E:/Biomedica Vol.23 Jul. – Dec. 2007/Bio-10 (A)

COMPARISON OF NEFIDIPINE WITH SOLBUTAMOL AS TOCOLYTIC AGENTS IN PRETERM LABOUR

KIREN K. MALIK
Department of Obstetrics and Gynaecology, Fatima Jinnah Medical College / Sir Ganga Ram Hospital, Lahore

This study was carried out to evaluate the tocolytic efficacy for prolongation of pregnancy with oral nifidipine in comparison to solbutamol, and to evaluate side effects of nefidipine. It was an interventional study and was performed for a period of one year in Sir Ganga Ram hospital, and in the department of obstetrics and gynaecology, Fatima Jinnah Medical College. Sixty women were enrolled in this study. A questionnaire was filled for each patient. Once randomised the women received oral nifedipine or intravenous solbutamol in recommended dosage for acute tocolysis. Measurements of maternal pulse, blood pressure and foetal heart rate were recorded for upto 24 hours and compared over the treatment course. Outcome measures were prolongation of pregnancy as a result of tocolysis and recorded in hours and days, along with maternal and foetal side effects. Delivery was deferred for 48 hours, 3 to 7 days and more than 7 days in 30%, 6.66% and 3.33% respectively in nifedipine group compared with 26.66%, 3.33% and 3.33% of women respectively in solbutamol group (no significant difference P > 0.05). Major maternal and foetal side effects were significantly less common in nifedipine group (0%) than in solbutamol group (13.33%) P value = 0.05. Nifedipine is almost as effective as solbutamol in suppressing preterm labour. Its use is associated with less frequent side effects.

Preterm labour is everyday's obstetrical problem. The 'early' baby requires intensive medical attention, which taxes our limited neonatal services. The earlier the delivery before completion of gestation the greater the risk to the newborn. Onset of labour after 24 weeks and before 37 weeks of the gestation is labelled as preterm labour.[1] The incidence of preterm birth has remained unchanged for years at about 8 - 10% per anum and prematurity remains the leading cause of neonatal mortality accounting for 70-85% of all neonatal deaths, so the prevention and treatment of preterm labour is a central issue in pregnancy care.[2] The percentage of perinatal deaths in Pakistan due to prematurity is 8.81%.[3]

Premature infants are at great risk for making it imperative to make efforts to stop the preterm labour. Management of threatened preterm labour includes: managing treatable predisposing factors of preterm labour and tocolysis. There are many tocolytic agents that are under consideration all over the world. The prevention of preterm labour by tocolytic agent aims to prolong pregnancy sufficiently to administer glucocorticoids and arrange transfer of women to a center with neonatal intensive care facilities.[4]

The perfect tocolytics do not exist however the large number of significant and occasionally potentially life threatening side effects of beta sympathomimetic agents if used inappropriately, have prompted the search for other tocolytic agents with their own foetomaternal side effects. Surveys of obstetricians indicate a high usage of tocolysis for preterm labour, but evidence that this treatment confers overall benefit is still lacking. Betamimetics are now, correctly, being abandoned in favour of nifedipine, which has superior tocolytic properties with better neonatal outcomes.[5]

The main problem with preterm labour is our lack of progress in the successful management of this condition. We as clinicians need to reassess our approach to this problem because preterm labour is not a disease, but an event, that may result from multiple independent pathways. The approach requires a close collaboration between clinicians and researchers in order to make significant progress in this difficult area and ultimately improve outcome.[6,7] Improvements in tocolysis with the recent introduction of new therapeutic agents have led to a tendency away from prescribing beta sympathomimetic agents.

In this study beta sympathomimetic agent (solbutamol) the standard group of drugs was compared with the newer agent nifedipine as a tocolytic agent.

MATERIALS AND METHODS

Study period:

The study was conducted from March 2006 to April 2007. It was carried out in Sir Ganga Ram Hospital, Lahore, in the department of obstetrics and gynaecology, Fatima Jinnah Medical College. Sixty women were included in the study, meeting the inclusion criteria.

Inclusion criteria

- The pregnant women presenting with preterm labour between 28 to 35 weeks of gestation.
- singleton pregnancy.

