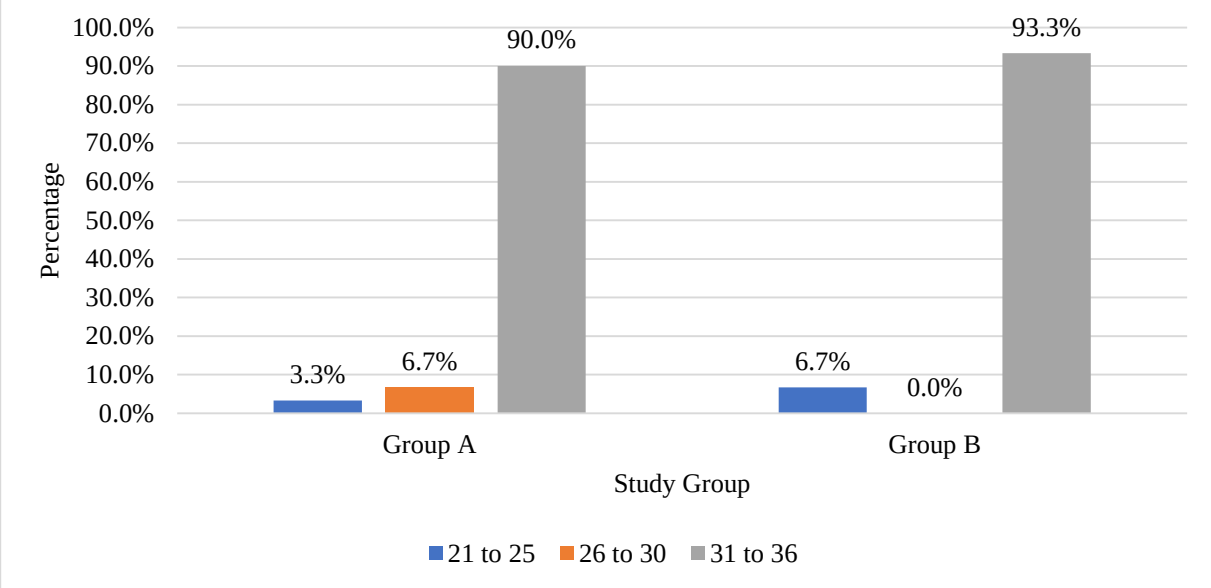


Table 17: Comparison of a nifedipine loading dose (in mg) between study group (N=60)

Nifedipine loading dose (In mg)	Study Group		Chi-square	P-value
	Group A (N=30)	Group B (N=30)		
20	15 (50%)	12 (40%)	0.807	0.668
30	7 (23.33%)	7 (23.33%)		
40	8 (26.67%)	11 (36.67%)		

Among the study population, the nifedipine loading dose was 20mg for 15 (50%) participants in group A and 12 (40%) participants in group B, 30mg for 7 (23.33%) participants in group A and group B and 40mg for 8 (26.67%) participants in group A and 11 (36.67%) participants in group B. (Table 17 & Figure 14)

Figure 14: Stacked bar chart of comparison of a nifedipine loading dose (in mg) between study group (N=60)

