ORIGINAL ARTICLE

Comparion of Effectiveness of Nifedipine with Progesterone Depot and Nifedipine Alone for Tocolysis in Preterm Labour

[1]KANWAL NOSHEEN, [2]SHAMSA HAMAYUN, [3]MEMOONA TAHIR
[1]Assistant Professor Department of Gynaecology FJMU/SGHR, [2]Professor/Head of Gynaecology, FJMU/SGRH, [3] Women Medical Officer, SGRH, Lahore.
Correspondence to: Dr. Kanwal Nosheen Assistant Professor Department of Gynaecology FJMU/SGHR, Lahore.

ABSTRACT

Many tocolytic agents are used to suppress preterm uterine contractions. These include: beta-agonists, calcium channel blockers, prostaglandin synthetase inhibitors, nitric oxide donars, oxytocin receptor antagonists. Among these the calcium channel blockers specifically nifedipine is constantly gaining importance due to its more effectiveness and lesser side effects as compared to the other drugs. In high risk pregnancies, Progesterones had also shown efficacy in reducing the incidence of recurrent preterm delivery . In this study the effectiveness of nifedipine with progesterone depot and nifedipine alone in the tocolysis of preterm labour was compared.

Objectives: To determine the efficacy of nifedipine alone (group-A) and nifedipine with progesterone depot (group-B) for tocolysis of preterm labour.

Study design: Randomized controlled trial

Setting: Obstetrics and Gynaecology unit-III, Sir Ganga Ram Hospital, Lahore.

Duration of study with dates: This study was conducted over period of six months from June 2015 to December 2015.

Subjects and Methods: The study was conducted on 92 patients; i-e: 46 in each group at gestational age of 28-36weeks.

Results: Age range in the study was from 18 to 35 years with mean age of 20.04 ± 5.12yaers. Majority of the patients 40 (43.48%) were between 18 to 25 years of age. The gestational age was from 28 to 36 weeks with mean age of 33.56 ± 2.23 weeks. Majority of the patients 51 (55.43%0were between > 32 to 36 weeks of gestation. 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 hours in 22 (47.83%) and no cessation in 24 (52.17%) patients in group-A, nifedipine only ; while in group-B ,nifedipine with progesterone depot, it was seen in 33 (71.74%) and 13 (28.26%) patients respectively. So, efficacy was 47.83% in group-A and 71.74% in group-B with p-value of 0.019.

Conclusion: Through this study it was concluded that nifedipine with progesterone depot was more effective in cessation of preterm uterine contractions as compared to oral nifedipine alone. So, it is recommended that nifedipine with progesterone depot should be used as a first line agent to inhibit the uterine contractions in preterm labour. Thus some benefit can be achieved by prolongation of preganacy , by accelerating fetal lung maturity through administration of corticosteroids. And this would help fetomaternal outcome and reduce the complications related to prematurity .

Keywords: Prematurity, tocolytics, uterine contractions, respiratory distress syndrome.

INTRODUCTION

Preterm labour is one of the frequently encountered problem in obstetrical practice. The incidence of preterm labour differs in different regions, the rate varying between 5 – 11%[1]. Preterm deliveries are the leading cause of infant morbidity and mortality[2]. Its exact mechanism is unknown but various causative factors include the following : decidual haemorrhage like abruption, mechanical factors such as uterine overdistension in multiple gestation or polyhydramnios, cervical incompetence, uterine distortion, cervical inflammation and uteroplacental insufficiency (e.g : hypertension, insulin dependent diabetes , drug abuse , smoking , alcohol consumption)[3]. Despite the introduction of new diagnostic and therapeutic technologies, there has been little reduction in the incidence of preterm birth over the past 30 years[4]. While no treatment has proven highly effective in preventing preterm delivery. In women who

experience preterm labour, diagnosis at an early stage allows the use of interventions that may delay delivery for 48 hours or more[5].

Preterm labour may be difficult to diagnose and a potential exists for the over treatment of uterine irritability. Various agents have been used for suppressing uterine contractions. Tocolytic agents currently in use are : beta-agonists , calcium channel blockers, prostaglandin synthetase inhibitors, nitric oxide donars and oxytocin receptor antagonists[6]. Tocolytic agents , if used in appropriate dosages are safe generally, with proper clinical monitoring. These should be used after consideration of the risks and benefits of such use due to their potential side effects. Tocolysis should be used with caution when the fetus is previable because the neonatal morbidity and mortality are generally affected by gestational age, especially when the pregnancy is less than 28 weeks' gestation. The neonate has a minimal chance of survival at less than 23 weeks. The likelihood of survival is further reduced if significant medical complications are present , such as intra-amniotic infection at these ages[7,8].

