Original Article

Comparison of Salbutamol and Nifedipine as a Tocolytic Agent in the Treatment of Preterm Labour

Naseem Junejo, Firdous Mumtaz and Bilal Ahmed Unar

ABSTRACT

OBJECTIVES: To compare the efficacy and safety of beta agonist salbutamol and calcium channel blocker nifedipine in inhibiting uterine contractions for prolongation of pregnancy and to evaluate the maternal side effects and neonatal outcome of the two drugs.

DESIGN: Quasi experimental study from November 2007 to March 2008.

SETTING: Maajee private hospital of Hyderabad and Department of Obstetrics & Gynecology (Unit –II), Liaquat University Hospital Hyderabad, Sindh - Pakistan. Total deliveries conducted in both settings were 6,360 per year.

METHODS: One hundred pregnant women having single fetus, with preterm labour (<37 weeks) were studied. A proforma was filled from each patient that included information regarding history, findings of clinical examination and investigations. These patients were divided into two groups. Group A received salbutamol (beta-agonist) treatment and group B nifedipine (calcium channel blocker). Salbutamol was given 4mg intravenously in 500cc of 5% dextrose solution, started at 10 drops per minute and increased at interval of 15-20 minutes until the contractions were stopped, then maintained with 4mg oral dose while nifedipine was given as 20mg oral tablets. Results were analyzed by SPSS version 10.0.

RESULTS: Total 100 patients were divided into two groups of 50 each. Mean age in group A was 27.64 ± 6.006 (20-33 years) and in group B, 27.84±6.60 (22-36 years). Mean parity in group A was 2.34± 1.97 (1-3) and group-B was 2.58 ± 1.99 (1-3). Mean gestational age in group A was 31.14±2.43 (28-36 weeks) and in group B, 32.34 ± 2.68 (28.36 weeks). In group A 35 (70%) of patients had stopped contraction in 1st hour as compared to group B where only 10 (20%) were tocolysed for the treatment, 40% of patients had no contraction in 3rd hour of treatment in this group. Two (4%) women suffered from hypotension and headache with nifedipine as compared to salbutamol group where 9 (18%) women had nausea, vomiting, palpitation and tachycardia. Neonatal outcome and pregnancy prolongation till 36 weeks were similar in both groups.

CONCLUSION: This study shows that tocolytic effect of prolongation of the pregnancy and the neonatal outcome of the two drugs are the same. However, calcium channel blockers are associated with less frequent side effects.

KEY WORDS: Salbutamol. Nifedipine. Preterm labour. Tocolysis effects.

INTRODUCTION

Onset of labour after 24 weeks and before 37 weeks of the gestation is labeled as preterm labour. This is associated with multiple complications and is the leading case of neonatal morbidity and mortality globally.[1,2] It complicates 6-10% of pregnancies.[3] The incidence of preterm labour was almost same since last 40 years and still persist regarding the best strategies for its management. It varies form 11% in North America, 5.6% in Oceania and 5.8% in Europe.[4] In Pakistan, perinatal mortality rate is 96 per thousand live births.[5] The preterm labour is diagnosed when there are palpable uterine contractions 3 in 10 minutes, at least 50% cervical effacement and dilatation <4cm with intact membranes. Its prevalence is affected by the way in which gestational age is assessed, by national differences in the registration of births, and perceived viability of extremely preterm infants. Early detection and effective management are important steps for preventing preterm labour which is leading cause of neonatal morbidity and mortality and accounts for 35% of all health care spending on the neonates as not only neonatal intensive care in short term but resource needed children in long term. It also results in serious sequelae of both mother and fetus including maternal and fetal infections and prolongation in hospital stay. The main aim of treatment is not only to inhibit the uterine contractions so that patients can be transferred to the tertiary care centre for best intensive neonatal care unit but also to prolong pregnancy for at least 48 hours so that corticosteroid may be given for fetal lung maturity. For preterm labour the drugs given are tocolytics, antibiotics though controversial and

corticosteroids.[6] Tocolytic agents available are beta mimetics, calcium channel blockers, prostaglandin synthatase inhibitors, magnesium sulphate, oxytocin receptor antagonist and uterine myometrial relexant, nitric oxide donar. Among this, salbutamol is commonly used drug, while other are terbutalin and ritodrine. Side effects noticed with beta sympathomimetics are palpitation, tremors, nausea, vomiting, headache, breathlessness and pulmonary edema. Because of these adverse effects close monitoring of the patients is mandatory. Measurement of maternal pulse, blood pressure and fetal heart rate are recorded up to 24 hours and compared over the treatment course while with calcium channel blockers' adverse effects are dizziness, flushing, headache, hypotension and peripheral edema. This study was conducted with the view to compare the efficacy and safety of a beta agonist and calcium channel blocker in a preterm labour and to compare the maternal side effects and neonatal outcome with the two drugs.