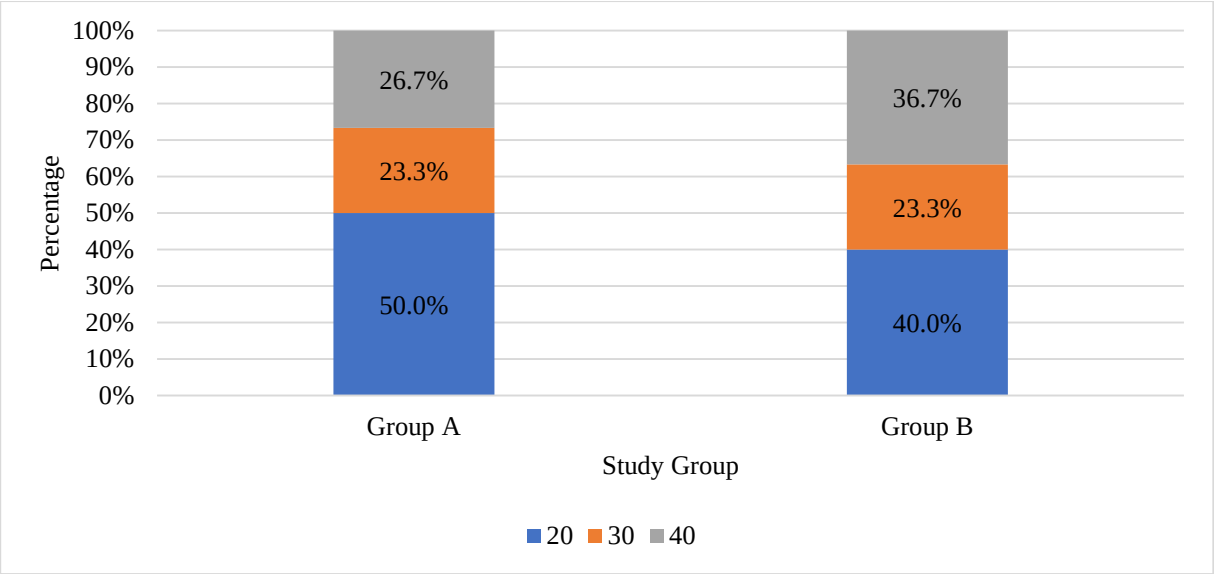
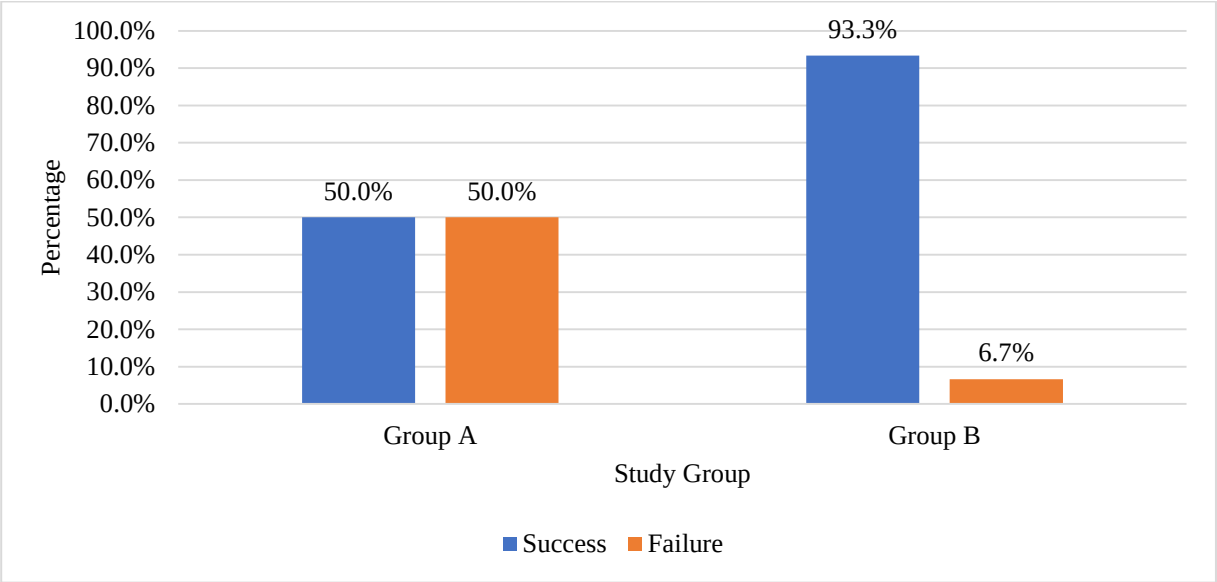


Table 18: Comparison of outcome between study group (N=60)

Parameter	Study Group		Chi-square	P-value
	Group A (N=30)	Group B (N=30)		
Success	15(50%)	28(93.3%)	13.871	<0.001
Failure	15(50%)	2(6.6%)		

Analysis of the tocolytic effect in the two groups showed the subgroup B 28 (93.3%) has a better success rate up to 1 week was seen. (Table 18 & Figure 15)

Figure 15: Stacked bar chart of comparison of outcome between study group (N=60)



DISCUSSION

DISCUSSION:

In developing nations, preterm birth is a leading cause of neonatal and infant illness and mortality. Major goal of an obstetrician is to postpone delivery for at least 24-48 hours in order to permit enough time for the administration of corticosteroids. It aids in lowering the occurrence and severity of newborn complications.