Contraindications to different tocolytic agents must be followed.

These agents should be used with caution in pregnant patients with serious comorbidities like : cardiac disease, cadiac surgery, significant pulmonary disease, renal failure or maternal infections e.g: pneumonia, appendicitis, pyelonephritis.

Till todate, no definite intervention proved to suppress uterine contractions compleletly, but nifedipine is the oral medication which was successfully reported to inhibit the uterine contractions in preterm labour[9(10]. Although Calcium channel blockers donot meet the criteria of ideal tocolytics but they reduce the incidence of preterm labour and they have certain properties that make them preferable to other tocolytics[10(11].

Progesterone is important to maintain uterine quiescence during pregnancy[11(15],suppress uterine contractility[12(16]. Therefore progesterone is also used as a prophylaxis in the prevention of preterm labour. Its use in acute preterm labour has not been proven[13(20]. Baumbach J et al[14(25] in his study has found that there is 40% inhibition of uterine contraction with nifedipine alone but if progesterone is added with nifedipine then this inhibits uterine contractions upto 70%.

Pretrerm labour is a common problem in developing as well as developed countries and prematurity is the leading cause of neonatal mortality and morbidity in developing countries due to inadequate nursery care. Due to limited data available on combined efficacy of progesterone and nifedipine, I aimed this study to evaluate the efficacy of nifedipine alone and nifedipine with progesterone depot in preterm labour in local population. This interm will provide a better regimen for inhibition of uterine contractions in order to prolong pregnancy so as to get maximum benefit of the corticosteroid cover for fetal lung maturity and hence the improved fetomaternal outcome.

METHODOLOGY

This randomized controlled trial was conducted in Obs & Gynae unit-III, of Sir Ganga Ram Hospital, Lahore, from Nov-2014 to April-2015 on 96 women,46 in each group using non-probability consecutive sampling technique.

All women of of 18-35yrs age, gestational age between 28-36 weeks by LMP and with single normal fetus with cephalic presentation were included in this study. And women with preterm premature rupture of membranes, severe anaemia (Hb<7gm/dl) , diabetes (BSF> & 2-hr postprandial >), pre-eclampsia (B.P >140/90, >300gm proteinuria in 24hrs), cardiac disease (based on clinical examination, ECG and echocardiography) and hepatic dysfunction (assessed by LFTs, total bilirubin > 2 IU/L, AST > 600 IU/L, ALT > 700 IU/L)

Multiple pregnancies, polyhydramnios, severe intrauterine growth retardation, anomalous fetus, patients allergic to nifedipine or pprogesterone and pts not willing to participate in the study were also excluded.

After approval from local ethical committee, 92 patients were selected and informed consent taken. Then the patients with preterm labour were offered to pick up a slip from mixed up slips half labelled 'A' and half 'B'. Baseline investigations : CBC, BSR, urine C/E, LFTs, ECG (if indicated) were done.

In group-A only nifedipine 20mg tablet was given and repeated after 20mins if uterine contractions were not stopped. After 30mins again 20mg tablet given if no response. After this nifedipine was continued 20mg twice a day for 2 days.

In group-B nifedipine 20mg tablet was given with single intramuscular injection of 250mg of 17-alpha-hydroxyprogesterone caproate. If uterine contractions were not stopped then nifedipine

20mg was repeated after 20 mins and 30 mins, with continuation as nifedipine 20mg twice a day for 2 days.

Thereafter all patients were evaluated after 48 hrs of the start of treatment, the treatment was successful if uterine contractions remain quiescence otherwise it was labelled as unsuccessful. All this data was recorded on a predesigned proforma, then 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 were 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 ≤ was considered as statistically significant.

RESULTS

The mean age of women in grouop-A was 26.11± 5.224 and in group-B was 25.97± 5.09 years. Majority of the patients 40 (43.48%) were between 18 to 25 years of age as shown in table-1.

Table 1 : Age distribution for group-A & B

Age (years)	Group-A (n=46)		Group-B (n=46)		Total (n=92)	
	No. of pts	% age	No. of pts	%age	No. of pts	% age
18-25	19	41.30	21	45.65	40	43.48
26-30	15	32.61	15	32.61	30	32.61
31-35	12	26.09	10	21.74	22	23.91
Mean ± SD	**26.11 ± 5.24**		**25.97 ± 5.09**		**26.04 ± 5.12**	

Table 2: % age of patients according to gestation age in both groups

Gestational age (weeks)	Group-A (n=46)		Group-B (n=46)		Total (n=92)	
	No. of pts	% age	No. of pts	% age	No. of pts	% age
28-32 weeks	21	45.65	20	43.48	41	44.57
32-36 weeks	25	54.35	26	56.52	51	55.43
Mean ± SD	**33.39 ± 2.16**		**33.67 ± 2.33**		**33.56 ± 2.23**	

