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Comparative Study between the Effect of Nifedipine, Ritodrine and Indomethacin Therapy on Doppler Indices of Fetal Umbilical and Middle Cerebral Arteries in Patients with Preterm Labour

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ABSTRACT

Background: The leading cause of neonatal and maternal morbidity is preterm delivery. Relevant hospitalization rates during pregnancy have been declining since 2007.

Aim of the work: Is to compare the effects of nifedipine, ritodrine, and Indomethacin tocolytic drugs on Doppler parameters of the foetal umbilical and middle cerebral arteries in instances of preterm labour in order to choose the safest and most effective drug.

Patients and methods: : In a cohort study, 132 patients with preterm labour symptoms, intact membranes, and a singleton gestation between 28 and 34 weeks of pregnancy were divided into three groups and admitted to the Obstetric Department at Ahmad Maher Teaching Hospital between May 2020 and October 2021.

Results: Nifedipine and Ritodrine caused an increase in the maternal heart rate and fetal heart rate, but a statistically significant only in the ritodrine group. With a p-value less than 0.05, the ritodrine group had greater maternal tachycardia, palpitation, and dyspnea. The three drugs caused cessation of uterine contractions; however, was more in the nifedipine group. The three drugs showed a statistically non-significant difference in fetal umbilical artery PI and cerebroplacental ratio changes before and after treatment. The middle cerebral artery PI following therapy in the ritodrine and indomethacin groups was statistically non-significant, whereas the nifedipine group showed a statistically significant decrease with a P value of 0.027.

Conclusion: The pulsatility index (PI) of the umbilical and middle cerebral arteries was not clinically significant in a foetal Doppler study, ensuring the medications' safety in both the mother and fetus aspects.

Keywords: *Nifedipine; ritodrine; indomethacin therapy; fetal umbilical; middle cerebral arteries.*

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INTRODUCTION

The presence of uterine contractions of sufficient frequency and strength to cause progressive effacement and dilatation of the cervix before to term gestation is characterised as preterm labour (between 20 and 37 week). Preterm labour is associated with about half of all preterm births in the United States, as well as preterm birth infant mortality. Preterm birth also accounts for 70% of neonatal illness, mortality, and health-care expenses spent on the neonate, owing to the 2% of American women who deliver very premature infants (less than 32 weeks) [1].

After 34 weeks of gestation, the risk of infant mortality and morbidity is low; yet, a trial of acute tocolysis may be started; however, vigorous tocolytic therapy is generally not suggested beyond 34 weeks due to probable maternal problems. Tocolytic therapy is generally acknowledged to outweigh the risk of maternal and/or foetal problems between 24 and 33 weeks of pregnancy, and these medicines should be started if no contraindications present. Although aggressive tocolysis is not commonly employed beyond 34 weeks' gestation, practitioners are urged not to deliver patients at this gestation without reason because babies delivered between 34 and 36 weeks of pregnancy have a greater risk of neonatal morbidity than those delivered at 37-40 weeks' gestation [2].

In a 2012 systematic review and network meta-analysis of 95 randomized studies of tocolytic treatment for preterm labour, all of the frequently employed tocolytic drugs (cyclooxygenase inhibitors (Indomethacin), beta-agonists (Ritodrine), calcium channel blockers (Nifedipine), magnesium sulphate, and oxytocin receptor antagonists) have been

statistically more effective than placebo/no tocolytic in delaying birth for 48 h [3].

The goal of this research is to examine the effects of oral nifedipine, IV ritodrine administration, and Indomethacin employed as tocolytics in instances of preterm labour on Doppler parameters of the fetus' umbilical and middle cerebral arteries, as well as their impacts on the mother and the fetus, to select the safest and most efficient medicine before the initial dose and 24 hours after the therapy.

PATIENTS AND METHODS

This prospective observational analytical group research has been carried on 132 patients admitted to the Ahmad Maher Teaching Hospital's Obstetric Department with preterm labour symptoms, intact membranes, and a singleton gestation between 28 and 34 weeks of pregnancy during May 2020 and October 2021.

