Original Article

COMPARISON BETWEEN NIFEDIPINE AND RITODRINE AS AN EFFECTIVE TOCOLYTIC AGENT FOR PRETERM LABOUR

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Abstract

Background: Preterm labour is not uncommon and its incidence is 10% of all the pregnancies. It can be a cause of maternal and fetal morbidity and mortality. Of many available tocolytic agents, ritodrine is frequently used but it can leads to maternal and fetal complications which include tachycardia or hypertension. Nifedipine is considered to avoid from these complications. However, its efficacy is still under debates.

Objectives: The objective of the study was to compare the efficacy of nifedipine with ritodrine in tocolysis of preterm labor.

Study Design: It was a randomized controlled trial.

Place and Duration of Study: This study was conducted at unit 111 Lady Willingdon Hospital Lahore and duration was one year from 1.1.2014 to 31.12.2014.

Methodology: One hundred and twenty patients were randomly divided in two equal groups. Group A patients were given nifedipine and in group B received ritodrine for prolongation of labor. The two groups were compared with each other for efficacy. Data was collected on a specially designed Performa.

Results: The efficacy of nifedipine was 71.1% and ritodrine was 31.1%. The results were statically significant (p-value < 0.05).

Conclusions: Nifedipine was proved to be more effective than ritodrine and the results were statistically significant

Key Words: Preterm labor; ritodrine; nifedipine; prolongation of labor.

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Introduction

Traditionally the definition of Preterm labor is the occurrence of regular uterine contractions before 37 completed weeks of gestation. This is one of the major causes of perinatal mortality and morbidity.[1] The reported incidence of preterm delivery by different studies lies between 5% to 10% of pregnancies but it is responsible for 70 – 80% of perinatal deaths.[1,2]

Even after the dedicated efforts, spending lot of money and inclusion of new medications for the management, neonatal mortality rates in the developed countries are still high i.e. 5 per 1,000 babies in United

States.[3]

The exact etiology of preterm labor is unknown but there are certain causative factors which are supposed to be associated with the onset of preterm labor, which include decidual hemorrhage due to placental abruption, over distension of uterus from multiple gestation or by polyhydramnios, cervical factors like cervical incompetence or cervical trauma due to forceful dilatation and Curettage or local procedure like cone biopsy, congenital uterine abnormalities and other conditions like fibroid uterus leading to uterine distortions and genital tract infections such as bacterial vaginosis. Maternal fever due to urinary tract infection, hormonal changes mediated by maternal or fetal stress and finally the uteroplacental insufficiency like hypertension, drug abuse, smoking, alcohol consumption and insulin dependent diabetes.[4]

Perinatal morbidity and mortality due to prematurity can be reduced if there is a clear agreement and understanding of the etiology, mechanism of preterm labour and psychological risk factors responsible for the preterm labor. There is also a need for accurate identification of pregnant women at risk for premature labor and delivery. It has been proved by the recent studies that early identification of the pregnant women having risk of preterm labor and if they are timely referred to obstetrical units dedicated for the management of such labors decrease the extreme prematurity (< 32 wk) rate, ultimately reducing the perinatal morbidity and mortality due to preterm delivery and the cost involved for the care of such babies.[5]

The major aim of management of preterm labor is twofold, firstly to inhibit the uterine contractions so that the mother can be transferred to a centre where the best neonatal intensive care facilities are available, secondly to prolong the pregnancy for at least 48 hours so that corticosteroid can be effective to enhance fetal lung maturity. No studies have shown that tocolysis can improve infant outcomes.[6] Three kinds of drugs are used for this purpose which are tocolytics, antibiotics (though controversial) and corticosteroids.[7]

