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A PROSPECTIVE COHORT COMPARATIVE STUDY OF NIFEDIPINE AND ISOXSUPRINE IN THE TREATMENT OF PRETERM LABOR

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ABSTRACT

Introduction: A prospective cohort study was conducted to compare the efficacy of nifedipine against isoxsuprine in preventing preterm labor and to evaluate maternal side effects and neonatal outcome. **Methods:** This was a Randomized Prospective cohort comparative Study. 156 eligible preterm labor women with gestational age between 28-36 weeks, who fulfilled the inclusion and exclusion criteria for the study, were randomly assigned to receive either Nifedipine or Isoxsuprine treatment. **Results:** Successful tocolysis was achieved in 92% of Nifedipine treated group and 84.6% of Isoxsuprine treated group. Delivery of women in Nifedipine group was delayed for 48hr, 7days and equal to or more than 21 days in 72 (92%), 72 (92%), 72 (92%), cases respectively compared with 66(84.8%), 17(21.7%) and 14(17.9%) women in Isoxsuprine group. The observation was significant for 7 days and equal to or more than 21 days except 48hrs which was insignificant. All the side effects were more common in isoxsuprine group compared to nifedipine group. Neonatal outcome was better with nifedipine in comparison to isoxsuprine group. **Conclusion:** The present study found that nifedipine has better tocolytic efficacy, less side effects and better tolerability as compared to isoxsuprine.

KEYWORDS: Preterm Labor; Nifedipine; Isoxsuprine; Tocolytics.

INTRODUCTION

Preterm labor is a huge problem for the entire family and for society as a whole because it commonly results in a premature baby. Preterm delivery affects 11% in U.S.[1] and it effects even greater in developing countries (23.3% in India)[2] and it is the precursor for 40–75% of

neonatal deaths. The lower the gestational age of the baby at birth, the higher is the risk of complications. This risk is still very high for those infants born extremely preterm despite recent advances in neonatal intensive care. Thus, prevention or early treatment of preterm labor could potentially be of tremendous importance. Beta adrenergic receptor blocking agent Isoxsuprine and Nifedipine a calcium channel blocking agent is the most widely used tocolytic agents,[3] in India. Several non-randomized and randomized trials suggest that Nifedipine is effective in suppressing preterm labor with minimal side effects on the mother and fetus.[4, 5, 6, 7] However, in all studies numbers are too small to prove equal efficacy of nifedipine with betamimetic drugs. The studies have been criticized for not having enrolled women now thought to be the ones most likely to benefit from tocolytic therapy ie, those still very early in their pregnancy, those needing transfer to a center that can provide neonatal intensive care, or those who have not yet received a full course of antenatal corticosteroids. What is needed now is a well-designed, appropriately sized studies comparing nifedipine restricting enrolment to women whose fetuses are most likely to benefit from a few extra days in utero. The objective of this prospective cohort study was to compare the efficacy of nifedipine against isoxsuprine in preventing preterm labor, and to evaluate maternal side effects and neonatal outcome. Understanding that we need huge number of patient's data to statistically detect the difference in efficacy of both the therapies the current attempt has been made to contribute to future meta-analyses.

METHODS

This is a prospective cohort study conducted between July 15, 2009 (first patient enrolled date) and - December 14, 2013 (Last patient follow up date) at CSI Kalyani Multi Specialty Hospital Chennai in India. Patients above 18 years old with singleton pregnancies and cervical dilatation not more than 4cm and intact membranes who were admitted for preterm labor at CSI Kalyani Multi Specialty hospital at 28 and 36 weeks' gestation were considered eligible for the study. Last menstrual period and ultrasonography examination was used to estimate the gestational age of the patients. Preterm labor was diagnosed on the basis of regular uterine activity, defined as regular uterine contractions 4 per 20 min, each lasting 30 s, and cervical dilatation of 0–3 cm for nulliparous and 1–3 cm for multiparous with cervical effacement of 50%.[8] The institutional review board approved the study, and written informed consent was obtained from the entire patient prior to their enrollment in to the study.

