ORIGINAL ARTICLE

Comparison of Efficacy of Nifedipine Alone and with Progesterone Depot for Tocolysis in Preterm Labour

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ABSTRACT

Background: Preterm birth is one of the leading causes of perinatal mortality. The incidence of preterm birth varies across the globe, the rate being between 5-11 %. If threatened preterm labour is recognized and managed in time, perinatal mortality can be reduced.
Aim: To compare efficacy of nifedipine alone and with progesterone depot for tocolysis of preterm labour.
Methods: This randomized controlled trial was carried out at Department of Obs & Gynae, Lady Willingdon Hospital Lahore from November 2017 to April 2018. A total of 92 patients of preterm labour, fulfilling the inclusion criteria were included in the study. Non-probability, consecutive sampling was done. The selected patients were placed randomly into two groups. In each group, if uterine contractions remained stopped till 48 hours after start of treatment, the treatment was regarded successful; otherwise it was labelled as unsuccessful.
Results: The mean age of women in group A was 26.11±5.24 and in group B was 25.97±5.09 years. The mean gestational age in group A was 33.39±2.16 weeks and in group B was 33.67±2.33 weeks. Mean parity in group A was 2.34±1.51 while in group B was 2.46±1.39. There was cessation of uterine contractions till 48 hrs in 22(47.83%) patients in Group A while in Group B, it was seen in 33 (71.74%) pts with p-value of 0.019
Conclusion: Nifedipine along with progesterone depot was associated with higher efficacy for cessation of uterine contractions in preterm labour as compared to oral nifedipine only.
Key words: Cessation, Uterine contractions, Progesterone, Calcium

INTRODUCTION

Threatened preterm labour is one of the leading clinical problems encountered in labour ward. It is a prominent cause of hospitalization during pregnancy.[1,2] Almost 50% of the women with diagnosis of threatened preterm labour would finally end up in preterm labour[1,3]. The precise mechanism of preterm labor is not known but is supposed to include; abruption, mechanical problems such as overstretching of uterus from multiple pregnancy or excessive liquor, cervical weakness and infection, uterine anomalies, and decreased blood supply to the fetus due to raised blood pressure, diabetes, smoking and alcohol and drug use[3]. Inspite of the introduction of new modalities, the figures for preterm birth over the past three decades haven't changed much[4]. While no treatment has proven very fruitful in stopping preterm delivery in those who have premature contractions, diagnosis at the earliest allows the use of medications that may delay delivery for 48 hours or more[5].

Preterm labor may not be easy to diagnose and there is a chance of over treating the problem. A number of drugs have been proposed for keeping uterus quiscent. Those used presently include beta-agonists, calcium channel blockers, prostaglandin synthetase inhibitors, nitric oxide donors, and oxytocin receptor antagonists[6]. Agents for tocolysis should be used cautiously keeping fetomaternal effects in mind. Neonatal outcome is compromised, especially when the pregnancy is less than 28 weeks. The chances of survival are further compromised if other element like intra-amniotic infection (IAI) is present[7].

Nifedipine is a drug which was reported for stopping uterine contractions in preterm labour[8]. Although it is not an ideal agent for tocolysis, calcium channel blockers have some qualities that make them a better choice as compared to others. They decrease calcium entry through cell membranes, so controlling muscle contractility in various tissues like uterus. Ulmsten et al[9] first used nifedipine for the treatment of preterm labor in a study comprising of 10 patients, with stoppage of uterine activity for 72 hours in all patients treated. Ferguson et al[10] indicated that nifedipine was as effective as ritodrine in preventing preterm labour, but had lesser side effects. A study by Naz et al[11] indicated that use of oral nifedipine stopped uterine contractions in 74.1% in 48 hours.

Progesterone has a significant role in pregnancy. It not only helps to keep uterus quiet during the pregnancy but also acts on cervical function. Moreover, it also prevents of preterm delivery. Progestins (vaginal or intramuscular) are thought to be effective in reducing preterm delivery in predisposed groups.[12] The combined effect of 17-α-hydroxyprogesterone caproate and nifedipine was not better than that of nifedipine alone (26.8% versus 20.4%) in a clinical trial done by Tan et al[13]. But other hand, Baumbach et al[14] found that there was 40% reduction of uterine contractions with nifedipine alone but with progesterone, uterine contractions were inhibited upto 70%.

