ORIGINAL ARTICLE

Efficacy of Calcium Channel Blocker as A Tocolytic Agent

SAADIA S, SHAMAYELA H, ASIFA A

ABSTRACT

Objective: This study was planned to determine the efficacy of calcium channel blocker as a tocolytic agent in pre-term labour and to evaluate the frequency of adverse effects of the drug

Study design: Descriptive cross-sectional study

Place and duration of study: Department of Obstetrics and Gynaecology. Fatima Memorial Hospital from March 2011 to August 2011

Sampling technique: Non-probability convenient sampling

Method: All pregnant women irrespective of booking status, age and parity presenting with preterm labour with cervical dilatation less than 3 cm between 28 to 36 weeks with singleton and twin pregnancy and intact membranes were included in the study. A proforma was formulated to document the details of each patient. Nifedipine was started as a tocolytic agent in these patients. The efficacy of the drug to postpone the delivery was recorded and both major and minor side effects were observed.

Results: During the study period 46 patients were enrolled. Delivery was successfully delayed upto 48 hours in 9 patients(19.5%) cases. Twenty seven cases (58.6%) delivered between 48 hours to 7 days. Thirteen cases (28.2%) remained undelivered till 7 days. Ca channel blocker failed to prolong pregnancy in 8.6% cases. Minor side-effects of the drug were observed in 5 cases (2.3%) like headache, nausea hypotension and flushing. No major serious adverse effect was seen in any women.

Conclusion: Results of our study are highly encouraging for the use of nifedipine as tocolytic agent. It is safe and effectively prolongs pregnancy. It was associated with few minor side effects which were tolerable.

Key Words: Tocolytic agents, calcium channel blocker, pre term labour, adverse effects

INTRODUCTION

Preterm birth is one of the leading cause of perinatal morbidity and mortality both in developed and under developed countries.[1] Preterm labour affects almost 12.8% of pregnancies.[2] The preterm births is responsible for 70% of neonatal morbidity and mortality. As a result it has a high impact on financial resources.[3]

Much work has been done to reduce its incidence but progress is still limited. Benefits can be anticipated even through gaining minimal pregnancy prolongation to allow the transfer of woman to centres with neonatal intensive care unit (NICU) and to administer corticosteroids for lung maturity.[4]

The aim of management of preterm labour is to identify the etiological cause and to prevent untimely uterine contractions.[5] Many agents have been used for the purpose of tocolysis including beta sympathomimetic agents, calcium channel blockers, prostaglandin synthetase inhibitors, magnesium sulphate (MgSo4) and oxytocin inhibitors. Beta agonists are still used by many obstetricians but due to concerns about its safety Royal College of Obstetrician & Gynaecologists (RCOG) have reservations considering it as first line tocolytic agent. [6] Research has shown that both Atosiban (oxytocin receptor inhibitor) and calcium channel blocker have less side effects but at the same time improved efficacy in prolonging preganancy. RCOG recommends atosiban & ca channel blockers as first line management of preterm labour.[7]

Calcium channel blockers as the name show target calcium channels in smooth muscles & cardiac muscle and slow the influx of extracellular calcium into the cell thus reducing muscular activity.[7] Decrease in intracellular calcium also results in vasodilatation, decrease in blood pressure (BP) with resulting tachycardia. Calcium channels are also present in myometrial cells and it has been seen that Ca channel blocker work more on smooth muscles as compared to cardiac muscles. [8] Peak levels of nifedipine reaches within 45-60 min after oral administration with half life of 2-3 hrs. [9]

Tocolysis with Ca channel blockers have shown a good safety profile and have positive effects on perinatal outcomes.[9,10] Commonly reported side effects are headache, palpitations,

transient hypotension, dizziness, flushing & oedema. [10]

However with increasing use of Calcium channel blockers, potentially serious side effects have been noticed sporadically like pulmonary edema, dyspnoea, hypoxia, myocardial infarction, atrial fibrillation and severe hypotension.[11] Recent reports have shown that chances of developing these serious side effects are enhanced when Ca channel blockers were used in women with multiple gestation, cardiac diseases, infection and diabetes mellitus. It is therefore advisable to use Ca channel blockers with great caution in such patients.[12,13,14]

This present study aims to evaluate the efficacy of Ca channel blocker in prevention of preterm labour and to evaluate the adverse effects.

MATERIAL AND METHODS

This descriptive cross-sectional study was carried at Fatima Memorial Hospital, Lahore, from March 2011 to August 2011.

All pregnant women irrespective of booking status, age, parity presenting with preterm labour between 28 to 36 weeks with singleton and twin pregnancy and intact membranes were included in the study. Women presenting with preterm labour with associated problems like cardiac disesase, antepartum haemorrhage, intauterine growth restriction & oligohydramnios, chorioamnionitis, fetal anomalies, preterm premature rupture of membranes, triplets and high order pregnancies were excluded from the study.