The study included patients ranging in age from 21–35 years with singleton pregnancy, gestational age between 28 and 34 weeks, intact membranes, and labour who had been given a diagnosis of painful, frequent uterine contractions (3-5 contractions every ten minutes for more than 60 minutes) linked to cervical modifications.

Before 20 weeks of pregnancy, all patients were precisely dated using a gestational age depending on the last menstruation cycle, and if possible, a 2nd trimester ultrasonography report was conducted. They have been split into three groups and given the following medications:

Regimens of administration of tocolytics:

Group A: women received ritodrine by intravenous infusion commenced by 50 µg/minute. Maternal heart rate should not exceed 120 beats/minute. The dose was increased by 50 µg every 20 minutes intervals to a maximum of 25 µg/min until contractions stopped or unacceptable side effects occurred [4].

Group B: women received nifedipine orally. Nifedipine treatment has been started with a 20–30 mg dose taken orally that has been repeated every 20 minutes if contractions do not decrease, up to a total dosage of 60 mg. For up to 48 hours, a maintenance dosage of 20 mg has been taken orally every 3 to 8 hours.

The maximum recommended dose is 180 mg/Day [5].

Group C: For women who received Indomethacin, if contractions remain, a 100-mg dosage of indomethacin could be administered via rectum and repeated after 1 to 2 hours. For the next 48 hours, take another dosage of 25 mg every 4–6 hours. Its application is restricted to preterm labour occurring before 32 weeks of pregnancy in women who have normal renal functions and amniotic fluid content. The maximum recommended dose is 200 mg/Day [6].

All patients were subjected to: Consent: a written consent was obtained from each candidate after explanation of the procedure in details. History taking: Personal history, current history, obstetric history, menstrual history, previous history, and family history.

General examination: With particular attention to pulse, blood pressure, and temperature every 20 minutes until a stable dose is achieved, and then every 4 hours. Prior to the start of therapy, all patients had blood pressures of more than 80/50 mmHg. The following equation was used to calculate the mean arterial pressure (MAP): MAP = Diastolic BP + 1/3 (Systolic BP - Diastolic BP)

Abdominal examination: Monitor the fetal heart rate and palpate the uterine contractions to determine the fundal level.

Pelvic examination: To evaluate the status of the membranes and rule out rupture using a sterile Cusco speculum, to rule out vaginal haemorrhage, and to evaluate the condition of the cervix and measure the bishop score.

Sonographic assessment: (using GE Logiq P5 Ultrasound Machine): To calculate the gestational age and volume of liquor, as well as to rule out placenta previa, placental abruption, and significant foetal congenital abnormalities.

Electronic monitoring of uterine contractions and fetal heart rate until the uterine contractions disappear (by Avalon FM20 Fetal Monitor, Philips): Afterwards, during hospital admission, the fetal heart rate and uterine contractions have been observed for 1 hour every 12 hours.

Administration of tocolytic drug, such as indomethacin, intravenous ritodrine or oral nifedipine: If uterine contractions stop within two hours of starting tocolytic therapy, this is considered an initial response. Therapy was continued until contractions ceased for 48 h, maximal dosages had been reached without response, unacceptable adverse effects occurred, or labor proceeded. The term "effective therapy" refers to the cessation of contractions for at least 24 hours and the absence of cervical alterations. Tocolytic failure is characterised by the continuation of symptomatic uterine contractions despite receiving the highest possible dosage of treatment, the rupture of previously intact membranes, or the onset of significant adverse impacts requiring therapy discontinuation. Then she was discharged with no maintenance therapy.

To enhance foetal lung maturity, all participants got 6 mg of IM dexamethasone, followed by another dosage 12 hours later for 48 hours.

Before and 24 hours after the first dose of tocolytic drug therapy, pregnant women and foetuses had their umbilical and middle cerebral artery Doppler waveforms measured (nifedipine, ritodrine, and indomethacin).

Statistical analysis

All statistical computations have been carried out employing the computer programmes Microsoft Excel 2003 (Microsoft Corporation, USA) and SPSS (Statistical Package for the Social Science; SPPS Inc., Chicago, IL, USA) version 15 for Microsoft Windows. A p value greater than 0.05 denotes statistically significant results.

