A comparative study between nifedipine and isoxsuprine in the suppression of preterm labour

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Abstract
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 none have been found to be completely effective with the choice being further limited by troublesome side effects. This study compares in a prospective and randomised design the efficacy and safety of the calcium antagonist Nifedipine with the β-mimetic Isoxsuprine. 81.25% of patients receiving Nifedipine and 70% of those receiving Isoxsuprine achieved successful tocolysis. The mean prolongation of pregnancy with Nifedipine was 25.19.85 days and with Isoxsuprine it was 19.18.17.82 days. Maternal side effects were similar in both groups with hypotension and tachycardia being the commonest. Discontinuation rates were also similar with pulmonary oedema and severe hypotension being the reasons for foregoing tocolysis. It can be concluded that Nifedipine is a safe and effective alternative to Isoxsuprine for suppressing preterm labour.

Key words: Nifedipine, Isoxsuprine, tocolysis, efficacy.

Preterm labour remains one of the unconquered frontiers in present day obstetrics. It is defined as the occurrence of regular uterine contractions every 5 – 8 minutes or less, lasting 30 seconds or more, with progressive cervical change, after 28 and before 37 weeks of pregnancy. Preterm birth affects 8 – 10 % of pregnancies and after exclusion of genetic and anatomic defects, it accounts for 75 – 80 % of perinatal morbidity and mortality. Throughout the years, a variety of drugs with different pharmacologic principles have been used to suppress preterm labour. However, the choice is limited by their efficacy, safety and side effects thus necessitating a continuous search for effective drugs with minimal side effects. Currently, the most commonly used tocolytic agents are beta-adrenergic agonists. However, the incidence of troublesome side effects and limited efficacy has led to a continuous search for alternatives.

There is a growing body of evidence that Nifedipine, a calcium channel blocker is an effective, potentially safer and better-tolerated tocolytic agent with no known fetal side effects. This study compares in a prospective design, the efficacy and safety of Nifedipine with that of Isoxsuprine, a beta-adrenergic agonist in the suppression of preterm labour.

Methodology
This was a prospective randomised study conducted at Kasturba Medical College, Manipal from 1 May 1997 to 30 May 1999. 62 patients with preterm labour were included in the study of which 32 received Nifedipine and 30 received Isoxsuprine. The patients were matched for age, parity, socio-economic status, previous obstetric history, gestational age and cervical status before tocolysis.

Selection Criteria
Patients with pregnancies between 28 to 36 weeks with intact membranes, presenting with threatened or established preterm labour diagnosed on the basis of painful uterine contractions, at least once every 10 minutes, with even minimal cervical changes in the form of effacement and dilatation (not exceeding 3 cm). Patients with severe preclampsia and eclampsia, antepartum haemorrhage, hydramnios, chorioamnionitis, cardiac disease, thyroid disorder and advanced labour were excluded. The fetal factors for exclusion were severe IUGR, IUD, oligoamnios or any fetal anomalies incompatible with life. However, maternal diabetes and an otherwise uncomplicated twin pregnancy were not a basis for exclusion from Nifedipine tocolysis. Two patients with maternal diabetes and one twin pregnancy were included in the study.

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Nifedipine Tocolysis (Group A)
32 patients received nifedipine in the following manner:
Prehydration: 500ml of crystalloid solution infused over 30 – 45 minutes. Maintenance at 100ml / hour.
Loading dose: Nifedipine 10mg sublingually. The same dose repeated every 20 minutes for up to 4 doses.
Maintenance dose: 4 – 6 hours after the last sublingual dose, Tab Nifedipine 10 – 20mg orally, 6 – 8 hourly for not more than 7 days.

Isoxsuprine Tocolysis (Group B)
Patients 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 depending on the status of uterine contractions and occurrence of side effects. After discontinuation of IV infusion, patients were maintained on oral Isoxsuprine 10mg 8hourly for up to 7 days.

Monitoring during acute tocolysis
Vital signs, uterine contractions and FHS were monitored ½ hourly and side effects were noted until the patient discharged from labour ward and started on maintenance doses.

All patients received oral antibiotics, Inj. Dexamethasone 12mg intramuscular (2 doses 12 hours apart) and complete bed rest with footend elevation.
Tocolysis was considered successful if delivery was postponed for more than 48 hours.

Results
During the study period, a total of 2492 deliveries took place. Of these 186 (7.46%) were preterm deliveries. Some of these patients had to be excluded as per the selection criteria. 5 patients were lost to follow up after tocolysis and these too were eliminated from the analysis. Hence, the final sample size was 62, of which 32 received Nifedipine and 30 received Isoxsuprine.

The patients in each group were matched for age, parity, gestational age, socio-economic status and previous obstetric history. The mean age of patients in Group A was 26 years and in Group B was 25.12 years. The mean gestational age in Group A was 32.22 weeks and in Group B was 32.64 weeks. The efficacy of tocolysis was analysed under four categories according to prolongation of pregnancy (Table 1). Although the efficacy was notably better with Nifedipine the results were not statistically significant (p>0.05).

