Comparison of Nifedipine Versus Indomethacin for Acute Preterm Labor

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Objective:

Our objective is to compare the prolongation of pregnancy by 48 hours after women are diagnosed with preterm labor prior to 32 weeks gestational age and treated with either nifedipine or indomethacin. We hypothesize that indomethacin will significantly arrest preterm labor by 48 hours in more women compared to nifedipine. The primary outcomes measured will be delaying preterm delivery by 48 hours; secondary outcomes measured will include delay of delivery by 7 days and decreasing delivery before 37 weeks.

Background:

Preterm birth accounts for 70% of neonatal deaths, and 25-50% of cases of long term neurologic impairment in children. About 12% of all live births occur before term and 50% of these were preceded by preterm labor.[1] Tocolytics have been well described in the literature and are recommended to provide time for corticosteroid administration, transfer to a tertiary facility and allow time for magnesium infusion. There are four main categories of tocolytics described by ACOG: calcium channel blockers, prostaglandin inhibitors, magnesium sulfate and B2 agonists. B2 agonists are no longer used outside of an acute setting due to significant maternal side effects; a black box warning has been issued by the US Food and Drug Administration as a result. Magnesium sulfate serves dual purposes in obstetrical medicine: it is used for neonatal neuroprotection and as a tocolytic. However, a recent meta-analysis revealed that it is a weak tocolytic agent compared to other tocolytics. It also revealed that both calcium channel blockers and prostaglandin inhibitors are consistently ranked among the top three tocolytics in delaying delivery by 48 hours, decrease RDS, neonatal mortality and maternal side effects.[2] The most commonly used and studied tocolytic within the calcium channel blocker class is nifedipine. The most commonly used and studied tocolytic within the prostaglandin inhibitor class is indomethacin.There have been only two published randomized control studies that directly compares nifedpine and indomethacin.[3,4] These two studies did not have the power or standardization of enrollment to guide us clinically. Here we propose a multi-institutional randomized controlled study directly comparing nifedipine to indomethacin in the setting of preterm labor. We plan to capitalize on the developing network for obstetrical clinical trials within the University of California Fetal Therapy Consortium, and involve all five medical campuses in the state.

Outcomes:

1. To compare the prolongation of pregnancy by 48 hours after women are diagnosed with threatened preterm labor prior to 32 weeks gestational age and treated with either nifedipine or indomethacin. The primary outcome measured will be delay of (preterm

delivery) by 48 hours. Secondary outcomes will be delay of delivery by 7 days and rate of delivery before 37 weeks.

2. Other secondary maternal outcomes included will be maternal adverse side effects significant enough to stop or delay medication use, need for a second tocolytic to halt preterm contractions. Neonatal outcomes measured will be respiratory distress syndrome (RDS), interventricular hemorrhage (IVH), patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), intubation, number of NICU days and neonatal mortality.

Existing Knowledge:

Specifically we intend to answer the question of which of these two tocolytics should be used as afirst line agent. Again there is much evidence showing that calcium channel blockers and prostaglandin inhibitors are the two classes of medications that are superior in delaying delivery for up to 48 hours, decrease RDS, neonatal mortality and maternal side effects compared to other medications.[2] There has been one poorly designed small study directly comparing nifedipine to indomethacin.[3] Another study compared magnesium to nifedipine and to indomethacin. Again, this study had an inadequate sample size. In addition, there was crossover of tocolytic groups, which does not allow for direct comparison. Women in preterm labor typically present with painful contractions and some degree of cervical dilation. There is a small window to treat these patients in an attempt to arrest preterm labor. Using the optimal tocolytic agent initially can potentially prevent or delay preterm birth with its resultant neonatal morbidity and mortality.

Previous Research:

Nifedipine is a well-studied tocolytic. A Cochrane review in 2011 evaluated data on all calcium channel blockers used for tocolysis; over 1029 women were included in the review. When compared to other tocolytic agents, calcium channel blockers decrease delivery within 7 days, decrease delivery less than 34 weeks, and have less need to stop medication for maternal adverse effect. Furthermore calcium channel blockers (compared to other tocolytics) decreased the incidence of RDS, NEC, IVH and neonatal jaundice in the newborn.[5] Nifedipine has thus shown benefit as a tocolytic. One meta-analysis demonstrated that nifedipine compared to B2 agonists had a reduction of preterm labor within 7 days, delivery before 34 weeks and reduction of RDS, NEC, IVH, neonatal jaundice, admission to the NICU and NICU stay. Compared to magnesium, nifedipine was associated with fewer maternal side effects. Although no difference in major neonatal outcomes were demonstrated, there was a significant decrease in NICU admission and NICU length of stay with nifedipine.[6]

