Efficiency of Celecoxib versus Magnesium Sulfate to Arrest Preterm Labor: Randomized Controlled Trial

Hosam M. Hemeda, Mohammad A. Nasr Addeen and Mohamamd K. Nazeer

Department of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University
Hosam1973md@gmail.com

Abstract: ***Background:*** Preterm birth occur in 7% to 12% of all deliveries, but accounts for over 85% of all prenatal morbidity and mortality The benefit of keeping the fetus in-utero long enough to enable administration of a full course of corticosteroids to assist in fetal lung maturation, and to organize transfer to an appropriate neonatal care unit is very important. the primary aim of tocolysis is to delay delivery for at least 48 hours to allow time for these measures to be implemented. Several methods and drugs are used for the primary tocolysis. Magnesium sulphate is one of the most successfully widely used tocolytic agents worldwide; it is conceivable that magnesium sulfate tocolysis delay delivery for 24 to 48 hours. Newer drugs are regularly added to the list of tocolytics searching for the more efficient and the better side effects profile. ***Aim of the work****:* is to compare the efficiency of oral Celecoxib, a preferential COX-2 inhibitor, versus Magnesium Sulfate to arrest preterm labor. ***Methods:*** a randomized controlled trial including Two hundred pregnant women with preterm labor between 24 and 34 weeks of gestation randomly assigned into two groups whether to receive Celecoxib 100 mg b.i.d. for 48 hrs or intravenous Magnesium Sulfate ($MgSO_4$) for maximum of 48 hrs. ***Results:*** Labor was successfully arrested for 48 hrs in 84 (84%) and 86 (86%) of the patients in the Celecoxib and Magnesium Sulfate groups respectively (p=**0.381**). ***Conclusion:*** Celecoxib is almost equally effective as magnesium sulfate for primary tocolysis.
[Hosam M. Hemeda, Mohammad A. Nasr Addeen and Mohamamd K. Nazeer. **Efficiency of Celecoxib versus Magnesium Sulfate to Arrest Preterm Labor: Randomized Controlled Trial] .** *J Am Sci* 2013;9(12):969-973]. (ISSN: 1545-1003). http://www.jofamericanscience.org. 123

Keywords: Celecoxib, Cox 2 inhibitors, preterm labor, Magnesium sulphate.

1.Introduction

Preterm birth complicates 10–15% of all pregnancies. It is the most important cause of neonatal morbidity and mortality and causes 75% of neonatal deaths that are not due to congenital anomalies [(1).]

The WHO in 1993 has recommended that preterm is defined as gestational age less than 37 completed weeks of pregnancy or less than 259 days of the LMP.[(2)]

Premature labor can be understood as a syndrome with a number of underlying-causes including infection, maternal stress, uterine distention, placental hypoxia, and decidual bleeding. Infection is probably the most important factor at lower gestational ages. [(3).]

Several drugs aiming to suppress preterm labor have been invented. These drug families include: Beta-sympathomimetics, Calcium Channel Blockers, Magnesium Sulfate, Prostaglandin Synthetase Inhibitors, Oxytocin Antagonists, Nitric Oxide Donors, Methylxanthines and Progestins. [(4).]

The aim of tocolysis is to delay preterm delivery to allow time (usually 48 hours) for maternal administration of corticosteroids and in utero transfer to a tertiary perinatal centre, thereby reducing neonatal morbidity and mortality**.** [(5).]

Magnesium sulphate is one of the world wide well recognized effective tocolytic agents. It acts by competing with calcium for entry into the muscle cell through voltage operated calcium channels (calcium antagonist). It is proposed also that magnesium competitively binds with calcium storage sites in the myometrium endoplasmic reticulum [(6).]

PGs are now recognized as the ‘‘triggers’’ of labor because the myometrium contracts in response to exogenous PGs *in vivo* and *in vitro* [(7).] Prostaglandin synthetase (COX) inhibitors are another well recognized tocolytic agents. inhibitors of PG synthesis decrease uterine contractility, *in vitro*, and delay birth and prolong pregnancy, *in vivo* [(8).] Most of the currently available NSAIDs inhibit both COX-1 and COX-2 [(9).]

