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Effectiveness of Melatonin in combination with Sildenafil in treatment of intrauterine growth restriction: a double-blind, randomized clinical trial

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Abstract

Background: Intrauterine Growth Restriction (IUGR) is a common obstetrical diagnosis associated with high risks of perinatal mortality and morbidity. Some studies have suggested that either sildenafil or melatonin may improve IUGR outcomes; but we found no evidence on the effects of concomitant sildenafil and melatonin therapy on IUGR fetuses. Therefore, the aim of the present study was to investigate whether simultaneous intake of melatonin and sildenafil can be more effective in alleviating IUGR outcomes.

Methods: Patients with idiopathic IUGR referred to Yasuj Women's Clinic during 2019 and 2021 were enrolled in the current double-blind, randomized clinical trial. Out of 140 participants, a total of 120 pregnant women were included, 100 pregnant women with confirmed IUGR (gestational age between 26 to 32 weeks) were randomly assigned into four groups as fellows: sildenafil group (25 mg three times a day), melatonin (3 mg three times a day), sildenafil plus melatonin, and placebo. The patients received the drugs for at least 4 weeks. Doppler ultrasound was used to evaluate some outcomes on factors such as fetal weight, systolic/diastolic (S/D), PI, and RI of the umbilical, cerebral and uterine arteries. Neonatal outcomes (anthropometric characteristics of the infant, Apgar scores, meconium aspiration, and NICU admission) were also recorded.

Results: S/D of the middle cerebral artery was lower in the sildenafil plus melatonin subjects than in the other groups ($p< 0.05$). Sildenafil plus melatonin significantly increased infant weight and decreased the risks of preeclampsia and hospitalization compared to other treatments ($p < 0.05$).

Conclusion: The results confirmed that the concomitant prescription of melatonin and sildenafil increases birth weight, normalizes middle cerebral artery indices, and reduces the incidence of preeclampsia and neonatal hospitalization for IUGR. Therefore, Melatonin plus sildenafil can be a simple and economic treatment for IUGR.

Key Words: IUGR, Melatonin, Neonate, Sildenafil.

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1- INTRODUCTION

Intrauterine Growth Restriction (IUGR) is a term that refers to a range of scenarios in which a fetus does not reach its full growth potential during the pregnancy. There are certain genetic or environmental factors contributing to the impairment of fetus development in IUGR (1). The prevalence of IUGR varies according to the type of population, race, and pathogenesis; however, IUGR generally accounts for 5-7% of all pregnancies. The incidence of IUGR in developing countries is six times higher than that in developed countries (1, 2). It is linked to fetal death, iatrogenic preterm birth, and prolonged stays in the neonatal critical care unit, neonatal mortality, and long-term morbidity (3). Serious early-onset fetal growth restriction has also been shown to be connected with neurodevelopmental impairment later in life (4). Currently, there are no effective treatments for increasing fetal growth, and the management consists of intensive monitoring to determine when the fetus should be delivered, balancing the advantages of preterm delivery with the disadvantages of hypoxia and undernutrition (3, 5).

The pathophysiology of IUGR has not been thoroughly elucidated, hence the root driver of IUGR remains uncertain. However, most research has revealed that the placenta's Endothelial Cells (ECs) malfunction is present in many patients (6). Nitric Oxide (NO) is one factor produced in normal pregnancies in women and facilitates blood flow through the placenta to the fetus (7).

Although adequate NO levels dilate blood vessels and transfer nutrients via the bloodstream to the fetus, NO levels in IUGR patients are lower than those in the general population. As a result, employing NO-synthesizing medications to minimize vascular smooth muscle resistance and enhance blood flow to the placenta is one of the most common options for IUGR patients (8). Sildenafil, a cyclic GMP phosphodiesterase inhibitor, increases NO production by preventing cGMP degradation. Animal studies provide some evidence that sildenafil is beneficial in the treatment of EC dysfunction in the placenta (9). Furthermore, there is no significant negative impact associated with this medication for pregnant women. Its precise mechanism of action on patients with IUGR has not yet been identified. There has been no consensus on the effectiveness of sildenafil as a treatment for IUGR. In other studies, sildenafil improved the clinical states of both the mother and the fetus, but its ability to prevent preterm birth has not been supported by empirical studies (5, 10).

