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EFFECT OF NIFIDIPINE, RITODRINE AND MAGNESIUM SULFATE THERAPY ON DOPPLER STUDY OF FETAL UMBILICAL AND MIDDLE CEREBRAL ARTERIES IN CASES OF PRETERM LABOR

By

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ABSTRACT

Background: Spontaneous preterm labor (SPTL) and preterm birth (PTB) is defined as birth before 37 completed weeks, and is the single most important cause of perinatal mortality and morbidity in highincome countries. Ritodrine is a betasympathomimetic drug that is frequently used for the prevention of preterm birth. One of the most important side effects of ritodrine is pulmonary edema. The lower incidence of side effects in comparison with ß-agonists undoubtedly has been the prime incentive to start the use of calcium channel blockers for tocolysis. The side effects also appear to have less impact on maternal wellbeing and are of shorter duration. Contrary to ritodrine, nifedipine had minimal effects on maternal pulse rate, systolic and diastolic blood pressure, serum potassium concentrations and blood glucose levels.

Objective: To assess and compare the effects of nifedipine, ritodrine and magnesium sulfate on Doppler parameters of fetal umbilical and middle cerebral artery in cases of preterm labor.

Patients and methods: A prospective cohort study conducted on pregnant women in the department of Obstetrics and Gynecology of Al-Ayat Central Hospital. A total of 150 cases coming to the casualty unit with preterm labor pains had been included in the study. Patients had been divided into 3 equal groups: Group A received intravenous ritodrine infusion, Group B received oral nifedipine, and Group C received intravenous magnesium sulfate infusion

Results: There was no statistically significant difference between groups regarding to demographic data. Bishop score before and after treatment. However, there was a statistically significant difference between groups according to maternal heart rate after treatment. Also, significant difference between before and after treatment according to maternal heart rate in ritodrine group. There was no statistically significant difference between groups regarding to contraction frequency at starting and at maintenance tocolytic, time from starting the drug till delivery, failure rate and cessation of contractions but there was a statistically significant difference between groups regarding to stopping the drug due to side effect. According to fetal umbilical artery PI in magnesium sulfate, group C showed significant difference between before and after the treatment. Also, significant difference between before and after treatment according to fetal middle cerebral artery PI in nifedipine (group B), and magnesium sulfate group (group C). There was a significant difference between before and after treatment according to cerebroplacental ratio in magnesium sulfate group (group C).

Conclusion: There was no overall difference between ritodrine, nifedipine, and magnesium sulfate in their efficacy as tocolytic for preterm labor. In addition, it showed that the maternal side effects profile was fewer with nifedipine and magnesium sulfate than with ritodrine.

Keywords: Nifidipine, Ritodrine, Magnesium Sulfate, Doppler Fetal Umbilical, Middle Cerebral Arteries, Preterm Labor.

INTRODUCTION

The exact mechanism(s) of preterm labor is largely unknown but is believed to include decidual hemorrhage, uterine over distension, cervical incompetence, uterine distortion, cervical inflammation, maternal medical disorders, and\or uteroplacental insufficiency *(Chung et al., 2015).*

American College of Obstetricians and Gynecologists issued a Committee Opinion stating that progesterone supplementation for the prevention of recurrent preterm birth should be offered to women with a singleton pregnancy and a prior spontaneous preterm birth due to spontaneous preterm labor or premature rupture of membranes. Progesterone supplementation for asymptomatic women with an incidentally identified very short cervical length (<15 mm) may be considered *(Mesiano, 2011).*

The administration of steroids is recommended in the absence of clinical infection whenever the gestational age is between 24 and 34 weeks. An attempt should be made to delay delivery for a minimum of 12 hours to obtain the maximum benefits of antenatal steroids. However, a randomized clinical trial showed that treatment with corticosteroids at 34-36 weeks of pregnancy does not reduce the incidence of respiratory disorders in newborn infants *(Porto et al., 2011).*

Although the use of repeated doses of corticosteroids remains controversial, a meta-analysis concluded that repeated doses of prenatal corticosteroids in women who remained at risk for preterm birth- 7 or more days after an initial course- reduced the risk of developing respiratory distress syndrome with serious infant outcomes. In view of these conclusions, the authors suggest that the clinicians may consider use of repeated doses of corticosteroids if the patient remains at significant risk for preterm delivery within the next 7 days *(Crowther et al., 2011).*

All patients in cases of preterm labor should be considered at high risk for neonatal GBS sepsis. Patients with high potential to be delivered should receive prophylactic antibiotics against GBS, unless GBS culture is negative. Prophylactic antibiotics should be administered and continued until delivery or for a minimum of 72 hours *(Verani et al., 2010).*