There is abundant evidence that the NSAIDs anti-inflammatory activity is largely the result of COX-2 inhibition, although many of their adverse effects (e.g. GI toxicity and nephrotoxicity) are due primarily to COX-1 inhibition. Familiarity with the function of the COX-2 isoenzyme led to the hypothesis that selective inhibition of COX-2 might retain the potent anti-inflammatory and analgesic effects of the NSAIDs without affecting COX-1 and its important physiologic functions. The availability of a new therapeutic class of highly selective COX-2 inhibitors may pave the way for safer, effective tocolytic [(10).]

Indomethacin is a non selective cyclo-oxygenase inhibitor that is used in the treatment of preterm labor. Although it has fewer maternal side effects, it is

associated with potential fetal risks including premature closure of ductus arteriosus with persistent pulmonary hypertension, renal and cerebral vasoconstriction and necrotizing enterocolitis. A recent 5-year retrospective study concluded that antenatal indomethacin could result in significant prolonged renal insufficiency in the preterm infant [(11)].

These side effects are more likely seen with higher dosage and prolonged treatment. It may be advisable to limit treatment for less than 48 hours and not to exceed 200 mg/day. Currently, in the light of these adverse and potentially serious fetal side effects, it may only be used as a second line agent in early gestational age preterm labor. There may be a place to use this as a first line agent in preterm labor secondary to polyhydraminos as it may reduce the formation of amniotic fluid [(11)].

Celecoxib, a selective cyclo-oxygenase 2 inhibitor has also been tried in the treatment of preterm labor. A recent prospective randomized controlled trial comparing celecoxib with indomethacin concluded that celecoxib has a better safety profile than indomethacin [(12)].

2. Subjects and methods

This study is a randomized controlled trial, which was conducted in Ain-Shams Maternity Hospital. Two hundred pregnant women with threatened preterm labor were included in the study .One hundred pregnant women with preterm labor received intravenous Magnesium sulfate and assigned as group A, and the other one hundred women received oral Celecoxib and assigned as group B. Randomization was conducted by serially numbering patients: even numbers received magnesium sulfate intravenously and odd numbers received celecoxib orally.

Diagnosis of preterm delivery was accomplished according to the criteria of ***(ACOG, 2001)***: contractions occurring at a frequency of four in twenty minutes or eight in sixty minutes with progressive change in the cervix, cervical dilatation greater than 1cm and less than 4 cm, cervical effacement of 80% or greater[(13)]. Patients included in the study were with gestational ages between 24-34 weeks, having singleton pregnancy, with intact membranes. Any patient with any contraindication for continuation of pregnancy e.g. intra amniotic infection, IUFD, non-reassuring fetal heart rate tracing, multiple congenital fetal malformations and any severe maternal condition necessitating pregnancy termination like renal or hepatic severe dysfunction or severe preeclampsia was excluded from the study.also patients with PPROM and those with cervical dilatation more than 4 cm were excluded. Also patients with known peptic ulcer were excluded.

After preterm labor is diagnosed, every patient was counseled about the study, patients who agreed and consent to join the study were subjected to full history taking ,full general examination including calculation of body mass index (BMI) and local examination for cervical changes as dilatation and effacement, any vaginal bleeding or amniotic fluid dripping.

Subjects were fully informed that they were randomly assigned to 1 of the 2 tocolytic techniques.

Those randomly assigned to the Magnesium Sulfate (group A) received our hospital traditional protocol consisting of 6 g in Magnesium sulfate 20% solution as an intravenous loading dose followed by a continuous infusion at a rate of 2 g/hour. The second group (group B) received 100 mg Celecoxib capsule orally twice daily. ([14]).

The medication was given for a maximum of 48 hours.

Numbers of uterine contractions were counted by palpation.

All subjects were offered pharmacological acceleration of fetal pulmonary maturation at 28 weeks or more of pregnancy, which consists of 6 mg of intramuscular dexamethasone every 12 hours for four doses.

Success was defined as the arrest of labor and no delivery within 48 hours in women who received only their random medication [(1)]

Therapy was considered unsuccessful If the medication was switched, or another agent added before 48 hours to arrest uterine contractions or if tocolysis was continued after the initial 48 hours study period due to persistent preterm labor contractions [(13)] or if the patients progressed to established preterm labor.

