International Journal of Medical and Health Research
ISSN: 2454-9142
Impact Factor: RJIF 5.54
www.medicalsciencejournal.com
Volume 3; Issue 11; November 2017; Page No. 34-39

Original Research Article: Side effect profile of nifedipine for tocolysis in pregnancy

[1] Dr. Chhavi Raman Baid, [2] Dr. Norman D Morris
[1] Assistant Professor, Department of Obstetrics and Gynaecology, Mata Gujri Memorial Medical College and Lions Seva Kendra Hospital, Kishanganj, Bihar, India
[2] Additional Professor, Department of Obstetrics and Gynaecology, BPKIHS, Dharan, Nepal

Abstract
Objective: Our study was to evaluate the incidence and severity of the side effects of nifedipine, and the management of suspected preterm labour.
Methodology: All women in whom it was decided to start tocolysis were given capsule nifedipine orally by using the following regimen-30 mg stat followed by 10 mg three times a day for 48 hours. Blood pressure along with temperature, respiratory rate and pulse rate were taken half an hour after the administration of the initial dose of nifedipine and repeated again after half an hour. And observations were recorded by the investigators.
Results: Data was analyzed using SPSS (PC+) version 11.0. Associations between the variables and outcome were evaluated using different significant tests like Fisher exact test and Pearson co-relation.
Conclusions: Most common clinical presentation was abdominal pain. Primigravida was commonly seen in women with preterm labour. Palpitation was the most significant side effect. Majority of cases were satisfied by the using of nifedipine treatment as a tocolytic.

Keywords: pregnancy, nifedipine, tocolysis

Introduction

Preterm birth is the most important single determinant of adverse fetal outcome in terms of both survival and quality of life. Preterm delivery complicates nearly 10% of all the pregnancies throughout the world. As there are long-term squeal for the infants in terms of growth, pulmonary function and neurological outcome, the prevention and treatment of preterm labour is important, not as an end in itself but as a means of reducing adverse events in the infant. The neonatal outcome is dependent upon gestational age at delivery, lower the gestational age, the higher the morbidity and mortality. Some cases of preterm labour occur because of obstetrics complications, e.g. multifetal pregnancy, polyhydramnios and antepartum hemorrhage. Most however are idiopathic.

In order to predict preterm delivery, various risk scoring systems have been proposed. One such risk scoring system, devised by Papiernik and modified by Creasy *et al.* [1] has been tested in the USA. This scoring system includes socio-economic factors, previous reproductive history of preterm birth, [2] daily habits and current pregnancy complications. As recently reviewed by Main and Gabbe, [3], the risk scoring system tested successfully on one population cannot be extrapolated on the other without being evaluated. So, it should be used in that community from which it has been evolved [4].

Not only is the identification of the risk factors difficult but the early diagnosis of preterm labour has remained an enigma. Because prediction and primary prevention of preterm delivery is so difficult, we must resort to inhibition of uterine contractions if and when woman present with symptoms suggesting preterm labour.

If we wait until labour is clinically established (with progressive dilation) it is usually too late to expect any inhibition of uterine activity to be effective. It is well recognized that even though most women presenting with preterm contractions without cervical changes do NOT deliver early, some do and, because we cannot identify which are at high risk of progressing quickly to deliver, we need to attempt tocolysis in all such women.

Medical management of preterm labour includes tocolytics which are drugs used to suppress uterine contractions. Tocolysis is important because even short term postponement of preterm birth (before 37 weeks) can help improve the outcome for babies as the mother can take corticosteroid therapy. This helps to accelerate fetal lung development. Such postponement also enables transfer of the baby in-utero to a tertiary health care center for better management, if necessary.

For a very long time, the most widely used group of tocolysis was beta memtics. Although they have been shown to improve the neonatal outcome, they have unpleasant and even potentially fatal maternal side effects. Similarly, magnesium sulphate, used frequently for tocolysis in the USA, has maternal and foetal side effects and requires close monitoring. The oxytocin antagonist, Atosiban, has been recommended in the U.K., but it also has short coming Non steroidal Anti-inflammatory Drugs (NSAIDS) are also used but are associated with deterious cardiovascular side effects for the infant. Another group of tocolytics are nitric oxide donors but they have not been used widely. In recent years there has been a growing interest in the used of calcium channel blockers

(CCB) because of their apparent effectiveness as tocolytics and their ease of administration. In our institution nifedipin is the first line drug used for tocolysis in the management of preterm labour. Aim of our study was to ascertain the incidence and severity of the side effects of nifedipine, as currently used at BPKIHS in the management of suspected preterm labour.