In the past, Beta-mimetic agents, such as ritodrine, were the agents of choice, but in recent years their use has been significantly curtailed due to maternal and fetal side effects. The use of these agents might lead to pulmonary edema, myocardial ischemia, and cardiac arrhythmia *(Nijhawan et al., 2012).*

Magnesium sulfate is widely used as the primary tocolytic agent; Common maternal side effects include flushing, nausea, headache, drowsiness, and blurred vision. The mother should be monitored for toxic effects, such as respiratory depression or even cardiac arrest that can occur at supratherapeutic levels. In addition, magnesium sulfate readily crosses the placenta and may lead to

respiratory and motor depression of the neonate. Several observational studies have reported an association of antenatal treatment with magnesium sulfate for preterm labor or preeclampsia with a decreased risk of cerebral palsy in low birth weight or preterm infants *(Conde-Agudelo et al., 2011).*

Since the primary therapeutic goal of tocolysis is to delay preterm delivery within 48 hours from the initiation of steroid prophylaxis, little evidence suggests that extended $MgSO_4$ therapy is beneficial. The authors recommend discontinuing magnesium sulfate therapy after 48 hours in most patients unless the gestational age is less than 28 weeks when a gain of an additional 3-4 days may significantly reduce neonatal morbidity and mortality. Since no clinical evidence suggests that oral betamimetics or oral magnesium compounds are effective in delaying preterm birth, alternative tocolysis is not currently recommended after the discontinuation of IV $MgSO_4$ therapy *(Kawagoe et al., 2011).*

Nifedipine, a calcium channel blocker, is commonly used to treat high blood pressure and heart disease because of its ability to inhibit contractility in smooth muscle cells by reducing calcium influx into cells. Consequently, nifedipine has emerged as an effective and safe alternative tocolytic agent for the management of preterm labor. Despite its unlabeled status, several randomized studies have shown that the use of nifedipine in comparison with other tocolytic is associated with a more frequent successful prolongation of pregnancy, resulting in significantly fewer admissions of newborns to the neonatal intensive care unit, and may be associated with a lower incidence of RDS, necrotizing enterocolitis, and intraventricular hemorrhage *(Conde-Agudelo et al., 2011).*

The aim of the present study was to assess and compare the effects of nifedipine, ritodrine and magnesium sulfate on Doppler parameters of fetal umbilical and middle cerebral artery in cases of preterm labor.

PATIENTS AND METHODS

There was a prospective cohort study conducted on pregnant women at the Department of Obstetrics and Gynecology of Al-Ayat Central Hospital. A total of 150 cases coming to the casualty unit with preterm labor pains had been included in the study between May 2019 and May 2020.

Inclusion criteria: Age: 20-35, singleton pregnancy, gestational age: 28-34 weeks, intact membranes, and presence of painful regular uterine contractions associated with cervical changes.

Exclusion criteria: Multiple pregnancy, evident intrauterine infection, congenital fetal anomalies, fetal growth restriction, fetal distress or fetal demise, abruptio placenta or placenta previa with life threatening bleeding, maternal medical disorders such as severe preeclampsia, heart disease or hyperthyroidism, and patients in active phase of the first stage of labor (cervix dilated more than 4cm).

Sampling:

- **Frame:** Pregnant women at the department of Obstetrics and Gynecology of Al-Ayat Central Hospital.

- **Method:** Non-probability convenience sampling method was conducted.
- **Sample size:** The sample size was calculated using the following formula *(Buderer, 2010)*:

$$n = \frac{\left[z_\alpha\sqrt{(1+1/m)\bar{p}(1-\bar{p})} + z_\beta\sqrt{p_0(1-p_0)/m + p_1(1-p_1)}\right]^2}{(p_0-p_1)^2}$$

- N = Sample size.
- $\alpha = 0.05$
- m = number of control subjects per experimental subject.
- P0 = probability of event in controls = 23.4% (Kamel et al., 2019).
- P1 = probability of event in experimental subjects = 48%.
- N= 150 subjects.
- On light of the above calculations, patients had been divided into the 3 equal groups: Group A received intravenous ritodrine infusion, Group B received oral nifedipine, and Group C received intravenous magnesium sulfate infusion.

Patients of each group had been subjected to:

- **History taking:**

- Personal history.
- Present history; especially onset of labour pains, vaginal gush of fluids, vaginal bleeding or febrile illness.
- Obstetric history.
- Menstrual history.
- Past history.
- Family history.

- **General examination:**

- Pulse, blood pressure, temperature.