Exclusion criteria

- Ruptured membranes.
- Intrauterine demise.
- intrauterine growth restriction.
- cervical dilatation more than 3 cm.
- Maternal or foetal condition necessitating immediate delivery.
- treatment with another tocolytic agent in preceding 24 hrs.
- Sensitivity to nifedipine.
- in cases of solbutamol cardiac patients.
- Diabetics.
- thyrotoxicosis.

The Apparatus

The two tocolytic agents were used for the two comparative groups. The whole information including baseline data, drug used and the outcome measures were filled in the proforma, nifedipine was used (calcium channel blocker) as capsule adalat 10 mg. For beta antagonist (solbutamol) intravenous ventolin injections were used. On ordinal data chi square test was applied to calculate p value and on numerical data student t test was applied.

Methodology

In this experimental study sixty women who presented at Sir Ganga Ram hospital with preterm labour and met inclusion and exclusion criteria, were included from March 2006 to April 2007.

Preterm labour was defined as three or more contractions per 30 minutes or serial change in bishop score as assessed by senior medical officer. Informed consent was taken from women, WHO were randomly selected to receive either glyceryl trinitrate patch or solbutamol infusion on alternate basis after assessment by a senior medical officer.

The protocol of assessment consisted of:

- Assessment of duration and frequency of palpable uterine contractions.
- Cervical examination in order to calculate bishop score.

The women then prophylactically received: a 1000 ml intravenous infusion of 0.9 % saline or ringer lactate over 30 - 60 minutes, sedation injection beta methasone 12mg intra-muscular, antibiotic cover augmentin / ampicillin. A second cervical examination was then performed and uterine contractions were assessed by the same doctor and bishop score calculated. If the contractions persisted or was a change in bishop score the women were randomised to receive either nifedipine or intravenous solbutamol. In this way two groups were formed including women on alternate basis that is in group 1 women received nifedipine (i.e. patient no. 1,3,5) and in group 2 received intravenous solbutamol.

Group 1:

In group 1 patients meeting inclusion and exclusion criteria and after assessment by senior medical officer destined to receive tocolytic therapy were included. Data were entered in standardised proforma and filled as the treatment proceeded. The women receive nifedipine therapy after initial hydration, sedation, corticosteroid and antibiotic cover.

A 10 mg capsule of adalat was given every 20 – 30 minutes for the first hour sublingually. If contractions had not decreased in strength or frequency after one hour dose repeated till contractions stopped maximum upto 4 hours then 60–90 mg/ day of slow release nifedipine depending on uterine activity.

- Continuous foetal heart rate was monitored.
- Maternal pulse and blood pressure was recorded every ten minute for up to 30 to 60 minutes thereafter half hourly for 12 hours.
- Blood samples for complete blood and high vaginal swab were taken at admission.

Treatment was carried out until contractions had completely subsided, usually this happened within 24 to 48 hours or when treatment fails. End point of treatment was delivery in hours or days from the start of tocolytic therapy and was considered successful if delivery was deferred for at least 48 hours. The women remained admitted for at least 72 to 96 hours after tocolysis and were then discharged and oral dose given for one week and advise follow up untill delivery. Side effects were observed and recorded, they included maternal hypotension, headache, flushing, and foetal heart rate changes.

Group 2:

In group 2 pregnant women received tocolytic therapy in the form of beta sympathomimetic agent solbutamol (ventolin). Thirty women were rando mised to receive solbutamol infusion that was started at a rate of 50 micrograms per minute i.e. 8 ampules of solbutamol injection (4 mgm) per 500 ml of 0.9% normal saline infusion at 8 drops per minute (0.5 ml/ min). The dose was increased by 15 microgram per 30 minute up to a maximum of 300 microgram per minute or until contractions stopped or unacceptable side effects appear.

The effective tocolytic dose was maintained for 12 hours and then tapered over 2 to 4 hours. Treatment was considered successful if delivery was deferred for 48 hours. Women in whom beta agonists failed were not treated with an alternate drug. Women in whom quiescence was maintained beyond 72 hours were discharged and instructed to continue bed rest and follow up. Monitoring was done as in GTN therapy group and chest auscultation was also performed on hourly basis. Side effects were carefully recorded which included maternal tachycardia, pulmonary oedema, headache, tremours, palpitations, chest discomfort, ECG changes, hypotension and foetal heart rate changes.