PATIENTS AND METHODS

This study was conducted from November 2007 to March 2008 at a private hospital of Hyderabad (Maajee) and Department of Obstetrics & Gynecology (Unit – II), Liaquat University Hospital Hyderabad. Total number of deliveries conducted in both hospitals was 6,360 per year. All patients were admitted either from out patient department or in emergency from casualty. The inclusion criteria includes gestational age between 28-36 weeks, single normal fetus with cephalic presentation, the palpable uterine contractions 3 in 10 minutes, at least 15% cervical effacement and cervical dilatation <4cm with intact membranes and no history of pre-eclampsia, cardiac disease and diabetes while patients who had severe intra-utrine growth retardation, fetal distress and antepartum hemorrhage were excluded from study. The informed consent was taken and the proforma filled. Group A included 50 patients for salbutamol treatment and group B for nifedipine treatment. In group A, salbutamol was given intravenously as follows, 4mg of salbutamol was diluted in 500cc of 5% dextrose solution started at 10 drops per minute. The dose was increased at interval of 15-20 minutes until the contractions stopped or the maternal pulse increased 140 beats per minutes or above, then it was maintained on oral salbutamol 4mg twice a day for further 5 days. Nifedipine was given as 20mg tablet stat if uterine contraction was not stopped within 20 minutes, then 20mg tablet was repeated. If there is no response then after 30 minutes another 20mg was given. Once the contractions stopped, nifedipine was enterea 20mg twice a day for further 5 days. The data from filled prorforma was filled in SPSS version 10.0. The scale measurement such as number of uterine contractions, time of delivery or neonatal outcome was compared for the two groups by Student's t-test.

RESULTS

Total 100 patients with diagnosis of preterm labour were studied. Demographic profile and clinical characteristics of the labour for both groups are shown in **Tables I** and **II** with no significant findings. The tocolysis was effective within one hour in 35(70%) patients in group A and 10(20%) in group B, while in consecutive 2,3,4 hours showed the pain was relieved in group B as compared to group A (**Table III**). The P-value showed a significant change (p<0.001). **Table IV** shows the period for prolongation of pregnancy, In group A, 11 (22%) patients delivered in less than 24 hours, while 12 (24%) delivered between 24-48 hours, 9 (18%) delivered between 48 hours to 1 week and 18 (36%) delivered after 1 week. In group B, 10 (20%) delivered in less than 24 hours, 18 (36%) delivered between 24 – 48 hours and 6 (12%) delivered between 48 hours and 1 week, and 16 (32%) delivered after 1 week. The P value was non significant. The side effects such as headache, palpitation and tachycardia were found in 9 (18%) cases, while in group B, 2(4%) had hypotension and tachycardia and the P value showed a significant change (p<0.04) (**Table V**) Neonatal outcome did not show any dependency on mortality and survival, and showed statistically non significant P value in both groups. Similarly, hospital stay at nursery showed no significant difference in two groups (P= 0.67). Perinatal mortality in salbutamol group was 160/1000 and nifedipine 80/1000 live births.

TABLE I:
DEMOGRAPHIC PROFILE

Mean±SD	Group A (n=50)	Group B (n=50)	t-value	p-value
Age (years)	27.64 ± 6.06	27.84 ± 6.16	0.16	0.87
Parity	2.34 ± 1.97	2.58 ± 1.99	0.61	0.545
Gestational Age (weeks)	31.94 ± 2.43	32.34 ± 2.68	0.78	0.436
Delivery interval	121.36 ± 106.19	455.04 ± 274.41	7.78	0.001