So, a number of studies have been conducted worldwide to find a suitable agent for arresting threatened preterm labour. Some of them supported the use of Nifidipine and the others that of progesterone. The rationale for this study was to come up with a regime of tocolysis which is safe & effective to be used in our set up.

MATERIALS AND METHODS

This randomized controlled trial conducted at Department of Obstetrics & Gynaecology, Lady Willingdon Hospital, Lahore from November 2017 to April 2018 and comprised 92 patients. All patients with single normal fetus with cephalic presentation having preterm labor with gestational

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age between 28-36 weeks as calculated by LMP and patients 18-35 years of age were included in the study. Patients with preterm premature rupture of membranes , chorioamnionitis, cervical dilatation >4cm, antepartum hemorrhage, H/o severe anemia (HB<7g/dl), diabetes mellitus, pre-eclampsia, cardiac disease and hepatic dysfunction, multiple pregnancy, polyhydramnios, severe intra-uterine growth retardation, anomalous fetus, those who were allergic to nifedipine or progesterone or not willing to participate in study were excluded from the study.

All patients with preterm labor were offered to pick up a slip from total mixed up slips (half-slips were contained letter 'A' and other half slips were contained letter 'B') and she was placed in that respective group. Base line investigations were done in every patient on admission. In the Group A, only nifedipine was given as 20 mg tablet stat if uterine contractions were not stopped within 20 minutes, then 20 mg tablet was repeated. If there was no response then after 30 minutes, another 20 mg was given. After this, nifedipine was continued 20 mg twice a day for further 2 days. While in Group B patients, nifedipine was given as 20 mg tablet stat along with single intramuscular injection of 250 mg of 17-alpha-hydroxyprogesterone caproate, if uterine contractions were not stop within 20 minutes, then 20 mg tablet of nifedipine was repeated. If there was no response then after 30 minutes, another 20 mg was given. After this, nifedipine was continued 20 mg twice a day for further 2 days. All patients in both groups were evaluated by the researcher herself for prolongation of gestation and prolongation of gestation at 48 hours after the start of treatment. In each group, if uterine contractions were remained cease till 48 hours after the start of treatment, the treatment was regarded successful; otherwise it was labeled as unsuccessful. All the data was entered and analyzed by using SPSS version 16.0. Quantitative variables like age, gestational age and parity were presented as mean and standard deviation. Frequency and percentage was calculated for efficacy of nifedipine alone and nifedipine with progesterone depot. Comparison between the efficacy of both groups were compared by chi-square for any difference and p-value ≤0.05 was considered as statistically significant. Effect modifiers like age, parity and gestational age were controlled through stratification and post-stratification. chi-square was applied to see effect of these factors on efficacy.

RESULTS

The efficacy was 47.83% in group A (nifedipine only) and 71.74% in group B (nifedipine plus progesterone depot) with p-value of 0.019 as shown in Table 1. Stratification of efficacy between two groups according to age of patients and gestational age has shown in Table 2 & 3 respectively while Table 4 has shown the stratification of efficacy between both groups according to parity.

Table 1: Comparison of Efficacy between both Groups (n=92)

Efficacy	Group A (n=46)		Group B (n=46)	
	No.	%	No.	%
Yes	22	47.83	33	71.74
No	24	52.17	13	28.26
P value	<0.019			

Table 2: Stratification of efficacy of both groups according to age

Age (years)	Group A (n=46)		Group B (n=46)		p-value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
18-25	9 (47.37%)	10 (52.63%)	15 (71.43%)	6 (28.57%)	0.121
26-30	8 (53.33%)	7 (46.67%)	11 (73.33%)	4 (26.67%)	0.256
31-35	5 (41.67%)	7 (58.33%)	07 (70.0%)	3 (30.0%)	0.184

Table 3: Stratification of efficacy of both groups according to gestational age

Gestational age (weeks)	Group A (n=46)		Group B (n=46)		p-value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
28-32	8 (38.10%)	13 (61.90%)	15 (75.0%)	5 (25.0%)	0.017
>32-36	14 (66.67%)	11 (33.33%)	18 (69.23%)	8 (30.77%)	0.329