Women were diagnosed to have preterm labour if there were four uterine contractions in 30 minutes and cervical dilatation was less than 3cm informed consent was taken and data recorded on proforma. Proforma included information regarding age, parity, gestational age and risk factors for preterm labour. A detailed history especially focusing onto risk factors of preterm labour was taken. Complete examinatiom of blood and urine was sent for each women and high vaginal swab sent in those women who complained of vaginal discharge. Calcium channel blocker with the name of nifedipine was started with a loading dose of 20 mg followed by 10 mg twice daily. In women where uterine activity still persisted after the loading dose, an additional 10 mg nifedipine was given orally 4-6 hourly depending on the uterine activity. Case was considered as treatment failure when uterine contractions persisted 12 hours after initiation of treatment. Fetomaternal monitoring was done by recording maternal pulse, blood pressure, temperature and palpable uterine contractions. Fetal health was assessed by cardiotocography in pregnancies beyond 32 weeks of gestation. The efficacy of the drug to successfully postpone delivery by 48 hours, 7 days and beyond 7 days was recorded. Minor and major side effects of the drug were also assessed.

RESULTS

During the study period 46 patients were enrolled in the study. The demographic characteristics of the study group are given in Table-1. Most of the women with preterm labour had age range between 26-30 years (39.1%), followed by age group of 21-25 years (34.7%), 31-35 years (17.3%) and 35 years (8.6%).

Table-1: Demographic characteristics of study group

Characteristics	Number	Percentage
Age (years)		
21-25	16	34.7
26-30	18	39.1
31-35	8	17.3
>35	4	8.6
Parity		
Primigravida	15	32.6
Para 1-3	19	41.3
>Para 3	12	26.0
Gestational Age (weeks)	8	17.3
28-32	28	60.8
32-34	10	21.7
34-36		
Risk factors of preterm labour	6	31.5*
Previous preterm	6	31.5*
delivery	4	21.0*
Twin pregnancy		
Infections (bacterial	2	10.5*
vaginosis & urinary	1	5.26*
tract infection)		
Fibroid pregnancy		
Polyhydramnios		

*Percentages calculated against 19 that is number of women with identified risk factors

In our study group most of the women were para 1-3 (41.3%), followed by primigravidas (32.6%) and women more than para 3 (26.0%). Majority of the women presenting with preterm labour had a gestational age of 32-34 weeks being

60.8% followed by 21.7% with gestational age of 34-36 weeks and 17.3% with gestational age between 28-32 weeks.

Previous preterm delivery and twin pregnancy were the commonest risk factors identified in the study group (31.5%). Infections both urinary tract infection and bacterial vaginosis, fibroid pregnancy and polyhydramnios were the other risk factors identified with frequencies of 21%, 10.5% and 5.26% respectively.

The efficacy of Ca-channel blocker was assessed by delay in delivery time. Delivery was successfully delayed upto 48 hours in 19.5% cases. Twenty seven cases (58.6%) delivered between 48 hours to 7 days. Thirteen cases (28.2%) remained undelivered till 7 days. Ca channel blocker failed to prolong pregnancy in 8.6% cases.

Minor side-effects of the drug were observed in 5 cases (2.3%) which are summarized in Table-3. Most women experienced more than one side-effect. The commonest adverse effect was headache followed by hypotension, tachycardia and nausea. No major serious adverse effect was seen in any women.

Table-2: Delay in delivery time

Delivery interval time	Number	Percentage
Upto 48 hours	9	19.6
48 hours-7 days	27	58.6
>7 days	13	28.2
Treatment failure	4	8.6

Table-3: Frequency of side-effects of Ca-channel blocker

Side-Effects	Number	Percentage
Headache	2**	40*
Hypotension	1**	20*
Nausea/vomiting	1**	20*
Tachycardia	1**	20*

*Percentages calculated against 5 that is number of women who had side-effects

**Due to multiple responses the total does not add to 5

DISCUSSION

Preterm birth continues to be the chief cause of both perinatal morbidity and mortality. Different pharmacological agents have been used as tocolytic agents that differ in their efficacy and potential side-effects.[15] Ca-channel blocker is regarded as effective tocolytic agents with minimal side effects. Nifedipine has gained popularity due to its oral route of administration and cheap cost and low incidence of adverse maternal and fetal effects.[16]

Iffat[17] found the tocolytic efficacy of calcium channel blocker to be 82% in a study recruiting 35 women. Another study conducted by Nikolar also concluded that calcium channel bloker is an effective tocolytic agent[18]. Tstaris after analyzing 9 randomised controlled trials concluded that calcium channel blocker was more effective than beta sympathomimetic in prolonging delivery for 48 hours.[19] These results are analogous to various studies using beta sympathomimetic and magnesium sulphate as tocolytic agent.

In our study the success rate of calcium channel blocker to prolong pregnancy turned out to be 92.4%. These results are compareable to a study carried out by Glock and Morales[20] who reported the efficacy of calcium channel blocker as 92%.

Several randomized controlled trials have concluded that nifedipine is safe and even superior to beta agonists. All agreed that nifedipine has a better side effect profile and very few women stop treatment because of its adverse effects. [21]

A study from Hong Kong assessed the side effect profile of calcium channel blocker in 212 women. Calcium channel blocker was discontinued in 2% of the cases due to severe adverse events whereas in our studies no major adverse event was seen. Milder side effects like headache and flushing were seen in 4% of cases and nausea/dizziness in 1%.[22] whereas in our study these side effects were seen in 5 (2.3%) patients out of 46.