RESULTS

When comparing the three study groups, it was found that the mean gestational age in weeks on admission for the nifedipine group was 31.03 ± 1.474,for the indomethacin group 31.13 ± 1.592 and for the ritodrinegroup it was 30.97± 1.629. The p-value for the three groups = 0.918 which is statistically non- significant.

	Nifedipine	
	Before treatment	**After treatment**
Number of cases	44	**44**
Range	74-99	**82-102**
Mean	86.93	**90.83**
Standard deviation	5.747	**4.893**
P value (before to aftertreatment)	**0.061**	
	Indomethacin	
	Before treatment	**After treatment**
Number of cases	44	**44**
Range	75-85	**75-90**
Mean	80.87	**84.37**
Standard deviation	5.090	**6.542**
P value (before to aftertreatment)	**0.058**	
	Ritodrine	
	Before treatment	**After treatment**
Number of cases	44	**44**
Range	75-90	**90-115**
Mean	80.23	**100.7**
Standard deviation	6.383	**8.276**
P value (before to aftertreatment)	**0.001**	

Table 1: Comparison of the three study groups as a change in maternal heart rate before and after treatment.

	Nifedipine	
	Before treatment	**After treatment**
Number of cases	44	**44**
Range	122-164	**126-166**
Mean	142.63	**146.97**
Standard deviation	9.704	**10.997**
P value (before to aftertreatment)	**0.061**	
	Indomethacin	
	Before treatment	**After treatment**
Number of cases	44	**44**
Range	122-158	**124-160**
Mean	140.13	**142.23**
Standard deviation	10.438	**10.054**
P value (before to aftertreatment)	**0.080**	
	Ritodrine	
	Before treatment	**After treatment**
Number of cases	30	**30**
Range	118-154	**130-168**
Mean	135.77	**153.1**
Standard deviation	12.492	**11.241**
P value (before to after treatment)	0.001	

Table 2: Comparison of the three study groups as a change in fetal heart rate before and after treatment

	Nifedipine	**Indomethacin**	**Ritodrine**	**Total**	**P Value**
Tachycardia, palpitation	4 (13.3%)	9 (30%)	25 (83.3%)	38 (42.2%)	**0.001**
Dyspnea	**0 (0%)**	**0 (0%)**	**4 (13.3%)**	**4 (4.4%)**	**0.015**

Table 3: Maternal complications.

	Nifedipine	**Indomethacin**	**Ritodrine**	**Total**	**P value**
Cessation of contractions	**35 (80%)**	**31 (70%)**	**26 (60%)**	**92 (70%)**	**0.24**

Table (4): Comparison of the three study groups regarding cessation of contractions after treatment

	Nifedipine	
	Before treatment	After treatment
Number of cases	44	44
Range	0.9-1.3	0.9-1.3
Mean	1.131	1.128
Standard deviation	0.099	0.098
P value (before to aftertreatment)	0.281	
	Indomethacin	
	Before treatment	After treatment
Number of cases	44	44
Range	0.8-1.4	0.8-1.4
Mean	1.03	1.07
Standard deviation	0.151	0.127
P value (before to aftertreatment)	0.016	
	Ritodrine	
	Before treatment	After treatment
Number of cases	44	44
Range	0.9-1.3	0.9-1.3
Mean	1.117	1.117
Standard deviation	0.125	0.126
P value (before to aftertreatment)	0.161	

Table 5: Comparison of the three study groups as regards a change in fetal umbilical artery PI before and after treatment.

	Nifedipine	
	Before treatment	After treatment
Number of cases	44	44
Range	1.16-1.5	1.15-1.5
Mean	1.3	1.29
Standard deviation	0.082	0.081
P value (before to aftertreatment)	0.027	
	Indomethacin	
	Before treatment	After treatment
Number of cases	44	44
Range	1.2-1.7	1.3-1.8
Mean	1.34	1.56
Standard deviation	0.143	0.135
P value (before to aftertreatment)	0.000	
	Ritodrine	
	Before treatment	After treatment
Number of cases	44	44
Range	1.1-1.6	1.1-1.6
Mean	1.37	1.371
Standard deviation	0.121	0.122
P value (before to aftertreatment)	0.26	

Table 6: Comparison of the three study groups as regard change in fetal middle cerebral artery PI before and after treatment.