The effect of melatonin on the immune system, particularly at a cytokine level, is currently being researched extensively. Melatonin inhibits the inflammatory response in sepsis by decreasing interleukin-10 (IL-10) levels and lowering stress-induced inflammation (11). A recent study found that maternal melatonin levels dramatically drop in the event of IUGR, resulting in increased pro-inflammatory immunity as seen by an increase in TNF-α, IL-1, and IL-6 levels in a pregnant woman's blood. IUGR also induced an increase in anti-inflammatory cytokines such as IL-4 and IL-10. (8, 10, 12, 13). On the other hand, melatonin levels have decreased in many patients, including IUGR (14).

It was found that reducing melatonin levels in patients with IUGR causes its progression, so its use can prevent the occurrence and progression of IUGR by inhibiting inflammatory reactions and oxidative stress (15). Also, in the study of Palmer et al., it was shown that the use of melatonin could prevent nerve damage in patients with IUGR by inhibiting inflammation and oxidative stress (16).

In spite of the fact that few studies have examined the effect of sildenafil and melatonin separately on the treatment of IUGR patients, no study has examined the combination of sildenafil and melatonin in IUGR patients. The purpose of this study was to determine if Melatonin and Sildenafil, either alone or together, could affect patients with idiopathic IUGR.

2- MATERIALS AND METHODS

2-1. Design and participants

The current study was designed as a double-blind, randomized clinical trial conducted on 140 patients with IUGR diagnosis between 2019 and 2021. The web-based randomization was 1:1, with random block sizes ranging from two to six, and classified by the participating center. The treatment allocation was concealed from participants, doctors, researchers, and outcome assessors.

Demographic information including age, patient weight, height and education, Gravid, Parity, abortion, and others were collected at recruitment.

2-1-1. Inclusion and exclusion criteria

The diagnosis of IUGR based on patients' history and clinical examinations were assigned to those who had estimated weight below the fifth percentile in Ultrasound, or estimated fetal weight (EFW $<5^{th}$) percentile compared to the previous Ultrasound or Doppler. Moreover, patients were enrolled if it was possible to continue the pregnancy, and there were no danger signs for the fetus.

Inclusion criteria was defined as single pregnancy with IUGR; gestational age of 26 to 32 weeks; mother’s age of 15 to 45 years; no consumption of alcohol, cigarettes and tobacco; normal scan anomaly; absence of any known or suspected anomaly of the fetus; absence of gestational or chronic diabetes; no use of other vasodilators such as nitric oxide and calcium channel blockers.

Exclusion criteria included reluctance to continue research; complications such as leakage due to rupture of the bladder; vaginal bleeding and intrauterine infection; patients with any heart, lung, liver, and kidney diseases; patients taking a nitrate; and hypersensitivity to sildenafil and intolerance to its side effects (hot flashes, visual disturbances, severe hypotension and hearing impairments). Also, fetuses with chromosomal abnormalities were excluded.

2-1-2. Procedure

a) Initially, 140 patients with IUGR diagnoses were included in the study. 20 patients were excluded due to unwillingness to participate in the study and lack of inclusion criteria. Then, the 120 patients were randomly divided into four groups (each group n=30) (**Fig. 1**). In the only sildenafil receiving group (group I), 3 patients were excluded due to lack of follow-up and 2 due to discontinuation of the intervention. In the only melatonin receiving group (group II), 3 patients were excluded due to lack of follow-up and 6 due to discontinuation of the intervention. In the group that received Melatonin and sildenafil simultaneously (group III), 3 patients were excluded due to lack of follow-up, and 2 discontinued the intervention. One patient was excluded from the study in the placebo receiving group (group IV) due to a lack of follow-up (**Fig. 1**).