<table>
<thead>
<tr>
<th>Prolongation of pregnancy</th>
<th>Nifedipine (N = 32)</th>
<th>Isoxsuprine (N = 30)</th>
<th>‘p’ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>Percentage</td>
<td>Number</td>
<td>Percentage</td>
</tr>
<tr>
<td>&lt;48 hrs.</td>
<td>6</td>
<td>18.75%</td>
<td>9</td>
</tr>
<tr>
<td>48 hrs – 7 days</td>
<td>8</td>
<td>25%</td>
<td>9</td>
</tr>
<tr>
<td>&gt;7 days and &lt;37 wks</td>
<td>11</td>
<td>34.38%</td>
<td>8</td>
</tr>
<tr>
<td>&gt;37 wks</td>
<td>7</td>
<td>21.88%</td>
<td>4</td>
</tr>
</tbody>
</table>

‘p’ value < 0.05 – statistically significant

The most important factor determining success was cervical status and the results are shown in Table 2.

<table>
<thead>
<tr>
<th>Cervical Status</th>
<th>Dilatation (cm)</th>
<th>Effacement (% )</th>
<th>Nifedipine</th>
<th>Isoxsuprine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine</td>
<td></td>
<td></td>
<td>Number</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(&lt; 1.5 cm)</td>
<td>?50%</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.5 – 3 cm)</td>
<td>&gt;50%</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(&gt; 3 cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoxsuprine</td>
<td></td>
<td></td>
<td>Number</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(&lt; 1.5 cm)</td>
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<td>(&gt; 3 cm)</td>
<td></td>
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</tr>
</tbody>
</table>

The outcome of tocolysis is shown in Table 3. Successful tocolysis (prolongation of pregnancy >48hrs) was 81.25% in Group A and 70% in Group B. The difference was not statistically significant (p value>0.05). The mean prolongation of pregnancy was not significantly different in the two groups (analysed by students ‘t’ test). The mean gestational age at delivery and mean birth weight was
significantly more in Group A. This probably reflects the longer prolongation of pregnancy in patients with a more advanced gestational age in Group A (Fig.3). The perinatal mortality was similar in both groups.

There was one neonatal death in Group A and two in Group B (p = 0.535) which was not statistically different.

**Table 3. Outcome of tocolysis**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nifedipine</th>
<th>Isoxsuprine</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean prolongation of pregnancy</td>
<td>25.71 ± 19.5</td>
<td>19.18 ± 17.82</td>
<td>t = 1.366</td>
</tr>
<tr>
<td>Mean Gestational age at delivery</td>
<td>34.98 ± 2.33</td>
<td>33.46 ± 2.16</td>
<td>t = 2.66</td>
</tr>
<tr>
<td>Mean birth weight (gm)</td>
<td>2383 ± 482.14</td>
<td>2042 ± 412.66</td>
<td>t = 2.823</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>1 (3.13%)</td>
<td>2 (6.66%)</td>
<td>p = 0.535</td>
</tr>
<tr>
<td>Successful tocolysis</td>
<td>26 (81.25%)</td>
<td>21 (70%)</td>
<td>p = 0.301</td>
</tr>
</tbody>
</table>

*Statistically significant: Student’s ‘t’ > 2; p value < 0.05*

The outcome of tocolysis was also analysed according to period of gestation in terms of mean prolongation of pregnancy and gestational age at delivery as shown in Fig. 3a and 3b.

**Fig 3a. Mean Prolongation of Pregnancy**

**Fig 3b. Mean gestational age at delivery**

The side effects noted during tocolysis were headache, flushing, tachycardia (defined as increase in pulse rate by more than 20bpm), hypotension (defined as drop in diastolic BP by more than 15mmHg), nausea, vomiting, palpitations and pulmonary oedema as shown in Fig.4. The commonest side effects were tachycardia (18.75% in Group A and 26.66% in Group B) and hypotension.
(18.75% in Group A and 13.33% in Group B). Pulmonary oedema was noted in one patient receiving Isoxsuprine. She was, however asymptomatic.

In patients with failed tocolysis, postpartum haemorrhage was noted in 1 (16.66%) patient in Group A and 2 (22.22%) patients in Group B.

Discontinuation rates were similar in both groups. Two patients in Group A were discontinued after the second sublingual dose of Nifedipine due to severe hypotension whereas in Group B, one had pulmonary oedema and the other severe hypotension both requiring discontinuation of the Isoxsuprine infusion.

Discussion

Isoxsuprine was the first beta sympathomimetic drug used to inhibit preterm labour in 1961. Many studies have shown it to have limited therapeutic value in light of unpleasant side effects and efficacy.\textsuperscript{1-4} Nifedipine, a calcium channel blocker was first used clinically as a tocolytic by Ulmsten et al.\textsuperscript{5} in 1980. Since then it has emerged as a safe and effective tocolytic.\textsuperscript{6,7} Randomised controlled trials comparing Nifedipine with ritodrine (another betamimetic agent) found it a superior tocolytic both in term of efficacy and safety.\textsuperscript{8-12} It was also found to compare favourably to other betamimetic agents, terbutaline and Isoxsuprine\textsuperscript{2,3,13}. Glock and Morales\textsuperscript{16} compared it with magnesium sulphate in a randomised trial and it was found to have similar efficacy and side effects.