	Nifedipine	
	Before treatment	After treatment
Number of cases	44	44
Range	1.04-1.37.	1.04-1.37
Mean	1.15	1.148
Standard deviation	0.96	0.091

P value (before to aftertreatment)	**0.37**	
	Indomethacin	
	Before treatment	**After treatment**
Number of cases	44	**44**
Range	1.08-1.55	**1.25-1.77**
Mean	1.32	**1.48**
Standard deviation	0.11	**0.13**
P value (before to after treatment)	**0.000**	
	Ritodrine	
	Before treatment	**After treatment**
Number of cases	44	**44**
Range	1.08-1.44	**1.08-1.44**
Mean	1.23	**1.22**
Standard deviation	0.079	**0.081**
P value (before to after treatment)	**0.5**	

Table 7: Comparison of the three study groups as regard a change in cerebroplacental ratio before and after treatment.

DISCUSSION

The following results were obtained from an analysis of the features of the investigated population in the current study, which involved 132 patients separated into three groups.

The mean maternal age for nifedipine, indomethacin, and ritodrine was determined to be 25.67 ± 5.268 (16-39), 25.97± 4.115 (17-36), and 27.97±6.278 (19-42) years old, respectively. When those data were compared, the p-value was 0.968, which is statistically non-significant.

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The women in the nifedipine group had a mean gestational age of 31.03±1.474 weeks, the indomethacin group had a mean gestational age of 31.13± 1.592 weeks, and the ritodrine group had a mean gestational age of 30.97±1.629 weeks at admission. When the results of the three study groups were compared, the p-value was 0.918, which is statistically insignificant.

Various characteristics of the study population were similar to those of Conde-Agudelo et al. [7] examined the effectiveness of nifedipine and ritodrine in extending gestation beyond 48 hrs., 1 week, and 36 weeks by separating 80 patients into 2 groups. In this study, the average mother age for the ritodrine group was 26.2 6.5 years and 26.9 6.1 years for the nifedipine group. The ritodrine group had an average gestational age of 32.1 2.1 weeks on admission, while the nifedipine group had an average gestational age of 32.2 2.2 weeks. The mean bishop score for the ritodrine and nifedipine groups was 2.9 1.9 and 2.7 1.8, respectively. However, the parity for both groups ranged from 0-3, which is logically lower than that found in our study due to higher parity in impoverished nations such as Egypt than in industrialised countries such as Ireland, where the study was conducted. Nifedipine, indomethacin, and ritodrine were found to be beneficial in the management of premature labour in a series of investigations. The majority of the research compared only two medications to each other. However, in this study, we compared the effectiveness, maternal, and foetal side effects of the three medicines.

Regarding the cardiovascular changes that occurred after the three medicines were given, we found that both Nifedipine and Ritodrine produced an increase in the maternal heart rate after they were given. Only in the ritodrine group did it reach a statistically significant level. The mean mother heart rate in the ritodrine group was 80.23 6.383 bpm before the drug was given and increased to 100.70 ± 8.276 bpm afterward. The p-value was 0.001, indicating that the result was statistically significant. The mean maternal heart rate in the nifedipine group was 86.93±5.747 bpm before therapy and 90.83± 4.893 bpm after treatment, with a p-value of 0.061 reflecting a statistically non-significant value. Furthermore, the maternal heart rate changed from 80.87 5.090 bpm to 84.37± 6.542 bpm in the indomethacin group, with a p-value of 0.058, which is statistically non-significant. Before the medications were administered, there was no statistical difference in maternal heart rate between the three groups (p-value = 0.172). At all time points during treatment, a statistically significant difference was seen between the ritodrine group and the other two groups (p-value = 0.015).

When comparing the changes in maternal mean blood pressure before and after therapy, all three medications resulted in a statistically significant reduction in maternal mean blood pressure after administration. In the nifedipine, ritodrine, and indomethacin groups, maternal mean blood pressure decreased from 85.63 5.962, 88.03± 4.514, and 91.01± 10.423 mm Hg before treatment to 77.03± 5.183, 86.4 5.21, and 84.83± 10.787 mm Hg after treatment, respectively. The nifedipine and indomethacin groups had a p-value of 0.042, while the ritodrine group had a p-value of 0.028, all of which were statistically significant.