Indomethacin has also been well studied. The Cochrane review looked at COX inhibitors and their use as a tocolytic. Of the 13 trials included, 10 specifically used

indomethacin. When compared to placebo, there was reduction in birth before 37 weeks gestation, an increase in gestational age at time of delivery and increase in birth weight. When compared to other tocolytics there was a reduction in birth before 37 weeks as well as reduction in maternal drug reaction.[7]

There have been two large meta-analyses comparing tocolytics to determine the optimal first line agent. The first was published in 2009 to compare the outcomes of delaying delivery at 48 hours, 7 days and until 37 weeks. A decision tree was created using the highest efficacy to toxicity ratio. The study concluded that all tocolytics were superior to placebo for delaying delivery for 48 hours and 7 days. In addition, prostaglandin inhibitors were superior to other tocolytic agents.[8] As described above, the second open network meta-analysis reviewed all tocolytics to determine the best probability for delaying delivery by 48 hours, and to decrease RDS, neonatal mortality and maternal side effects. Both prostaglandin inhibitors and calcium channel blockers were ranked among the top three medication classes for each category. Specifically prostaglandin inhibitors were ranked the best tocolytic in delaying preterm delivery within 48 hours and maternal side effect.

Calcium channel blockers ranked the best tocolytic for neonatal outcomes.[2] As discussed above, there have been two randomized control studies comparing nifedipine versus indomethacin. The first study included a total of 79 patients comparing nifedipine to indomethacin. This study found that nifedipine was superior for arresting contractions during the first two hours; however, if there was a response to indomethacin within the first two hours, there was no difference in delivery at 48 hours or up to 7 days. There are several design flaws in the study including the small sample size for which a calculation was not described, use of dosing regimens for both nifedipine and indomethacin that are not commonly used, and generous, non-standard inclusion criteria for preterm labor.[3]

The second randomized control study compared 3 different tocolytics: nifedipine, indomethacin and magnesium. This study had several flaws as well, including a small sample size (approximately 90-114 in each group) and tocolytic group cross over. Although tocolytic cross over was allowed, the subjects remained in their initial group for analysis and for this reason this study does not allow for direct comparison. In addition, twin gestations were included. This group is at high risk for preterm delivery and neonatal morbidity at baseline, are thought to have a different mechanism for preterm delivery, and likely have a different response to tocolytic agents, all of which could potentially skew data. They also reported a gestational age of enrollment from 20 to 32 weeks. As the main goal of tocolytic therapy is to administer corticosteroids (given between 24-34 weeks gestation) and allow transfer to a tertiary center, inclusion of patients less than 23 weeks gestation – who fall within the non-viable range and typically are not considered candidates for intervention, with tocolytic treatment or corticosteroid administration, was problematic in this study.[4]

This proposed study will be a multi-institutional study to directly compare the two tocolytics that have been shown to be superior in meta-analysis. Determining a first line treatment will help guide clinicians in the treatment of preterm labor.

1. Management of preterm labor. Practice bulletin No. 127. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012; 119: 1308-17.

2. Haas DM, Caldwell DM, Kirkpatrick P et al. Tocolytic therapy for preterm delivery: systematic review and network meta-analysis. BMJ 2012;345:e6226

3. Kashanian M, Bahasadri S, Zolali B. Comparison of the efficacy and adverse effects of nifedipine and indomethacin for the treatment of preterm labor. International Journal of Gynecology and Obstetrics 2011:113; 192-195

4. Klauser CK, Briery CM, Martin RW. A comparison of three tocolytics for preterm labor: a randomized clinical trial. J Matern Fetal Neonatal Med 2013, Early online: 1-6.

5. King JF, Flenady V, Papatsonis D et al. Calcium channel blockers for inhibiting preterm labour. Cochrane Database of Systematic Reviews 2003, issue 1.

6. Conde-Agudelo A, Romero R, Kusanovic P. Nifedipine in the management of preterm labor: a systematic review and meta-analysis. Am J Obstet Gynecol 2011;204:134.e1-20.

7. King JF, Flenady V, Cole S, Thornton S. Cyclo-oxygenase (COX) inhibitors for treating preterm labour. Cochrane Database of Systematic Reviews 2005, Issue 2.

8. Haas DM, Imperiale TF, Kirkpatrick PR. Tocolytic therapy A meta-analysis and decision analysis. Obstet Gynecol 2009;113:585-94

Methods:

This is a randomized controlled open-label trial comparing two groups of women with preterm labor who are treated with either indomethacin or nifedipine as a tocolytic agent. The study will be conducted at each of the five University of California medical center hospitals. In order to be admitted to the hospital for tocolytic treatment, subjects will have to be in preterm labor defined as regular uterine contractions (at least 6 per hour) associated with changes in cervical dilatation and/or effacement, cervical dilatation of > 2 cm at presentation or a change in cervical dilatation of > 1 cm, and > 25 to 50% effacement and/or a short cervical length (per institution's policy) as obtained by transvaginal cervical sonography with or without a positive fetal fibronectin. All women will be treated in a uniform fashion with initial hydration, evaluation for etiologic infection, administration of antenatal corticosteroids to accelerate fetal maturity, and magnesium sulfate for neuroprotection. Magnesium will be administered according to each institution's magnesium for neuroprotection protocol. Women will be randomized to either tocolytic therapy with nifedipine or indomethacin by using computerized randomized block sequencing.