Materials and Methods

This prospective study was conducted during a period from april 2006 to march 2007 at BPKIHS, Dharan, Nepal. The attendents/patients signed an informed consent approved by institutional ethical committee of B. P. Koirala Institute of Health Sciences, Dharan, Nepal was sought.

Subjects

A total of 60 pregnant women with threatened or established preterm labour presenting in the obstetric emergency was taken for this study. Inclusion criteria of this study were all pregnant women in whom it had been decided by the doctor to administer nifedipine as the tocolytic agent, for the medical management of preterm labour. And exclusion criteria were women in whom already some other tocolytic it started, Women on any other medication which can interact with nifedipine. ($MgSO_4$), Cardiac disease, known diabetes mellitus or impaired glucose tolerance., liver dysfunction, renal dysfunction.

Recruitment of cases

The cases were recruited in the emergency and were investigated as per the current institute guidelines. All the cases were reviewed and the treatment started as per the protocol.

A detail history was taken to all the patients enrolled in the study. Demographic features like age, address were noted. Booking status and immunization status were noted and the period of gestation was calculated. If the woman was not sure of her dates then by other investigations already done by her like former USG, the best dates were calculated and were taken as the period of gestation. The number of times the women had got pregnant (gravid), the number of times she had got viable pregnancy (para), number of living children, number of abortions and number of previous preterm labour deliveries were all noted. A detail history was taken about the presenting complains and history of presenting illness. Woman was asked about any other medical illness a history taken about any other form of tocolytic treatment.

Examination

Patients vital parameters were noted including pulse, blood pressure, respiratory rate, temperature, pedal oedema, flushing. General examination was done and signs of pallor, icterus, lymphadenopathy, cyanosis, clubbing were noted. Examination of the chest and cardiovascular system was done to rule out any pathology. This was followed by per abdominal examination in which the fundal height was measured and cross checked with the dates. Fetal heart rate was looked for; lie and presentation were also been. By manual (using hand) method contractions were noted and in per speculum examination cervical changes, show, discharge and leaking were noted. Pre vaginal examination was not done. A non stress for documentation of the fetal cardiac activity and contractions was taken. Corticosteroid therapy was also started.

Methodology

All women in whom it was decided to start tocolysis were given capsule nifedipine orally by using the following regimen-30 mg stat followed by 10 mg three times a day for 48 hours. Blood pressure along with temperature, respiratory rate and pulse rate were taken half an hour after the administration of the initial dose of nifedipine and repeated again after half an hour.

These observations were made personally by the investigator using the same sphygmomanometer and thermometer. The same observations were recorded by the nursing staff four hourly.

There was also a questionnaire administered personally by the investigator on two occasions for each patient. First time, it was taken in 6 to 12 hours after the initial dose of nifedipine; the second in 12 to 24 hours.

Data Analysis

Data was analyzed using SPSS (PC+) version 11.0. validity of the data was done. Associations between the variables and outcome were evaluated using different significant tests like Fisher exact test and Pearson co-relation.

Observation and Results

Out of total 60 patients, maximum number of patients were from Sunsari district, having a percent of 46.7 %. The total number of booked patients were 26(43.3%). The frequency of immunized patients were 51(85%). Out of the study population the total number of primigravida who presented with preterm labour were 35 and multigravida were 25. The range of gravidity was from 1 to 6 with a mean of 1.78 and standard deviation of ±1,21.

Out of all the patients, 10 patients had previous abortion with total percent of 15.5% and a total number of previous living children were 19 in number having a percent of 31.5 %. In the study population, the range of period of gestation was from 28.4 weeks to 36.2 weeks. Mean period of gestation = 32.67 weeks, having a standard deviation ± 1,664.