Table 3: Comparison of efficacy between both groups (n=92)

		Group A (n=46)		Group B (n=46)	
		No. of patients	% age	No. of patients	% age
Efficacy	Yes	22	47.83	33	71.74
	No	24	52.17	13	28.26

P value is 0.019 which is statistically significant

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

Age of patients	Group A (n=46)		Group b (n=46)		P – value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
18 -25 yrs	09(47.37%)	10(52.63%)	15(71.43%)	06(28.57%)	0.121
26 – 30 yrs	08(53.33%)	07(46.67%)	11(73.33%)	06(28.57%)	0.256
31 – 35 yrs	05(41.67%)	07(58.33%)	07(70.0%)	04(26.67%)	0.184

Table 5: Stratification of efficacy of both grouos according to gestational age

Gestational age	Group A (n=46)		Group b (n=46)		P – value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
28 - 32 yrs	08(38.10%)	13(61.90%)	15(75.0%)	05(25.0%)	0.017
>32 – 36 yrs	14(66.67%)	11(33.33%)	18(69.23%)	08(30.77%)	0.329

Table 6 : 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	07(53.85%)	06(46.15%)	11(73.33%)	04(26.67%)	0.283
Para - 2	08(50.0%)	08(50.0%)	10(71.43%)	04(28.57%)	0.232
Para – 3	04(40.0%)	06(60.0%)	08(72.3%)	03(27.27%)	0.130
Para - > 3	03(42.86%)	04(57.14%)	04(66.67%)	02(33.33%)	0.391

Gestational age was from 28 to 36 weeks with mean age of 33.56 ± 2.33 weeks. Majority of the patients 51 (55.43%) were between 32 to 36 weeks.

The efficacy was 47.83% in group-A (nifedipine only) and 71.74% in group-B (nifedipine with progesterone depot) with p-value of 0.019.

The stratification of efficacy between two groups according to age of patients and gestational age , parity are shown in tables.

DISCUSSION

In at risk pregnancies , the preterm birth may be prevented by taking progesterone during the antenatal period. With appropriate treatment approximately 75% of preterm infants would survive. Corticosteroids given between 24-34 weeks might improves the fetal outcome. Various tocolytics like nifedipine may gain time by delaying delivery, for the fetal lung maturity by corticosteroids or the mother can be shifted to a better obstetrical unit with good neonatal care facilities. As the neonate is born, immediate supportive care should be provided by keeping the baby warm through skin to skin contact, encouraging breast feeding, supporting breathing and treating infections.

In this study majority of the patients 40 (43.48%) were between 18-25years. Taherian AA et al[15(101] in his study had found a mean age of 26 years that is comparable to my study. Mean parity in group-A was 2.34 + 1.51 while in group-B was 2.46 + 1.39 . Contrary to these results, Lyell DJ et al[16(102] and Glock JL et al[17(103] have shown that preterm labour is usually associated with primiparity.

A range of tocolytic agents has been used to inhibit preterm labour in order to have the time for such cointervention. Several Cochrane reviews have compared individual tocolytic drugs with placebo or other tocolytics[18,19(105,106] A recent pooled meta-analysis and decision analysis of trials on tocolytics reported the effectiveness of prostaglandin inhibitors in delaying delivery for 48-hours to 7-days[20(8].In this study ,there was cessation of uterine contractions till 48 hours in 22 (47.83%) and no cessation of uterine contractions in 24 patients (52.17%) in group-A, nifedipine only while in group-B , nifedipine with progesterone depot , it was seen in 33 (71.74%) and 13 (28.26%) patients respectively.

Progesterone is thought to play a key role in the maintenance of pregnancy until term due to its inhibitory effect on uterine contractions.[21(107]. Baumbach J et al 19(25 in his study found that there is 40% inhibition of uterine contraction with nifedipine alone ,but if progesterone added with nifedipine this inhibits upto 70%.

Recent systematic views of literature have shown effectiveness of progesterone to reduce the incidence of preterm birth and low birth weight newborns, when used for suppressing preterm labour[22,23(109,110] and that women at risk of preterm birth should be recommended progesterone therapy[24(111].The probability of being ranked in the top three most efficacious classes was 96% for prostaglandin inhibitors, 63% for magnesium sulfate, 57% for calcium channel blockers, 33% for beta mimetics, 24% for nitrates, 14% for oxytocin receptor blockers, 13 % for others and 0% for placebo. The use of progestational agents resulted in a statistically significant reduction in preterm deliveries at less than 37 weeks of gestation. So, this study concluded that nifedipine with progesterone depot was associated with higher efficacy for cessation of uterine contractions in preterm labour as compared to oral nifedipine only and gives some benefit from prolongation of pregnancy by enabling corticosteroid administration to accelerate fetal lung maturation which would improve fetomaternal outcome.