Tocolytic therapy delays threatened preterm labor so that the patient can be transferred to a center with a newborn intensive care unit, or corticosteroids can be given. It aids in respiratory morbidity prevention. Nifedipine has been found to be more effective and safer for tocolytic therapy of impending preterm labor than ritodrine. This study was conducted to compare the effect of nifedipine and sildenafil citrate combination and nifedipine alone for the management of threatened preterm labor.

A total of 60 subjects were included in the final analysis. Group A (Nifedipine) were 30 participants, and Group B (Sildenafil +Nifedipine) were 30 participants.

In the present study, the mean age of the participants was identified as 21.07 ± 3.31 years in group A, and 22.87 ± 3.15 years in group B. Shoukat F, et al.[3] performed a randomized controlled in which 30.67±3.90 and 29.95±4.32 years were identified as the mean of age in the nifedipine and sildenafil + nifedipine group.

In another study by Yousef Abou- Elwan El-Sayed et al.[33] conducted on 192 women in which the mean of age was identified as 30.6±4.9 and 31.3±6.1 (years) in the nifedipine and sildenafil + nifedipine group. Elkattan R. et al.[38] performed a prospective study on 88 women

in which 26.75 years and 26.55 years were identified as the mean of age in the nifedipine and sildenafil groups, respectively.

Shoukat F et al.[3] Yousef Abou- Elwan El-Sayed. et al.[33] and Elkattan R. et al.[38] study showed an increased mean of age as compared to our study results.

Table 19: Comparison between the mean of age between various studies.

Study	Population	Mean of age (years)
Present study	60	Nifedipine group (21.07 ± 3.31) Nifedipine + sildenafil group (22.87 ± 3.15)
Shoukat F, et al.[3]	292	Nifedipine group (30.67±3.90) Nifedipine + sildenafil group (29.95±4.32)
Yousef Abou- Elwan El-Sayed. et al.[33]	192	Nifedipine group (30.6±4.9) Nifedipine + sildenafil group (31.3±6.1)

In the present study, the majority of the participants in group A belonged to the age group of < 20 years with 46.67%, followed by the age group between 21 to 25 years with 40%. Whereas, in group B majority of the participants were belonged to the age group between 21 to 25 years with 53.33%, followed by the age group of <20 years with 26.67%.

In the current study, there were 26.67% of booked pregnancies and 73.33% of unbooked pregnancies in group A. While in group B, booked and unbooked pregnancies were 50% of each.

In the present study, the majority of the participants in group A and group B were belonged to primigravida with 86.67% and 73.33%, respectively. Urmila Karya et al.[30] conducted a prospective randomized study on 80 women in which the majority of the participants in the nifedipine and sildenafil + nifedipine group were belonged to multigravida with 65% and 62.5%, respectively, which was contradictory to our study results.

Table 20: Comparison of gravida between various studies.

Study	Population	Gravida	
Present study	60	Nifedipine group Primigravida (86.67%) Multigravida (13.33%)	Sildenafil + nifedipine group Primigravida (73.33%) Multigravida (26.67%)
Shoukat F, et al.[3]	292	Nifedipine group Primigravida (54.5%) Multigravida (50.26%)	Sildenafil + nifedipine group Primigravida (45.5%) Multigravida (49.74%)

In the current study, 40% of the participants in group A had given a history of preterm birth, whereas; it was identified as 75% in group B. In Elham Mohammadi et al.[29] the history of preterm birth was identified as 9.1% in the nifedipine group while it was 21.2% in sildenafil + nifedipine group which was a decreased rate as compared to our study results.

The median period of gestation was 32.50 (30,34) weeks in group A while it was 34 (31,34.25) in group B. In Shoukat F, et al.[3] study 29.58±2.05 and 31.23±2.16 were identified as the mean period of gestation in the nifedipine and sildenafil + nifedipine group which was a decreased mean as compared to our study.

Most of the women had the gestational age between 33 to 35 weeks in groups A and B with 50% and 63.33%, respectively. In Urmila Karya et al.[30] study majority of the participants had the gestational age between 32-34 weeks in the nifedipine and sildenafil + nifedipine group with 60% and 55%, respectively, which resembles to our study results.