TABLE II:
CLINICAL CHARACTERISTICS OF LABOUR

Uterine Contractions	Group A (n=50)	Group B (n=50)
1-2	14(28%)	16(32%)
3-4	31(62%)	30(60%)
>4	5 (10%)	4(8%)
Cervical Dilatation		
<2cm	12(24%)	11(22%)
2-3cm	23(46%)	26 (52%)
3-4cm	15(30%)	13(26%)
Cervical Effacement		
Less than 50%	24(48%)	25(50%)
50 – 60%	16(32%)	18(36%)
50%	10(20%)	7(14%)

TABLE III: TIME FOR TOCOLYSIS

	Group A (n=50)	Group B (n=50)
1st hour	35 (70%)	10 (20%)
2nd hour	9 (18%)	14 (28%)
3rd hour	5 (10%)	18 (36%)
4th hour	1 (2%)	8 (16%)

P < 0.01

TABLE IV: PROLONGATION OF PREGNANCY

	Group A (n=50)	Group B (n=50)
24 hours	11 (22%)	10 (20%)
24 – 48 hours	12 (24%)	18 (36%)
48 – 1 week	13 (26%)	6 (12%)
After 1 weeks	14 (28%)	16 (32%)

TABLE V:
MATERNAL SIDE EFFECTS' FREQUENCY

Side effect	Group A (n=50)	Group B (n=50)
Headache	4 (8%)	0
Hypotension	0	1 (2%)
Nausea / Vomiting	2 (4%)	0
Palpitation / Tachycardia	3 (6%)	01 (2%)

P = 0.04

TABLE VI:
NEONATAL OUTCOME

	Group A (n=50)	Group B (n=50)
Alive	42(84%)	46(92%)
Neonatal Death	8(16%)	4(8%)
Stay In Nursery		
< 24 hours	15 (60%)	19 (70.4%)
24-48 hours	6(24%)	4(14.8%)
> 48 hours	4(16%)	4(14.8%)

DISCUSSION

Preterm birth is not singularly the consequence of preterm labour. There are three major etiological factors such as preterm rupture of membranes (25%), spontaneous preterm labour in pregnancy with intact fetal membranes (50%), complication of pregnancy that severely jeopardize fetal and maternal health (25%), and the life style factor. Approximately two thirds of all preterm occur spontaneously. Preterm birth[8] is classified in mild preterm (32-36 weeks), very preterm (28-31 weeks) and very extremely preterm (<28 weeks). Preterm delivery before 34 weeks gestation account for 75% cases of neonatal mortality, and mortality rate from 32 weeks of gestation are similar to those at term.[9] Various drugs have been used in inhibiting preterm labour with the aim of tocolytic therapy to prolong gestation long enough till maturation of fetus is completed. This is done to delay delivery for at least 48 hours so that corticosteroid administration is effective or for transfer of patient to tertiary care centre with neonatal intensive care facility. In this study, highest number of patients (53%) was in 25-30 years and lowest number (21%) among 20-25 years. This study was in similarity with the study of Iqbal J et al,[10] where no patient was below the age of 20 years. Mean age in this study for group A was 25.8 $\pm$ 5.2 and group B 27.0 $\pm$ 5.7 years which is comparable to the study of Ghazi A, et al.[5] But our study was in contrast to the study by Lockwood CJ et al who found the increased risk of preterm delivery in women <20 years and over 35 years of age.[11] This may be due to the lack of knowledge about the ages in female. In this study, most of the patients were of low parity which is contradictory to the results found in study of Copper L et al,[12] where incidence of preterm labour was high in multipara. This may be due to because all the patients

were low parity in our study or due to the fact that more multipara delivered at home and did not come to the hospital. In this study, mean gestational age was 32.0 ± 2.34 years in group A and for group B, it was 32.3 ± 2.34 years which is comparable to the study by Weerakul W et al, where mean gestational age was 31.7 ± 1.8 years. In this study, 43 (86%) patients with salbutamol delivered after 24 hours showing it to be an effective drug and this is comparable to other studies, whose results were 85%, 86% and 81% respectively.[12,13,14] In our study delivery with nifedipine was found comparable to salbutamol and this is also proved in many different studies.[12,13] In this study, 9 (18%) patients in group A as compared to only 2 (4%) in group B had side effects, thus as compared to salbutamol nifedipine had no serious maternal side effects. This is comparable to study by Kiran K Malik.[14] None of our patient had pulmonary edema but on review of literature one case of pulmonary edema among 582 women was reported treated with beta-agonist by Ferguson JE et al.[17] This is possibly because of small sample size. Regarding neonatal outcome in terms of stay was similar in nursery in both groups. This shows no significant difference in the birth related outcomes between groups. Similar results were found in different control trials. This study shows that nifedipine is a better choice for tocolysis[16], compared with salbutamol in view of less maternal side effects and comparable results regarding prolongation of pregnancy and neonatal outcome.