There are number of tocolytics available which include beta mimetic, prostaglandin synthetase inhibitors, calcium channel blockers, oxytocin receptor antagonist, magnesium sulphate and uterine myometrial relaxant like nitric oxide donor.[8] Among these, beta-adrenergic agonists like Ritodrine (trade name Yutopar) is utilized in the form of oral tablets or as an injection, and is typically used as the hydrochloride salt, ritodrine hydrochloride. It is widely used but is associated with potential side effects of maternal tachycardia, hypertension, palpitations and ischemic condition of heart.[9] B-adrenergic – receptor agonists rapidly cross the placenta and this transfer induces a stimulated β-adrenergic state in the fetus. This evokes roughly the same effects as it does in the mother. Fetal tachycardia is the most observed effect after initiation of treatment. In the long term effects, follow-up studies of infant and child development after in utero exposure of ritodrine showed no difference between these children and unexposed controls or when compared to nifedipine exposure.[10]

Nifedipine is claimed to avoid from these complications. However, it is not frequently practiced routinely.[11] Nifedipine (Adalat Retard) is type 2 calcium channel blocker which reduced calcium influx into the cells and delays delivery with a reduced risk of respiratory distress syndrome (RDS).[12] The recommended protocol of Nifedipine consists of 20 mg orally stat, followed by 20 mg orally after 30 minutes if contractions persist, followed by 20 mg orally every 3 – 8 hours.[13]

This study was designed for the comparison of the efficacy of nifedipine and ritodrine in tocolysis for preterm labor, Efficacy was described as ability to produce a desired effect by prolongation of labor for more than 48 hours.

Material and Methods

Randomized controlled trial was carried out in department of Obstetrics and Gynaecology unit 111 Lady Willingdon Hospital Lahore and duration was one year from 1.1.2014 to 31.12.2014. One hundred and twenty cases were recruited for the study (divided in two groups, 60 cases in each group) by non probability sampling technique taking Expected percentage of delay of preterm delivery was 48 hour i.e. 60% with nifedipine and 30% with ritodrine taking 96% power of the study, 5% margin of error and 95% confidence interval.

Inclusion Criteria was Patients with singleton pregnancy between 28 – 36 completed weeks of gestation on dating scan, intact membranes on speculum examination Preterm labor defined "as regular uterine contraction of at least 1 in 10 min during at least 1 hour with or without dilatation and effacement".

Exclusion Criteria: Presence of fetal distress, multiple pregnancies, fetal malformation requiring termination, Suspected chorioamnionitis, ruptured memb-

ranes with history of leaking, 1st or 2nd trimester vaginal bleeding/ proteinuric hypertension with (BP > 140/ 90) and sever preeclampsia. Mothers with cardiovascular disease, hyperthyroidism, with hypovolemia, diabetes mellitus, and asthma determined on history clinical examination and previous investigation.

After approval by research and ethical committee and written informed consent by patients in labor room, 120 women with singleton pregnancy were selected who full field the inclusion criteria being divided into two groups by using the random number table.

Nifedipine in (Group A) and Ritodrine (Group B) were kept under observation for 72 hours. Uterine activity cessation was noted. Nifedipine was given in the dose of 20 mg orally followed by 20 mg orally after 30 minutes if contractions persisted, followed by another 20 mg orally 12 hourly for 48 hours. Ritodrine by intravenous infusion (150 mg i.e. 3 ampoules in 500 cc of 5% dextrose gave 300 ug ritodrine/ml) started at the rate of 50 ug/minute until contraction stopped. Oral treatment was given for 3 day in all. Maternal outcome to be assessed was prolongation of labor for more than or equal to 48 hours.

All this information was recorded in a specially designed Performa .Analysis of the data was done by SPSS version 16.0. $P < 0.05$ was considered a significant. Quantitative variables as age, parity were presented as mean ± SD. Qualitative variables like group (A/B), labor prolongation for 48 hours (yes/no) were presented as frequency and percentage.

Results

In group A, 60 patients were included. The mean age of the patients in group A was 26.67 ± 5.08 years (range 18 – 35). Of these, there were 11 (18.3%) patients with the age ≤ 20 years, 31 (51.7%) patients with the age 21 – 30 years, 18 (30%) patients with the age 31 – 40 years (Table 1).

The mean age of the patients was 25.98 ± 5.62 years (range 18 – 35) in Group B. Among the 60 patients included in group B, there were 15 (25%) patients with the age ≤ 20 years. There were 26 (43.3%) patients of the age range from 21 – 30 years and 19 (31.7%) patients of the age range of 31 – 40 years. (Table 1).

