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TO COMPARE THE EFFECTIVENESS AND SAFETY OF NIFEDIPINE WITH BETA-SYMPATHOMIMETICS FOR SUPPRESSION OF PRETERM LABOUR

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Abstract:
Objective: *Preterm labour is defined as onset of labour after 24 weeks and before 37 completed weeks of gestation. About 13 million preterm births occur worldwide annually. Aim of the study was to compare the effectiveness and safety of Nifedipine with beta-sympathomimetic for suppression of preterm labour.*
Study Design: *Quasi-Experimental study.*
Place and Duration of Study: *This study was conducted at the Obstetrics and Gynecology Department of Jinnah Hospital Lahore for the duration of one year from July, 2019 to June, 2020.*
Materials and Methods: *A total of 120 admitted pregnant women in preterm labor were studied. Patients were divided into two groups of 60 each. The patients presenting with regular painful uterine contractions at frequent intervals and with appreciable cervical change, at gestation > 24weeks or < 37 weeks were admitted for tocolysis. Two groups were formed by using random numbers table. Group A was given Nifedipine and Group B was given Beta-sympathomimetic drug i.e. Terbutaline. All relevant information was written on proforma.*
Results: *During study period, 120 patients were enrolled. 60 patients were randomized to Nifedipine and 60 to Beta sympathomimetic treatment. The age distribution, gravidity and gestational age were same in both groups. Tocolysis was successful in 93 % of patients in Nifedipine group and 67 % of patients in Beta sympathomimetic group. It failed in 7% and 33% in Nifedipine and Beta sympathomimetic groups respectively. The mean gestational age achieved at delivery was 32.67 ± 2.248 and 32.43 ± 2.473 in Nifedipine group and Beta sympathomimetic group respectively. Nifedipine caused effective tocolysis in 83% patients within 24 hours whereas Beta sympathomimetic caused it in only 56% patients within 24 hours. Hypotension was the commonest side effect seen in 17% of patients in Nifedipine group and 43% in Beta sympathomimetic group. Tachycardia was observed in 70% of the patients and vomiting was observed in 12% of patients in Beta sympathomimetic group.*
Conclusion: *Nifedipine is more efficacious and safe as compared to Beta sympathomimetic in suppression of preterm labour with lesser side effects.*
Key Words: *Preterm labour, Prematurity, Cervical incompetence, Tocolysis.*

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INTRODUCTION:

Preterm labour is defined as onset of labour after 24 weeks and before 37 completed weeks of gestation.[1] About 13 million preterm births occur worldwide annually.[2] The incidence of preterm labour ranges from 5% in developed countries to 25% in developing counteries.[3] It is considered one of the major causes of perinatal morbidity and mortality and 70-80 % of perinatal deaths are due to preterm labour.[4],5 The perinatal mortality falls with advancing gestational age from being 66% at 28-31weeks, 38% at 32-33 weeks to 20% at 34-36 weeks.[6] Causes of preterm labour include smoking, previous or family history of preterm birth, psychological stress, multiple pregnancy, anemia, polyhydromnios, antepartum haemorrhage, uterine and fetal anomalies, trauma, medical disorders, systemic, vaginal and urinary tract infections, cervical incompetence, premature rupture of membranes.[1,3,7,8]