The patients were included in the study with Gestational age between 28-36 weeks, Singleton Pregnancies, Intact membrane and Cervical dilatation not more than 4 cms.[9,10] The patients were excluded from the study if with Dead fetus, Multiple Pregnancy, Rapture membrane, Polyhydramnios, Fetal distress, History of antepartum hemorrhage, Cervical dilatation of more than 4 cm, Severe pre eclampsia, Previously diagnosed congenital malformations, Cervical incompetence, Maternal heart disease, Chorio-amnionitis, Eclampsia, Severe IUGR, Other medical disorders which contraindicate the use of tocolytic drugs, Essential hypertension, Diabetes mellitus, Chronic nephritis, Severe anemia (Hb<5 gm%) , Maternal Thyrotoxicosis, Liver disease and History or medical condition that contraindicates the use of investigational drug.

After informed consent was obtained, the patient was assigned to either nifedipine or Isoxsuprine group. SAS version 9.2 Generated Randomization was used for allocation of treatment to patients. The allocation was done as and when patients were enrolled in the study until the required number of patients was achieved by the protocol. The sample size of 70 in each group was considered sufficient to achieve the statistical power as per previously reported studies on preterm labor. However considering the number of expected dropouts additional 8 subjects in each group was considered, hence 78 in each group was considered for this current study. The randomization code was blinded to the investigator performing the statistical analysis until the final report is submitted. The patients assigned to nifedipine group were administered with an initial oral loading dose of 30 mg (10 sublingual and 20 mg oral) and a maintenance oral dose of 20 mg every 6 h.[11] And patients assigned to isoxsuprine group were started on infusion of Inj. Isoxsuprine 40mg in 500ml Ringer lactate at 0.08mg/min, increasing the infusion rate up to 0.24mg/min. After discontinuation of IV infusion, patients were maintained on oral Isoxsuprine 10mg 8 hourly for up to 7 days. Either of the treatment was discontinued if no uterine contractions occurred within a 48 h period and was switched to indomethacin 25-50 mg every 6 hours, with a maximum daily dose 200 mg, for 48 hours.[12] If spontaneous rupture of membranes occurred within 48 hours of treatment, delivery was considered. To enhance fetal lung maturation, all the patients were given head low position and injection dexamethasone 12 mg im 12 hrly for two doses followed by weekly injections up to 36 weeks and Antibiotic prophylaxis was given in the form of erythromycin to patients. Rest and hydration for half an hour was applied as first line management in all cases, Normal saline infusion at a rate of 100-150ml/HR after an initial bolus of 200ml was given for hydration. Tocolysis was considered to have been achieved

when uterine activity decreased to <4 contractions/h with the absence of cervical change. Tocolytic failure was defined as delivery <48 hours after the initiation of a study agent. All patients were placed on a home uterine activity monitor (Tokos Medical Corp, Encino, Calif) at hospital discharge. All patients were followed up weekly in the outpatient research clinic until delivery. At each clinic visit the degree of cervical dilatation was determined, monitor recordings were reviewed. If a patient was readmitted because of preterm labor, tocolytic therapy was initiated with again with nifedipine or isoxsuprine previously demonstrated to be effective for that particular patient. Uterine activity was monitored twice daily. Fetal Heart rate measurement was done every 15min for the first 2hrs then hourly for the next 22hrs then twice daily thereafter when uterine quiescence had been achieved. Clinical signs and symptoms of intolerance to nifedipine used was assessed every 6hr. Several neonatal parameters, such as weight, Apgar score, umbilical venous cord PH values and presence of hyperbilirrubinemia was determined, neonatal complications such as hemorrhage or infections were recorded. All statistical analyses were performed using SAS version 9.2 or higher. The intention-to-treat (ITT) population is the full analysis set in which all patients were randomized to receive at least one of the study drugs. The per-protocol (PP) population would include patients from the ITT population who did not commit any protocol deviation. For evaluation of the primary endpoint Chi square test was used. A p value less than 0.05 ($p< 0.05$) was considered sufficient for the rejection of the null hypothesis. For Secondary endpoints a comparative analysis between the two treatment groups were performed by students-t test and chi square test for continuous and categorical data respectively. Ordinal data were analyzed with the Mann–Whitney U-test. The difference between the two groups were considered significant at $p < 0.05$. Safety outcomes were analyzed by descriptive statistics and qualitative analysis for all emergent adverse events, measured after initial and after the treatments.