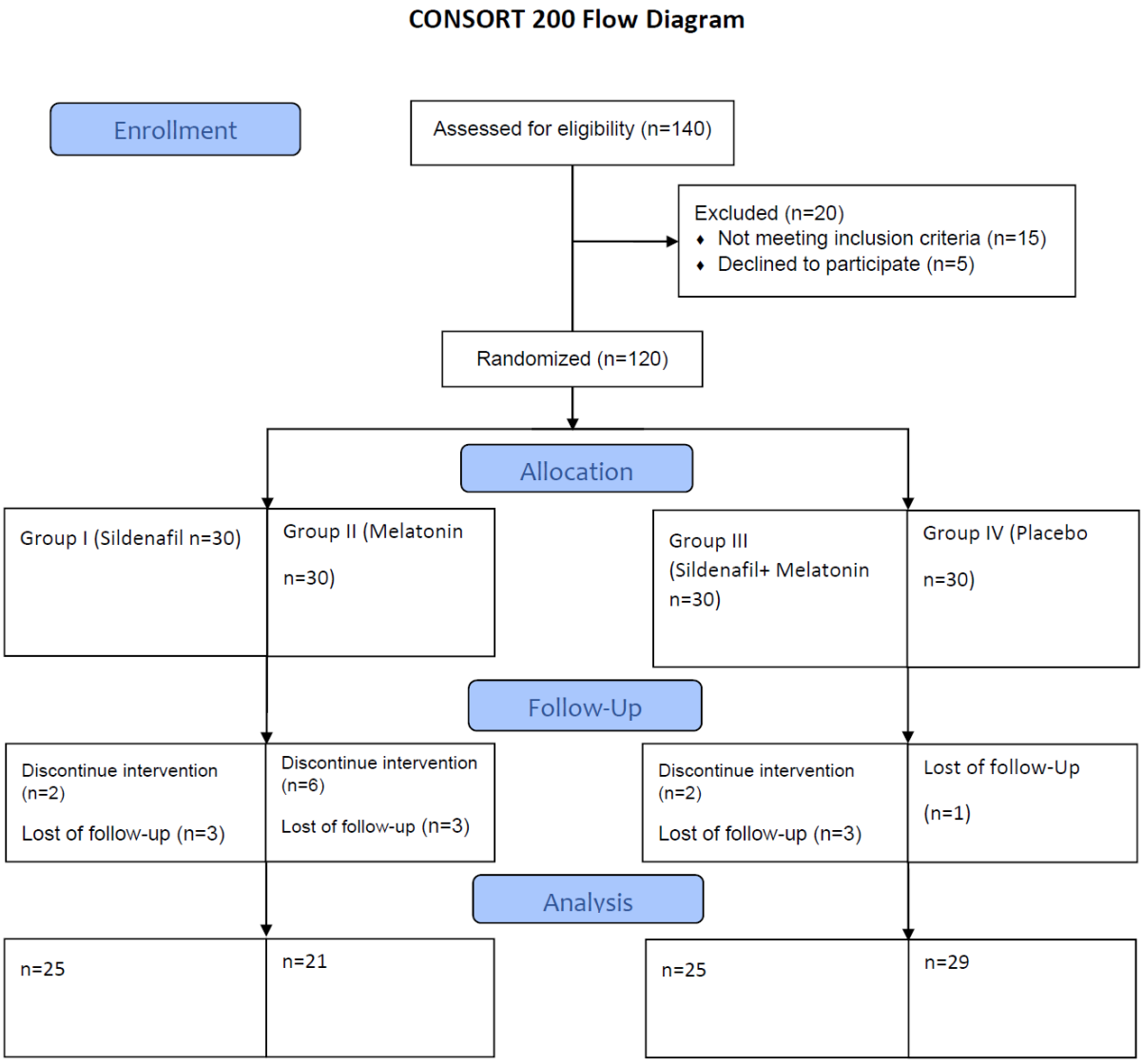

Fig. 1: Stages of conduct study.