Statistical Analysis

In baseline data the maternal variables are; age, parity, history of preterm delivery, gestational age at presentation, bishop score at presentation and at randomisation in two groups under study.

The statistical tests used for the baseline data are students t test for maternal age, gestational age at presentation, bishop score at presentation and at randomisation. Students t test is applied after calculating mean and standard deviation for each variable. Chi square test is used for parity and history of preterm delivery after calculating percentages in two groups. P value for each variable between two groups is calculated and given in results and Table 1.

In outcome measures variables are: delivery within 48 hours, from 3 to 7 days and beyond 7 days. The side effects of the two drugs are also included and Chi square test is applied on these variables to calculate the P value for each variable. The results are given in Tables 2, and 4. Degree of freedom for t test is taken as n – 2 and for chi-square as n-1.

RESULTS

A total of 60 women were included in the study and were randomised to receive nefidipine (n=30) or solbutamol (n=30) and followed up till delivery.

There was no difference in P value > 0.05 in base line data for nifedipine compared with salbutamol group. Table 1 presents base line data or characteristics on admission in two groups. Nifidipine tocolysis was successful (delivery delayed > 48 hours) in 9 women (30%). Delivery was delayed for 3 to 7 days in 2 women (6.66%) and beyond 7 days in 1 woman (3.33%). Failure of tocolysis occurred in 18 women (60%). Solbutamol tocolysis was successful {delivery delayed for > 48 hours} in 8 women (26.66%). Delivery was delayed for 3 to 7 days in 1 woman (3.33%) and beyond 7 days in 1 woman (3.33%). Tocolysis was unsuccessful in 19 patients (66.66%). There were no significant differences in the two groups as regard the delay in delivery for more than 48 hours, 7 days or beyond (P value more than 0.05). This information is presented in Table 2.

Headache was more common in nifidipine group but all other side effects were more common and subjectively more troublesome in solbutamol group. Statistically minor side effects were recorded in 13 women (43.33%) in nifidipine group and 19 women (63.33%) in the other group. No major side effects seen in nifedipine group but there was need to stop treatment in 4 women (13.33%) due to heart rate more than 130 beats per minute and chest pain – (P value = 0.05 so it is significant). In GTN group side effects subsided in a few hours and did not necessitate any special measures (Table 3). In statistical analysis, P value less than or equal to 0.05 is considered statistically significant.

DISCUSSION

This study shows that nifedipine is an effective tocolytic agent compared to beta agonist and it causes fewer side effects and less haemodynamic compromise. In order to evaluate critically the effect of nifedipine we included women with objective evidence of change in bishop score or persistent uterine contractions after supportive measures for more than one hour. Success of tocolysis was defined as delay of labour for at least 48 hours, to allow enhancement of foetal lung maturity with glucocorticoids. Using these criteria successful tocolysis was achieved in 40% of women treated with nifedipine. There is growing interest in calcium channel blockers as a potentially effective and well tolerated form of tocolysis. Studies suggest that nifedipine drugs may be effective tocolytic agents without significant foetal or maternal side effects. There were no adverse effects on foetal blood gas values, oxygen or substrate uptake, umbilical flow, cardiac output, blood pres-

Table 1: *Characteristics of women in preterm.*

Prolongation of pregnancy	Nifedipine	Beta agonist	Tests	P-value
For 48—72 HRS	9/30 (30%)	8/30 (26.66)%	Chi sq. 0.046	> 0.05
For 3—7 DAYS	2/ 30 (6.66%)	1/30 (3.33%)	0.32	> 0.05
For >7 DAYS	1/30 (6.66%)	1/30 (3.33%)	0	> 0.05
Delivery within 48 Hrs	18/30 (60%)	20/30 (66.66%)	0.064	> 0.05

sure or heart rate.