RESULTS AND DISCUSSION

Total of 212 patients reported with preterm labor and a total of 156 preterm labor diagnosed patients were enrolled into the study. Out of 156 patients (78 in Nifedipine group and 78 Isoxsuprine group) participated patients, 138 (72 in Nifedipine group and 66 in Isoxsuprine group) patients completed the study. In the current study all cases were between 19-38 yrs. of ages. The youngest was of 19 years age, eldest was 38 years of age. 51.27% were above 26 years of age. In the present study 90 cases (57.69%) were primigravida, 23.72% were secondgravida, 9.62% were thirdgravida, 5.77% were fourth gravida and 3.21% were

fifthgravida or more. The combined percentage of primigravida and second gravida was 81.4%. This finding is in accordance with finding of Griswold and Cavang (1966)[13], who observed in there 551 cases that premature labor was more common in first and second pregnancy in more than 70% of cases. 9.6% of patients were of low socio economic status, 60.2% were of low middle class, 5.7% of upper class, and only 24.35 % patient were of upper middle class. Most of the cases belong to lower middle class i.e. 56.25%. The combined percentage of patients belonging to lower middle and upper middle class was 84.55%. It may be due to the fact that patients belonging to higher class may prefer to be treated in private hospitals. Under circumstances of socio economic deprivation the mechanism of labor may be triggered prematurely through effect of chronic malnutrition, reproductive excess, life stress or infection of genital urinary tract (Whitehead NS 2012).[14] Meis and Colleagues and Janet Tucker et al found association of preterm labor and poverty. 73.7% of the patients were graduates 13.46% were matriculate, 2.5% were up to matriculate and 10% were illiterates.[15] It was found in present study that pre term delivery was more in mothers who were at educated which was more than the illiterate which is controversial to the study done by Fredrick and Anderson (1976)[16], and Creasy et al (1980).[17] This may be due to the fact that literacy rate in India have increased and moreover the culture of Indian woman who work at office and as well as at home. 74.35% of cases were from 28 weeks to 33 weeks of gestation. Maximum number of patients presented in gestation age of 28 – 33 weeks of gestation. Finding of Benson RC, (1986)[18] and Uma Singh et al (2007)[19] is comparable to present study. Benson observed in his study that most patients of preterm of labor were of gestational age less than 34 weeks and benefited most by tocolysis. 16.6% of patients had history of abortion. Fredrick and Anderson (1976) suggested that risk of developing preterm labor increases with history of previous abortion. Uma Singh et al (2007) found 49% of patients in their study had history of previous abortion. 10.10% of patient had previous history of preterm birth. Incidence of preterm labor increases in patients with previous history of preterm labor as per Griswold and Cavang 1966, Singh Uma et al (2007) and Janet Tucker et al (2004).[20] Car Hill and Hall (1985)[21] found that more the number of previous preterm delivery the incidence of preterm labor increases in the present pregnancy. Labor was successfully postponed by more than 48 hours in (92%) in nifedipine group as compared to 66 cases (84.6%) in isoxsuprine group. Labor could not be suppressed for more than 48 hours in 6 cases (3.84%) of nifedipine group and 12 cases (7.69%) of isoxsuprine group (Table-I). This observation is in accordance with Singh Nisha et al (2011)[22] in their study of preterm labor nifedipine had success rate of (80%) and isoxsuprine of 68%. The finding of

present study is comparable to finding of D Kalita et al (1998)[23] who also observed that nifedipine gave success rate of 84% as compared to 64% in isoxsuprine group. Thus it is seen that nifedipine as compared to isoxsuprine is better in suppression of preterm labor. 92% of nifedipine group and 84.6% of isoxsuprine group labor was postponed for 48 hours – 7 days. 92% of nifedipine group and 21.7% of isoxsuprine labor was postponed for 7-21 days. 92% of nifedipine group and 17.9% of isoxsuprine group labor was postponed for more than 21 days. This finding is comparable to that of A. D Kalita et al (1998) who found in their study that maximum prolongation of pregnancy in nifedipine group was 49 days. Adverse effects especially cardiovascular were less with nifedipine as compared to isoxsuprine. Tachycardia was seen in (4.17%) in nifedipine group and (33.33%) in isoxsuprine group and Hypotension in (4.17%) in nifedipine group and (28.79%) in isoxsuprine group. Hypotension and Tachycardia were commonest maternal side effect (Table-2). D Kalita et al (1998) have reported significantly higher incidence of side effects with isoxsuprine than with nifedipine.