- **Abdominal examination:**

- Fundal level between 28-34 weeks.
- Fetal heart sounds.
- Fundal grip, umbilical grip, 1st pelvic grip.

- **Vaginal examination:**

- Cervical dilation and effacement.
- State of membranes.

- **Sonographic assessment:**

- Estimation of gestational age.
- Assessment of amniotic fluid volume and placental site.
- Exclusion of major fetal anomalies.
- Electronic monitoring of fetal heart rate and uterine contractions.
- Fetal Doppler assessment: Assessment of the Doppler waveforms of the umbilical and middle cerebral arteries had been performed prior to, and 24 hours after starting drug therapy. Colour Doppler examination of both foetal middle cerebral and umbilical arteries using Ultrasound equipment capable of high-resolution grayscale, pulsed wave and color Doppler modes was used a 2-5MHz transabdominal probe (GE LOGIC p5, Japan and GE LOGIC p7, Japan).

- **Administration of the tocolytic agent:**

Group A received ritodrine by intravenous infusion commenced by 50 µg/minute (one ampoule 50 mg on 500 ml glucose 5 % at a rate of 10 drops/min, if contractions persisted increase rate by 5

drops every 5 min till no contractions). Maternal heart rate should not exceed120 beats/minute. The dose increased by 50 µg every 20 minutes intervals until contractions stopped or unacceptable side effects occurred. The lowest effective dose was maintained for 24 hours after cessation of contractions. The maximum recommended dose was 350 µg/minute.

Group B received nifedipine orally. Nifedipine therapy was initiated with a 10 mg capsule, if uterine contractions continued to persist after 15 minutes a second 10 mg dose was given and it was administered twice more if necessary up to a maximum dose of 40 mg nifedipine in the first hour of loading therapy. A maintenance dose of 80 – 120 mg nifedipine/ 24 hr.

Group C received magnesium sulfate infusion of the primary dose of 4 g followed by continuous infusion of 1 g/hras maintenance dose

- Initial response had been defined when uterine contractions are suppressed within 2 hours, after starting the drug therapy.
- Drug therapy had been continued for 24 hours after successful response.
- Drug therapy had been considered to fail if rupture of membranes occurs, painful regular uterine contractions still persist or evidence of any side effects with maximum drug dosage.

Ethical consideration:

After approval of the ethical committee, patients were properly counseled as regards the type, methodology and value of study and an informed consent had been taken.

Statistical analysis:

Recorded data were analyzed using the statistical package for social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA). The quantitative data were presented as mean± standard deviation and ranges when their distribution was parametric (normal) while non-normally distributed variables (non-parametric data) were presented as median with inter-quartile range (IQR). Also qualitative variables were presented as number and percentages. Data were explored for normality using Kolmogorov-Smirnov and Shapiro-Wilk Test. The following tests were done: A one-way analysis of variance (ANOVA) when comparing between more than two means and Post Hoc test: Tukey's test was used for multiple comparisons between different variables & Paired sample t-test of significance was used when comparing between related samples in parametric data, as for the non-parametric data was used Kruskall Wallis test: for multiple-group comparisons & Mann Whitney U test: for two-group comparisons, also Wilcoxon Signed-Rank Sum test comparison between differences by time for non-parametric data using; the Comparison between groups with qualitative data was done by using Chi-square test and Fisher’s exact test instead of Chi-square test only when the expected count in any cell less than 5. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the Probability P-value <0.05 was considered significant.

RESULTS

There was no statistically significant difference between groups regarding demographic data with p-value >0.05 NS, while BMI, previous preterm labor and hemoglobin significant difference between groups with p-value <0.05 S; as shown in **(Table 1)**.

Table (1): Comparison between the groups according to demographic data

Parameters \ Groups	Group A (ritodrine) (n=50)	Group B (nifedipine) (n=50)	Group C (MgSO4) (n=50)	P-value
Age (years)#				
Range	18-37	18-37	18-37	0.338
Mean±SD	26.43±5.51	26.95±5.21	28.01±5.61	
BMI (kg/m²)#				
Range	21.6–35	20.5–33.4	24.3–33.7	<0.001
Mean±SD	24.9±4.21‡	22.4± 3.37≠	26.2 ± 3.81†	
Parity▲				
Range	0-4	0-4	0-3	0.453
Mean±SD	1.81±1.02	2.12±0.62	1.64±0.72	
Abortion▲				
Range	0-2	0-3	0-2	0.364
Mean±SD	0.74±0.63	1.07±0.82	0.94±0.52	
Previous preterm labor▲				
Range	0-4	0-3	0-3	<0.001
Mean±SD	3.47±0.83†	2.72±0.53‡	2.21±0.48≠	
Urinary tract infection	11 (22%)	9 (18%)	13 (26%)	0.627
Hemoglobin (g/dl)#	11.2 ± 0.5‡	11.4 ± 0.5‡	10.9± 0.4†	<0.001
GA (week) on admission#				
Range	28-34	29-35	28-33	0.132
Mean±SD	31.8±1.76	32.5±1.90	32.2±1.52	
Mode of delivery§				
VD	10 (20%)	11 (22%)	9 (18%)	0.883
CS	40 (80%)	39 (78%)	41 (82%)	

