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Plausibility of the combination of 17 α hydroxyprogesterone injection and Nifedipine versus Magnesium sulfate in the management of preterm labor, RCT

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***Abstract*---**Background: Preterm birth is the leading cause of neonatal mortality and the most common reason for neonatal admission to the hospital. Although the causes of preterm labor are not well understood, the burden of preterm births is clear—preterm births account for approximately 70% of neonatal deaths and 36% of infant deaths as well as 25–50% of cases of long-term neurologic impairment in children. Objective: To compare the effectiveness of the tocolytic action of the standard protocol of Magnesium sulfate versus the combination of Nifedipine and 17 α hydroxyprogesterone injection in the term of acute tocolysis therapy on the perinatal outcome and to abrupt threatened preterm labor between 24 weeks to 33 weeks and 6 days. Patients and methods: A prospective randomized control trial study conducted at Zagazig Maternity Hospital, included 102 pregnant women who presented with threatened preterm labor at the Emergency Department of Zagazig University Maternity Hospital. The participants were divided into two groups, group (1) included 51 cases

who received the standard protocol of Magnesium Sulfate: loading dose 4 g IV; maintenance 2 g/hr for 24 hrs. Group (2) included 51 patients who received nifedipine with the initial dose of 20 mg nifedipine capsules, followed by 20 mg nifedipine retard per 6 hours for the next 48 hours along with 17 α hydroxyprogesterone(prolutone Depot 250 mg Bayer Schering Pharma) IM injection stat dose to be repeated twice weekly for 2 weeks. Both groups were given corticosteroids to enhance fetal lung maturity in the form of Dexamethasone 12 mg for 2 doses 24 hrs apart. Primary outcome: Postponement of birth for at least 48 hrs. after initiation of therapy and secondary outcome: neonatal outcomes and maternal adverse effects. Results: this study showed that there was a statistical difference between both groups in delivery 24 hours (p=0.02) and 72 hours (p=0.03) after admission with less early deliveries among group 2 combined Nifedipine with 17 α hydroxyprogesterone IM injection. There was a higher rate of delivered cases in group 1 magnesium sulfate compared to combined group 2. Regarding maternal outcome, there were statistically significant differences regarding maternal mean blood pressure before and after treatment in group 2 Nifedipine with 17 α hydroxyprogesterone IM injection. Maternal mean blood pressure decreased significantly after treatment than before treatment (P= 0.04). There was a statistically significant difference regarding maternal heart rate before and after treatment in Nifedipine with 17 α hydroxyprogesterone IM injection group 2 (P= 0.04).: Regarding the neonatal outcome, less neonatal respiratory distress was recorded among group 2 the nifedipine with 17 α hydroxyprogesterone (p= 0.02). Conclusion: The addition of 17 α hydroxyprogesterone injection as a uterine quiescent hormone to nifedipine was a very effective novel combination in the treatment of threatened preterm labor and improve neonatal outcomes without compromising maternal safety.

***Keywords*---**preterm labor, nifedipine, 17 α hydroxyprogesterone, Mgso4.

Introduction

Prematurity is a multifactorial complex antenatal risk and remains the main cause of perinatal deaths and related morbidity especially cerebral palsy and respiratory distress. [(1)]preterm babies represent a major health burden worldwide due to increased admission to neonatal intensive care units [(2),] The main value of tocolytic therapy is to prolong the pregnancy to allow giving the rescue corticosteroid injection to improve the respiratory function postnatally. Further, tocolytic therapy permits to transfer the of preterm parturient women to a tertiary hospital where good intensive care will be available [(3)]. Accordingly, many regimens had been suggested to stop preterm uterine activities. yet there is no consensus about the optimal tocolytic therapy. This reflects that the efficacy of these medications is not granted and a combination of multimodality drugs with a different mechanism of action might be able the solve the challenge of unexplained premature uterine contraction [(4),].