Clinical trials with nifedipine have reported either an insignificant decrease in blood pressure or no change in maternal heart rate or transient hypotension in 14 to 45% of patients. In a randomized trial between nifedipine and ritrodrine significantly more side effects were noted with ritodrine. Glock and Morales[24] also noted transient hypotension in 41% of nifedipine group although t resolve spontaneously in <10 minutes in most patients without evidence of prolonged maternal and fetal symptoms which led them to emphasize the need to ensure proper hydration of patients before starting Nifedipine therapy. Aarti Gulati et al[25] found in their study almost similar percentage of Tachycardia, 84% with isoxsuprine and 76% of nifedipine. Amit Patki et al (1993)[26] observed hypotension in 50% with isoxsuprine group and 15% in nifedipine group. The other side effects were noted were palpitation, headache, nausea, vomiting and flushing in 11.11%, 11.11%, 16.67%, 5.6%, 0% in nifedipine group and 25.76%, 18.18%, 51.52%, 40.91%, 12.12% in isoxsuprine group respectively (Table-II). Rayamajhi et al also noted that side effect was more in isoxsuprine group, the common side effects being hypotension and tachycardia. However, headache was more in nifedipine group as seen in the present study and that of Rayamajhi et al. The maximum change in pulse was more in isoxsuprine group i.e. 40 beats per minute as compared to nifedipine group i.e. 30 beats per minute. The present studies shows that fall in systolic and diastolic blood pressure was more in cases of isoxsuprine group than in nifedipine group. Maximum fall in systolic blood pressure was 18mm of Hg in nifedipine group and 26 mm Hg in isoxsuprine group. Maximum fall in diastolic blood pressure was 15mm Hg in nifedipine group and 20 mm of

Hg in isoxsuprine group. The finding is comparable to that of Aarti Gulati and Uma Rai et al (1993)[27] who observed fall in blood pressure in both groups but fall was more significant in isoxsuprine group. The adverse events observed in the present study and the change in maternal pulse, change in systolic and diastolic blood pressure suggests that all side effects especially cardiovascular side effects were less with nifedipine treated pregnant women as compared to isoxsuprine group. These observations are similar to Read & Wellby (1986)[28] who observed more cardiovascular side effects with beta adrenergic as compared to nifedipine. Granger et al (1985)[29] found that nifedipine exhibited greater selectivity for inhibition of uterine contractions relative to its cardiovascular effects. The effects of nifedipine on systolic and diastolic blood pressure in normotensive patients have not shown significant change and are only transient effects, Ulmstein et al (1984). The other side effects were more with isoxsuprine but percentage of hot flushes was more with nifedipine (5%) in comparison to none with isoxsuprine. This was similar to finding of Ulmstein et al (1984), Read & Wellby (1986). Aarti Gulati and Uma Rai (1993), D. Kalita (1998). They observed in their study that hot flushes were more common side effects of nifedipine but it was transient. In cases where cervical dilatation was less than 1.5 cm and effacement was less than 50% successful tocolysis was achieved in 100% of cases of both the groups. In cases were cervical dilatation was 1.5-3cm effacement more than 50% labor was suppressed was more than 48 hours in 83% of nifedipine group and 70% of isoxsuprine group. The finding is comparable to that of Rayamajhi et al who found 100% success with nifedipine when dilatation was less than 1.5 cm. There was 70% success in nifedipine group as compared to 61% in isoxsuprine group when dilatation was 1.5 to 3 cm. The mean prolongation of pregnancy in days at all weeks of gestation was more in nifedipine group than isoxsuprine group. The finding is comparable to that of Rayamajhi et al. The mean gestational age in all weeks of gestation at time of delivery was more in nifedipine than isoxsuprine. The finding is comparable to that of Rayamajhi et al except for 26-29 weeks of gestation where mean gestational was more in isoxsuprine group in Rayamajhi et al study. The present study shows that 97.22% of cases of nifedipine groups and 93.93% of isoxsuprine group delivered vaginally. 2 cases of nifedipine and 4 cases of isoxsuprine group had lower segment caesarean section. There was no mark difference of results in both groups. The finding of present studies is comparable to that of Preeti Dubey et al (1992) who observed that mode of delivery in mothers treated with nifedipine was more or less similar to that of mothers treated with isoxsuprine. The present study shows that neonatal outcome was comparatively better in mothers treated with nifedipine than those with isoxsuprine. In this study 75% of babies of