Regular uterine contractions at frequent intervals and documented cervical change or appreciable cervical dilatation or effacement are diagnostic.[9] Management includes bed rest, hydration, sedation, corticosteroid therapy, tocolysis, rescue cerclage and antibiotics. [8, 10] Tocolytics are the drugs used to suppress uterine contractions.[11] Aim is to enable transfer of mother to tertiary care center and to prolong pregnancy sufficiently so that corticosteroids can be given to enhance fetal lung maturity.[12] No studies have shown that tocolysis can improve fetal outcome. [13] A variety of tocolytic drugs are available including beta sympathomimetic (salbutamol, terbutaline, ritrodine), prostaglandin synthesis inhibitors,magnesium sulphate, progestins, cyclooxy genase inhibitors, calcium channel blockers (nifedipine), nitric oxide donors (glyceryl nitrates) and oxytocin receptor antagonists (atosiban).[7,14]
Beta-sympathomimetics, a phenylthylamine derivative, which was introduced in 1971 for obstetric use and was approved by FDA for tocolysis. [14] It relaxes uterus and uterine vessels.[9] These can be given orally or parentally. Maternal risks include palpitations, tremors, nausea, headache, tachycardia, hypotension, chest pain, hyperglycemia, hypokalemia and pulmonary oedema.[7-10],14 Fetal risks include tachycardia, hypoglycemia, ileus and intra ventricular hemorrhage.[7,9,14] Contraindications include cardiac disease, hyperthyroidism, uncontrolled hypertension or diabetes, asthma, and chronic hepatic or renal diseases.[9]

Nifedipine is calcium channel blocker and inhibits influx of calcium into myomatrial and other cells and reduces muscle contraction.[9] It can be given by mouth or sublingually. Various forms include immediate-release capsules of 10 mg and extended-release tablets of 20, 30, 60 and 90 mg.[14] Maternal risks include hypotension, tachycardia, headache, flushing and vomiting.[9,14] Fetal risks include tachycardia and hypotension.[10] Caution should be taken when the maternal cardiovascular condition is compromised, such as with intrauterine infection, twin pregnancy, maternal hypertension, cardiac disease, hyperthyroidism.[14]

MATERIALS AND METHODS:

The Quasi- experimental study was carried out in the Obstetrics and Gynecology Department of Jinnah Hospital Lahore for the duration of one year from July, 2019 to June, 2020.

Data Collection: After history, examination and investigations two groups were formed by using random numbers table. Group A was given Nifedipine 20 mg (Adalat retard) stat by mouth then 10mg every 6 hours until the patient was well tocolyzed. Group B was given beta-sympathomimetic drug i.e. Terbutaline (Bricanyl) by intravenous infusion containing 5 ampules of Terbutaline (0.5mg/1ml ampule) in 500ml of normal saline solution initially at the rate of 8-10 drops per minute. The dose was titrated with reference to suppression of contractions, increase in pulse rate and change in blood pressure. A maternal heart rate of more than 135 beats /min was avoided. The patients were tocolysed by one of these drugs for maximum period of 48hours. Fetal heart was monitored half hourly. Monitoring of pulse rate, blood pressure and uterine contractions were done initially hourly for 4-6hrs then 4 hourly. If uterine contractions persisted then vaginal examination was repeated after 2 hours. Duration of tocolysis was also noted. Side effects like nausea or vomiting, tachycardia and hypotension were observed.

Inclusion Criteria: The patients presenting with regular uterine contractions at frequent intervals and or with appreciable cervical change, at gestation > 24weeks or < 37 weeks were admitted for tocolysis and included in study.

The exclusion criteria: Patients with cardiovascular disease, cervical incompetence, intrauterine infections, twin pregnancy, maternal hypertension or severe pre-eclampsia, placental abruption, diabetes mellitus and hyperthyroidism were excluded from study.

Data Analysis: All data was analyzed on SPSS version 10. Side-effects i.e. vomiting, tachycardia and hypotension were presented by frequencies. Mean ± S.D. were calculated for age of patient and duration of tocolysis. For comparison of qualitative variables (vomiting, tachycardia and hypotension) chi-square test was applied. P <0.05 was taken as statistically significant.

RESULTS:

During the study period 120 patients were enrolled in the study; 60 were allocated to Nifedipine (Group A) and 60 received Terbutaline (Beta sympathomimetic - Group B).