Values are expressed as mean±SD and Number (Percent%)
#One way Analysis of Variance test was performed & Multiple comparison between groups through Post Hoc test: Tukey's test
▲Kruskal–Wallis was performed & Multiple comparison between groups through Mann-Whitney test
§Chi-square test
Values in each row which have different symbols are significantly different at (P<0.05).

There was no statistically significant difference between groups according to bishop score before and after treatment.

There was a statistically significant difference between groups according to maternal heart rate bfore treatment. Also, significant difference between before and after treatment according to maternal heart rate in ritodrine group (group A).

There was a statistically significant difference between groups according to fetal heart rate bfore treatment. Also statistically significant difference between before and after treatment according to fetal heart rate in ritodrine group (group A).

There was a statistically significant difference between groups regarding to

side effect regardin Tachycardia, palpitation and Dyspnea. Also, statistically significant difference between groups according to maternal heart rate before treatment.

There was a highly statistically significant difference between groups regarding to contraction frequency at starting tocolytic (min); contraction frequency at maintenance tocolytic (min) and time from starting the drug till delivery (hour).

There was no statistically significant difference between groups regarding to Failure, Stopped drug due to side effect and Cessation of contractions **(Table 2)**.

Table (2): Comparison between groups according to Bishop's score, maternal heart rate, fetal heart rate, side effect, drug effectiveness

Parameters \ Groups	Group A (ritodrine) (n=50)	Group B (nifedipine) (n=50)	Group C ($MgSO_4$) (n=50)	P-value
Bishop score▲:				
Before treatment	6.98±2.39	6.33±2.36	6.09±2.08	0.107
After treatment	7.51±2.48	6.87±2.14	6.23±2.11	0.079
P-value using Wilcoxon test	0.428	0.533	0.453	
Maternal heart rate#				
Before treatment	75.13±5.81‡	83.89±4.56†	86.72±5.98†	<0.001
After treatment	91.2±7.08	89.72±3.13	90.02±4.90	0.338
P-value using Paired sample t-test	<0.001	0.054	0.065	
Fetal heart rate#				
Before treatment	139.08±11.92	143.13±10.12	142.11±9.07	0.134
After treatment	152.8±11.07†	146.2±9.41‡	141.30±10.81≠	<0.001
P-value using Paired sample t-test	<0.001	0.081	0.121	
Maternal complications				
Tachycardia, palpitation	27(54%)	7(14%)	10(20%)	<0.001
Dyspnea	5(10%)	0(0%)	0(0%)	0.006
Nausea and vomiting	19 (38%)	9 (18%)	13 (26%)	0.078
Pulmonary edema	1 (2%)	0 (0%)	0 (0%)	0.365
Myocardial ischemia	0 (0%)	0 (0%)	0 (0%)	NA
Others	2 (4%)	1 (2%)	1 (2%)	0.774
Drug effectiveness:				
Contraction frequency at starting tocolytic (min)▲	15.5±3.51‡	14.8±3.26‡	12.4±3.12†	<0.001
Contraction frequency at maintenance tocolytic (min)#	85.3±9.14≠	93.2± 10.12‡	102.4±12.53†	<0.001
Time from starting the drug till Delivery (hour)#	42.2±7.33≠	51.8±5.16†	47.1±5.73‡	<0.001
Failure	21(42%)	20 (40%)	22(44%)	0.921
Stopped drug due to side effect	9 (18%)	3 (6%)	5 (10%)	0.156
Cessation of contractions	20(40%)	27(54%)	23(26%)	0.371

Values are expressed as mean±SD and Number (Percent%)

#One way Analysis of Variance test was performed & Multiple comparison between groups through Post Hoc test: Tukey's test

▲Kruskal–Wallis was performed & Multiple comparison between groups through Mann-Whitney test

■Fisher's exact test; §Chi-square test

Values in each row which have different symbols are significantly different at (P<0.05).

There was a statistically significant difference between groups according to fetal umbilical artery PI before and after treatment. Also, significant difference between before and after treatment according to fetal umbilical artery PI in magnesium sulfate group (Group C).