In threatened preterm labor with cervical dilatation less than 4 cm, there will place to use a single tocolytic drug or a combination of them to prolong pregnancy. [5] Coordinating with the Royal College of Obstetrics and Gynecology guideline RCOG, it is recommended between 24- to 33 weeks and 6days gestation, with expected or scheduled preterm delivery to give a single course of steroid injection to enhance the fetal lung maturity. Thus, tocolytic therapy benefits are accepted and outweigh the risk of maternal adverse effects and/or fetal complications. Generally, these agents should be initiated provided no contraindications exist like evidence of chorioamnionitis or congenital fetal malformation. [6] Nevertheless, aggressive combined tocolysis is not typically used beyond 34 weeks gestation, but before this date, a combination could be wise to guard against the complication of prematurity, especially in low resources countries where there are shortages of NICU facilities. [7]

A tocolytic drug is a medication used to inhibit uterine contraction. Knowing the facts about the mechanism of labor and uterine contraction, varieties of medications were used to stop the preterm labor pains including oxytocin receptors antagonist, calcium channel blockers, beta-agonists, magnesium sulfate, and hormonal support like progesterone. The ideal tocolytic agent should be easy to administer, inexpensive, without significant maternal, fetal, or neonatal side effects, effective at delaying preterm birth, and long enough to permit the use of antenatal corticosteroids [8]. Calcium channel blockers exert their tocolytic effects through inhibition of the calcium influx inside muscle hurdling their contraction. Nifedipine has emerged as a cheap and effective tocolytic drug. [9] Although it is off-labeled status, several randomized studies have shown that the use of nifedipine in comparison with other tocolytics is associated with a more frequent successful prolongation of pregnancy. [10] In addition, it may be associated with a lower incidence of respiratory distress syndrome (RDS), necrotizing enterocolitis, and intraventricular hemorrhage. [11] . Magnesium sulfate was described as influencing uterine contractility by increasing the duration of labor. The exact mechanism of magnesium sulfate as a tocolytic agent is only partially understood.

Magnesium decreases the depolarization of smooth muscle, by modulating calcium uptake, binding, and distribution in smooth muscle cells. The added value of magnesium sulfate is neuroprotection for preterm babies before 30 weeks. Magnesium sulfate, by its peripheral vasodilator effects, when infused intravenously, produces flushing, sweating, and a sensation of warmth. Reported maternal side effects relate to dosage and speed of infusion including nausea, vomiting, headache, palpitations, and rarely, pulmonary edema [12]. Both natural progesterone and 17 α hydroxyprogesterone had been used widely as a prophylactic tocolytic medication in women with a short cervix and with a history of preterm labor. Progesterone is the predominant pregnancy hormone responsible for uterine quiescence; thus, it has been studied in two large, randomized trials as an effective therapeutic modality in terms of acute tocolysis [13,14]. National and international obstetrical societies have different recommendations regarding progesterone formulation for the prevention of recurrent preterm birth. 17-hydroxyprogesterone caproate (Makena) is licensed by the US Food and Drug Administration (FDA)to reduce the risk of preterm birth for women with a singleton pregnancy who have a history of singleton

spontaneous preterm delivery [15]. Supporting evidence for the licensing of intramuscular 17-hydroxyprogesterone caproate was provided by the trial of Meis et al [16] . Being an effective, affordable medication in low resources countries, our study aimed to compare the efficacy of the combined use of 17 α hydroxyprogesterone intramuscular injection and Nifedipine versus Magnesium sulfate in the management of preterm labor and the impact of this combination of neonatal outcomes and maternal adverse effect.

Patients and Methods

Sitting

This was a prospective randomized study conducted at the Obstetrics & Gynecology Department, of Zagazig University Maternity Hospital on pregnant women who attended the emergency room with preterm labor pain.