CONCLUSION

This study concluded that nifedipine with progesterone depot was associated with higher efficacy interms of cessation of uterine

contractions in preterm labour as compared to nifedipine alone. So it is recommended to be used as first line agent for the tocolysis in preterm labour, hence sone benefit can be gained from prolongation of pregnancy by enabling corticosteroid administration to accelerate fetal lung maturity. This would improve the fetomaternal outcome and the complications related to prematurity.

REFERENCES

1. Lisonkova S, Sabr Y, Butler B, Joseph KS. International comparison of preterm birth : higher rates of late preterm birth are associated ith lower rates of stillbirth and neonatal death. Br J Obstet Gynecol. 2012;119:1630-639.
2. Haas DM, Caldwell DM, Kirkpatrick P, McIntosh JJ, Welton NJ. Tocolytic therapy for preterm delivery : systematic review and network meta-analysis. Br Med J. 2012:345:e6226.
3. Conde-Agudelo A, Romero R, Kusanovic JP.Nifedipine in the management of preterm labor : a systematic review and meta-analysis. Am J Obstet Gynecol. 2011:204(2):134.e1-2.
4. Berghella V, RaaelTj, Szychowski JM. Cerclage for Short Cervix onUltrasonography in women with singleton gestations and previous preterm birth : a meta-analysis. Obstet Gynecol. 2011;117(3):663-71.
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. Renzo GCD, Roura LC. Guidelines for the management of spontaneous preterm labor. J Perinat Med. 2006;34:359-66.
7. Simhan HN, Caritis SN. “Prevention of Preterm delivery”. N Engl J Med. 2002;357(5):477-87.
8. Haas DM, Caldwell DM, Kirkpatrick P, McIntosh JJ, Welton NJ. Tocolytic therapy for preterm delivery : systematic review and network meta-analysis. Br Med J. 2012:345:e6226.
9. Chawanpaiboon S, Kanokpongsakdi S. Comparison of Nifedipine and Bed Rest for Inhibiting Threatened preterm Labour. Gynecol Obstet. 2012;2(5):131-34.
10. Gaspar R, Hajagos-Toth J. Calcium Channel Blockers as Tocolytics : Principles of Their Actions, Adverse Effects and Therapeutic Combinations. Pharmaceuticals. 2013;6:689-99.
11. Smith R. Parturition. N Engl J Med. 2007;356:251-83.
12. Csapo A. Force of labor. In:Iffy L, Kaminetzky HA, eds. Principles and practice of obstetrics and perinatology. John Wiley and Sons Inc; 1981:7610-99.
13. Godenberg RL. The management of preterm labor. Obstet Gynecol. 2002;100:1020-37.
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.el-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 randomized controlled trial. Obstet Gynecol. 2001;110(1):61-7.
17. Glock JL, Morales WJ. Efficacy and safety of nifedipine versus magnesium sulfate in the management of preterm labor : A randomized study. Am J Obstet Gynecol. 1993;169:960-4.
18. Fuchs AR, Peryasamy S, alexandrova M, Soloff MS. Correlation between oxytocin receptor concentration and responsiveness to oxytocin in pregnant rat myometrium : effects of ovarian steroids. Endocrinol. 1983;113:742-9.
19. Roberts JM, Insel PA, Goldfien RD, Goldfien A. Alpha adrenoreceptors but not beta adrenoreceptors increase in rabbit uterus with oestrogen . Nature. 1977;270:624-7.
20. Haas DM, Caldwell DM, Kirkpatrick P, McIntosh JJ, Welton NJ. Tocolytic therapy for preterm delivery : systematic review and network meta-analysis. Br Med J. 2012:345:e6226.
21. Thorburn GD, Challis JRG. Endocrine control of parturition. Physiological Rev. 1979:59(4):863-6.
22. Dodd JM, Flenady VJ, Cincotta R, Crowther CA. Progesterone for the prevention of preterm birth : a systematic review. Obstet Gynecol. 2008;112(1):127-34.
23. Farine D, Mundle WR, Dodd J, Basso M, Delisle MF, Farine D, et al. The use of progesterone for prevention of preterm birth. Journal of Obstetrics and Gynaecology Canada : JOGC. 2008;30(1):67-77.
24. Coomarasamy A, Thangaratinam S, Gec H, Khan KS. Progesterone for the prevention of preterm birth : a critical evaluation of evidence. Eur J Obset Gynecol Rerod Biol. 2006;129(2):111-8.