Of the total 60 patients in group A, there 9 (15%) patients who were primigravida and 51 (85%) patients who were multigravida. None (0%) patients were grand multipara (Table 2).

Among the 60 patients in group B, there were 11 (18.3%) patients who were primigravida. There were 49 (81.7%) patients who were multigravida and 0 (0%) patients who were grand multipara (Table 2).

As long as distribution of patients for the parameter of the prolongation of labor for 48 hours was concerned. Of the 60 patients in group A, prolongation of labor for 48 hours was seen among 43 (71.1%) patients, while in 27 (28.8%) patients it was not observed (Figure 1).

There were 19 (31.7%) patients in whom the prolongation of labor for 48 hours was observed in Group B, while in 41 (68.3%) patients, no prolongation of labor was seen (Figure 1).

Regarding Efficacy of both groups. In group A, the efficacy of the drug (Nifedipine) was observed in 43 (71.1%) patients, while in 27 (28.8%) patients, the drug was not effective (Figure 2). While in groups B, there were 19 (31.7%) patients in whom the drug (Ritodrine) was found effective, while in 41 (68.3%) patients, the drug was not effective (Figure 2).

When two groups were compared regarding efficacy of drugs, Nifedipine was better than Ritodrine. The results were statistically significant ($P < 0.05$).

Table 1:
Distribution of patients by age (n = 120).

Age in Years	Group A		Group B	
	Patients No	Percentage	Patients No	Percentage
≤ 20	11	18.3	15	25
21 – 30	31	51.7	26	43.3
31 – 40	18	30	19	31.7
Mean + SD	26.67 ± 5.08		25.98 ± 5.62	
Range	18 – 35		18 – 35	

Table 2:
Distribution of patients by Parity
(n = 120)

Parity	Group A		Group B	
	Patients No (n = 60)	Percentage	Patients No (n = 60)	Percentage
Primigravida	9	15	11	18.3
Multigravida	51	85	49	81.7
Grand multipara	0	0	0	0

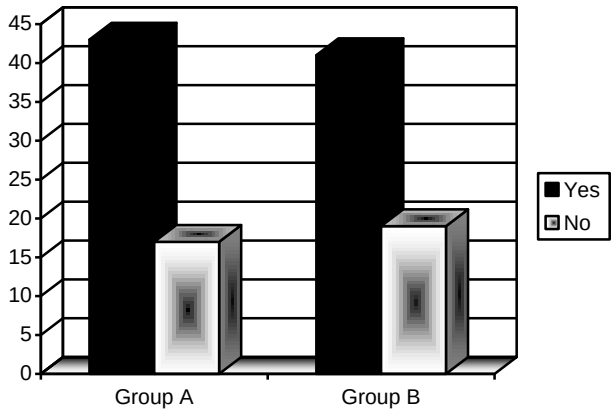

Figure 1: Distribution of patients by Prolongation of labor for 48 hours (n = 120)

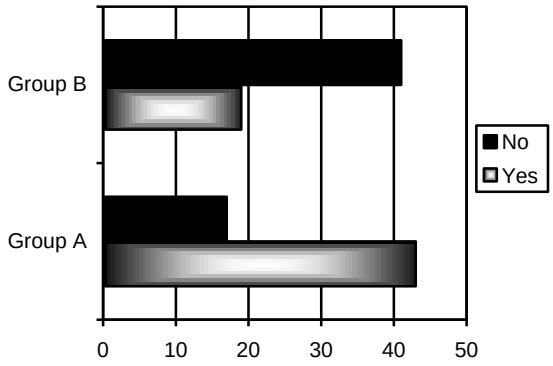

Figure 2: Distribution of patients by Efficacy (n = 120).