During therapy, the foetal heart rate was considerably higher in the ritodrine group. The foetal heart rate

rose from 135.77 ±12.492 to 153.1 ±11.241 beats per minute (p-value 0.05, statistically significant). The foetal heart rate increased from 142.63 9.704 bpm to 146.97 10.997 bpm in the nifedipine group (p-value 0.061, statistically non-significant). Furthermore, the foetal heart rate in the indomethacin group increased slightly from 140.13±10.438 bpm to 142.23±10.054 bpm (p-value 0.08, statistically non-significant).

After treatment, all significant differences in maternal and foetal hemodynamic measures between the three groups disappeared. This is consistent with the results of Black et al. [8] who compared the cardiovascular effects of GTN to those of ritodrine for acute tocolysis. This study included sixty women who were in the early stages of pregnancy. Following the RCOG standards, the women were given either transdermal GTN or intravenous ritodrine. The maternal pulse, blood pressure, and foetal heart rate were measured for up to 24 hours and compared over the course of the treatment. The GTN group had a lower mean maternal heart rate (p0.01), while the GTN group had a considerably lower mean foetal heart rate (p=0.008). Ritodrine reduced mean arterial pressure by a significant amount. Over the course of GTN treatment, mean arterial pressure did not change considerably.

After administration of the medications, contractions stopped in all three trial groups, with the nifedipine group showing the most improvement (80 percent). When the presence of contractions in the three groups was compared to each other after treatment, the difference was determined to be insignificant (P value 0.24). This indicated that all three medications had approximately same efficacy in stopping contractions.

When we looked at the Doppler changes in the foetal umbilical and middle cerebral arteries following administration of the three medicines in our trial, we found that the mean umbilical PI was 1.017±0.115 before indomethacin administration and 1.097±0.125 afterward in the indomethacin group. The p-value was 0.157, indicating that the result was not statistically significant. The mean umbilical PI in the ritodrine group was 1.117 0.125 before ritodrine delivery and increased to 1.117 0.126 afterward. The p-value was 0.161, indicating that the result was statistically insignificant. The mean umbilical PI in the nifedipine group was 1.131 0.099 before therapy and 1.128 0.098 after treatment, with a p-value of 0.281 indicating a statistically non-significant value.

The study found no statistically significant difference in middle cerebral artery PI following therapy in the indomethacin group (P = 0.112) and a statistically significant drop in the nifedipine group (P = 0.027), both of which were within clinically acceptable values. The mean MCA PI in the nifedipine group was 1.3 0.082 before nifedipine treatment and 1.29 0.081 afterward. The p-value was 0.027, indicating that the result was statistically significant. The mean MCA PI in the ritodrine group was 1.37 0.121 before therapy and 1.371 0.122 after treatment, with a p-value of 0.26 indicating a statistically non-significant result.

When the cerebroplacental ratio in the three groups was compared pre and post therapy, the study found a statistically non-significant difference in the cerebroplacental ratio following therapy in the indomethacin group, with a P value of 0.116. The mean cerebroplacental ratio in the nifedipine group was 1.15±0.96 before nifedipine was given, and it was 1.148±0.091 afterward. The p-value was 0.370, indicating that the result was statistically insignificant. The mean cerebroplacental ratio in the ritodrine group was 1.23±0.079 before therapy and 1.22±0.081 after treatment, with a p-value of 0.5 suggesting a statistically non-significant value.

CONCLUSION

The current investigation found no significant differences in the efficacy of ritodrine, nifedipine, or indomethacin as tocolytics for premature labour.

Furthermore, it was discovered that nifedipine and indomethacin had fewer maternal adverse effects than ritodrine.

The three medicines were not linked to a significant change in maternal blood pressure or foetal heart rate after 24 hours in our study. The pulsatility index (PI) of the umbilical and middle cerebral arteries was not clinically significant in a foetal Doppler study. There was also no change in cerebro-placental ratio 24 hours following indomethacin administration, indicating that the medications are safe for both the mother and the foetus.

Conflict of interest : none

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