In the current study, the median prolongation of pregnancy was observed as 2 (2,5) days in group A, and 7 (2.75,20) in group B. Saima Ayub et al.[28] performed a study on 176 women in which the majority of the participants had prolongation of pregnancy between 48 hours to 1 week in nifedipine group with 37.50% followed by > 1 week with 30.68% while, in sildenafil

group majority of the women had > 1-week prolongation of pregnancy with 32.95% followed by 48 hours to 1 week with 20.65%.

Saima Ayub et al.[28] studies showed similar results to our study.

The cause of preterm was identified as idiopathic in the majority of the women in group A with 83.33%, followed by infection with 13.33%. Similar causes were identified in group B with 70% and 16.67%, respectively.

Maternal side effects in group A were tachycardia, palpitations, nausea, and vomiting with 26.67%, 3.33%, and 16.67%, while in group B, tachycardia, facial flushing, palpitations, and headache were identified with 10%, 6.67%, 10%, 6.67%. In Urmila Karya et al.[30] study, facial flushing, palpitations, headache, and nausea were the side effects identified within the nifedipine group with 22.5%, 10%, 25%, and 7.5%, while; it was identified with 42.5%, 7.5%, 40%, and 5% respectively which resembles to our study results.

In the current study, the birth weight was 2090 ± 372.64 grams in group A. While it was 2381.67 ± 492.44 grams in group B. Elham Mohammadi et al.[29] conducted a randomized study on 139 women in which 1609.0±204.3 and 2154.5±221.3 (grams) were the means of birth weight identified in the nifedipine and sildenafil + nifedipine group which was a decreased mean of birth weight as compared to our study results.

In the current study, respiratory distress syndrome, NICU admission, perinatal death, alive and healthy neonates were identified with 16.67%, 23.33%, 20%, and 53.33% in group A, whereas it was identified with 23.33%, 36.67%, 3.33%, and 56.67% respectively. In Urmila Karya et al.[30] study the respiratory distress and perinatal death were identified with 22.5%,

35%, and 12.5% in the nifedipine group while it was 10%, 22.5%, and 5% in the sildenafil + nifedipine group.

Abd El-Naser. Et al.[31] performed a study on 300 pregnant women in which respiratory distress, sepsis, perinatal mortality were observed with 7.40%, 4.20%, and 1.06%, while it was identified with 8.30%, 4.10%, and 2.08% in the sildenafil group.

Urmila Karya, et al.[30] Abd El-Naser. Et al.[31] Elham Mohammadi et al.[29] and our study showed similar neonatal outcomes.

Table 21: Comparison of neonatal complications between various studies.

Study	Population	Neonatal complications	
Present study	60	Nifedipine group Respiratory distress syndrome (16.67%) NICU admission (23.33%) Neonatal mortality (20%)	Sildenafil + nifedipine group Respiratory distress syndrome (23.33%) NICU admission (36.67%) Neonatal mortality (3.33%)
Elham Mohammadi, et al.[29]	139	Nifedipine group Respiratory distress syndrome (25.8%) NICU admission (66.7%) Neonatal death (4.5%)	Sildenafil + nifedipine group Respiratory distress syndrome ((7.6) NICU admission (36.4) Neonatal death (7.6%)

Betensol was given to 83.33% of participants in group A and 96.67% in group B. In the current study, cervical length was 32 (31,33) in group A.

The majority of the participants had a cervical score between 31 to 36 in group A and group B with 90% and 93.33%, respectively.

while it was 32 (31.75,34) in group B. In Elham Mohammadi et al.[29] 29.50±3.51 and 28.62±3.90 (cm) were identified as the mean of cervical length in the nifedipine and sildenafil + nifedipine group which was a decreased mean as compared to our study.

In the current study, the nifedipine loading dose was 20mg for the majority of the women in groups A and B with 50% and 40%, respectively.

The rate of success was higher with group B (93.3%) than with group A (50%).

SUMMARY

SUMMARY:

Preterm labor is defined as the commencement of regular painful uterine contractions with effacement and dilation of the cervix before the completion of 37 weeks of pregnancy, counting from the first day of the last menstrual period and ending after the time of viability. It causes 75% of neonatal mortality and 50% of long-term morbidities such as respiratory disease and neurodevelopmental impairment.