Discussion

Preterm labor is a significant cause of maternal and fetal mortality and morbidity. The prolongation in labor have been claimed to show certain benefits like, by enabling corticosteroid administration to accelerate fetal lung maturation, and the ability to transfer the pregnant woman to a center with excellent neonatal intensive care facilities. In literature, several drugs have been discussed for prolongation of labor like nifedipine, ritodrine, magnesium sulfate, nitrous oxide donor and isoxaprine etc, but none has been recommended as a standard protocol.[14]

The results of our study favored the use of Nifedipine over Ritodrine for prolongation of labor i.e. nifedipine was effective in 71.7% patients and Ritodrine in 31.7% patients for prolongation of labor. Eventually the results were statistically significant ($p < 0.05$).

Al-Qattan F, et al, compared the efficacy of Nifedipine with Ritodrine among 60 patients. Efficacy was measured by cessation of the labor for more than 48 hours. This was the same parameter as in our study. It was found that eighteen patients (60%) in the nifedipine group had cessation for more than 48 h compared to 7 (30.4%) in the ritodrine group ($p < 0.05$). Like our study, the results of this study were in favor of nifedipine. They concluded that nifedipine is safe, more efficacious, easy to administer and they recommended the use of nifedipine over ritodrine.[15]

Kupferminc, et al compared the efficacy of Nifedipine with Ritodrine in 71 patients and revealed 83% success with Nifedipine and 77% with ritodrine for prolongation of labor for 48 hours.[16] The results of this study showed that efficacy of ritodrine were higher than our study i.e. 77% and 31.7% in our study. However, again, like our study and other studies, the efficacy of nifedipine was higher than ritodrine. In another study by Read, et al, reported a success rate of 83% with Nifedipine vs.45% with ritodrine.[17]

In a study by Paptsonis DNM, the efficacy of nifedipine was compared with ritodrine and it was noted that nifedipine was effective in 77.9% patients and ritodrine in 62.1% patients. The results were significant statistically. This study also favored nifedipine as tocolytic agent.[18]

There are two systematic reviews which have compared nifedipine with different beta mimetic including ritodrine. In the one they included 607 women and 679 women in other were compared to see the efficacy of nifedipine with ritodrine. In both, there was

insufficient evidence for reaching on the conclusions about the effect on neonatal mortality. Nifedipine was more effective and had a better chance of delivery being delayed for over 48 hour (RR 1.13; 95% CI 1.01 – 1.26).[19,20]

In a study by Van De WM, et al, the efficacy of both the agents was compared and they found that nifedipine was more effective. However, they evaluated the efficacy on the basis of mean duration of prolongation of labor i.e. Birth was delayed for an average of 4.3 weeks in the ritodrine group and 5.0 weeks in the nifedipine group ($p = 0.4$).[21]

According to age distribution of the patients, the difference in the two groups was not significant. And the mean age of the patients in both groups was almost similar i.e. 26.67 ± 5.08 years in nifedipine group and 25.98 ± 5.62 years in ritodrine group. In study by Paptsonis DNM et al, the mean age of patients was 29.8 ± 5.0 years in nifedipine group and 28.7 ± 5.8 years in ritodrine group.[18]

According to distribution of patient by parity, majority of patients in our study were multipara i.e. 85% in nifedipine group and 81.7% in ritodrine group. This finding is in contradiction to study by Paptsonis DNM et al, in which, most of the patients were multigravida i.e. 55.7% in nifedipine group and 57.4% in ritodrine group.[18]

In literature, different studies have used different parameters for the assessment of efficacy. Most of the studies have used prolongation of labor for 48 hours, while others have used prolongation for 1 week or more and side effects and maternal and fetal outcome etc. Most of the studies have used the outcome variable as prolongation for 48 hours which is the same as that of our study.

The above discussion suggests that the efficacy of the nifedipine ranges from 71.7% to 83% and that of ritodrine from 31.7% to 62.1%. Although theses digits are variable in some studies the results are not significant, nifedipine is superior to ritodrine.

This study had certain limitations. This was not a double blind study, as it was not possible because one of the agent i.e. nifedipine was administered by oral route and the other agent ritodrine was administered by intravenous route.

Conclusion

The efficacy of nifedipine is better than ritodrine and the results are statistically significant. It is recommended to use nifedipine for prolongation of labour in preterm labor.

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