The age distribution among the two groups was found to be similar. In both the groups most of the patients i.e. 28 (47%) were in the age group 25-30 years. Nifedipine group (Group A) included 20 (33%) patients whereas Beta sympathomimetics group (Group B) included 24 (40%) patients in the age group between 20-25 years. The mean age of the patients was 27.40 ± 4.49 years in Nifedipine group and 27.40 ± 4.09 years in Beta sympathomimetics group with p value of 1.000. (Table 1)

Table No.1: Comparison of demographic profiles of patients in two groups:

Parameter	Nifedipine (mean ± std) (n=60)	Beta Sympatho-mimetics (mean ± std) (n=60)	P-Value
Age (years)	27.40 ± 4.492	27.40 ± 4.098	1.000
Gestational age (weeks)	32.67 ± 2.248	32.43 ± 2.473	0.704
Gravidity	2.56 ± 1.165	2.80 ± 1.672	0.593

The gestational age between the two groups was also taken into consideration. In Nifedipine group 18 (30%) patients were < 32 weeks of gestation whereas in Beta sympathomimetics group 16 (27%) patients were of same gestational age. In Nifedipine group 28 (47%) patients were between 32-34 weeks and in Beta sympathomimetics group 32 (53%) were of same gestational age. In Nifedipine group 14 (23%) patients were > 34 weeks of gestational age whereas 12 (20%) in Beta sympathomimetics group were of same gestational age. The mean Gestational age of the patients who presented with preterm labour was 32.67 ± 2.248 years in Nifedipine group and 32.43 ± 2.473 years in Beta sympathomimetics group with p value of 0.704.

The mean gravidity of the patients who presented with preterm labour was 2.56 ± 1.165 in Nifedipine group and 2.80 ± 1.672 in Beta sympathomimetics group with p value of 0.593. (Table 1)

Effectiveness of tocolysis was studied in these groups. Tocolysis was successful in 56 (93%) patients of Nifedipine group and 40 (67%) of Beta sympathomimetics group. It failed in 4 (7%) patients of Nifedipine group and 20 (33%) patients of Beta sympathomimetics group. The difference in response between the two treatment groups was statistically significant with P- value of 0.0098. (Table 2)

Table No.2: Comparison of Efficacy of Drugs in both groups

Drugs	Successful		Failed		P Value
	n	%	n	%	
Nifedipine (n=60)	56	93	4	7	
Beta-Sympatho-mimetics(n=60)	40	67	20	33	0.0098

In Nifedipine group tocolysis was achieved successfully within 12 hours of administration of drug in 22 (36%) patients and 02 (03%) patient of Beta sympathomimetics group. Tocolysis was established between 13-24 hours in 30 (50%) patients in Nifedipine group and 20 (33%) patients in Beta sympathomimetics group. Tocolysis was achieved between 25-36 hours in 02 (03%) patient in Nifedipine group and 06 (10%) patients in Beta Sympathomimetics group. Tocolysis was established in 37-48 hours in 02 (03%) patient in Nifedipine group and 12 (20%) patients in

Beta sympathomimetics group. Tocolysis was unsuccessful in 4 (07%) patients in Nifedipine group and 20 (33%) patients in Beta sympathomimetics group. The mean duration of achievement of tocolysis was 13.67 ± 10.886 hours in Nifedipine group and 35.63 ± 13.319 hours in Beta sympathomimetics group with p value of 0.000.

Very few side effects were seen in both groups, commonest being hypotension. It was seen in 10 (17%) patients in Nifedipine group and 26 (43%) patients in Beta sympathomimetics group with p value of 0.0798. Other side effects are shown in table 3.

Table No. 3: Comparison of complications of two groups:

	Nifedipine (n=60)		**Beta Sympatho-mimetics (n=60)**		
Side Effects	**Yes (n)**	**%**	**Yes (n)**	**%**	**P Value**
Vomiting	02	03	24	40	0.00056
Tachycardia	02	03	42	70	0.00000
Hypotension	10	17	26	43	0.0798