A major goal of the obstetrician is to postpone delivery for 24-48 hours to permit time for the administration of corticosteroids. It helps to prevent neonatal complications. In a meta-analysis, nifedipine was identified as more effective and safer than other traditional tocolytics agents whereas, another meta-analysis study concluded it as a drug of choice for threatened preterm labor. This study was conducted to compare the effect of nifedipine and sildenafil citrate.

A total of 60 subjects in the final analysis. Group A (Nifedipine) were 30 participants, and Group B (Sildenafil +Nifedipine) were 30 participants.

The mean age of the participants was identified as 21.07 ± 3.31 years and 22.87 ± 3.15 years in groups A and B. Majority of the participants in group A age group between 18-20years with 46.67%. Whereas, in group B majority of the participants were belonged to the group between 21 to 25 years with 53.33%. There were 26.67% of booked pregnancies and 73.33% of un booked pregnancies in group A. While in group B, booked and un booked pregnancies were 50% of each.

The majority of group A and group B were belonged to primigravida with 86.67% and 73.33%, respectively. Around 40% of the participants in group A had a previous history of preterm birth whereas, it was identified as 75% in group B. The median period of gestation was 32.50 (30,34) weeks in group A while it was 34 (31,34.25) in group B. Most of the women had the gestational age between 33 to 35 weeks in group A and B with 50% and 63.33%, respectively. The median prolongation of pregnancy was observed as 2 (2,5) days in group A and 7 (2.75,20) in group B. The cause of preterm was identified as idiopathic in the majority of the women in group A with 83.33%, followed by infection with 13.33%. Similar causes were identified in group B with 70% and 16.67%, respectively.

Maternal side effects in group A were tachycardia, palpitations, nausea, and vomiting with 26.67%, 3.33%, and 16.67%, while in group B, tachycardia, facial flushing, palpitations, and headache were identified with 10%, 6.67%, 10%, 6.67%. The birth weight was 2090 ± 372.64 grams in group A. While it was 2381.67 ± 492.44 grams in group B. Respiratory distress syndrome, NICU admission, perinatal death, alive and healthy neonates were identified with 16.67%, 23.33%, 20%, and 53.33% in group A, whereas, it was identified with 23.33%, 36.67%, 3.33%, and 56.67% respectively. Betnesol was given to 83.33% of participants in group A and 96.67% in group B.

The cervical length was 32 (31,33) in group A. while it was 32 (31.75,34) in group B. Majority of the participants had a cervical score between 31 to 36 in group A and group B with 90% and 93.33%, respectively. The nifedipine loading dose was 20mg for the majority of the women in groups A and B with 50% and 40%, respectively. The rate of success was higher with group B (93.3%) as compared with group A (50%). Our study found that a combination of sildenafil citrate and nifedipine is more effective than nifedipine alone in avoiding premature labor.

CONCLUSION

CONCLUSION:

An ideal tocolytic agent should be safe ,well tolerated , easily administered , rapidly absorbed and should relax myometrium to prevent threatened Preterm labor**.**

Effect of tocolytic are intensified through the synergistic effect of sildenafil citrate with nifedipine combination.

In our study, a combination of sildenafil citrate and nifedipine was found to be more beneficial than nifedipine alone in preventing preterm labor.

The combination of sildenafil citrate and nifedepine has better efficacy in maternal and neonatal outcome , compared to nifedepine alone , both are well tolerated.

LIMITATIONS:

The study was performed in a single center. So, more studies are required with a fixed dose of the drug and on a larger scale.

RECOMMENDATIONS:

Larger studies at multiple centers are required to gain a better understanding of the benefit of this therapeutic intervention. Adverse effects of this combination regimen on fetus and mother as a prophylactic agent in preterm labor can also be determined.

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ANNEXURE

ANNEXURES

CASE PROFORMA

NAME: **IP NO:**

AGE: **DOA:**

OCCUPATION: **DOD:**

ADDRESS:

EDUCATION:

HUSBANDS

OCCUPATIN:

SOCIOECONOIC

STATUS:

CHIEF COMPLAINTS:

HISTORY OF PRESENT ILLNESS:

OBSTETRIC HISTORY:

Marital life: Consanguinity:
Gravida: Para: living: Abortion: Dead: Details of

previous pregnancy: Details of present pregnancy:

MENSTRUAL HISTORY:

Last menstrual period: Age of menarche:

Expected delivery date:

Period of gestation:

Period of gestation according to

early scan: Past menstrual cycles:

