Oral nifedipine and parenteral isoxsuprine in arresting preterm labor: A comparative study

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ABSTRACT

Objective: To compare the efficacy of oral nifedipine and parenteral isoxsuprine in arresting preterm labor. Considering the paucity of studies comparing these two agents, a comparative analysis is obligatory. Materials and methods: Eighty antenatal women in the gestational age range of 28–37 weeks, with regular uterine contractions, cervical dilatation ≤3 cm, and <50% cervical effacement, admitted with complaints of preterm labor pain were randomized to receive either 40 mg isoxsuprine or 20 mg nifedipine. Efficacy of the drugs was measured in terms of arrest of preterm labor, prolongation of pregnancy, and the days gained by infant before birth. Results: Isoxsuprine showed increased lowering of systolic blood pressure (SBP), diastolic blood pressure (DBP), and slightly higher maternal pulse rate, but higher fetal pulse rate post-administration in comparison to nifedipine (P < 0.05). Isoxsuprine was significantly associated with more side effects. Pregnancy was more prolonged in the nifedipine group (25 days) than in the isoxsuprine group (19 days) (P < 0.05). The birth weight of neonates in group B was more than that of neonates in group A (P < 0.05). At 5 min after birth, none of the neonates in group B had an Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) abnormal score <7, compared to neonates in group A. Majority of neonates in group A showed tachycardia and respiratory distress syndrome (RDS) (17.5% and 12.5%, respectively), compared to group B (12.5% and 7.5%, respectively). The overall success rate was better in group B (86.8%) compared to group A (80%). Conclusion: Nifedipine was slightly more effective in arresting preterm labor with fewer side effects, compared to isoxsuprine.

Keywords: Gestational Age, isoxsuprine, nifedipine, pregnancy, tocolysis

Introduction

Preterm labor threatens the maternal and fetal health and life and is thus considered the most significant clinical challenge faced by obstetricians globally. The incidence of preterm labor ranges from 8% to 10% globally, accounting for about 80% of neonatal morbidity. India has a very high incidence (23.3%) of preterm labor and preterm delivery (10%–69%). An essential intervention for arresting preterm labor is the use of tocolytics, which relax the uterine myometrium and inhibit uterine contractions by various mechanisms causing arrest of preterm labor. Furthermore, they delay preterm delivery, providing time for administration of antenatal corticosteroids, which cause fetal lung maturity.

Different classes of drugs such as β-agonists are used as tocolytics in the management of preterm labor. They tend to decrease the intracellular calcium ion availability through various mechanisms, causing inhibition of interaction between actin and myosin.

Among them, isoxsuprine relaxes the uterine smooth muscles and arrests preterm labor. Previous studies have demonstrated that isoxsuprine, when administered intravenously along with maintenance therapy (oral administration), is effective in pregnancy prolongation in women at risk of preterm delivery.
Studies have shown that nifedipine suppresses preterm labor with minimum fetal and maternal side effects.[12] Its administration has been associated with decreased blood flow in the uterus, causing fetal hypoxia and acidosis, maternal palplation, and headache, and the safety data is not well established.[13]

The available literature does not contain adequate number of studies comparing the effects of nifedipine and isoxsuprine as tocolytic agents.[14] The better tocolytic agent among the two still needs to be explored. Therefore, the present study focused on comparing the efficacy of oral nifedipine and parenteral isoxsuprine in arresting preterm labor.

Materials and Methods

Study Design

With the institutional ethics committee's approval, this single-centered, hospital-based, prospective, comparative study was conducted in the Department of Obstetrics and Gynecology at a tertiary care hospital in Karad, Maharashtra (EC approval: KIMS/U/EIC/01/2015 dated: 05/03/2015) over a period of 23 months (June 2014–May 2016). A written informed consent was obtained from all the patients included in the study.

Sample Size

Based on the World Health Organization (WHO) data,[8] the estimated prevalence of preterm births globally ranges from 5% to 18%. Hence, considering an average of 11.5% (P) and an error of 10%, the sample size was estimated by using the following formula:

$$N = \frac{4 P Q}{d^2}$$

A minimum sample size of ~39 participants was required for each group. Therefore, to round off, we recruited 40 patients in each group, making a total of 80 patients.