nifedipine group mothers had Apgar score of 8-10, in comparison to 62.5% babies of isoxsuprine mothers. There was no neonatal death in both the groups, (Table-III). This finding is comparable to that of Papatsonis DNM et al (2003) group who found that neonatal outcome was better in nifedipine that ritodrine group.

The present study shows that mean gestational age at the time of delivery was 35.95 weeks in nifedipine groups and 33.15 weeks in isoxsuprine group. Mean prolongation of pregnancy was 31.26 days in nifedipine group and 14.47 days in isoxsuprine group. Mean birth weight was more in nifedipine group i.e. 2.11 kg as compared to isoxsuprine groups that is 1.8 kg. Tewari et al[30] have reported significantly more term deliveries with nifedipine but similar mean gestational age and mean birth weight in both groups. Kalita et al have reported mean birth weight of 2.5 ± 0.5kg with nifedipine and 2.27 ± 0.63kg with isoxsuprine. The perinatal mortality was similar in both groups as also noted by others. Clinical trials have demonstrated no harmful side effects on the fetus with nifedipine. D Kalita et al have reported mean prolongation of pregnancy as 31.16 days with nifedipine and 23.06 days with isoxsuprine. These results were similar to those reported by read et al. Tewari et al reported mean prolongation of pregnancy as ± 25.5 days with nifedipine and 25.5 ± 15.7 days with isoxsuprine. In the present study Successful tocolysis was achieved in 72 cases of nifedipine group i.e. 92.3% as compared to 66 cases of isoxsuprine group i.e. 84.61%. Tewari et al considered successful tocolysis as delay of delivery beyond 72 hours and found 56.6% success with nifedipine vs. 50% success with isoxsuprine. Read et al reported success rate of 83% of nifedipine vs. 45.5% with ritodrine. Kupferminc et al reported 53% success with nifedipine and 77% with ritodrine. The finding of this study are comparable to that of Rayamajhi et al (2003) who found better outcome with tocolysis in nifedipine group as compared to isoxsuprine group.

Table-I: Duration of postponement of labor after therapy in both groups

Postponement of labor in hours/days	**Group A n = 78**	**Group B n = 78**	***P***
Upto 48 – 7 days	72 (92%)	66 (84.6%)	ns
Upto 7 – 21 days	72 (92%)	17 (21.7%)	<0.001
More than 21 days	72 (92%)	14 (17.9%)	<0.001

Postponement of Labor was more in Nifedipine than in isoxsuprine group and this observation was significant in both 7-21 days and more than 21 days of postponement of delivery.

Table-II: Table showing side effect of drugs in both groups.