PAST HISTORY:

Hypertension /Diabetes Mellitus/Bronchial Asthma/Tuberculosis /Blood

Dyscrasias/ Epilepsy/ Thyroid Disorder/ Cardiac Disease/Allergy

H/O blood transfusions:

H/O Surgeries or hospitalization:

PERSONAL HISTORY:

Sleep and appetite:

Diet:

Bowel and bladder:

FAMILY HISTORY:

DRUG HISTORY:

GENERAL EXAMINATION:

General condition:

Fair/ moderate/ Poor

Built: Nourishment:
Ht: cms Wt: kgs BMI:

Pallor: Icterus: Cyanosis:

Clubbing:

Lymphadenopathy:

Edema:

VITALS:

Pulse rate: Respiratory rate:

Blood pressure:

Temperatur

e: Breast: Spine: Thyroid:

SYSTEMIC EXAMINATION:

Cardiovascular system: Respiratory system: Central nervous system:

Per abdomen: Uterus size:

Relaxed / Irritable / Acting

Presentation: cephalic/ Breech/ other FHS:

LOCAL EXAMINATION:
Per Speculum: leaking PV Vaginal discharge

Per Vaginum: Effacement:

Dilatation:

Station:

Membranes:

Consistency

OS POSITION

PROVISIONAL DIAGNOSIS:

EFFECT OF TOCOLYSIS:

PROLONGATION OF TOCOLYSIS WITH NIFEDIPINE ALONE OR COMBINED SILDENAFIL
CITRATE.

PROLONGATION OF PREGNANCY	**NIFEDIPINE ALONE**	**SILDENAFIL CITRATE WITH NIFEDIPINE**
LESS THAN 48 HRS		
UP TO 48 HRS		
UP TO TO 7 DAYS		

SIDE EFFECTS ASSOCIATED WITH TOCOLYSIS TREATMENT:

ACHYCARDIA FACIAL FLUSHING

PALPITATION HEADACHE

NAUSEA AND VOMITING

DETAILS OF THE NEONATE:

Sex: Date: Time: Birth weight: APGAR

score: 1’- 5’-

Admission to NICU:

Neonatal resuscitation

Perinatal

morbidity/mortality

INVESTIGATIONS:

Blood group and Rh typing:

CBC: HB: HIV:

PCV: HbsAG:

RBC: VDRL:

WBC:

PLT: RBS:

Urine analysis: Albumin-

Su ga

OBSTETRICS SCAN:

PATIENT INFORMATION SHEET

Study title: EFFECT OF ORAL NEFIDIPINE OR COMBINED WITH SILDENAFIL CITRATE FOR MANAGEMENT OF THREATENED PRETERM LABOUR: RANDOMIZED TRIAL

Study location: R L Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar.

Details-

Pregnant women admitted to the labor room with threatened preterm labor were on a group

Will receive nifedipine alone, and one group will receive nifedipine along with sildenafil

Citrate, and the outcome is noted.

Patients in this study will have to undergo a complete general physical examination, obstetric examination, routine blood investigations such as complete blood count, viral serology, urine routine, and random blood sugar levels. To assess fetal wellbeing, a cardiotocograph and an obstetric ultrasound with a biophysical profile will also be done.

Please read the following information and discuss with your family members. You can ask any questions regarding the study. If you agree to participate in the study, we will collect information (as per proforma) from you or a person responsible for you or both. Relevant history will be taken. This information collected will be used only for dissertation and publication.

All information collected from you will be kept confidential and will not be disclosed to any outsider. Your identity will not be revealed. This study has been reviewed by the Institutional Ethics Committee, and you are free to contact the member of theInstitutional Ethics

Committee. There is no compulsion to agree to this study. The care you will get will not change if you don't wish to participate. You are required to sign/ provide a thumb impression only if you voluntarily agree to participate in this study.

For further information, contact

Dr. SHREYA SINGH

Postgraduate,

Department of obstetrics and gynecology,

Sri Devaraj Urs Medical College,

Kolar.