Selection Criteria and Grouping

Eighty pregnant women at 28–35 weeks of gestation, with regular uterine contractions (≥2/10 min, with each lasting for at least 15–25 s), cervical dilatation ≤3 cm, and cervical effacement ≤50% with intact membrane, admitted to the labor room complaining of preterm labor pain with no previous administration of tocolytics in the last 7 days were included in the study. These women were observed to ensure that they were in preterm labor by tracking any cervical change and/or descent of the presenting part. Pregnant women with cervical dilatation ≥4 cm with strong contractions, multiple gestation, antepartum hemorrhage, polyhydramnios, hypo or hyperthyroidism, pregnancy with diabetes mellitus, fetal malformation or complications, heart disease, chronic obstructive pulmonary disease, and bronchial asthma were excluded from the study.

All the patients were randomly allocated to two groups by assigning them odd and even outpatient department (OPD) (outside patient) numbers. Group A (n = 40) received 40 mg isoxsuprine in 500 mL of 5% dextrose at eight drops per minute (0.04 mg/min) and group B (n = 40) received 20 mg nifedipine capsule orally stat.

Data Collection

Data regarding patient's age, parity, previous history of abortions and preterm deliveries, last menstrual period, gestational age, and time of onset of preterm labor was collected from all the patients through interviews before the procedure.

Clinical data such as vital signs, general examination, systemic examination, examination of external genitalia, and per vaginal (PV) examination was also collected.

Study Procedure

Group A (isoxsuprine)

The patients were given 40 mg isoxsuprine in 500 mL of 5% dextrose at eight drops per minute (0.04 mg/min). After every 30 min, the drop rate was increased by eight drops per minute until uterine quiescence was attained or the patient developed adverse effects in the form of maternal tachycardia (>120/min), hypotension (systolic blood pressure [SBP] <80 mmHg or diastolic blood pressure [DBP] <40 mmHg), intolerable nausea and vomiting, or fetal tachycardia (fetal heart rate >160/min). The intravenous drip was continued for 24 h even after attaining uterine quiescence. After discontinuation of intravenous infusion, patients were maintained on intramuscular (IM) isoxsuprine 10 mg/8 h for up to 3 days.

Group 2 (nifedipine)

The patients were given 20 mg nifedipine capsule orally stat, and then 5 mg was repeated every 20–30 min for up to four doses if contractions persisted after giving stat dose (maximum 40 mg dose was administered). Nifedipine 20 mg capsule was given orally every 6 h for not more than 3 days as a maintenance dose.[14]

Patients in both groups were administered antibiotic (dexamethasone) in case of any noted infection. Dexamethasone 24 mg injection was given IM in two divided doses, 24 h apart. Uterine contractions, fetal heart rate, and vital signs were monitored in both the study groups. For vaginal infections, KOH slide test was done to differentiate between candidiasis and vaginosis.

Treatment was considered successful if there was abolition of uterine contractions, no progression of cervical dilatation, and contractions did not recur within 7 days of cessation of therapy. Vitals of the patient (pulse and blood pressure) were monitored every 30 min. Maternal side effects such as tachycardia, hypotension, palpitation, headaches, flushing, nausea, and dizziness, related to the tocolytic agent, were assessed. Data regarding efficacy of the drugs in terms of arrest of preterm labor, prolongation of pregnancy, and the days gained in utero was noted. Details of the mode of delivery, gestational age at the
time of delivery, birth weight, and Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score were also recorded.

**Statistical Analysis**

Statistical analysis was performed by using R software (Version 3.6.0). Data was recorded in Microsoft Excel and expressed as mean ± standard deviation, along with frequency and percentage. Qualitative variables were analyzed using Chi-square test of independence, two-sample proportion test, and paired t-test for continuous variables. Data was considered statistically significant when \( P \leq 0.05 \).

**Results**

Table 1 presents data on the distribution of demographic and clinical variables. Majority of the pregnant women in both the groups were young and multiparous, with low socioeconomic status, and were in their third trimester [Table 1]. Maximum number of patients in both the groups had unfavorable Bishop score for induction of labor, indicating preterm labor pain [Table 1].