CONCLUSION

This study concludes that salbutamol and nifedipine are equally effective regarding delay of delivery, prolongation of gestation and neonatal outcome but nifedipine is more effective in view of easy intake, less active maternal and fetal monitoring and very few side effects as compared to salbutamol which requires strict monitoring of both mother and fetus. Salbutamol has further disadvantage of an intravenous route.

REFERENCES

1. Ahmad K, Malik A, Yousuf W. Perinatal morbidity and mortality in cases of preterm labour, an antegarde study conducted at Lady Wellington Hospital, Lahore. Biomedica. 2000; 16: 74-7.
2. Fahim F, Mehrunnisa. Contribution of preterm delivery to perinatal mortality. J Postgrad Med Inst. 2004; 18(2): 275-9.
3. Whitworth M, Quenby S. Prophylactic oral betamimetics for preventing preterm labour in singleton pregnancies. Cochrane Database Syst Rev. 2008; (1): CD006395.
4. Ronnie F, Lamon M, Mason R, Paul E, Adinkra. Advances in use of antibiotics in the prevention of preterm birth, In: Bonnar J. editor. Recent advances of obstetrics and gynecology. 21st ed.. London; Churchill Livingstone 2001: 36-7.
5. Ghazi A, Jabbar S, Siddiq NM. Preterm labour – still a challenge! Pak J Surg. 2006; 22(4): 222-6.
6. Haas A, Maschmeyer G. Antibiotic therapy in pregnancy. Dtsch Med Wochenschr. 2008; 133 (11): 511-5
7. Kam KY, Lamont RF. Development in the pharmacotherapeutic management of spontaneous preterm labour. Expert Opin Pharmacother. 2008; 9 (7): 1152-68.
8. De Haas, Harlow BW, Cramer D, Frigoletto FD. Spontaneous preterm birth: A case-control study. Am J Obstet Gynaecol 1991; 165:1290-6.
9. Draper ES, Manktelow B, Field DJ, James D. Prediction of survival of preterm births by weight and gestational age: Retrospective population based study. BMJ. 1999; 319: 1093-7.
10. Iqbal J, Nausheen F, Bhatti FA. Management of preterm labour. Annals. 2004; 10:423-6.
11. Lockwood CJ, Kuczyuski E. Risk stratification and pathological mechanisms in preterm delivery. Paediatr Perinat Epidemiol. 2001; 15 (Suppl 2): 78-89.
12. Copper RL, Goldenberg RL, Creasy RK. A multicentre study of preterm birth weight and gestational age specific neonatal mortality. Am J Obstet Gynecol. 1993; 168: 78-84.
13. Weerakul W, Chittacharoen A, Suthutvorauvt S. Nifedipine versus terbutaline in management of preterm labour. Int J Gynaecol Obstet. 2002; 76: 311-3.
14. Malik KK. Comparison of Nefidipine with Salbutamol as tocolytic agents in preterm labour. Biomedica. 2007; 23: 111-5.
15. Papatsonis DN, Van Geijn HP, Ader HJ, Lange FM, Bleker OP, Dekker GA. Nifedipine and ritodrine in the management of preterm labour: a randomized multicenter trial. Obstet Gynecol. 1997; 90: 230-4.
16. de Veciana M, Porto M, Major CA, Barke JI. Tocolysis in advanced preterm labour: impact on neo-

natal outcome. Am J Perinatol. 1995; 12(4):294-8.
17. Ferguson JE, Dyson DC, Holbrook RH, Schutz T, Stevenson DK. Cardiovascular and metabolic effects associated with nifedipine and ritodrine tocolysis. Am J Obstet Gynecol. 1989; 161: 788-95.
18. Ferguson JE 2nd, 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.

AUTHOR AFFILIATION:

Dr. Naseem Junejo *(Corresponding Author)*
Consultant Obstetrician and Gynaecologist
Hyderabad, Sindh-Pakistan.

Dr. Firdous Mumtaz
Department of Obstetrics and Gynaecology
Liaquat University of Medical & Health Sciences,
Jamshoro, Sindh-Pakistan.