INFORMED CONSENT FORM

Case no:

I have read the foregoing information, or it has been read to me and has been explained to me in my own understanding language. I have had the opportunity to ask questions about it, and any questions that I have asked have been answered to my satisfaction. I have understood that I have the right to refuse consent or withdraw it at any time during the study, and this will not affect my treatment in any way. I consent voluntarily to participate in this study **"EFFECT OF ORAL NIFEDIPINE OR COMBINED WITH SILDENAFIL CITRATE FOR MANAGEMENT OF THREATENED PRETERM LABOUR: RANDOMIZED TRIAL"**

Name of Participant_____

Signature/ thumbprint of Participant _____

Date _____

R.L Jalappa Hospital Tamaka, Kolar.

MASTER CHART

MASTER SHEET

S.no	UHID	Study group	Age (in years)	U/B	Gravida	Previous history of PTB	Period of gestation (in weeks)	Prolongation of pregnancy (in days)	Cause of preterm	Maternal side effect	Birth weight (in kg)	Neonatal complication	perinatal death	Be Tensol	Cervical length	Nifedipine loading dose (in mg)
1	745426	Group A	20	Unbooked	Primi		34	10	Lower genital tract infection	Tachycardia	2400	RDS	No	Yes	32	20
2	820058	Group A	27	Unbooked	Multi	Yes	32	15	idiopathic	Tachycardia	2200	NICU/RDS	No	Yes	35	20
3	818083	Group A	19	Unbooked	Primi		28	1	idiopathic	Tachycardia	1600	perinatal death	Yes	No	31	20
4	777640	Group A	23	Booked	Primi		31	2	idiopathic	Nausea and vomiting	1800	perinatal death	Yes	Yes	34	40
5	820058	Group A	18	Booked	Primi		30	2	idiopathic		2100	NICU	No	Yes	32	30
6	843064	Group A	18	Unbooked	Multi	No	33	10	Lower genital tract infection		2300	A&H	No	Yes	32	20
7	820058	Group A	26	Unbooked	Primi		35	1	idiopathic		2200	A&H	No	Yes	33	20
8	837539	Group A	21	Unbooked	Primi		31	2	idiopathic		1800	NICU/RDS	No	Yes	32	20
9	837535	Group A	16	Unbooked	Primi		29	1	idiopathic	Nausea and vomiting	2200	A&H	No	No	31	30
10	841969	Group A	21	Unbooked	Multi	Yes	32	2	Cervical incompetence		2400	A&H	No	Yes	21	20
11	868209	Group A	19	Unbooked	Primi		35	2	idiopathic	Tachycardia	2400	A&H	No	Yes	29	30
12	863790	Group A	26	Unbooked	Primi		31	8	idiopathic		3200	A&H	No	Yes	31	20
13	855114	Group A	19	Unbooked	Primi		34	4	idiopathic		2400	A&H	No	Yes	33	20
14	871779	Group A	26	Unbooked	Primi		34	5	idiopathic		2200	NICU/RDS	No	Yes	32	40
15	873671	Group A	18	Unbooked	Primi		34	6	idiopathic		2100	NICU/RDS	No	Yes	33	40
16	871792	Group A	24	Unbooked	Primi		30	2	idiopathic	Nausea and vomiting	2200	A&H	No	Yes	34	20
17	881172	Group A	16	Unbooked	Primi		34	3	idiopathic	Tachycardia	2300	A&H	No	Yes	33	30
18	889103	Group A	18	Booked	Primi		32	2	idiopathic		1700	perinatal death	Yes	No	32	20
19	870114	Group A	20	Booked	Primi		28	1	idiopathic		2100	NICU	No	Yes	32	30
20	873842	Group A	23	Booked	Primi		35	2	idiopathic	Tachycardia	2200	A&H	No	Yes	33	40
21	914592	Group A	18	Booked	Primi		35	2	idiopathic		1600	perinatal death	Yes	Yes	30	20
22	914198	Group A	22	Booked	Primi		29	2	idiopathic	Tachycardia	2100	A&H	No	Yes	31	40
23	916317	Group A	21	Unbooked	Primi		34	4	Lower genital tract infection	Tachycardia	1900	A&H	No	Yes	31	20
24	916675	Group A	25	Unbooked	Multi	No	30	1	idiopathic	palpitations	1900	A&H	No	Yes	33	20
25	918379	Group A	19	Unbooked	Primi		35	4	idiopathic		2100	A&H	No	No	35	20