CONCLUSION

Nifedipine is an effective and safe tocolytic agent. It successfully prolongs the pregnancy for more than 48 hours in most of the cases to gain time for steroids. However, during its use, monitoring of vital signs is necessary to prevent and decrease the complications associated with its use. In this study nifedipine is used in minimal dosage and no serious side effect is seen except for few minor complications like headache. Lastly it is prudent not to combine nifedipine with other tocolytic agents particularly beta-agonist as this combination of drugs is associated with very serious complications like pulmonary oedema and myocardial infarction.

REFERENCES

1. Nasser AH, Aound, USTA IM-AmJ Perinatop. 2011 Jan; (28(1):57-66,Epub 2010 Jul 16.
2. Martin JA, Hamiltion BE, Sutlon PD, et al Centers for Disease control and prevention National Centre for Health statistics. National vital statistics system, Bitrhs: final data for 2005, Nati Vital stat Rep 2007;56:1-103
3. ACOG Commitee on practice bulletins-obstetrics, ACOG practice bulletin, Management of pretem labor, Number 43,May 2003. Int J Gynaecol Obstet 2003; 82:127-135
4. Tocolytic Drugs for Women in Preterm Labour. Clinical Guideline No. 1(B). Royal college of Obstetricians and Gynecologists, 2002. Available at:http://www.rcog.org.uk/files/rcog-corp/GT1BTocolyticDrug2002revised/pdf. Accessed December 28,2009
5. Nayler WG, Poole-Wilson P. Calcium antagonists: definition and mode of action. Basic Res Cardiol 1981;76:1-15
6. Hearne AE, Nagey DA. Therapeutic agents in preterm labor; tocolytic agents. Clin Obstet Gynecol 2000;43:787-801
7. Nakajima H, Hoshiyama M, Yamashita K, Kiyomoto A. Effect of diltiazem on electrical and mechanical activity of isolated cardiac ventricular muscle of guinea pig. Jpn J Pharmacol 1975;25:383-392
8. Braunwald E. Mechanism of action of calcium-channel-blocking agents. N Engl J med 1982;307:1618-1627.
9. Giles W, Bisits A. Preterm labour. The present and future of tocolysis. Best Pract Res Clin Obstet Gynaecol 2007;21:857-868
10. Oei SG. Calcium channel blockers for tocolysis: a review of their role and safety following reports of serious adverse events. Eur J Obstet Gynecol Reprod biol 2006;126:137-145.
11. Oei SG, Oei SK, Brolmann HA. Myocardial infarction during nifedipine therapy for preterm labor. N Engl J Med 1999;340:154. Bal L, Thierry S, Brocas E, Adam M, Van de Louw A, Tenaillon A. Pulmonary edema induced by calcuim-channel blockade for tcolysis. Anestth Analg 2004;99:910-911.
12. Vaast P, Dubreucq-Fossaert S, Houfflin-Debarge V, et al. Acute pulmonary oedema during nicardipine therapy for preterm labour, report of five cases. Eur J Obstet Gynecol Reprod Biol 2004;113:98-99. Hodges R, Barkehall-Thomas A, Tippett C. Maternal hypoxia associated with nifedipine for threatened preterm labour. Br. J Obstet Gynaecol 2004;111:380-381.
13. Van Geijn HP, Lenglet JE, Bolte AC. Nifedipine trials: effectiveness and safety aspects. Br. J Obstet Gynaecol 2005;112:79-83.
14. Psaty BM, Heckbert SR, Koepsell TD, et al. The risk of myocardial infarction associated with antihypertensive drug therapies. JAMA 1995;274:620-625.
15. De Heus R, Mol BW, Erwich JJ, et al. Adverse drug reactions to tocolytic treatment for preterm labour: prospective cohort study. BMJ 2009;338:b744
16. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturity for women at risk of preterm birth. Cochrane Database Syst Rev 2006;3:CD004454
17. Nuzhat Rasheed, Iffat Yasmin, Sumaira Siddique. Role of nifedipine in comparison to salbutamol in the management of preterm labour. Pak J Med Health Sci Jan –Mar 2011;5(1):64-7
18. Nikolar Ginekol (Sofiia). Treatment of preterm delivery with calcium channel blocker. 2007:46(9):18-22
19. Mercer BM, Merlino AA; Society for Maternal Fetal medicine. Magnesium sulphate for preterm labor and preterm birth.Obstet Gynecol2009;114:650-668
20. Glock JL, Morales WJ. Efficacy and safety of nifedipine versus magnesium sulphate in the management of preterm labour : a randomized study . Am J Obstet Gynecol 1993; 169: 960-964
21. Bracero L.A, Leikin E, Tejani N. Comparison of nifedipine and ritodrine for the treatment of preterm labor. Am J Perinatol 1991;8:365-396
22. Chan LW, Sahota DS, Yeung SY, et al. Side effect and vital sign profile of nifedipine as a tocolytic for preterm labour. Hong Kong Med J 2008;14:267-272