There was a statistically significant difference between groups according to fetal middle cerebral artery PI before and after treatment. Also, significant difference between before and after treatment according to fetal middle cerebral artery PI in nifedipine (group B) and magnesium sulfate group (group C).

There was a statistically significant difference between groups according to cerebroplacental ratio after treatment. Also, there was significant difference between before and after treatment according to cerebroplacental ratio in magnesium sulfate group (group C).

There was a statistically significant difference between groups according to birth weight at admission.

There were no statistically significant differences between groups regarding to need for incubation, Gestational age at admission, NICU stay, and causes for NICU admission **(Table 3)**.

Table (3): Comparison between groups according to fetal umbilical artery PI before and after treatment, fetal middle cerebral artery PI before and after treatment, cerebroplacental ratio, need for NICU admission and causes for NICU admission

Parameters \ Groups	Group A (ritodrine) (n=50)	Group B (nifedipine) (n=50)	Group C ($MgSO_4$) (n=50)	P-value
Fetal umbilical artery PI#				
Before treatment	1.21±0.128‡	1.27±0.125†	1.06±0.148≠	<0.001
After treatment	1.23±0.130‡	1.31±0.126†	1.17±0.119≠	<0.001
P-value using Paired sample t-test	0.243	0.281	0.012	
Fetal middle cerebral artery PI#				
Before treatment	1.38±0.13†	1.31±0.11‡	1.38±0.149†	0.010
After treatment	1.36±0.13‡	1.27±0.12≠	1.62±0.136†	<0.001
P-value using Paired sample t-test	0.289	0.042	<0.001	
Cerebroplacental ratio▲:				
Before treatment	1.25±0.11	1.18±0.89	1.34±0.12	0.101
After treatment	1.23±0.09‡	1.16±0.24‡	1.51±0.13†	<0.001
P-value using Wilcoxon test	0.163	0.188	<0.001	
Need for NICU admission				
NICU admission§ Yes No	 38(76%) 12(24%)	 30(60%) 20(40%)	 35(70%) 15(30%)	0.219
Gestational age at admission (week)#	30.2± 5.31	31.8± 5.82	31.2± 5.51	0.349
Birth weight at admission (gram)#	1957.5±215.33‡	2140.6±225.31†	2126.2±219.24†	<0.001
NICU stay (days)▲	11.4± 3.51	9.2± 2.17	9.8 ± 2.37	0.554
Causes for NICU admission:				
RDS No (%)§	26(68.4%)	24 (80%)	26(74.2%)	0.899
IVH No (%)■	2(5.4%)	1 (3.3%)	1(2.9%)	0.774
NEC No (%)■	5(13.3%)	2 (6.7%)	4(11.4%)	0.503
Sepsis No (%)■	3(7.9%)	3 (10%)	3(8.5%)	1.000

Values are expressed as mean±SD and Number (Percent%)

#One way Analysis of Variance test was performed & Multiple comparison between groups through Post Hoc test: Tukey's test

▲Kruskal–Wallis was performed & Multiple comparison between groups through Mann-Whitney test

■Fisher's exact test; §Chi-square test

Values in each row which have different symbols are significantly different at (P<0.05).

DISCUSSION

In the present study, which was held on 150 patients divided into three groups, analysis of the characteristics of the studied population showed that the mean maternal age found to be 26.43±5.51, 26.95±5.21 and 28.01±5.61 years old for Ritodrine, Nifedipine, and Magnesium Sulphate groups respectively. The difference in age between groups was insignificant. The mean parity for the ritodrine group was 1.81±1.02, for the magnesium sulfate group 1.64±0.72 and for the nifedipine group it was 2.12±0.62, which was statistically non-significant. Also, the mean number of previous preterm labors for the nifedipine group was 0.60±0.87, for the magnesium sulfate group 0.57±0.59, and for the ritodrine group was 0.76±0.59 (0-3) with statistical insignificant difference. The mean gestational age at nifedipine group was 31.5±1.90 weeks, magnesium sulfate group was 31.2±1.52 weeks, and for the ritodrine group it was 31.8±1.76 weeks with statistical insignificant difference.

In agreement, *Mousa et al. (2019)* reported that comparing the mean maternal age was 26.44±5.01, 26.75±4.24, 27.81±6.47 years old for Nifedipine, Magnesium Sulphate and Ritodrine groups respectively. The difference in age between groups was insignificant. The mean parity for the nifedipine group was 1.79±1.14, for the magnesium sulfate group 2.01±0.87 and for the ritodrine group it was 1.69±0.65, which was statistically non-significant. In addition, when we compared the three study groups, it was found that the mean number of previous preterm labors for the nifedipine group was 0.66±0.81, for the magnesium sulfate group 0.74±0.68, and for the ritodrine group it was 0.53 ± 0.64, which was statistically non-significant. The mean gestational age at admission for the women included in the nifedipine group was 31.96±1.52 weeks, for the magnesium sulfate group the mean gestational age at admission was 32.06±1.64 weeks, and for the ritodrine group was 31.9±1.68 weeks. When comparing the results of the three study groups, no statistically significance.

