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Study to compare safety and efficacy of nifedipine and isoxsuprine in suppression of preterm labour

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Abstract
Preterm birth and its consequences constitute a major health problem in India and worldwide imposing a huge burden on the healthcare cost as preterm labor is one of the leading causes of perinatal mortality and morbidity. This prospective randomized study has compared the safety and efficacy of 2 widely used tocolytics, Nifedipene and Isoxsuprine. 82% of patients who received nifedipine achieved successful tocolysis. While only 72% of patients who received Isoxsuprine received successful tocolysis. Maternal side effects like tachycardia, hypotension and pulmonary edema were more frequently observed in patients receiving isoxsuprine than those receiving nifedipine. This study proves nifedipene to be a better tocolytic than Isoxsuprine in terms of mean gestational age at birth, success rate and side effects.

Keywords: Tocolytic, nifedipene, isoxsuprine, tidilan, preterm, safety, efficacy

Introduction
Preterm labor is defined as regular uterine contractions occurring at least once every 10 minutes and resulting in cervical dilatation or effacement before 37 weeks' gestation. Preterm birth and its consequences constitute a major health problem in India and worldwide imposing a huge burden on the healthcare cost as preterm labor is one of the leading causes of perinatal mortality and morbidity. Children who are born prematurely have higher rates of cerebral palsy, sensory deficits, learning disabilities and respiratory illnesses compared with children born at term. The morbidity associated with preterm birth often extends to later life, resulting in enormous physical, psychological and economic costs. Of all early neonatal deaths (deaths occurring within first 7 days of life) that are not related to congenital malformations, 28% are due to preterm birth. Delaying preterm labor has been tried by physicians since long. Tocolytic drugs inhibit contractions and delay delivery in the hope of improving survival and preventing handicap. Simultaneous administration of glucocorticoids promotes fetal lung maturation and antibiotics help to treat infections, if present.

Methodology
A prospective randomized study was carried out at C. U. Shah Medical College and Hospital hospital from January 2017 to January 2018 on 100 patients with preterm labor. A total of 100 cases of preterm labor who fulfilled the inclusion and exclusion criteria were selected. These 100 cases had been randomly allocated into 2 groups, Group A and Group B of 50 cases each and were matched appropriately.

Inclusion Criteria
1. Patients with pregnancies between 28 to 37 weeks gestation
2. Regular uterine contractions with or without pain (at least one in every 10 minutes)
3. Presence of cervical changes in form of effacement and dilatation (not exceeding 3 cm); even minimal cervical changes are taken into consideration.

Exclusion Criteria
1. Parturients suffering from uncontrolled diabetes, thyrotoxicosis, severe hypertension, cardiac disease, placenta previa or abruption, anemia.
2. Parturients with fetal distress, fetal death, fetal anomalies, chorioamnionitis, and pregnancy beyond 36 weeks.

3. Patients in advanced stage of labor.

Method of tocolysis

(Group A) Nifedipene

Patients were preloaded or prehydrated with 500ml of crystalloid solution infused over 30 – 45 minutes and then maintained at 100ml / hour in order to prevent hypotension caused by nifedipine. A loading dose of 10 mg nifedipine was then given orally and repeated upto maximum 4 doses over an interval of 20 minutes till contractions cease. Once uterus is quiescent, a maintenance dose of nifedipine 10-20 mg orally every 6-8 hourly is started for not more than 7 days.

(Group B) Isoxsuprine

Patients were put on infusion of Inj. Isoxsuprine 40mg in 500ml of lactated ringer solution at rate of 0.08mg/min, increasing up to 0.24mg/min depending on the status of uterine contractions and occurrence of side effects. Once uterus is quiescent patient is put on oral isoxsuprine 10 mg 8 hourly for up to 7 days.

Monitoring

Patients pulse, Blood pressure, FHS and uterine contractions were monitored till patient was admitted and later on patient was discharged on maintenance doses. Apart from tocolytics, pateints were given antibiotics, Injection Betamethasone.

Patients whose labor got delayed by >48 hours were considered successful.

Results

In this study, incidence of unbooked (59%) cases was more than that of booked (41%) cases. Most of the booked cases had attended antenatal OPD regularly and had undergone required investigations.

Table 1: *Comparision in terms of prolongation of days*

Drugs	Prolongation of Pregnancy in Days								Mean
	0-2 (<48Hrs)	2-7	8-14	15-21	22-28	29-35	36-42	>42	
Isoxsuprine	14	01	02	04	06	06	08	09	24.3654
Nifedipine	08	00	05	01	01	8	09	18	32.1356

As evident from table 1, mean prolongation of pregnancy with isoxsuprine is 24.3654 days with a standard deviation of 18.1071 days and with nifedipine is 32.1356 days with a standard deviation of 20.1595 days. Statistical analysis was done using unpaired student's (2 tail) t-test. P-value was found to be 0.044 which is < 0.05, hence statistically significant.

Table 2: *case distribution according to mean birth weight*

Drugs	Mean birth weight in Kg						Mean weight
	1.6 to 1.79	1.8 –to 1.99	2.0 to 2.19	2.2 to 2.39	2.4 to 2.59	2.6 to 2.8	
Isoxsuprine	04	13	19	12	02	00	2.02 kg
Nifedipene	00	09	18	16	05	02	2.17 kg

As evident from table 2 mean birth weight with isoxsuprine is 2.0221 Kg with a standard deviation of 0.3662 Kg and with nifedipine is 2.1705 Kg with a standard deviation of 0.3884 Kg. Statistical analysis was done using unpaired student's (2 tail) t-test. p value was found to be 0.049 which is < 0.05, hence statistically significant.