Distribution of clinical presentation

The frequency of abdominal pain was 53(88.8%) which was the maximum complaint that shows that maximum number of patients present with abdominal pain in pre term labour. Discharge p/v was seen in 32 patients followed by backache seen in 22 patients then burning micturition seen was 20 patients and then leaking p/v seen in 6 patients and lastly. The frequency of show per vaginum was 5(8.3%) which was the minimum complain.

There was a gradual increase in the pulse rate from the time of admission till one hour (loading dose) of giving the drug. The mean pulse at the time of admission was 90.33 with standard deviation of ±9.55. The mean of half hour pulse was 101.4, standard deviation ±11.83. The mean of 1 hour pulse was 106.4 and standard deviation was ±12.65.

The pulse readings taken by the nursing staff at four hourly difference was having a mean reading more than 100 which meant that most women were tachycardia during the course of the therapy. This is distributed in table 1.

Table 1: Nursing readings four hourly

Nursing pulse readings	Mean	Standard deviation	minimum	maximum
Nursing 1	108.17	13.77	82	136
Nursing 2	108.24	13.97	84	140
Nursing 3	109.05	14.64	80	140
Nursing 4	107.36	13.68	82	142
Nursing 5	105.04	11.48	82	142
Nursing 6	103.47	11.75	82	128
Nursing 7	102.38	11.53	80	122
Nursing 8	100.04	9.79	86	130

The blood pressure reading taken by the nursing staff taken at a four hourly difference is distributed in table 2.

Table 2: Blood pressure reading four hourly

B.P	Sys mean	Sys std dev	Dys mean	Dys std dev
Nursing 1	107.42	9.74	68.51	±9.45
Nursing 2	109.07	9.86	66.34	±9.34
Nursing 3	112.35	9.34	67.86	±10.4
Nursing 4	113.61	9.28	72.39	±6.89
Nursing 5	111.92	9.31	69.79	±9.08
Nursing 6	116.64	9.23	72.6	±8.15
Nursing 7	117.17	10.15	71.38	±8.88
Nursing 8	115.06	10.14	72.94	±7.97

The respiratory rate reading and temperature readings taken by the nursing staff at four hourly intervals is distributed in table 3.

Table 3: respiratory rate and temperature four hourly recordings

Reading	RR mean	Std deviation	Temp mean	Std deviation
Nursing 1	20.03	2.18	97.97	0.29
Nursing 2	20	2.28	97.907	0.39
Nursing 3	19.51	2.5	97.2	0.36
Nursing 4	19.64	1.95	95.97	1.9
Nursing 5	19.58	2.01	97.63	0.53
Nursing 6	19.51	1.84	97.72	0.5
Nursing 7	19.32	1.6	97.66	0.4
Nursing 8	19.17	1.33	97	0.56

The number of patients who had tachycardia (pulse 100/minute or more) after the loading dose was 43 in number, having a percent of 71.7%. The number of patients who had hypotension (blood pressure equal to or less than 90/60) was 10 in number, having a percent of 16.7% after loading dose.

The number of patients who remained tachycardia after the completion of the course were 25 in number out of 53 in total, having a percent of 41.7%. The number of patients who were hypotensive after the completion of the course were only 1 out of 53 patients, having a percent of 1.7%.

The side effect profile from six to twelve hours of therapy

It was noted that frequency of palpitations was highest which was in 51 patients out of 60 in total. This was followed by nausea which was seen in 50 patients followed by headache and dizziness seen equal in frequency. They were seen in a frequency of 43 each. Flushing was present in a total of 25 patients. Inability to sleep after the administration of the drug was present in 34 patients. Altered bowel habit and difficulty in passing stools was seen in 18 patients while 9 had change in appetite (decrease).

The side effect profile of the patients between 12 to 24 hours of therapy

It was seen that palpitation remained the leading side effect after 24 hours of therapy. The frequency was seen in 28 patients out of 53 it total. The percentage calculated was 46.7%. This was followed by inability to sleep properly, which was seen in 25 patients. Nausea was next on the list with a frequency of 22 patients and it was not fluctuate much from the six hour readings.