These characteristics also were not different from *Abdellateef et al. (2018)* who assessed the effect of Nifidipine on fetal and maternal circulation. The maternal age in their study ranged between 18 and 40 with the mean 25.70±4.94. Gravidity ranged between 1 and 5 with the mean 2.44±1.20. Parity ranged between 0-4 with the mean 1.33±1.15. Gestational age on admission ranged between 25 and 34 with the mean 30.33±2.54. Fetal weight ranged between 780-2432 with the mean 1611.56±459.73 *(Abdellateef et al., 2018)*.

Most of the deliveries in the current study were, by cesarean sections, 78% for Nifidipine group, 82% for Magnesium sulfate group and 80% for ritodrine group. There were no significant differences between groups regarding mode of delivery. *Mousa et al. (2019)* showed that cesarean sections were 80% for Nifidipine group, 84% for Magnesium sulfate group, and 78% for ritodrine group. There were no significant differences between groups regarding mode of delivery.

In our study, the mean apgar score was 4.32±0.73 for Nifedipine group, 4.45±0.62 in Magnesium sulfate group and 4.61±0.59 in Ritodrine group. The

difference between groups insignificant. The mean birth weight was 1709.5±272.3; 1652.2±270.3 and 1691.6±260.2; for Nifedipine, Magnesium sulfate and Ritodrine groups respectively. The differences between groups in birth weight were also non-significant.

This was consistent with *Lyell et al. (2011)* who compared fetal adverse effects resulting from administration of Nifedipine versus Magnesium sulfate. They found that mean birth weight was 2,55±802 grams among Nifedipine group, and 2,65±698 grams among Magnesium sulfate. This difference in birth weight was insignificant.

This was in agreement with *Mousa et al. (2019)* who found that the mean apgar score was 4.56±0.64 for Nifedipine group, 4.43±0.62 in Magnesium sulfate group and 4.14±0.58 in Ritodrine group. The difference between groups was insignificant. The mean birth weight was 1783.9±237.1; 1718.5±245.9 1650.9±254.8; for Nifedipine, Magnesium sulfate and Ritodrine groups respectively. The difference between groups in birth weight was non-significant.

In our study, when we observed the cardiovascular changes that occurred after administration of the three drugs, it showed that all of the three drugs caused an increase in the maternal heart rate after their administration. However, it reached a statistically significant value only in the ritodrine group.

These results came in agreement with *Kamel et al. (2018)* study that showed that all of the three drugs caused an increase in the maternal heart rate after their administration. However, it reached a statistically significant value only in the ritodrine group.

This was in agreement with *Kamel et al. (2018)* who found no statistical difference in the maternal heart rate between the three groups before administration of the drugs, while after their administration a statistically significant difference was noted between ritodrine group and the other two groups at all-time points of treatment.

Our study found a statistically significant difference between groups according to maternal heart rate after treatment. Also, significant difference between before and after treatment according to fetal heart rate in ritodrine group (group A).

Similarly *Mousa et al. (2019)* study which showed that fetal heart rate increased which was statistically significant. In the nifedipine group, the fetal heart rate increased non-significantly. In the magnesium sulfate group the fetal heart rate slightly changed insiginficantly. Moreover, there was a significant difference between the three groups in fetal heart rate and after treatment.

Kamel et al. (2018) compared the effect of each tocolytic drug on fetal heart rate, separately; and found that fetal heart rate was significantly greater in the ritodrine group at all points during treatment. However; this was in disagreement with previous literature that showed no significant difference in fetal heart rate after tocolytic administration *(Guclu et al., 2010).*

The current study results showed that there was a statistically significant

difference between groups according to maternal complications. Ritodrine group participants had significantly highest rate of maternal complications in the form of tachycardia and palpitation compared to other two groups. Dyspnea occurred in 10 % of Ritodrine group participants, while no dyspnea was observed among mothers in Magnesium sulfate and Nifedipine group. This difference between groups was significant.

In agreement, *Mousa et al. (2019)* showed that Ritodrine group participants had significantly highest rate of maternal complications in the form of tachycardia and palpitation compared to other two groups (84 % of Ritodrine group, compared to 30 % and 14 % in Magnesium sulfate and Nifedipine respectively). Dyspnea occurred in 14 % of Ritodrine group participants, while no dyspnea was observed among mothers in Magnesium sulfate and Nifedipine group; this difference between groups was significant.