The duration and number of supplements and placebo used in each group were as follows:

b) Group I: Patients received 25 mg of sildenafil citrate (Actover Pharmaceutical Company, Iran) three times daily for four weeks.

c) Group II: In this group, 3 mg melatonin tablets (Razak Pharmaceutical Company, Iran) were prescribed three times per day (morning, noon, night) for four weeks.

d) Group III: Both sildenafil and Melatonin were administered three times a day for four weeks.

e) Group IV: A starchy placebo was administered three times a day for four weeks.

All treatments continued from the time of IUGR diagnosis (26 to 32 gestation weeks) to a minimum of 4 weeks or a maximum of 6 weeks (The duration of 4 to 6 weeks was chosen because the most weight gain of the fetus occurred in the third trimester and also in cases where emergency termination is needed, medication can endanger the life of the fetus. (, unless

there was a severe problem requiring emergency delivery (**Fig. 1**).

2-2. Outcome assessment

The patients were evaluated with the following criteria, and the results were recorded using pregnancy and neonatal outcomes checklists.

a) Ultrasound (estimated fetal weight, Amniotic Fluid Index (AFI), fetal abdomen circumference) after intervention

b) Color Doppler Ultrasound of the artery, umbilical vein, and middle cerebral artery before and after intervention

Pregnancy Outcomes Checklist included gestational age, ultrasound characteristics, and Ultrasound Doppler, including fetal weight percentage, percentage of abdominal growth percentage, indicators of Ultrasound of color Doppler vein, placental artery, and middle cerebral artery, and amniotic fluid index.

Neonatal Outcome Checklist consisted of anthropometric characteristics of the infant (height, weight, and head circumference), first and fifth minute Apgar scores, meconium aspiration, and NICU admission.

2-3. Doppler ultrasonographic measurement

Ultrasonography and Doppler velocimetric assessment were performed using GE Voluson E8 (General Electric Company). The semirecumbent position for all participants was used to evaluate Doppler velocimetry. Finally, Pulsatility Index (PI), Resistance Index (RI), and Systolic/Diastolic (S/D) ratios were calculated.

2-4. Data analysis

The study findings of Maged et al. (2018) and the following formula were used to estimate the sample size (17). The final sample volume was estimated to be 25 people per group, taking a 20% withdrawal into account. The final sample size was 100 people.

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 (S_1^2 + S_2^2)}{(\mu_1 - \mu_2)^2}$$

The Shapiro-Wilk test examined the normality of data distribution, and descriptive analyses were used to describe qualitative and quantitative data. Chi-square, Fisher exact test, and Krus-KalWallis samples were carried out for inferential data analysis. SPSS software (version 23) was applied for data analysis. P-value < 0.05 was considered as the significance level.

3- RESULTS

3-1. Demographic characteristics of patients

The median age of the patients enrolled in this study was 28.50 years (range: 24-34). There was no significant relationship between weight, occupation, education, and BMI between the four groups. In addition, no significant relationship was observed between the patients in terms of Gravid, parity, abortion, and termination of pregnancy ($p > 0.05$). However, it was found that there was a significant relationship between gestational age and indication of termination between groups ($p<0.001$) (**Table 1**).

3-2. Evaluation of Doppler ultrasonographic indexes before and after the intervention

In this study, Pulsatility Index (PI), Systolic/Diastolic (S/D) ratio, and Resistance Index (RI) were examined before and after the intervention. These indices were evaluated in three sections: the middle cerebral artery, umbilical artery, and uterine artery. There was no significant relationship between the patients in terms of PI, S/D, and RI indices before the intervention ($p > 0.05$) (**Table 2**).