Headache was reduced in patients with a frequency of 18 in number only. Percentage of dizziness was also reduced from 71% to 35% after 12 hours of therapy. 85% patients were satisfied with the treatment and thought that they were well taken care for.

Reasons of stopping the therapy

Nifedipine was stopped in three patients because of severe tachycardia and three patients delivered within 48 hours of receiving tocolysis. In one patient the drug was stopped due to atrial fibrillation, this effect was reversed after stopping of the drug within 24 hours.

Analytical Results

During the analysis of the side effect profile within six hours of the commencement of the treatment it was found that most of the women who had headache in 6-12 hours also had tachycardia which persisted throughout the therapy and remained after the completion of the course. It had a significant p-value of 0.018 by the application of fisher exact test.

It has already been seen that the maximum frequency of side effect that occurred in the 6-12 hours was palpitation but it did not have a significant p-value when associated with tachycardia whereas woman who had palpitations after 12 hours of therapy had tachycardia which persisted even after completion of the therapy. It had a significant p-value of 0.004. It means that most of the women who were tachycardia by the end of the therapy also had palpitations.

When the side effect nausea after twelve hours was associated with tachycardia which persisted after completion of the therapy (48 hours) it had a significant P value of 0.015,

showing that most of the women who had nausea also had tachycardia by the end of the therapy. When the side effect flushing after twelve hours was associated with tachycardia which persisted after the completion of the therapy, had a significant P value of 0.032, showing that most of the women who had flushing till 12 hours also had tachycardia by the end of the therapy. This was done by using Fisher exact test.

None of the other side effects could be significantly associated with tachycardia either after the loading dose or after the completion of the therapy.

It was also analyzed that most of the significant associations were of the side effects after 12 hours of therapy with tachycardia which persisted till the end of the therapy rather than tachycardia after one hour of the therapy. This showed that the duration of the treatment had significant associations of the side effects with tachycardia.

By the application of the test it was seen that the readings of the pulse taken by the doctor after one hour of the loading dose was significantly different from the readings taken within first hours by the nursing staff. The p-value was 0.000.

Similarly the blood pressure reading had a highly significant P value when associated the doctor's readings with the readings of the nursing staff.

P value 0.000 and 0.039 for systolic and diastolic blood pressure respectively. This also applied to the respiratory rate and temperature taken p value of each being 0.001 and 0.018.

This shows a significant inter observer variation. And also that by the time the nurses took the readings most of the effects had subsided. Indicate that most side effects were seen in first hour of therapy.

By analyze the side effect profile of six hours with that of twelve hours. Using the Fisher exact test it was found that headache had reduced significantly with a p- value of 0.02. It was seen that flushing also had reduced significantly from 6 to 12 hours, with a p value 0.015. It was also seen that number women who were also to sleep properly had also reduced significantly with a p value of 0.04.

Table 4: Comparison of side effect profile of nifedipine at 6 hours with 12 hours and p value.

Variable	6 hours	12 hours	P Value
Headache	43	18	0.02
Palpitation	51	28	0.42
Nausea	50	22	0.18
Flush	25	11	0.015
Dizzy	43	21	0.16
Normal sleep	34	28	0.04
Stools	34	7	0.09
Appetite change	9	4	0.46
No care	5	2	0.88
No sat	6	2	0.81

There was no significant difference in the care and satisfaction of the patients. With the help of Pearson Correlation comparison of the pulse by taking admission pulse as the baseline, one hour pulse and pulse at the end of the therapy it was found that the rate of rise of pulse from the admission to one hour of therapy was highly significant having a p value of 0.000.

It was also found that there was a significant rise in the pulse rate from the time of admission till the end of the therapy p value 0.02 but it was less than the rise seen in one hour.

During analysis of the women who presented with pre term labor 15 primigravida's were booked and 12 multigravida's were booked. It was seen that most of the primigravida were significantly associated with the complained of discharge per vaginum. The p value 0.048. Nine other complain was significantly co related to the gravidity. It was also analyzed by using the fisher exact test that most of the multigravida who had increased period of gestation but obviously below 37 weeks had more chances of pre term labour. Had a significant p value of 0.017.