Nifedipine Treatment: Subjects will be given nifedipine 10mg orally and repeated every 20 minutes for a maximum dose of 30mg in the first hour followed by 20mg every 6 hours for the first 48 hours of treatment. This is a commonly used dose and has been described in a large meta-analysis reviewing nifedipine in the management of preterm labor by Conde-Agudelo et al.[1] Of the 26 studies reporting on nifedipine as an acute tocolytic, the dosing ranged from a loading dose of 10 to 30mg orally or sublingually, followed by 10 to 20mg orally every 4-8 hours. 12 of those studies used a repeat loading dose every 15-20 minutes. The decision was made to proceed with nifedipine 10mg orally and repeated every 20 minutes for a maximum dose of 30mg followed by 20mg every 6 hours since it a commonly prescribed dosing for acute tocolysis.

Indomethacin Treatment: Those randomized to indomethacin will be given 100mg orally as a loading dose followed by 50mg every 6 hours for the first 48 hours of treatment. This regimen was decided after reviewing the Cochrane review on COX inhibitors for treating preterm labor.[2] 10 of the 13 trials included in the review used indomethacin. The dosing ranged from 50 to 100mg loading dose followed by 25mg to 50mg orally every 4-6 hours. The loading dose was mostly given rectally. A recent randomized control trial compared indomethacin vs. two other tocolytics.[3] The indomethacin dosing used was an initial 100mg suppository, repeated one time if contractions persisted after two hours, followed by 50mg orally every 6 hours. This regimen was associated with increased incidence of fetal ductal constriction (13/97) and oligohydramnios (5/97) when compared to the other two treatment groups. Therefore, we propose using a one time loading dose of 100mg orally followed by 50mg every 6 hours, which is a commonly prescribed dosing. Using the lower end of the normally prescribed dosing range should have decrease fetal and maternal side effects.

Tocolytic failure will be defined as delivery within 48 hours of initiation or the start of magnesium for neuroprotection. Magnesium for neuroprotection is started when delivery is deemed imminent, so when initiated, it is implied that there has been tocolytic treatment failure. That being said, it is difficult to predict preterm birth, especially in the setting of preterm labor, and some clinicians may start magnesium for neuroprotection without labor proceeding to delivery. There is a theoretical risk of neuromuscular blockade with the concurrent use of magnesium and nifedipine, and there have been 2 case reports of reversible neuromuscular blockade in this setting.[4,5] One of these case reports used a total dose of 500mg of magnesium[5] – which is significantly more than what would be administered for our neuroprotective dosing. There are studies, albeit small, that show concurrent use of nifedipine and magnesium is safe in the setting of preeclampsia.[6,7,8] One such study describes expected hemodynamic changes with the concurrent use of nifedipine and magnesium including a decreased mean arterial pressure, systemic vascular resistance and increase in cardiac index.[7] The magnesium dosing in the study was 5 grams over 20min followed by 3g/hr which is a higher maintenance dose than any of the campuses uses for neuroprotection.

One of the largest studies that examined maternal and neonatal outcomes in the setting of preeclampsia was the Magpie trial,[8] which had about 30% concurrent use with nifedipine and magnesium with no adverse effects reported. While on magnesium, all 5 campuses have mechanisms in place to monitor closely for magnesium toxicity including serial neurologic exams and/or magnesium levels. If any early adverse signs are seen, magnesium will be discontinued and/or calcium gluconate administered to reverse any neuromuscular blockade. For this reason, concomitant use of magnesium with either nifedipine or indomethacin is left to the judgment of the providers at each institution.

After 48 hours from the first dose of antenatal corticosteroids, the tocolytic agent will be discontinued. Maintenance tocolysis for longer than 48 hours will not be used on study patients. The study time required from each subject is the duration of hospital admission during which she is enrolled in the study and the duration of the birth hospitalization for each infant. To clarify, secondary outcomes measured will include delay of delivery by 7 days and decreasing delivery before 37 weeks as outlined in section 1 on page 2. Section 3 specifically asks the time required by study participants. Gestational age at delivery is an endpoint we plan to collect and the end of the study participants' time in the study. Gestational age at delivery will be collected as data but analyzed in a dichotomous fashion i.e. prior to 37 weeks. End points for tocolytic treatment are arrest of preterm labor (cervical dilation) or completion of betamethasone administration (e.g. 48 hours from the first dose). The primary study outcome is extension of pregnancy by 48 hours after admission. The secondary outcome is gestational age at delivery. We will also evaluate pregnancy extension by 7 days after treatment initiation. It is likely that some patients are discharged still pregnant and return later in gestation for delivery. Although no actual study time between these two time points are required of the subject or during subsequent hospitalization(s), data would be collected at the time of delivery.