Adverse Event	Time after tocolysis was started	Nifedipine (Group-A)		Isoxsuprine (Group-B)		*P*
		N	n (%)	N	n (%)	
Nausea	2hrs	72	5 (6.94%)	66	10(15.15%)	0.17
	24hrs	72	3(4.17%)	66	12(18.18%)	0.01
	7days	72	4(5.56%)	66	12(18.18%)	0.03
Vomiting	2hrs	72	1(1.39%)	66	8(12.12%)	0.01
	24hrs	72	2(2.78%)	66	10(15.15%)	0.01
	7days	72	1(1.39%)	66	9(13.64%)	0.008
GIT upset	2hrs	72	0(0%)	66	3(4.55%)	0.08
	24hrs	72	0(0%)	66	2(3.03%)	0.15
	7days	72	0(0%)	66	1(1.52%)	0.31
Headache	2hrs	72	3(4.17%)	66	4(6.06%)	0.70
	24hrs	72	4(5.56%)	66	6(9.09%)	0.51
	7days	72	1(1.39%)	66	2(3.03%)	0.56
Flushing	2hrs	72	0 (0%)	66	3(4.55%)	0.08
	24hrs	72	0 (0%)	66	3(4.55%)	0.08
	7days	72	0 (0%)	66	2(3.03%)	0.15
chest pain	2hrs	72	0 (0%)	66	3(4.55%)	0.08
	24hrs	72	0 (0%)	66	1(1.52%)	0.31
	7days	72	0 (0%)	66	0 (0%)	NS
Dyspnea	2hrs	72	2(2.78%)	66	4(6.06%)	0.40
	24hrs	72	2(2.78%)	66	2(3.03%)	NS
	7days	72	1(1.39%)	66	2(3.03%)	0.56
Hypotension	2hrs	72	2(2.78%)	66	9(13.64%)	0.02
	24hrs	72	1(1.39%)	66	8(12.12%)	0.01
	7days	72	0(0%)	66	2(3.03%)	0.15
Tachycardia	2hrs	72	1(1.39%)	66	10(15.15%)	0.004
	24hrs	72	2(2.78%)	66	9(13.64%)	0.02
	7days	72	0(0%)	66	3(4.55%)	0.08
Palpitation	2hrs	72	4 (5.56%)	66	9(13.64%)	0.14
	24hrs	72	3(4.17%)	66	4(6.06%)	0.70
	7days	72	1(1.39%)	66	4(6.06%)	0.17
Syncope	2hrs	72	2(2.78%)	66	0 (0%)	0.15
	24hrs	72	0(0%)	66	0 (0%)	NS
	7days	72	0(0%)	66	0 (0%)	NS
One or More AE's	2hrs	72	8(11.11%)	66	15(22.73%)	0.11
	24hrs	72	2(2.78%)	66	10(15.15%)	0.01
	7days	72	3(4.17%)	66	4(6.06%)	0.70

It is observed in this study that side effects were more in patients treated with isoxsuprine (Group B) in comparison to nifedipine (Group A).

Table-III: Neonatal outcome in different group of patients.

	Nifedipine (Group A)		Isoxsuprine (Group B)		
	N	Value	N	value	p
Birth weight	72	2112 ± 854	66	1856 ± 855	0.185**
Apgar Score in 1 min	72	8.5 (7-9)	66	7 (4-8)	0.002*
Apgar score in 5 min	72	10 (9-10)	66	9 (7.75 – 9)	0.001*
Venous Cord PH	72	7.28 ± 0.07	66	7.27 ± 0.13	0.736**
Neonatal Death	72	0	66	0	ns

*Median and 25th and 75th Quartiles, analysis with Mann-Whitney U-test

*Mean and Standard deviation

CONCLUSION

The present study found that nifedipine has better tocolytic efficacy, less side effects and better tolerability as compared to isoxsuprine. In view of the increasing evidence of its efficacy and safety combined with its ease of administration, it appears likely that Nifedipine will play an expanded role in the suppression of preterm labor.

REFERENCE

1. Martin JA, Kochank KD, Strobino DM, et al. Annual summary of vital statistics 2003. Pediatrics. 2005; 115: 619–39.
2. Begum F, Buckshee K, Pande JN. Risk factors associated with preterm labor. Bangladesh Med Ras Coune Bull. 2003; 29: 59–66.
3. Singh Nisha, Singh Uma, Seth Shikha. Comparative Study of Nifedipine and Isoxsuprine as Tocolytics for Preterm Labor The Journal of Obstetrics and Gynecology of India. 2011; 61:512–515.
4. Ulmstein, U. Treatment of normotensive and hypertensive patients with preterm labor using oral nifedipine. Arch Gynaecol. 1984; 236:69-72.
5. Kupfermine M, Lessing JB, Yaron Y, Peyser MR, Nifedipine versus ritodrine for suppression of preterm labor. Br. J. Obstet Gynecol. 1993; 100:1090-1094.
6. Ferguson JE, Dyson DC, Holbrook HR et al. Cardiovascular and metabolic effects associated with nifedipine and ritodrine tocolysis. Am J Obstet Gynecol.1981; 161: 788–795.
7. Ulmstien U, Andersson K, Wingerup L, Treatment of premature labor with the calcium antagonist nifedipine. Arch Gynecol. 1980; 229:1–5.
8. Moutquin JM, Sherman D, Cohen H et al. Double-blind, randomized, controlled trial of atosiban and ritodrine in the treatment of preterm labor: a multicenter effectiveness and

safety study. Am J Obstet Gynecol. 2000; 182: 1191–1199.