DISCUSSION

Preterm birth is the leading cause of neonatal mortality and the most common reason for antenatal hospitalization.[14] Reduction in the rate of preterm birth can decrease neonatal morbidity and mortality and as obstetrician we need to find effective and safe method to prolong pregnancy. On reviewing the national as well as international literature many studies were found in which different tocolytic agents were compared with each other. Nifedipine was introduced as a tocolytic agent at a time when beta-agonists and magnesium sulphate dominated the arena for the prevention of preterm birth. The oral rout of administration, availability of immediate and slow-release preparations, low incidence of (mild) side effects and its limited costs explain the attraction to this medication from the obstetric field and its rapid and widespread distribution. However no study have shown that tocolysis can improve fetal outcome. [13]

In my study the two drugs Nifedipine and Beta sympathomimetics were compared with each other to find out a safe and effective tocolytic agent to reduce the neonatal morbidity and mortality.

The association of preterm birth with extremes of maternal age was not significant in my study as most of the patients (47% in Nifedipine and Beta sympathomimetics group) in our study were in the range of 26-30 years. This is comparable to study done in India in 2017 by Dr Burkha Gujjar who compared Nifedipine, Ritrodine and Isoxsuprine as to colytic agent and majority of cases were between 21-25 years of age.[15] Similarly a study by Nadeem Shahzad also showed that 51.7 % patients in Nifedipine group and 43.3 % patients in terbutaline group were between 21-30 years of age.[16] Mean age of patients who presented to preterm labour in our study was 27 years in both groups and this is comparable to other studies. [15,16,17,18] While comparing parity of patients in both groups, in my study, 60% patients in Nifedipine group and 53 % in Terbutaline group were G2-G3.This is comparabale to study by Nadeem Shahzad [16].However contrasting results are shown by Bai G D where 66.7 % patients in Nifedipine group and 56.7 % in Ritrodine group were primigravida [17]

In our study, efficacy was defined as prolongation of pregnancy for ≥ 48 hours. It was achieved in 93 % of patients in Nifedipine group and 67 % patients in Terbutaline group and difference is statistically significant (p value 0.0098). A study in India also showed success rate of 80% and 68% in both groups. [15] However contrasting results were shown in a study done by Kiren K. Malik in which tocolytic success rate was only 40% with Nifedipine and 30 % with beta agonist group. [18] Two systematic reviews compared efficacy of Nifedipine and Ritrodine. In one review 607 women and in other review 679 women were compared. In both reviews Nifedipine was more effective in prolonging pregnancy > 48 hours [19, 20] A meta-analysis in 2002, reviewed 12 randomized-controlled studies involving 1029 women and found that Nifedipine is more effective than Ritrodine and is more safe. Because each individual trial has been small, this is the best evidence to date that nifedipine can be used for tocolysis. Cessation of treatment due to adverse reaction occurred in 1 of

419 patients, vs. 29 of 414 with other tocolytic. In our study no patient had such an adverse effect to stop the treatment. Van De MW, also compared both agents and concluded that Nifedipine is more effective. However, when they evaluated efficacy on basis of prolongation of labour and delaying fetal birth ,it showed that birth was delayed for an average 5.0 weeks with Nifedipine and 4.3 weeks with Ritrodine (p value 0.4) Both tocolytic agents have fetomaternal side effects. Nifedipine has fewer side effects as compared to Terbutaline. In our study, while comparing maternal side effects, vomiting, tachycardia and hypotension was more profound with Terbutaline as compared to Nifedipine. Same results were shown by an Indian study in 2017 where none of the patient treated with Nifedipine had hypotension and fetal tachycardia and 10% patients in Ritrodine group had hypotension and fetal tachycardia. Overall side effects were 20% in nifedipine group and 28% in ritrodine group. [15] A study conducted in 2011 also concluded that overall side effects were 30% (especially headache) in Nifedipine group were and 80% (especially palpitations) in Salbutamol group.

CONCLUSION:

On the basis of better efficacy and lesser complications with Nifidepine as compared to Beta sympathomimetics, it is concluded that Nifedipine can be used with more confidence and safety as compared to Beta sympathomimetics for tocolysis.

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