Sample size

The sample was calculated to be 102 cases (51 cases in each group), using OPEN-EPI with a power of 80% and confidence interval of 95%. • All statistical comparisons were two tailed with significance Level of P-value ≤ 0.05 indicates significant, p 0.05 indicates non-significant difference.

Methodology

The enrolled patients were 102 cases who attended the emergency room with preterm labor pains and were diagnosed with preterm labor according to the following criteria: singleton pregnancy gestational age between 24-33weeks'6 days gestation with intact membranes. The diagnosis of labor was made if persistent uterine contractions occurred 3 times in 10 minutes recorded through clinical examination and confirmed with cardiotocography. cervical examination showed active cervical changes when the dilatation was less than 4 cm and an effaced cervix 80 % with an intact membrane. The following cases were excluded from the study: multiple pregnancies, congenital malformation, ruptured membranes, fetal death, maternal cardiac disease, and allergy to any of the used medications.

After concurring Ethical Committee took an interest in this investigation and marked an educated assent, informed consent was obtained from all participants. Patients introduced to the Emergency Room of the Obstetrics and Gynecology Department for work and meeting the criteria of choice specified above were subjected to detailed history taking, full clinical examination involving general, obstetric, and local examinations, laboratory investigations, and sonographic examination. Trans-abdominal sonography for fetal biometry (including BPD, HC, FL, and AC), placental site and grading, amniotic fluid volume, and fetal anomalies as well as Trans-vaginal sonography for cervical length measurement were performed in all selected cases the cervical length was less than 25 mm. When preterm Labor was diagnosed through painful regular uterine contractions (3-5 contractions in 10 minutes for more than one hour) associated with cervical changes per vaginal examination Dexamethasone injection was given in a dose of 12 mg; two doses 24 hours apart unless administered previously.

Patients were randomly allocated to receive either group (1) included 51 cases who received Magnesium Sulfate: loading dose 4 g IV; maintenance 2 g/hr for 24 hrs. Group (2) included 51 patients who received nifedipine with the initial dose of 20 mg nifedipine capsules, followed by 20 mg nifedipine retard per 6 hours for the next 48 hours along with 17 α hydroxyprogesterone caproate, IM injection (prolutone 250 mg IM stat dose followed by twice weekly injection for 2 weeks until 37 weeks or earlier delivery) while Nifedipine continued only for 48–72 hours. Throughout the treatment observation, maternal (pulse rate, blood pressure, uterine contractions) and fetal (heart rate) monitoring were performed every 30 minutes during the first 4 hours following the start of therapy, then every 4 hours during the rest of the treatment.

Patients in both groups whose contractions stopped were observed for an additional 24 hours to detect whether contractions appeared again; if they remained stable, they were discharged and come for the following week in the antennal clinic in the same hospital. All discharged patients were instructed to have enough oral fluids, rest, and seek medical advice if they have any regular lower menstrual-like cramps. The primary outcome is the efficiency of tocolytic therapy in each arm through the whole period of hospitalization. Treatment failure was considered in participants who delivered during this period. The secondary outcomes were admission to the NICU and maternal adverse effects.

Statistical analysis

Data were checked, entered, and analyzed using SPSS version 23 for data processing. Student "t" test, Chi-square test (X^2), and Paired T-test were used for the analysis of the results of the present study. For all statistical tests done, the threshold of significance was fixed at a 5% level (P-value). A p-value of > 0.05 indicates non-significant results, and the P value of < 0.05 indicates significant results. The smaller the P value obtained the more significant the results.

Results

Both groups were similar distributions regarding age and Body Mass Index (BMI). The patients' age in group 1 ranged from 20 to 42 years with a mean ± SD of 29.7±4.9 years while in group 2 ranged from 20 to 41 years with a mean ± SD of 31.3±6.1years. Body mass index (BMI) was 27.7±4.6 and 28.6±5.7 kg/m^2 in groups 1&2, respectively.