9. Caritis SN, Toig G, et al. A double-blind study comparing ritodrine and terbutaline in the treatment of preterm labor. Am J Obstet Gynecol. 1984; 150: 7-14.
10. Papatsonis DN, Van Geijn HP, Ader HJ et al. Nifedipine and ritodrine in the management of preterm labor: a randomized multicenter trial. Obstet Gynecol. 1997; 90: 230-4.
11. Deulofeu P, Carmona F, Martinez S et al. Tratamiento tocolı´tico con nifedipina en la amenaza de parto prete´rmino. Prog Obst Gin. 1992; 35:74–81.
12. Rayamajhi R, Pratap K, A comparative study between nifedipine and isoxsuprine in the suppression of preterm labor. Kathmandu University Med J. 2003; 1: 85-90.
13. Griswold DM, Cavanagh D. Eclampsia and the weather. Am J Obstet Gynecol 1965; 91:847-51.
14. Whitehead NS. The relationship of socioeconomic status to preterm contractions and preterm delivery. Matern Child Health J. 2012; 16:1645-56.
15. Meis PJ, Michielutte R, Peters TJ, et al. Factors associated with preterm birth in Cardiff, Wales. II. Indicated and spontaneous preterm birth. Am J Obstet Gynecol, 1995; 173: 597-602.
16. Frederick J, Anderson ABM. Factors associated with spontaneous preterm births. Brit. J. Obst. Gynec. 1976; 83:342–350.
17. Creasy RK, Gummer BA, Liggins GC. A system for predicting spontaneous preterm birth. Obstet Gynecol 1980; 55: 692–5.
18. Benson RC. Preterm Labor. In D.H. Danforth and J.R. Scott (Eds.) Obstetrics and Gynaecology; Philadelphia; JB Lippincott Company. 1986; 682-689.
19. Uma Singh, Singh Nisha, Seth Shikha. A prospective analysis of etiology and outcome of preterm labor J Obstet Gynecol India. 2007; 57: 48-52.
20. Janet Tucker, William McGuire. Epidemiology of preterm birth, clinical review. Brit Med J. 2004; 329: 675-8.
21. Carr-Hill RA, Hall MH. The repetition of spontaneous preterm labour. Br J Obstet Gynaecol. 1985; 92:921-8.
22. Singh Nisha, Singh Uma, Seth Shikha . Comparative Study of Nifedipine and Isoxpurine as Tocolytics for Preterm Labor.The Journal of Obstetrics and Gynecology of India. 2011; 61:512–515.
23. Kalita D, Goswami A, Mazumtar KL. A comparative study of nifedipine and isoxsuprine hydrochloride in the management of preterm labour. J Obstet Gynecol India. 1998; 48: 47-50.

24. Glock JL, Morales WJ. Efficacy and safety of nifedipine versus MgSO4 in the management of preterm labour : A randomized study. Am J Obstet Gynecol. 1993; 169:960-964.
25. Aarti Gulati, Uma Rai. Suppression of preterm labour with nifedipine J. Obstet. Gynaecol of India. 1993; 43: 2.
26. Ameet Patki et al Comparison between Nifedipine and isoxsuprine J. Obstet Gynaecol. Of India. 1993; 43: 5.
27. Aarti Gulati, Uma Rai. Suppression of preterm labour with nifedipine J. Obstet. Gynaecol of India. 1993; 43: 2.
28. Read MD, Wellby DE. The Use Of Calcium Antagonist To Suppress Pre Term Labour Br. J. Obstet. Gynaecol. 1986; 93:933-937.
29. Granger SE, Hollings WM, Weston AH. A comparison of several calcium antagonists on uterine vascular and cardiac muscles from the rat. Brit. J. harmac. 1985; 85:255.
30. Tewari S, Sachan A, Gulati N. A study in department of obstetrics and Gynaecology, Pt. BD Sharma PGIMS, Rohtak. The Indian Practitioner. 1997; 50: 307-10.