During the study period, no patient received other tocolytics other than the study agent.

An ultrasound examination was performed before the start of treatment, and at the end of the study to calculate the amniotic fluid index (AFI).

Throughout the treatment, the investigators reviewed incidence of maternal side-effects, such as headache, nausea, emesis, indigestion, shortness of breath, palpitations, local pain at the intra-venous site, or flushing.

The main outcome variables were either success to delay delivery for 48 hours, or maternal and fetal side-effects or developing oligohydramnios.

3. Results

No significant statistical difference was found between group A (magnesium sulphate group) and group B (Celecoxib group) regarding age, parity, BMI and gestational age at admission. Table (1).

Table (1): Comparison between group A (patients received magnesium sulfate) and group B (patients received celecoxib) as regard demographic data.

Variable		Group A (Magnesium Sulfate group) N=100	Group B (Celecoxib group) N=100	t	X^2	*P*
Age(ys)		28.9±5.2	28.2±4.4	1.2		0.521
BMI (kg/m2)		25.3±1.9	25.4±0.9	0.6		0.087
Gestational age: Mean ±SD range (weeks)		30±2 24-34	29.8±3 24-34	0.9		0.273
Parity	**Pg**	18(18%)	34(34%)		6	0.153
	P1	44(44%)	36(36%)			
	P2	30(30%)	22(22%)			
	P3	4(4%)	8(8%)			
	P4	4(4%)	0			

Magnesium Sulphate could suppress 86 preterm deliveries out of the 100 women in group A and Celecoxib could suppress 84 in group B. The difference is not significant statistically (p=0.293).

Comparing the time elapsed since initiation of tocolytic therapy till stoppage of uterine contractions in both groups showed that the mean time for group A was (7.76±0.4 hrs) while in group B it was (9.7 ± 0.6 hrs). The difference was statistically significant (p=0.003). Table(2)

Studying the complications of therapy magnesium sulfate group mainly had flushing while celecoxib group had mainly compliant of vomiting and diarrhea, with statistically highly significant difference between both groups. Table (2)

Table (2): Difference between group A (Magnesium Sulfate group) and group B (Celecoxib group) as regard time for cessation of contractions and side effects.

variables		Group A (Magnesium Sulfate group) N=100	GROUP B (CELECOXIB GROUP) N=100	t	X^2	*P*
Time (hrs): Mean ±SD Range		7.76±0.49 4-12	9.76±0.6 6-18	6.2		0.003
Side effects	**No**	85(85%)	92(92%)		14	0.002
	Flushing	15(15%)	0			
	Vomiting	0	6(6%)			
	Diarrhea	0	2(2%)			

AFI ultrasound studies in our study noticed that among group A (Magnesium Sulphate group) the mean AFI before treatment was 17±1cm and after treatment it was 18±1 cm with no statistical difference between the two values while in group B (Celecoxib group) the mean AFI before treatment was 18.3±3cm and after treatment it was 15±2 cm with significant statistical difference between the two values using paired t-test. (p=0.0231)

4.Discussion

Celecoxib, showed comparable clinical efficacy in delaying delivery for 48 hours in direct comparison with Magnesium Sulfate. The results of this study showed that delivery was delayed for 48 hours in 84 patients (84%) and 86 patients (86%) in the Celecoxib and Magnesium Sulfate groups, respectively and no significant difference was identified between the two groups. The failure rate within 48 hours of starting the treatment of the Celecoxib group and the Magnesium sulfate group were 16% and 14%, respectively (10 patients of Celecoxib group delivered and 6 patients required shift to other line of tocolysis), (while in magnesium sulfate group 7 patients delivered and the other 7 patients required shift to other line). No significant difference was identified between the two groups as regard success of tocolysis, (p value was >0.05)

This is consistent with the findings of ***McWhorter et al. in 2004*** study. Who compared oral Rofecoxib with intravenous magnesium sulfate as a tocolytic. In that study, Two hundred fourteen patients were randomly assigned (105 received Rofecoxib and 109 received Magnesium Sulfate). Delivery was delayed for 48 hours in 95 (90.4%) and

96 (88%) of the patients in the Rofecoxib and Magnesium Sulfate groups, respectively [15].