This also in agreement with *Haas et al. (2013)* and *Alfirevic (2012)*, in their metanalysis, who stated that Calcium channel blockers, including Nifedipine had only a 15% probability of being ranked in the top three drug classes for maternal side effects, whereas beta mimetics (including Ritodrine and Magnesium sulfate), showed statistically significant harmful effects on mothers. Moreover, Nifedipine was associated with significantly fewer mild and severe maternal adverse effects, compared to Magnesium sulfate *(Nassar et al., 2011)*.

In the present study, there was cessation of contractions in the three study groups after administration of the drugs, which was more evident in nifedipine group (54%) which was In agreement with the study of *Mousa et al. (2019)* study.

In our study, when we observed the Doppler changes on fetal umbilical and middle cerebral arteries that occurred after administration of the three drugs, it showed increase in umbilical artery PI after treatment in the magnesium sulfate group only, which was statistically significant.

This was in agreement with *Kamel et al. (2019)* and *Mousa et al. (2019)* who found significant increase in umbilical artery PI after treatment in the magnesium sulfate group only, whereas no significant differences in mean umbilical PI were observed before and after treatment in case of ritodrine, nor in case of treatment with nifedipine.

Our study found statistically significant difference between groups according to fetal middle cerebral artery PI after treatment. Also, significant difference between before and after treatment according to fetal middle cerebral artery PI in nifedipine (group B) and magnesium sulfate group (group C).

Mousa et al. (2019) stated that the mean PI of fetal middle cerebral artery showed significant differences between the three groups before treatment, and after treatment. Also, there was a significant difference before and after treatment in Nifedipine group and in magnesium sulfate group.

These results were in agreement with *Nhan-Chang et al. (2010)* and *Kamel et al. (2019)*; whose studies found significant increase in middle cerebral artery PI after treatment in magnesium sulfate group and

showed statistically significant decrease in nifedipine group, and the decrease was within clinically acceptable levels.

Cerebroplacental ratio in this study had statistically significant difference between groups after treatment. Also, there was significant difference between before and after treatment according to cerebroplacental ratio in magnesium sulfate group (group C).

Mousa et al. (2019) showed that cerebroplacental ratio before treatment showed no statistical difference between the three groups in the current study while there was a significant difference between the groups. Magnesium sulfate group showed a significant difference in cerebro-placental ratio before and after treatment. Meanwhile, *Guclu et al. (2010)* stated that Nifedipine maintenance was associated with a significant fall in the cerebroplacental Doppler ratio was maintained beyond 24 h.

The mean bishop score was calculated before and after treatment in our study; and the difference was insignificant.

The insignificant difference between groups before treatment was in agreement with *Kamel et al. (2019)* who found insignificant differences between the three groups in admission with p value was 0.045.

The current study results showed that the majority of newly born needed incubation after birth; indicating high rate of neonatal morbidity. The highest proportion was among Ritrodrine group (76%), followed by Magnesium sulfate group (70 %) and lowest was among Nifedipine group (60%). There wasn`t a significant difference between the three groups. This was in partial agreement with results of an open randomized controlled trial conducted to assess neonatal effects of oral nifedipine (n= 95) and intravenous Ritodrine (n = 90); that Nifedipine was found to be associated with a lower incidence of neonatal morbidity (neonatal intensive care unit admissions, intracranial hemorrhage, respiratory distress syndrome, and neonatal jaundice); similar to the current study results. However this difference was significant *(Nassar et al., 2011)*.

Similarly, while comparing adverse effects in neonates as an outcome of Nifidepine versus Magnesium sulfate administration, neonatal morbidities were similar between groups, but neonatal intensive care admission rate was higher in newborns in the magnesium sulfate group (52%) compared to Nifedipine (37%), and this result was significant *(Haas et al., 2013)*. Moreover, when comparing side effects of Nifedipine versus Ritodrene; the number of admissions to the neonatal intensive care unit (NICU) in the nifedipine group was significantly lower than in the ritodrine group (68.4 versus 82.1%). Several literature demonstrated that nifedipine treatment did not influence either fetal or uteroplacental circulation *(Nikbakht et al., 2014)*.

CONCLUSION

There was no overall difference between ritodrine, nifedipine, and magnesium sulfate in their efficacy as tocolytic for preterm labor. In addition, the maternal side effects profile was fewer with nifedipine and magnesium sulfate than with ritodrine.