Table 1
Comparison between the studied groups in gestational age on admission, cervical length, and cervical dilatation

Variable	Group (1) No. (51)	Group (2) No. (51)	Test	P
Gestational age on admission (weeks) Mean ± SD (range)	30.7±2.2 (24-34)	30.4±2.1 (27-34)	t-test 0.5	0.6
BMI kg/m^2	27.7±4.6	28.6±5.7	0.5	0.34

Mean ± SD (range)		(25-34)		(26-35)		
Cervical length (TVU/S)					t-test	0.6
Mean ± SD (range)		2.4 ±0.16 (1.6-2.4)		2.5 ±0.13 (1.5-2.5)	0.5	
Cervical dilatation					test	
1 cm	28	52.1	22	58.3	$x^2$1.7	0.06
2 cm	10	27.1	16	20.8		
3 cm	10	20.8	10	20.8		

There was a statistically significant difference regarding maternal heart rate and blood pressure before and after treatment in Nifedipine with 17 α hydroxyprogesterone group 2, but no difference in both observations in Magnesium sulfate group 1 p values respectively (P= 0.04& 0.7). (Table 2).

Table 2
Comparing maternal heart rate mean blood pressure before and after treatment in the studied groups

Maternal heart rate	Before treatment n (51)	After treatment n (51)	Paired t-test	P
Group (1) Mean ± SD (range)	74.5±6.2 (70-100)	79.6±4.1 (71-107)	2.1	0.7
Group (2) Mean ± SD (range)	75.5±8.4 (62-100)	82.3±9.1 (67-100)	3.4	0.04*
Maternal mean blood pressure	Before treatment No. (51)	After treatment No. (51)	Paired t-test	P
Group (1) Mean ± SD (range)	75.5±2.6 (70-95)	76.9±4.1 (71-99)	1.3	0.7
Group (2) Mean ± SD (range)	76.1±4.5 (72-97)	74.3±2.3 (72-95)	2.5	0.04*

Table 3 shows that there was a statistically significant difference between the two studied groups in delivery 24 hours (p=0.02) and 72 hours (p=0.03) after admission with less early deliveries among the Nifedipine with 17 α hydroxyprogesterone group 2 with less undelivered patients until discharge with higher deliveries among Magnesium sulfate groups.

Table 3
Comparison between the two studied groups as regards delivery 24 hours 48 hours 72 hours after admission

Delivery 24 hours after admission	Group (1)		Group (2)		test x^2	P	Odds (CI 95%)
	n (51)	%	n (51)	%			
No	38	77.1	44	89.6	3.7	0.02*	0.4 (0.1-1.2)
Yes	13	22.9	7	10.4			
Delivery 48hours after admission	Group (1)		Group (2)		test x^2	P	Odds (CI 95%)
	n (38)	%	n (44)	%			
No	30	75.6	38	86.1	0.9	0.3	0.6 (0.2-1.6)
Yes	8	24.4	6	13.9			
Delivery 72 hours after admission	Group (1)		Group (2)		test x^2	P	Odds (CI 95%)
	No (30)	%	No (38)	%			
No	23	82.1	36	94.6	3.8	0.03*	0.4 (0.2-1.1)
Yes	7	17.9	2	6.5			
Cases delivered from discharged to 1 week	Group (1)		Group (2)		test x^2	P	Odds (CI 95%)
	No (23)	%	No (36)	%			
Yes	13	56.5	31	85.7	9.2	0.002*	4.6 (1.4-9.2)
No	10	43.5	5	14.3			

Table 4 shows that neonatal respiratory distress with less reported among the nifedipine with and 17 α hydroxyprogesterone group 2 (p= 0.02).