In the present study, successful tocolysis, defined as prolongation of pregnancy by more than 48% during which parenteral corticosteroids were given to hasten lung maturity was achieved in 81.25% with Nifedipine and 70% with Isoxsuprine. Kalita et al\textsuperscript{3} reported a success rate of 84% with Nifedipine and 64% with Isoxsuprine. Tewari et al\textsuperscript{2} considered successful tocolysis as delay of delivery beyond 72 hours and found 56.6% success with Nifedipine versus 50% success with Isoxsuprine (Table 4). Read et al\textsuperscript{7} reported a success rate of 83% with Nifedipine vs.455 with ritodrine. Kuperminc et al\textsuperscript{12} reported 83% success with Nifedipine and 77% with ritodrine.

The mean prolongation of pregnancy in the present study was 25.71\(\pm\)19.85 days with Nifedipine and 19.18\(\pm\)17.82 days with Isoxsuprine. Kalita et al\textsuperscript{3} reported mean prolongation of pregnancy as 31.16\(\pm\)10.2 days with Nifedipine and 23.06\(\pm\)days with Isoxsuprine(Table 4). These results were similar to those reported by Read et al.\textsuperscript{7} Tewari et al.\textsuperscript{2} reported mean prolongation of pregnancy as 39.26\(\pm\)25.5 days with Nifedipine and 25.5\(\pm\)15.75 days with Isoxsuprine.

The present study found a similar incidence of maternal side effects in the two groups, hypotension (18.75% in Group A and 13.33% in Group B) and tachycardia (18.75% in Group A and 26.66% in Group B) being the commonest. However, both drugs were generally well tolerated. The discontinuation rates due to severe side effects were also similar. Kalita et al\textsuperscript{3} have reported a significantly higher incidence of side effects with Isoxsuprine than with Nifedipine and Tewari et al\textsuperscript{2} have reported a much higher incidence of tachycardia in both groups.

Clinical trials with Nifedipine have reported either an insignificant decrease in blood pressure and no change in maternal heart rate\textsuperscript{7,8} or transient hypotension in 14 – 41% of patients.\textsuperscript{10,16} In a
randomised trial between Nifedipine and ritodrine, significantly more side effects were noted with ritodrine. This may in part be attributed to the use of prehydration in the nifedipine regime in this study, hence its inclusion in our study. Glock and Morales also noted transient hypotension in 41% of patients in the Nifedipine group, although it resolve spontaneously in <10 minutes in most patients without evidence of prolonged maternal and foetal symptoms which led them to emphasize the need to ensure proper hydration of patients before starting Nifedipine therapy.

The mean gestational age at delivery and mean birth weight was significantly more in the nifedipine group (34.98±2.33 weeks vs.33.46±2.16 weeks and 2383±482.14 gm vs. 2042±412.16gm ) in our study. Tewari et al reported significantly more term deliveries with Nifedipine but similar mean gestational age and mean birth weight in both groups. Kalita et al reported a mean birth weight of 2.5±0.5kg with Nifedipine and 2.27±0.63 kg with Isoxsuprine. The perinatal mortality was similar in both groups as also noted by others. Clinical trials have demonstrated no deleterious side effects on the foetus with Nifedipine.

In the present situation, the results of meta analyses indicate that a more achievable goal of tocolytic therapy is to delay delivery for at least 48 hours, an important interval during which the mother may be transferred to a tertiary centre for delivery, administer corticosteroids to the mother as well as treat maternal infection when present. These measures have been shown to reduce neonatal morbidity and mortality and aggressive pursuit of these achievable goals may be expected to lead to further improvements in neonatal outcome. Our study found a favourable outcome with nifedipine in this aspect (81.25% v. 70%) though it was not statistically significant.

The reported experience with Nifedipine as a tocolytic has been found to be reassuring. 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 labour.

References

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**On age and ageing**

No body grows old by merely living a number of years; people grow old only by deserting their ideals. Years wrinkle the skin, but to give up enthusiasm wrinkles the soul. Worry, doubt, self-distrust, fear and despair – these are the long years that bow the heat and turn the growing spirit back to the dust.

------Samuel Ullman

It is sad to see so many men and women are afraid of growing old. They are in bondage to fear. Many of them, when they find the first gray hair, are alarmed. Now one really ought not to be alarmed when one’s hair turns gray; if it turned green or blue then one ought to see a doctor. But when it turns gray, that simply means there is so much gray matter in the skull there is no longer room for it, it comes out and discolors the hair. Don’t be ashamed of your gray hair; wear it proudly, like a flag. You are fortunate, in a world of so many vicissitudes, to have lived long enough to earn it.

------William Lyn Phelps

Age is quality of mind,
If you have left your dreams behind,
If hope is cold,
If you no longer look ahead,
If your ambitions fires are dead –

THEN YOU ARE OLD.

But if from life you take the best,
And if in life you keep the jest,
If LOVE you hold;
No matter how the years go by,
No matter how is the birthdays fly –

YOU ARE NOT OLD.

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