Fetal Doppler study found no clinically significant effect on the pulsatility index (PI) of umbilical and middle cerebral artery, while with magnesium sulfate therapy, there was increase in cerebroplacental ratio 24hr after treatment, and these findings ensure safety of the drugs on the maternal and fetal aspects.

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تأثير عقار نيفيدبين و ريتودرين و سلفات الماغنسيوم على دراسة دوبلر شريان الحبل السري, وشريان المخ الأوسط للجنين في حالات الولادة المبكرة

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خلفية البحث: يتم تعريف المخاض العفوي قبل الأوان والولادة قبل الأوان على أنهما ولادة قبل 37 أسبوعاً كاملاً وهو السبب الوحيد الأكثر أهمية للوفيات والمراضة في الفترة المحيطة بالولادة في البلدان ذات الدخل المرتفع. ريتودرين دواء محاك للبيتا الودي يستخدم بشكل متكرر للوقاية من الولادة المبكرة. أحد أهم الآثار الجانبية للريتودرين هو الوذمة الرئوية. لا شك أن معدل حدوث الآثار الجانبية الأقل مقارنة بمنبهات بيتا كان الحافز الرئيسي لبدء استخدام حاصرات قنوات الكالسيوم لحل المخاض. يبدو أيضًا أن الآثار الجانبية لها تأثير أقل على صحة الأم وتكون مدتها أقصر. على عكس الريتودرين، كان للنيفيديبين تأثير ضئيل على معدل نبض الأم، وضغط الدم الانقباضي والانبساطي، وتركيزات البوتاسيوم في الدم ومستويات السكر في الدم.

الهدف من البحث: تقييم ومقارنة آثار النيفيديبين والريتودرين وكبريتات المغنيسيوم على معلمات دوبلر للشريان السري والوسطي المخي للجنين في حالات الولادة المبكرة.

المريضات وطرق البحث: دراسة جماعية مستقبلية أجريت على النساء الحوامل في قسم النساء والتوليد بمستشفى العياط المركزي. وتم تضمين 150 حالة قادمة مع آلام مخاض قبل الأوان. وتم تقسيم المرضى إلى ثلاث مجموعات متساوية: المجموعة أ تلقت الريتودرين عن طريق الوريد، المجموعة ب: تلقي نيفيديبين عن طريق الفم، والمجموعة ج: تم تسريب كبريتات المغنيسيوم عن طريق الوريد.

نتائج البحث: لم تظهر الدراسة أن هناك فرقا معتدا به إحصائيا بين المجموعات فيما يتعلق بالبيانات الديموغرافية. وفي درجة الأسقف قبل العلاج وبعده، ولكن

كان هناك فرق ذو دلالة إحصائية بين المجموعات وفقًا لمعدل ضربات قلب الأم بعد العلاج. أيضا، هناك فرق إحصائي قبل العلاج وبعده حسب معدل ضربات قلب الأم في مجموعة الريتودرين. فيما يتعلق بالأعراض الجانبية أظهرت الدراسة فروقا ذات دلالة إحصائية بين المجموعات و لم يكن هناك فروقا ذات دلالة إحصائية بين المجموعات فيما يتعلق بتكرار الانكماش عند البدء وفي حالة المداومة للمخاض، والوقت من بدء الدواء حتى الولادة، ومعدل الفشل ووقف الانقباضات ولكن هناك فرق معتد به إحصائياً بين المجموعات فيما يتعلق بإيقاف الدواء بسبب التأثير الجانبي. وفقا للشريان السري للجنين في مجموعة كبريتات المغنيسيوم، أظهرت المجموعة (ج) فرقا معنويا بين قبل وبعد العلاج. أيضا، هناك فرق معنوي بين قبل وبعد العلاج حسب الشريان الدماغي الأوسط للجنين في مجموعة نيفيديبين (المجموعة ب) ومجموعة سلفات المغنيسيوم (المجموعة ج). وكان هناك فرقا معنويا بين قبل العلاج وبعده حسب نسبة المشيمة الدماغية في مجموعة كبريتات المغنيسيوم (المجموعة ج).

الاستنتاج: لا يوجد فرق إجمالي بين ريتودرين، نيفيديبين، وكبريتات المغنيسيوم في فعاليتها كمحللة للمخاض من أجل الولادة المبكرة. بالإضافة إلى ذلك، اظهر أن الآثار الجانبية للأم كانت أقل مع النيفيديبين وكبريتات المغنيسيوم مقارنة بالريتودرين.

الكلمات الدالة: نيفيديبين، ريتودرين، كبريتات المغنيسيوم، دوبلر الجنين السري، الشرايين الدماغية الوسطى، الولادة المبكرة.