Table 4
Comparison between the two studied groups' neonatal outcomes

Variable	Group (1) No. (51)		Group (2) No. (51)		Tests	P
Fetal heart rate b/min						
mean ± SD (range)	150.5±13.4 (110-166)		153.4±11.4 (115-166)		t-test= 1.1	0.2
	%	Fetal outcome %				
Normal	37	77.1	34	66.6	test	0.8
distressed	11	21.5	13	27.1	x^2=1.3	
Death	3	6.3	4	8.3		
Intranasal	0.0	0.00	1	1.1		
Postnatal	3	6.3	3	6.2		
% Neonatal infection %						
No	40	78.4	45	88.5	test	0.8
Yes	11	16.7	6	12.5	x^2=0.06	
% Neonatal respiratory distress%						
Absent	33	68.7	43	84.3	test	0.02*
present	18	35.2	8	15.6	x^2=6.6	
% Incubator admission %						
No	37	77.1	35	68.6	1.3	0.2
Yes	14	27.4	16	33.3		
Gestational age on incubator admission						

	(14)	%	(16)	%	1.9	0.07*
25 – 30 W	8	57.1	8	50.0		
30 – 32 W	2	14.2	5	31.3		
32 – 34 W	2	14.2	3	18.7		
Neonatal birth weight (Kg)						
mean ± SD (range)	2.8±0.3 (1.4-3.9)		2.6±0.4 (1.3-3.7)		t-test= 1.1	0.5

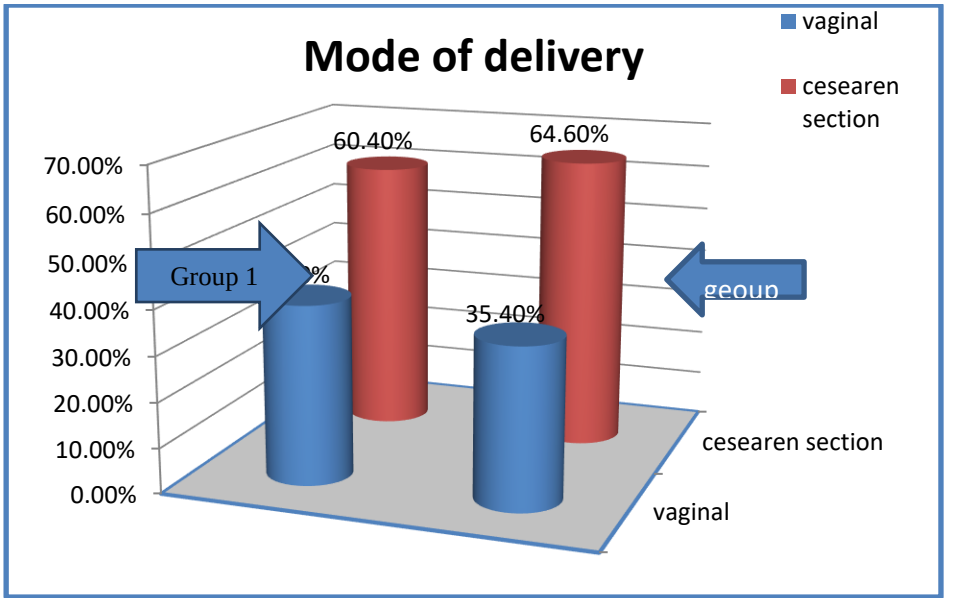

Figure 1. Bar chart for comparing the mode of delivery between the two studied groups

Discussion

Progesterone plays a role in the maintenance of pregnancy, and the lack or withdrawal of its concertation in the blood is one of the theories of initiation of preterm labor. [17] Preterm infants are particularly prone to complications due to impaired respiration, difficulty in feeding, poor body temperature regulation, and a high risk of infection. [18] There is a diversity of tocolytics medications with different mechanisms of action. The obstetrician's choice of medication usually occurs in the context of the case, available medication, cost, and expected maternal side effects. A combination of tocolysis with a different mechanism of action is deemed to have better control of the patient's symptoms due to synergism. Importantly large, randomized study studied the use of Progestogens (vaginal progesterone and intramuscular 17-hydroxyprogesterone acetate) for women at high risk of preterm delivery. The endorsed regimen of 17-hydroxyprogesterone caproate (250 mg intramuscularly weekly), starting at 16–20 gestational weeks until 36 weeks or delivery for women with a singleton gestation and a history of spontaneous preterm birth, for women with cervical incompetence, cervical length ≤25 mm) [19]