Table 4: Stratification of efficacy of both groups according to parity

Parity	Group A (n=46)		Group B (n=46)		p-value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
Para-1	7 (53.85%)	6 (46.15%)	11 (73.33%)	4 (26.67%)	0.283
Para-2	8 (50.0%)	8 (50.0%)	10 (71.43%)	4 (28.57%)	0.232
Para-3	4 (40.0%)	6 (60.0%)	8 (72.73%)	3 (27.27%)	0.130
Para->3	3 (42.86%)	4 (57.14%)	4 (66.67%)	2 (33.33%)	0.391

DISCUSSION

Preterm labour is defined as the onset of regular effective uterine contractions resulting in effective cervical change before 37 completed weeks of pregnancy. In those at risk of prematurity, progesterone, if taken during pregnancy, may prevent the eventuality. Trials do not support the efficacy of bed rest. It is estimated that at least three quarters of preterm infants survive with appropriate management .In patients who deliver between 24 and 34 weeks, steroids improve survival. A number of agents including nifedipine and progesterone preparations may delay delivery so that a mother can be transported to a well equipped facility and the steroids can work[14].

Age range in this study was from 18 to 35 years with mean age of 26.04±5.12 years. Taherian et al[15] in a similar study had found a mean age of 26 years which is very much comparable to our study. In the same study, mean gestational age was found to be 32 weeks.[15] In our study

the majority of the fetuses were born between 34-36 weeks which fits in the category of late preterm. Lyell et al[16] have shown that most of the patients in preterm labour are primigravidas but in our study they are second gravidas.

Several cochrane reviews have compared the tocolytic drugs with placebo and others[17]. In our study, the uterine contractions stopped for 48 hours in 47.83% patients nifedipine only group while in nifedipine plus progesterone depot group the contractions ceased in 71.74%. So the difference was statistically significant. Baumbach et al[14] found that there is less inhibition of uterine contraction with nifedipine alone but if progesterone added with nifedipine this inhibits moreuterine contractions. A local study done in Bahawalpur has results that meet closely with ours[18].

Progesterone is thought to play a key role in prolongation of pregnancy until term. In animal studies, progesterone reduces oxytocin and alpha-adrenergic receptors in the myometrium, as well as production of prostaglandins. It brings about changes in myometrium which nduce muscle contraction. A study done by Chawanpaiboon[8] showed that when used for inhibition of premature labour, proluton depot was more effective than nifidipine. Same results were shown in a study conducted by Haghighi[1]. Another study conducted in India bore the same results[19]. Many reviews have shown that progesterone, when used for preterm labour is an effective tocolytic[20]. Caution is needed as few studies have indicated that progesterone might affect the cognitive development of the newborn[21].

Nifidipine has been shown to be very effective in prevention of preterm labour in many studies[9,10,11,22,23] They all came to the conclusion that in threatened preterm labor, maintenance tocolysis with nifedipine may reduce perinatal mortality. Preterm birth remains one of the leading causes of neonatal mortality the world over and interventions are direly needed.[24] So, this study showed that nifedipine when coupled with progesterone depot was associated with higher success rate in arresting threatened preterm labour. This opens a promising avenue of research for developing countries like ours.

CONCLUSION

Nifedipine with progesterone depot was associated with higher efficacy as compared to oral nifedipine only. So, we recommend that nifedipine with progesterone depot should be used as a first line agent for inhibition of uterine contractions in preterm labourin order to gain maximal benefit in terms of neonatal outcome.