By associating the difference in results with adding women with leaking or subtracting them when compared to frequency of tachycardia, it was found to be insignificant.

Secondary Results

Only 5.3% of the patients in our study delivered before 48 hours where as in the study done by Rayamajhi. R. the percentage was 18.75%. There was no case of in-utero fetal death or fetal tachycardia or fetal distress or abandoning of the procedure. Successful tocolysis (more than 48 hours) seen 95% patients with our protocol regimen.

Discussion

Preterm labour and delivery remains a major cause of perinatal morbidity and mortality. Numerous drugs and interventions have been used to prevent and inhibit preterm labour but non have been found to be completely effective with the choice being further limited by troublesome side effects.

In Nepal only 9.8% of the population has hospital deliveries and access to health services is very less and rate of preterm labour is high specially in the rural areas of Nepal.[5] Inspite of this huge burden very less information is there regarding the most commonly drug used in our setup for managing preterm labour and our is a tertiary health centre situated in eastern Nepal covering a radius of 300 kilometers in health associated problem. So with this background our descriptive study attempts to highlight the safety aspects the calcium channel blocker, nifedipine is managing preterm labour. During the study period of one year 60 cases of preterm labour were admitted at BPKIHS, Dharan. In all the cases Nifedipine was started as the tocolytic agents. In this study, it was seen that more of primigravida's of earlier age group presented with preterm labour, which was similar to a study done in Nepal by Christine. P. Stewart *et al.* [6]

In our study the most two common clinical presentation were of pain abdomen 53% followed by discharge p/v similar were the results shown by Copper and colleagues, 1990: Iams and associates, 1990 [7]. Therefore these sign and symptoms are important as they are the harbinger of labour. The most important side effect was tachycardia which was seen in 43(71.6%) patients in first hour of therapy, this tachycardia persisted till the end of therapy in 25(41.6%) patients. When compared to a different study done by Rayamajhi R and Pratap K [8] it was seen in 18.75 % of the patients only. This can be explained by the difference in the protocol of giving nifedipine. It was also seen in a study done by Ferquson. J.E.

et al. [9] that tachycardia was the most common side effect which was seen in 13.6% of the patients in their study.

It was seen that in our study the rate of hypotension was in 15.5% patients after one hour of the therapy and remained in 1.5% of the patients in by the end of the therapy. Study done by Ryamajhi. R *et al.* the rate of hypotension was more 18.75%. This can be explained because they had used sublingual doses of nifedipine in the loading dose protocol of the therapy. In a study done by Vicenc *et al.* in 2006 [10] it was seen that headache was seen in 10.3% of the cases where as in our study it was seen in 30% of the cases. In our study we have found that most of the side effects decreased in number as time passed. Although most of the studies was not reported dizziness as a side effect but Ryamajhi. R. reported anxiety in 2 % of the cases. In our study, it was seen in 35% of the cases. In our study, there was also a considerable amount of flushing 16% whereas one important side effect was palpitations although a subjective observation but it was quite uncomfortable to most of the patients. Palpitation was seen in 46.5% of the patients.

In the study done by Vicenc Cararach *et al.* nausea was seen in 5.2% of the cases where as in our study nausea was seen in 36% of the cases by the end of the therapy.

In our study there was only one case of atrial fibrillation that was trnansient because by the time E.C.G was done although there were no significant changes of patients conditions improved after stopping nifedipine. In a study done by Oei *et al.* [11] there was a case of myocardial infarction with nifedipine. There was another case of myocardial infarction in a study done by Verhaert and Vanhacker *et al.* [12] There was also a case of severe maternal hypoxia seen by Hodges *et al.* [13] on 20 mg B.D.S doses of nifedipine.

In our study there was no case of pulmonary oedema but in a study done by Vaast *et al.* [14] there was a case of acute pulmonary oedema I.V. nifedipine was used in that case. In study done by Van Geign in 2005 [15] there were seven reported cases of dyspnoea in whom 6 were twin gestation. In our study there was no such recorded case. In our study we were seen that there was no case of foetal death or abandoning of the treatment because of foetal tachycardia or foetal distress.