Table 3: *Case distribution according to gestational age*

Drugs	Mean gestational Age at delivery in weeks					Mean Gest Age
	28 to <30	≥30 to <32	≥32to <34	≥34 to <36	≥36	
Isoxsuprine	08	10	12	07	13	32.38
Nifedipene	02	07	09	14	18	33.80

As evident from table 3, mean gestational age at birth with isoxsuprine is 32.28 weeks with a standard deviation of 2.7108 weeks and with nifedipine is 33.80 weeks with a standard deviation of 2.5951 weeks. Statistical analysis was done using unpaired student's (2 tail) t-test. p value was found to be 0.005 which is < 0.05, hence statistically significant.

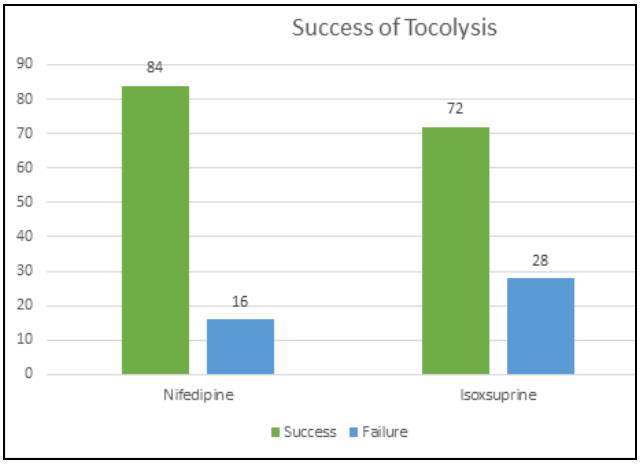

Fig 1: *Success of tocolysis*

As it is evident from figure1, patients on nifedipine had an 82% success rate, while patients on Isoxsuprine had just 72% success rate.

Discussion

Isoxsuprine has been used for years together as a tocolytic without going questioned. Studies have failed to appreciate its true potential [1-4]. A prospective randomized study was conducted from January 2017 to January 2018 on 100 patients with preterm onset of labor. To suppress preterm labor, tocolytics were administered. Data was collected. Following observations were recorded. Detailed analysis has been done and the results have been compared with the statistics available from Indian authors and other authors around the world.

Table 4: *Success rates according to different studies*

Studies	Nifedipene	Isoxsuprine
Prerna Jain *et al*. [5]	90%	76%
Rayamajhi R *et al*. [6]	81.25%	70%
Nisha Singh *et al*. [7]	80%	68%
Seema BN *et al*. [8]	96%	75%
Farzana Zakir *et al*. [9]	100%	70%
Present Study	84%	72%

As it is evident from table 4, in this study success rates with nifedipine is 84% and with Isoxsuprine is 72%. Other studies from India have shown similar success rates for both drugs.

Table 5: *Prolongation of pregnancy according to different studies*

Studies	Nifedipene	Isoxsuprine
Rayamajhi R *et al*. [6]	25.71±19.5 days	19.18±17.82 days
Prerna Jain *et al*. [5]	22.4±15.6 days	16.5±4.5 days
Seema BN *et al*. [8]	31.68 days	27.54 days
Farzana Zakir *et al*. [9]	46.13±17.78 days	27.34±20.60 days
Present Study	32.13±20.15 days	24.36±18.10 days

The mean prolongation of pregnancy in the present study is 32.13 ± 20.15 days for nifedipine and 24.36 ± 8.10 days with p value < 0.05. According to study by Prerna Jain *et al*. [32], mean prolongation of pregnancy is 22.4±15.6 days for nifedipine and 16.5±4.5 days for isoxsuprine According to study by Seema BN *et al*. [35], mean prolongation of pregnancy is 31.68 days for nifedipine and 27.54 days for isoxsuprine. According to study by Farzana Zakir *et al*. [36], mean prolongation of pregnancy is 46.13±17.78 days for nifedipine and 27.34±20.60 days for isoxsuprine All other studies mentioned here have a greater prolongation with nifedipine which is similar to present study. This denotes that nifedipine is more efficacious than isoxsuprine in terms of prolongation of pregnancy.

Table 6: *Comparison of birth weight according to different studies*

Studies	Nifedipene(Group A)	Isoxsuprine(Group B)
Rayamajhi R [6]	2.38±0.48 Kg	2.04±0.41 Kg
Farzana Zakir [9]	2.618±0.366 Kg	2.156±0.62 Kg
Present Study	2.17±0.38 Kg	2.02±0.36 Kg

In present study, the mean birth weight in group A is 2.17±0.38 Kg, while mean birth weight in group B is 2.02±0.36 Kg. According to study conducted by Rayamajhi R[6], mean birth weight in group A is 2.38±0.48 Kg, while mean birth weight in group B is 2.04±0.41 Kg. According to study conducted Farzana Zakir mean birth weight in group A is 2.618±0.366 Kg, while mean birth weight in group B is 2.156±0.62 Kg. In present study, the mean birth weight achieved at birth using nifedipine as a tocolytic is more than the mean birth weight achieved at birth using Isoxsuprine. Similar results were obtained in other studies carried out previously.

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