However, in 2003 the Cochrane database of systematic reviewer's conclusion was when tocolysis is indicated for women in preterm labour, calcium channel blockers are preferable to other tocolytic agents compared, mainly betamimetics. Further research should adderss the effects of differrent dosage regimens and formulations of calcium channel blockers on maternal and neonatal outcomes.[8-10] Treatment with beta agonists however often required discontinuation due to severe side effects and complications. The ability to prolong pregnancy by inhibiting uterine contractions bwas similar to beta agonist in this study.[11]

Table 2: *Prolongation of pregnancy with tocolytic therapy.*

Base Line Data	**Nifedipine n= 30**	**Beta agonist n = 30**	**Statistical test**	**P-value**
Maternal Age	Mean(SD) 25.27 (4.58)	Mean (SD) 26.6 (5.40)	Student t test 1.01	>0.05
Multiparity	22/30 (73.33)	10/30 (66.66%)	Chi sq test .056	> 0.05
History PTD	45.45%	30%	Chi sq test 0.479	>0.05
Gestainal Age	Mean (SD) 32.63 (2.04)	Mean (SD) 32.3 (2.02)	0.62 students t test	>0.05
Bishop Score 1	Mean (SD) 4.1 (0.81)	Mean (SD) 4.3 (0.8)	Student t test 1	>0.05
B.S 2	5.1 (1.2)	5.3 (1.24)	0.625	>0.05

Table 3: *Side effects of the drugs.*

	GTN	**Beta agonist**	**Tests**	**P Value**
Minor side-effects	43.33% 13/30	63.33% 19/30	Chi sq.0.0736	>0.05
Major side-effects	0%	13.33% 4/30	3.76	=0.05

The limitations of this study were that nifedipine or its metabolites levels were not measured in maternal or foetal blood. Fetal monitoring with electronic foetal monitoring alone was done. Facilities of Doppler artery studies for feto placental blood flow and foetal blood sampling to measure calcium channel blockers levels were not available. Furthermore, foetus was followed till delivery and after birth any effect of drugs on neonate immediately and later on were not studied. The rapid and effective action obtained with the nifedipine, its simplicity of administration and safety suggest that prospective randomised comparison of nifedipine with established therapy or placebo should be carried out in larger study populations. This study clearly showed that solbutamol has a pronounced effect on maternal and foetal cardiovascular systems than nifedipine. Nifedipine excellent safety record it might be an alternative to beta agonist for preterm labour and could make a major contribution to the management of preterm labour.

This study **Concludes** that nifedipine is a useful tocolytic agent comparable in efficacy to beta agonist but with a fewer side effects. There is a need for further clinical trials to establish an unequivocal evidence base for tocolysis, which requires placebocontrolled trials, and for comparative trials to identify the agent with superior characteristics. So, it is suggested that oral nifedipine may be promising as a safe, effective means for tocolysis.

REFERENCES

1. Ahmed K, Malik A, Yusuf W. Perinatal morbidity and mortality in cases of preterm labour, an antegrade study conducted at lady willingdon hospital, Lahore. Biomedica 2000; 16: 74-7.
2. Kolben M, Maritus J. Prevention and treatment of preterm labour. Geburtshilfe und Frauenheilkunde 2000; 60 (4): 206-211.
3. Rana S. Maternal and perinatal mortality. In: Rana S. Obstetrics and perinatal care for developing counteries. Islamabad Pakistan: Saf publications, 1998; 35-74.
4. Greenfield P J, Lamont R F. The contemporary use of tocolytics. Curr Obstet Gynaecol 1999; 10 (4): 218-224.
5. King JF. Tocolysis and preterm labour. Curr Opin Obstet Gynecol, 2004; 16 (6): 459-63.
6. McNamara HM. Problems and challenges in the management of preterm labour. BJOG 2003; 110 suppl 20: 79-85.
7. Lamont RF. Looking to the future. BJOG 2003; 110 (20): 131-5.
8. King JF, Flenady VJ, Papatsonis DN, Dekker GA, Carabane B. Cochrane Database Sys Rev. 2003; (1): CD 002255.
9. Giles W, Bisits A. The present and future of tocolysis. Best Pract Res Clin Obstet Gaenecol 2007; 23: (Epub ahead of print.

10. Coomarasamy A, Knox EM, Gee H, Song F, Khan KS. Effectivenes of nifedipine versus atosiban for tocolysis in preterm labour; a metaanalysis with n indirect comparison of randomized trials. BJOG 2003; 110 (12): 1045-49.

11. Tan TC, Devendar K, Tan LK, Tan HK. Tocolytic treatment for the management of preterm labour: a systematic review. Singapore Med J2006; 47 (5): 361-6.