In our study, Pregnancy prolongation of more than 48 hours was seen in 95% of the cases. In study done by Ryamajhi. R and Pratap. K the mean prolongation of pregnancy was 81.25%.

Summary & Conclusion

In our study, most of the women presenting with preterm labour were primigravida, women who presented with preterm labour which had younger age group had lesser period of gestation. Commonest presentation was abdominal pain but most of the primigravida presented with discharge p/v with a significant p value. There was a rapid rise of pulse in the first hour of therapy but it was decreased by the end of the therapy. There was no significant hypotension noted during the study. The most common side effect seen was palpitation which persisted till the end of the therapy. There was one woman who got transient atrial fibrillation. 95% women were satisfied with the treatment. Period of prolongation of gestation for more than 48 hours was 95%. There was no case of maternal mortality and no case of intrauterine foetal death. There was no case of abandoning the treatment due to fetal distress or fetal tachycardia. Hence we concluded that most of the women were abdominal pain and preterm labour women were primigravida. Palpitation was the most significant side effect. Majority of cases were satisfied by the using of nifedipine as a tocolytic.

Recommendations

1. As this study has been concluded at a tertiary care hospitals, the result may not be generalized to peripheral level hospitals (district hospitals, zonal hospitals) thus a need to conduct studies in peripheral areas to get a clearer picture.
2. The use of oral nifedipine rather than sublingual or i.v. nifedipine, can help reduce serious side effects with an similar rate of prolongation of pregnancy.
3. As we have seen that there is maximum side effects in the first hour of loading dose therefore there should be vitals monitoring every half hourly before we start with maintenance dose.

References

1. Creasy RK, Gummer BA, Liggins GC. System for predicting spontaneous preterm birth. Obstet Gynecol. 1980; 55:692.
2. Hoffman JD. K Ward. Genetic factors in preterm delivery. 1999; 54:203-210.
3. Main DM, Gabbe SG. Risk scoring for preterm labour-where do from here? Am J Obstet Gynecol. 1987; 157:789-793.
4. Iams JD, Johnson FF, Creasy RK. Prevention of preterm birth. Clinical Obstet Gynecol. 1988; 31:599-615.
5. Jahn, Alareche, Iang Maurein, Shah Usha. Maternity care in rural Nepal a health service analysis. Tropical medicine and international health. Blackswell publishing. 2000; 5:657-665.
6. Christine Stewart P, Joanne Katz, Subarna K. Khatry. Preterm delivery but not intra-uterine growth retardation is associated with young maternal age among primiparae in rural Nepal. Maternal and Child Nutrition. 2007; 3(3):174-184.
7. Iams JD. Prediction and early detection of preterm labour. Obstet Gynecol. 2003; 101:402.
8. Rayamajhi R, Pratap K. Kathmandu Univ Med J (KUMJ). 2003; 1(2):85-90.
9. Ferguson JE, Dyson DC, Holbrook RH, Schutz T, Stevenson DK. Cardiovascular and metabolic effects associated with nifedipine and ritodrine tocolysis. Am J Obstet Gynecol. 1989; 161:788-795.
10. Vicenc Cararan, Montse Patasio. Nifedipine versus ritorine for suppression of preterm labour comparison of their efficacy and and secondary effects. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2006; 127:204-208.
11. Oei SG, Oei SK, Bro Imann HAM. Myocardial infarction during nifedipine therapy for preterm labour. N Engl J Med. 1999; 340:154-155.
12. Verhaert D, Van Acker R. Acute myocardial infarcton during pregnancy. Acta Cardiol. 2004; 59:331-339.

13. Hodges R, Barkehall-Thomas A, Trippet C. Maternal hypoxia associated with nifedipine for threatened preterm labour. Br J Obstet Gynaecol. 2004; 111:380-381.
14. Vaast P, Dubreucq-Fossaert S, Houfflin-Debarge V, *et al*. Acute pulmonary oedema during nicardipine therapy for premature labour, report of five cases. Eur J Obstet Gynecol Reprod Biol. 2004; 113:98-99.
15. Van Geign HP, Lenglet JE, Bolte AC. Nifedipine trials: effectiveness and safety aspects. BJOG. 2005; 112(1):79-83.