Table-1: Demographic information of IUGR patients

Variables		Sildenafil (n=25)	Melatonin (n=21)	Sildenafil+ Melatonin (n=25)	Placebo (n=29)	p-value
Weight		31 (24-33)	26 (22-32)	29 (24-34)	29 (25-35)	0.46
Job	Employed	3 (12)	0 (0)	1 (4)	5 (17.2)	0.13
	housewife	22 (88)	21 (100)	24 (96)	24 (82.2)	
Education	Primary	2 (8)	0 (0)	1 (4)	6 (20.7)	0.37
	High school	16 (64)	13 (61.9)	11 (44)	11 (34.5)	
	University	7 (28)	8 (38.1)	13 (52)	12 (41.4)	
Termination of pregnancy	Term	15 (60)	14 (67)	18 (72)	18 (62)	0.20
	Pre-term	10 (40)	7 (33)	7 (28)	11 (38)	
C/S indication (N., %)	Non progress labour	0 (0)	0 (0)	-	2 (2.2)	0.1
	Other	4 (100)	11 (100)	-	7 (77.8)	
EFW		1714.4±342	2510±1615	1777.4±521	1870.1±525.1	0.312
Delivery (N., %)	Emergency	9 (40.9)	5 (29.4)	1 (5.3)	7 (36.8)	0.2
	Cesarean	5 (22.7)	5 (29.4)	7 (36.8)	4 (21.1)	
	Nvd	8 (36.4)	7 (41.2)	11 (57.9)	8 (42.1)	
BMI		24.34 (22.26-29.48)	27.38 (25.46-35.96)	25.63 (20.75-27.24)	26.44 (23.93-29.64)	0.07
Gravid		1 (1-2)	1 (2-2-)	1 (1-3)	1(1-1.75)	0.73
Parity		1 (1-3)	1 (1-2)	1 (1-2.5)	1 (0-1)	0.76
Abortion		1 (1-2)	0 (1-1.75)	1 (1-1)	1 (0-1)	0.95
Gestational age indication termination	FGR	9 (47.7)	1 (7.1)	3 (17.6)	12 (54.5)	<0.001
	Hypertension	1 (5.3)	3 (21.4)	0 (0)	1 (4.5)	
	Fetal heart decrease	2 (10.5)	2 (14.3)	1 (5.9)	0 (0)	
	LP	5 (26.3)	4 (28.6)	8 (47.1)	0 (0)	
	Other	1 (5.3)	4 (28.6)	2 (11.8)	0 (0)	
	FGR and Hypertension	0 (0)	0 (0)	3 (17.6)	7 (3.18)	
	FGR and Other	1 (5.3)	0 (0)	0 (0)	2 (9.1)	

Abbreviation: BMI: Body Mass Index, EFW: Estimate Fetal Weight.

Table-2: Summary of Doppler ultrasonographic index before intervention

Variables		Sildenafil (n=25)	Melatonin (n=21)	Sildenafil+ Melatonin(n=25)	Placebo (n=29)	p-value
Middle cerebral artery	S/D	5.70 (4.30-6.84)	6.22 (5.74-7.84)	4.90 (4.6-7)	5.40 (3.90-5.97)	0.13
	RI	0.81 (0.77-0.86)	0.83 (0.80-0.92)	0.78 (0.77-0.81)	0.81 (0.75-0.92)	0.21
	PI	1.90 (1.62-2.44)	1.90 (1.80-2.30)	1.90 (1.59-2.28)	1.66 (1.23-2.09)	0.21
Umbilical artery	S/D	2.31 (2-3.17)	2.39 (1.96-2.75)	2.45 (2.21-3.50)	2.21 (2-2.50)	0.32
	RI	0.59 (0.51-0.80)	0.61 (0.49-0.70)	0.63 (0.57-0.93)	0.58 (0.50-0.81)	0.54
	PI	0.80 (0.7-0.99)	0.81 (0.67-0.91)	0.89 (0.80-1.39)	0.74 (0.54-1.10)	0.30
Uterine artery	S/D	2.76 (2.50-3.87)	2.50 (2.29-3.15)	2.80 (2.66-3.70)	2.47 (2.13-2.50)	0.18
	RI	0.67 (0.63-0.74)	0.59 (0.55-0.69)	0.65 (0.58-0.70)	0.61 (0.51-0.70)	0.30
	PI	1 (0.9-1.14)	0.90 (0.82-1.02)	0.95 (0.90-1.50)	0.91 (0.81-1.10)	0.42

Abbreviation: S/D: Systolic/Diastolic Ratios; RI: Resistance Index; PI: Pulsatility Index

After the intervention, comparing the Doppler ultrasound information, the results showed that the S/D of the middle cerebral artery in group III, followed by group II, was significantly lower than that in the other groups ($p < 0.05$) (**Table 3**).