None of the symptoms and risk factors were significantly different between groups A and B \( (P > 0.05) \). In group A, three women came with symptoms of burning micturition and two with white vaginal discharge. In group B, two women had symptoms of burning micturition and four women had white vaginal discharge. Abdominal pain was the common symptom observed in all the pregnant women. Infection was the most common risk factor in most of the women in both the groups [Table 2].

In group B, the maximum loading dose of 40 mg nifedipine was required in 13 (32.5%) patients; 35 mg nifedipine was required in eight (20%) patients.

The mean post-drug SBP and DBP were significantly lower in both the groups \( (P < 0.001) \). However, group A showed more lowering of SBP and DBP post-administration in comparison to group B [Table 3]. Similarly, the mean maternal pulse rate and mean fetal pulse rate were significantly higher in both the groups \( (P < 0.001) \). However, group A showed slightly higher maternal pulse rate and mean fetal pulse rate post-administration in comparison to group B [Table 3].

By applying the Z test of difference between two proportions, the proportion of the side effects such as tachycardia and facial flushing was noted to be significantly higher in group A compared to group B \( (P < 0.05) \). Moreover, hypotension, nausea, and vomiting were noted only in group A [Table 4].

A significant difference was noted in terms of gestational age at delivery between the two groups \( (P < 0.05) \) as most of the patients in group A had a gestational age of <37 weeks at the time of delivery, compared to group B [Table 5]. Most of the women in both the groups had vaginal delivery, with group B women having higher number of vaginal delivery than group A. The prolongation of pregnancy was more in group B than group A with a significant difference \( (P < 0.05) \), indicating that nifedipine was more effective in arresting preterm labor and delaying delivery, compared to isoxsuprine [Table 5]. A significant difference was observed between the two groups in terms of birth weight of neonates, as the neonates in group B weighed more than the neonates in group A \( (P = 0.01542) \) [Table 6].

Additionally, majority of the neonates had an abnormal APGAR score \(<7\) at 1 min after birth in both the groups. However, at 5 min after birth, none of the neonates in group B had APGAR score in the abnormal range \(<7\), compared to neonates in group A. Majority of the neonates born in group A showed side effects such as tachycardia and respiratory distress syndrome (RDS) compared to neonates in group B, indicating that isoxsuprine had more side effects on neonates, compared to nifedipine. Due to more cases of RDS and low birth weight, the neonatal intensive care unit (NICU) admissions were more in group A compared...
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Table 3: Changes in the hemodynamic variables pre- and post-drug administration

|                      | Blood pressure (mmHg) | Maternal pulse rate (bpm) | Fetal pulse rate (bpm) | Group A (n=40) (Mean±SD) | Group B (n=40) (Mean±SD) | P     |
|----------------------|-----------------------|---------------------------|------------------------|---------------------------|---------------------------|-------|
|                      | Pre-administration    |                           |                        | Post-administration       |                           |       |
| SBP                  | 122.85±8.73           | 76.40±6.71                | 87.55±4.43             | 115.45±10.30              | 69.85±5.86                | 0.000 |
| DBP                  | 143.55±5.29           |                           |                        | 141.50±4.24               | 143.55±5.29               |       |

Table 4: Maternal side effects in both the groups

| Side effects                  | Group A (n=40) f(%) | Group B (n=40) f(%) | P  |
|-------------------------------|---------------------|---------------------|----|
| Tachycardia (>120 bpm)        | 15 (37.5)           | 7 (17.5)            |     |
| Headache                     | 3 (7.5)             | 2 (5)               |     |
| Hypotension (<90/60 mmHg)     | 4 (10)              | 0                   |     |
| Nausea                       | 2 (5)               | 0                   |     |
| Vomiting                     | 1 (2.5)             | 0                   |     |
| Facial flushing              | 15 (37.5)           | 10 (25)             |     |
| Palpitations                 | 7 (17.5)            | 4 (10)              |     |