Also this study is consistent with the study of ***Borna et al. in 2007*** who stated that Celecoxib is as effective as Magnesium Sulfate in stopping preterm labor by comparing one hundred four patients randomly assigned, 52 to the Celecoxib group and 52 to the Magnesium Sulfate group. The two groups were similar with respect to maternal age, parity, gestational age, amniotic fluid index, demographic characteristics. The times to the cessation of contractions during the initial medication were similar in both treatment groups (P=0.125). Delivery was delayed for 48 h in 42 (81%) and 45 (87%) patients in the Celecoxib and Magnesium Sulfate groups, respectively (P=0.298). Delivery before 48 hours was in 10 (19%) and 7 (13%) of the patients in the celecoxib and magnesium sulfate groups, respectively. Four of the patients in the Magnesium Sulfate group had side-effect such as headache, lethargy, and palpitations. There was no side-effect in the Celecoxib group. There were no severe maternal and neonatal complications in either group believed to be related to the study medications. [16]

As regard time needed for cessation of contractions we found that Celecoxib group required a longer time compared to Magnesium Sulfate group with statistically highly significant difference between the two groups(mean =9.76 h ±0.6 for Celecoxib group while it was 7.76 h ± 0.49 for Magnesium Sulfate group) and this may be due to the different route of administration as we give Celecoxib orally which requires a longer time for absorption from the gastrointestinal tract, as the Peak plasma levels of celecoxib occur approximately 3 hrs after an oral dose while Magnesium Sulfate is directly given intravenously.

This also gives an idea about the side effects which mainly was vomiting and diarrhea in celecoxib group while in magnesium sulfate was flushing.

We found highly significant difference as regard amniotic fluid index study between the start and the end of treatment in Celecoxib group. The mean AFI before treatment was 18.3±3cm and after treatment it was 15±2 cm with significant statistical difference between the two values using paired t-test. (p=0.0231)

This is consistent with the study of ***Holmes and Stone in 2000*** who stated that Selective cyclooxygenase-2 inhibitors (Nimesulide) might cause severe but transient oligohydramnios but if used only for rather long periods, however the present study showed no single case of oligohydramnios although there's a mild decrease in the amount of amniotic fluid among celecoxib group at end of treatment[17].

Also this study is consistent with the study of ***Locatelli et al. in 2001*** Who evaluated the efficacy and safety of Nimesulide (100 mg orally twice daily for > 48 hours) in a pilot series of five women (including two with twin pregnancies) at 24 weeks (range 21 – 27) in preterm labor. Nimesulide therapy was continued for eight days (5 – 16) and was associated with a prolongation of pregnancy for 27 days (6-69). Oligohydramnios occurred in all seven fetuses after three to nine days of therapy, and in the five pregnancies that continued after discontinuation of Nimesulide, but it resolved within four days (2-7). None of the babies manifested permanent renal damage[18].

This is inconsistent with the study of ***McWhorter et al. in 2004*** who stated that Short courses of COX-2 inhibitors, however, have not been associated with detectable adverse fetal or neonatal side effects as oligohydramnios when given after 22 weeks of gestation[15].

Also our study is inconsistent with the study of ***Borna et al. in 2007*** who stated that Amniotic fluid index after medication was not significantly different between the magnesium sulfate and Celecoxib groups (P=0.87)[16].

Our study also is inconsistent with the study of ***Sawdy et al. in 1997*** who used for the first time a COX-2 inhibitor (Nimesulide) to prevent preterm birth. He stated that exposure to 200 mg daily dose for short periods at 16 to 34 weeks did not result in a decreased amniotic fluid volume[19].

Conclusion

We conclude that Celecoxib (cox 2 inhibitor) is as effective as magnesium sulfate as a tocolytic. It appears to have no greater risk of maternal side-effects than magnesium sulfate.

We recommend that further research should be done on the potential long term fetal side-effects like fetal ductus arteriosus constriction , permanent decreased amniotic fluid volume or permanent fetal renal injury.