26	922760	Group A	22	Unbooked	Primi		33	2	Lower genital tract infection	Nausea and vomiting	2400	A&H	No	Yes	34	30
27	921830	Group A	25	Unbooked	Primi		34	4	idiopathic		2200	A&H	No	Yes	33	40
28	927013	Group A	18	Booked	Primi		34	5	idiopathic	Nausea and vomiting	2100	NICU	No	Yes	32	30
29	927385	Group A	24	Unbooked	Primi		28	7	idiopathic		1400	perinatal death	Yes	Yes	31	40
30	923456	Group A	23	Unbooked	Primi	No	24	1	idiopathic		1200	perinatal death	Yes	No	31	40
31	778686	Group B	26	Booked	Primi		31	7	idiopathic	Facial Flushing	1900	NICU	No	Yes	32	20
32	827231	Group B	22	Unbooked	Multi	No	32	28	Cervical incompetence	Headache	2200	A&H	No	Yes	24	30
33	838892	Group B	27	Unbooked	Primi		34	7	idiopathic		2050	NICU	No	Yes	34	20
34	840313	Group B	23	Unbooked	Primi		34	4	Lower genital tract infection		2300	NICU	No	Yes	35	20
35	853596	Group B	24	Booked	Multi	Yes	35	20	idiopathic		2800	A&H	No	Yes	32	30
36	842872	Group B	25	Booked	Primi		35	7	Lower genital tract infection	Facial Flushing, Tachycardia	2100	A&H	No	Yes	31	20
37	842774	Group B	20	Unbooked	Primi		35	2	idiopathic		2200	NICU	No	Yes	32	20
38	842702	Group B	25	Booked	Primi		29	7	Cervical incompetence		1800	NICU	No	Yes	21	20
39	841263	Group B	26	Unbooked	Multi	Yes	31	1	idiopathic		1600	NICU/RDS	No	No	32	30
40	867277	Group B	23	Unbooked	Primi		35	2	Lower genital tract infection	Tachycardia	2500	A&H	No	Yes	34	20
41	855384	Group B	22	Unbooked	Primi		35	20	idiopathic		3200	A&H	No	Yes	32	20
42	873842	Group B	27	Unbooked	Primi		30	15	Urinary tract infection		2600	NICU/RDS	No	Yes	32	30
43	886352	Group B	21	Booked	Primi		34	7	Urinary tract infection	palpitations	3200	A&H	No	Yes	32	20
44	823452	Group B	26	Booked	Primi		34	8	idiopathic		2400	A&H	No	Yes	35	30
45	845533	Group B	24	Booked	Multi	Yes	32	2	idiopathic		2200	RDS	No	Yes	35	20
46	824216	Group B	19	Booked	Primi		34	2	idiopathic	palpitations	2300	A&H	No	Yes	31	30
47	890232	Group B	23	Booked	Primi		29	1	idiopathic		1600	perinatal death	Yes	Yes	32	20
48	891496	Group B	29	Booked	Multi	Yes	33	12	Lower genital tract infection		2100	NICU/RDS	No	Yes	34	30
49	891408	Group B	22	Booked	Primi		29	20	idiopathic	Headache	1800	NICU/RDS	No	Yes	35	20
50	929787	Group B	18	Booked	Primi		33	15	idiopathic		2400	A&H	No	Yes	34	40
51	930835	Group B	18	Unbooked	Primi		34	7	idiopathic		2400	A&H	No	Yes	36	40
52	938679	Group B	24	Unbooked	Primi		34	7	idiopathic		2300	A&H	No	Yes	32	40
53	930886	Group B	25	Unbooked	Primi		35	6	idiopathic		2200	A&H	No	Yes	31	40
54	931268	Group B	20	Booked	Multi	No	34	20	idiopathic		3400	A&H	No	Yes	33	40
55	932012	Group B	18	Booked	Primi		30	3	idiopathic		2600	A&H	No	Yes	31	40
56	938365	Group B	18	Unbooked	Primi		34	20	idiopathic		3200	alive and healthy	No	Yes	32	40
57	969286	Group B	24	Unbooked	Multi	Yes	34	2	idiopathic		2200	NICU/RDS	No	Yes	33	40
58	933694	Group B	25	Unbooked	Primi		30	20	Lower genital tract infection	palpitations	2100	NICU/RDS	No	Yes	31	40
59	938952	Group B	20	Unbooked	Primi		35	20	idiopathic	Tachycardia	2400	A&H	No	Yes	34	40