REFERENCES

1. Haghigi L, Rashidi M , Najmi Z, Homam H, Hashemi N,. Comparison of intramuscular progesterone with Nifedipine for treating threatened preterm Labour: A randomized controlled trial. Med J Repub Iran 2017;31:56.
2. Vahdat M, Mehdizadeh A, Sariri E, Chaichain S, Najmi Z,. Placenta Percreta penetrating broad ligament and parametrium in woman with previous two cesarean sections: a case report. Case Rep Obstet Gynecol 2012; 251381.
3. Hassani V, Pazouki A, Nikoubakht, Chaichian S, Sayarifard A, Khankadi AS. The effect of Gabapentin in reducing pain after Laparoscopic gastric bypass surgery in patients with morbid obesity. Anaesthesia Pain Med 2015; 5 (1);e22372.
4. Gilani S, Ali SM, RA Umair, Mushtaq A, Asghar AH.To compare efficacy of nifidipine and nitroglycerine as tocolytic patients in preterm labour patients. PJMHS 2014 ; 8(1):80-82.
5. Chao TT, Bloom SL, Mitchell JS, McIntire DD, Leveno KJ. The diagnosis and natural history of false preterm labor. Obstet Gynecol 2011;118(6):1301-8.
6. Tabassum S, Shahzadi U, Khalid H. Comparitive study of Efficacy of Magnesium Sulphate and Nifidipine in suppression of Preterm Labour. PJMHS 2016; 10(4) :1307-12.
7. Haas DM, Caldwell DM, Kirkpatrick P, McIntosh JJ, Welton NJ. Tocolytic therapy for preterm delivery: systematic review and network meta-analysis. BMJ 2012;345:e6226.
8. Chawanpaiboon S, Kanokpongsakdi S. Comparison of Nifedipine and Bed Rest for Inhibiting Threatened Preterm Labour. Gynecol Obstet 2012;2(5):131-34.
9. Ulmsten U, Andersson KE, Wingerup L. Treatment of premature labor with the calcium antagonist nifedipine. Arch Gynecol 1980;229:1–5.
10. Ferguson JE II, Dyson DC, Schutz T, Stevenson DK. A comparison of tocolysis with nifedipine or ritodrine: Analysis of efficacy and maternal, fetal, and neonatal outcome. Am J Obstet Gynecol 1990;163:105–11.
11. Naz S, Majid E, Soomro S, Perveen R, Baloch R. Efficacy of nifedipine in suppression of preterm labour. Pak J Surg 2011;27(4):299-303.
12. Hassan SS, Romero R, Vidyadhari D. PREGNANT Trial. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multi-center, randomized, double-blinded, placebo-controlled trial. Ultrasound Obstet Gynecol 2011;38:18-31.
13. Tan PC, King AS, Vallikkannu N, Omar SZ. Single dose 17 alpha-hydroxyprogesterone caproate in preterm labor: a randomized trial. Arch Gynecol Obstet 2012;285:585–90.
14. Baumbach J, Shi S-Q, Shi L, Balducci J, Coonrod DV, Garfield RE. Inhibition of uterine contractility with various tocolytics with and without progesterone: in vitro studies. Am J Obstet Gynecol 2012;206:254.e1-5.
15. Taherian AA, Dehdar P. Comparison of efficacy and safety of nifedipine versus magnesium sulfate in treatment of preterm labor. J Res Med Sci 2007;12(3):136-42.
16. Lyell DJ, Pullen K, Cambell L, Ching S, Druzen ML, Chitkera V, et al. Magnesium sulfate compared with nifedipine for acute tocolysis of preterm labour: a ramdomized controlled trial. Obstet Gynecol 2007;110(1):61-7.
17. Dodd JM, Grivell RM, OBrien CM. Prenatal preterm birth in women in women with a singleton pregnancy. Cochrane Database of Systematic Reviews 2017, 1: CD 012531.
18. Jabeen S, Akhter M, Fatima N. Role of progesterone for prevention of preterm labour. PJMHS 2012; 6(1): 253-5.
19. Kamat S, Veena P, Rani R. Comparison of nifidipine and progesterone for maintenance tocolysis after arrested preterm labour . J Obstet Gynecol 2014;34(4):322-5.
20. Aggarwal A, Bagg R, Girish B, Kaira J, Kumar.Effect of maintenance tocolysis with nifidipine in established preterm labouron pregnancy prolongation and neonatal outcome. J Obstet Gynaecol 2018;38(2):177–184.
21. Willing J, Wagner CK. Exposure to synthetic progestin 17-alpha hydroxyprogesterone caproate during development affects cognitive flexibility in adulthood. Endocrinology 2016;157(1);77-82.
22. Conde –Agudelo A, Romero R, Kusanovic JP. Nifedipine for the management of preterm labour: A systematic review and metaanalysis. Am J Obstet Gynecol 2011;204(2):134.e1
23. Roos C, Marc E, Spndermaan A, Schult E. Effect of Maintenance Tocolysis with threatened preterm labour on Perinatal outcome. JAMA 2013; 309(1) :41-7.
24. Norman JE, Bennet PE. Preterm birth prevention: time to progress beyond Progesterone. Plos Med 2017; 14(9): e 1002391