Table 5: Comparison of various variables (during delivery) after intervention

| Variables                         | Group A (n=40) f(%) | Group B (n=40) f(%) | P    |
|-----------------------------------|---------------------|---------------------|------|
| Gestational age at delivery (weeks) |                     |                     |      |
| <37                               | 27 (67.5)           | 19 (47.5)           | <0.05|
| >37                               | 13 (32.5)           | 19 (47.5)           |      |
| Lost to follow-up                 | 0                   | 2 (5)               |      |
| Mode of delivery                  |                      |                     |      |
| Vaginal                           | 31 (77.5)           | 32 (80)             |      |
| LSCS                              | 9 (22.5)            | 6 (15)              |      |
| Lost to follow-up                 | 0                   | 2 (5)               |      |
| Prolongation of pregnancy (days)  | (Mean±SD)           | (Mean±SD)           |      |
|                                  | 19.92±11.66         | 24.89±13.66         | 0.021|

Discussion

The most common challenge faced by obstetricians is management of established preterm labor by using pharmacological agents like β-agonists. Therefore, the present prospective study was carried out to compare the efficacy and safety of oral nifedipine and parenteral isoxsuprine in arresting preterm labor.

All the women in both the groups complained of abdominal pain, and some of them had burning micturition along with white vaginal discharge. Infection was the most common risk factor in most of the women in both the groups. Similar observations have been noted in previous studies. Various attempts have been made to design a stratification tool to determine the risk of preterm delivery based on risk factors.

Our study showed that with the oral administration of nifedipine (group B), there was higher reduction of both SBP and DBP (post-administration), compared to isoxsuprine administration (group A). Group A showed slightly higher maternal and fetal pulse rate post-administration in comparison to group B. This is in accordance with the findings of Gurjar et al.'s study.

In a study conducted by Jaju et al., the most common side effects of isoxsuprine were maternal tachycardia, vomiting, and facial flushing, while tachycardia was the major side effect of nifedipine. Furthermore, peripheral vasodilation by isoxsuprine causes decreased peripheral vascular resistance. The tendency of isoxsuprine to cause tachycardia and hypotension is the major limiting factor in its use in comparison to nifedipine for arresting preterm labor.

In this study, the mean duration of prolongation of pregnancy was 25 days in nifedipine group and 19 days in isoxsuprine group, which is in accordance with Singh et al.'s study. This indicates that nifedipine is more successful in delaying delivery, compared to isoxsuprine. Nifedipine is a calcium channel blocker that works by blocking the calcium ions from moving into the uterine muscle cells, thus reducing the ability of the uterine muscles to contract. This, in turn, delays labor and causes prolongation of pregnancy.

Nifedipine group showed more improvement in the APGAR score at 5 min compared to isoxsuprine group, as all the neonates in nifedipine group had an APGAR score of >7 at 5 min. NICU admissions were also more in the isoxsuprine group than in the
nifedipine group due to more cases of low birth weight and RDS. The mean neonatal birth weight, improved APGAR scores, and fewer side effects in nifedipine group are in agreement with other studies. This comparatively high incidence of RDS, tachycardia, and low APGAR score in the isoxsuprine group could be due to the direct transplacental passage of the drug and a direct effect on the fetal myocardium, resulting in adverse neonatal outcomes after birth. \[16\]

The overall success rate was more in the nifedipine group (86.84%) compared to the isoxsuprine group (80%), indicating that nifedipine was more effective in arresting labor compared to isoxsuprine. Similar observations were made in previous studies. \[16][17\]

In the present study, the tendency of isoxsuprine to cause tachycardia and hypotension is the major limiting factor in its use in comparison to nifedipine for arresting preterm labor, and it should be given prime importance. In addition, nifedipine showed improvement in the APGAR score at 5 min as well. This indicates that nifedipine not only delays preterm delivery, but also decreases the chances of cesarean delivery by helping the women achieve full term. The study did not include twin pregnancies. Large-scale, randomized, controlled studies are warranted to substantiate the results.

**Conclusions**

Nifedipine was successful in prolonging pregnancy by 25 days with uterine quiescence more frequently than isoxsuprine, with an overall success rate of 86.84%. Additionally, it was slightly more effective than isoxsuprine in preventing delivery by cesarean section. It caused fewer maternal side effects like RDS and tachycardia compared to isoxsuprine, due to which it was better tolerated. NICU admissions and perinatal side effects were also less with nifedipine. Hence, nifedipine is recommended for use in arresting preterm labor.

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**Conflicts of interest**

There are no conflicts of interest.

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