For the neonates, data will be collected through discharge. No neonatal follow up is required. There may be subjects who deliver at another hospital. If the patient gives permission, then we will obtain records from the appropriate hospital.

Subject's privacy will be protected by using HIPPA guidelines by limiting access to data collection study personnel only. In addition, data will always be kept in a secured, locked location. Subject screening, enrollment and case report forms will be kept in a binder that will be locked in a room/drawer at all times. These case report forms will be uploaded to a secure online database run by a well-established company Tiatros. Tiatros uses online software to organize, analysis and allow communication among principal investigators in the study. Most importantly this is done securely and follows HIPPA regulations.

Summary

This comparative study of nifedipine versus indomethacin for acute preterm labor will be conducted at the 5 UC medical campuses (UC Irvine, UC Davis, UC San Diego, UC San Francisco, UC Los Angeles) using the Reliance Agreement. UCI is the reviewing IRB. UC Davis, UCSD, UCSF, UCLA are the relying IRBs. All tocolytic treatment will be given in the primary hospital at each campus. Medication is discontinued once there is arrest of preterm labor, 48 hours from first dose of betamethasone, or when delivery is deemed imminent or unavoidable, and depending on institution's policy at the time magnesium initiated for neuroprotection. No maintenance tocolytic medication will be given (i.e. longer than 48 hours) and none will be given as an outpatient.

1. Conde-Agudelo A, Romero R, Kusanovic P. Nifedipine in the management of preterm labor: a systematic review and meta-analysis. Am J Obstet Gynecol 2011;204:134.e1-20.

2. King JF, Flenady V, Cole S, Thornton S. Cyclo-oxygenase (COX) inhibitors for treating preterm labour. Cochrane Database of Systematic Reviews 2005, Issue 2.

3. Klauser CK, Briery CM, Martin RW. A comparison of three tocolytics for preterm labor: a randomized clinical trial. J Matern Fetal Neonatal Med 2013; early online: 1-6.

4. Ben Ami M, Giladi Y, Shalev E. The combination of magnesium sulphate and nifedipine: a cause of neuromuscular blockade. Br J Obstet Gynaecol. 1994;101:262-3.

5. Synder SW, Cardwell MS. Neuromuscular blockade with magnesium-sulfate and nifedipine. Am J Obstet Gynecol. 1989;161:35-6.

6. Magee LA, Miremadi S, Li J et al. Therapy with both magnesium sulfate and nifedipine does not increase the risk of serious magnesium-related maternal side effects in women with preeclampsia. Am J Obstet Gynecol. 2005;193:153-63.

7. Scardo JA, Vermillion ST, Hogg BB et al. Hemodynamic effects of oral nifedipine in preeclamptic hypertensive emergencies. Am J Obstet Gynecol ,1996; 175:336-8.

8. Altman D, Carroli G, Duley L et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie trial: a randomized placebo-controlled trial. Lancet 2002;359:1877-90.

Statistical Analysis:

The purpose of this study is to determine whether nifedipine or indomethacin is superior in arresting preterm delivery by 48 hours. We expect the nifedipine group to arrest preterm labor for 48 hours in 72% of cases[1] and the indomethacin group to arrest preterm labor for 48 hours 83% of cases.[2] Using a power of 80%, alpha of 0.05 we calculate 225 subjects are needed in each group.

The primary outcomes and other dichotomous outcomes will be evaluated using Chi-square. We also anticipate a 25% difference between groups based on prolongation of pregnancy by one week based on a small RCT using nifedipine vs. ritodrine conducted by Papatsonis et al.[3] Continuous variables will be compared using Student's t-test. Sub-group analyses will be done to compare differences across the sites. Regression analyses will be applied where appropriate such as for neonatal complications and the consideration of gestational age.

1. Lyell DJ, Pullen K, Campbell L et al. Magnesium sulfate compared with nifedipine for acute tocolysis of preterm labor: a randomized controlled trial. Obstet Gynecol 2007; 110:61-.

2. Zuckerman H, Shalev E, Gilad G, Katzuni E. Further study of the inhibition of premature labor by indomethacin. Part II double-blind study. Journal of Perinatal Medicine 1984; 12(1):25-9.

3. Papatsonis et al. Nifedipine and ritodrine in the management of preterm labor: a randomized multicenter trial. Obstet Gynecol 1997; 90:230-4.