Corresponding author
Hosam M. Hemeda
Obstetrics and Gynaecology department, Faculty of Medicine, Ain-Shams University, Cairo. Egypt
Hosam1973md@gmail.com

References

1. Alan H De Cherney, Lauren Nathan, T. Murphy Goodwin, Neri Laufer: Late pregnancy complications, textbook Current Obstet Gynaecol, 2006; chapter 15: 443-487.

2. WHO (World health organization): Preterm Labour: Managing Risk in Clinical Practice, Edited by Jane Norman and Ian Greer, Cambridge University Press, 1993.
3. Hagberg H and Wennerholm UB: Spontaneous premature birth: physio-pathology, predictors and management, Lakartidningen, 2000; Jan 26; 97(4):30 1-6.
4. Cunningham FM, MacDonald PC, Grant NF, *et al.*: Appleton, Lange, Norwalk, 2001; Williams Obstetrics, 21 ed.
5. American college of Obestetricians and Gynecologists: Procedure: Tocolysis Criteria. June 1998; Criteria Set No.34.
6. Guiet-Bara A, Bara M, and Duriach J: Comparative study of the effect of two tocolytic agents(Mg So4 and alcohol) on the tonic transfer through the isolated human amnion. Eur J Obstet Gynaecol Repord Biol, 1985; 20:297.
7. Hoff T, De Witt DL. Kaever V, *et al.*: Differentiation- associated expression of prostaglandin G/H synthase in monocytic cells. FEBS Lett. 1993; 320:3842.
8. De Witt DL, Meade E: Serum and glucocorticoid regulation of gene transcription and expression of prostaglandin H synthase- 1 and prostaglandin H synthase-2 isoenzymes. Arch Biochem Biophys. 1993; 306:94-102.
9. Vane JR: Mechanism of action of NSAIDs. Br J Rheumutol. 1996; 35(Suppl l): l-3.
10. Gierse JK, Hauser SD, Creely DP, Koboldt C, Rangwala SH, Isakson PC and Seibert K: Expression and selective inhibition of the constitutive and inducible forms of human cyclo-oxygenase. Biochem J, 1995; 305:479–484.
11. Stika CS, Gross GA, Leguizamon G *et al.*: A prospective randomized safety trial of celecoxib for treatment of preterm labor [Clinical Trial. Comparative Study.Journal Article. Randomized Controlled Trial. Research Support, Non-U S Gov't]. Am J Obstet Gynaecol 2002; 187: 653–660.
12. Stika CS, Gross GA, Leguizamon G *et al.*: A prospective randomized safety trial of celecoxib for treatment of preterm labor. Am J Obstet Gynaecol 2004; 187:653-60
13. American College of Obstetricians and Gynecologists: Assessment of Risk Factors for Preterm Birth. Clinical Management Guidelines for Obstetrician-Gynecologists, (Washington), 2001; Practice Bulletin No. 31. ACOG.
14. Sedigheh Borna and Fatemeh Mir Saeidi: Celecoxib versus magnesium sulfate to arrest preterm labor: randomized trial. J Obstet Gynaecol, 2007; Res.vol.33,No 5:631-634.
15. McWhorter J, Carlan SJ, O'Leary TD, Richichi K, O'Brien WF: Rofecoxib versus magnesium sulfate to arrest preterm labor: a randomized trial. Obstet Gynaecol 2004; 103: 923–930.
16. Borna s., Fatemeh Mir Saeidi :Celecoxib versus magnesium sulfate to arrest preterm labor: Randomized trial. Journal of Obstetrics and Gynaecology Research 2007 Volume 33, Issue 5, pages 631–634
17. Holmes RP, Stone PR: Severe oligohydramnios induced by cyclooxygenase-2 inhibitor nimesulide. Obstet Gynaecol, 2000; 96:810 –1.
18. Locatelli A, Vergani P, Bellini P, Strobelt N, Ghidini A: Can a cyclo-oxygenase type-2 selective tocolytic agent avoid the fetal side effects of indomethacin?, Br J Obstet Gynaecol, 2001; 108(3): 325-6.
19. Sawdy R, Slater D, Fisk N, Edmonds DK, Bennett P: Use of cyclo-oxygenase type-2-selective non steroidal anti-inflammatory agent to prevent preterm delivery. Lancet 1997; 350: 265–266.

12/22/2013