Here, in our study, we used the 17 α hydroxyprogesterone as a therapeutic intervention with a dose of 250 mg depot intramuscular injection twice weekly in combination with the standard Nifedipine protocol in terms of acute tocolysis and we plotted the results compared to magnesium sulfate tocolytic regimen. We recorded a statistically significant difference between the two studied groups in delivery 24 hours after admission with fewer early deliveries among the Nifedipine with 17 α hydroxyprogesterone group 2. However, there was no statistically significant difference between the two studied groups in delivery 48 hours after admission with fewer early deliveries among the Nifedipine with 17 α hydroxyprogesterone group this could be added value of the due timing of the second dose of 17 α hydroxyprogesterone. Similarly, delivery within 72 hours after admission was less among the same group 2. The statistical significance was in favor of the combined group, with 2 more undelivered patients till discharge; consequently, a higher number of patients delivered in group 1 magnesium sulfate.

Regarding neonatal outcomes: mode of delivery, fetal heart rate, fetal outcome, and neonatal infection were similar in both groups. Notably, neonatal respiratory distress was more frequently detected in group 1 than in group 2. Yet, the birth weight and the neonatal incubator admission rate were equal in both groups. Our results came contrary to the OPTIMUM trial (Norman et al. Lancet 2016; 387:2106–16), which evaluated the effect of progesterone prophylaxis in pregnancies at high risk of preterm birth, which has recently been reported. OPTIMUM showed that progesterone did not affect the three primary outcomes: birth before 34 weeks of gestation (odds ratio, OR 0.86; 95% confidence interval, 95% CI 0.61–1.22); neonatal death or short-term morbidity (OR 0.62; 95% CI 0.38–1.03); 2-year cognitive score in the progesterone group versus the placebo group [97.3 (SD 17.9) versus 97.7 (SD 17.5), respectively; the difference in means −0.48; 95% CI −2.77 to 1.81][20]. However our suggestion of the promising result of adding 17 α hydroxy progesterone to Nifedipine was based on experimental support from animal and in vitro studies, and empirical evidence from large, randomized placebo-controlled clinical trials, that treatment with progestins (group of steroid hormones that include natural progesterone and its analogs) minimize the risk of preterm birth [21].

The current study showed a statistically significant difference in maternal adverse effects regarding maternal heart rate and mean blood pressure (mm Hg) before and after treatment with Nifedipine with 17 α hydroxyprogesterone. Maternal mean blood pressure decreased significantly after treatment because of the synergistic vasodilator effects of Nifedipine and 17 α hydroxyprogesterone on the wall of the blood vessel. Additionally, the painful injection sites. The strength of our study to our knowledge this is the first study that used 17 α hydroxyprogesterone in acute phase treatment of preterm labor and it is combined with calcium channel blockers, the availability of medication and cost-effectiveness of medication is of great value. The limitation of the study we did not record the long-term effects for the baby of implementing these recommendations, had no subgroup analysis, small sample size.

Conclusion

Our study offers hope that the combination of nifedipine with 17 α hydroxyprogesterone is superior to Magnesium sulfate in controlling preterm labor and prolongation of pregnancy. Larger studies with different dosage regimens, multicenter, are needed to confirm our findings and gain a better understanding of the mechanism of action of this novel therapeutic combination.

Conflict of interest

All the authors declared that no conflict of interest.

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Authors' contribution

ANA shared by the conception of the research, and manuscript drafting. AMA: data collection, summarization, and analysis/. AMF revision of the manuscript.

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