Table-3: Summary of Doppler ultrasonographic index after intervention.

Variables		Sildenafil (n=25)	Melatonin (n=21)	Sildenafil+ Melatonin (n=25)	Placebo (n=29)	p-value
Middle cerebral artery	S/D	5.75 (3.95-5.82)	5.85 (4.86-7.15)	4.20 (3.36-5)	5.40 (4.50-7.14)	0.001
	RI	0.80 (0.75-0.83)	0.82 (0.79-0.96)	0.80 (0.80-0.88)	0.79 (0.71-0.84)	0.14
	PI	1.66 (1.30-1.92)	0.72 (1.50-1.90)	2 (1.49-2.09)	1.47 (1.26-1.88)	0.23
Umbilical artery	S/D	2.40 (1.89-3)	2.32 (2-2.60)	2.27 (2.27-2.50)	2.50 (1.66-2.70)	0.58
	RI	0.62 (0.50-0.70)	0.64 (0.55-0.70)	0.55 (0.55-0.58)	0.60 (0.47-0.70)	0.23
	PI	0.81 (0.77-1.21)	0.87 (0.67-0.93)	0.87 (0.72-0.93)	0.74 (0.58-1.10)	0.65
Uterine artery	S/D	2.80 (2.45-3.45)	2.70 (2.37-3.14)	2.70 (2.43-3.38)	2.30 (2.10-2.50)	0.70
	RI	0.66 (0.59-0.70)	0.62 (0.52-0.71)	0.62 (0.58-0.70)	0.61 (0.57-0.70)	0.72
	PI	0.97 (0.80-1.10)	1.07 (0.87-1.20)	0.97 (0.81-1.16)	0.86 (0.76-1.05)	0.18

Abbreviation: S/D: Systolic/Diastolic Ratios; RI: Resistance Index; PI: Pulsatility Index.

3-3. Evaluation of neonatal outcomes

The infants' head circumferences were almost the same (33 cm) in all four groups, and no significant difference was observed. Also, the infants' height was the same in all four groups (34 cm), and no significant difference was observed. Apgar scores at one and five minutes were also the same in all groups. Regarding NICU admission, the number of admitted patients in groups II and III was significantly lower than that of other groups (p:0.001). The weight of the neonates in the placebo group was 2400 g, while in the sildenafil and Melatonin group, it was 3092.5 g, showing a significant difference (p: 0.001). Preeclampsia was significantly higher in the placebo group than that in the other groups, and it was significantly lower in group III in comparison to the others (p: 0.007). The results also showed that Meconium aspiration did not occur in any of the patients receiving sildenafil and/or

Melatonin, while Meconium aspiration occurred in 97% of the patients receiving placebo, which was a statistically significant difference(p: 0.001) (**Table 4**).

Table-4: Neonatal outcomes after intervention

Variables		Sildenafil (n=25)	Melatonin (n=21)	Sildenafil+ Melatonin (n=25)	Placebo (n=29)	p-value
Weight at birth (g)		2500 (2400-2975)	3500 (3050-3600)	3092.5 (2762.5-3200)	2400 (1875-2875)	0.001
preeclampsia	Yes	3	3	1	9	0.007
	No	22	18	24	20	
Apgar score (min)	1	9 (9-9)	9 (9-9)	9 (9-9)	9 (9-9)	0.64
	5	10 (9-10)	9 (9-9)	9 (9-9)	9 (9-9)	0.07
Meconium aspiration	Yes	0 (0)	0 (0)	0 (0)	28 (97)	0.001
	No	25 (100)	21 (100)	25 (100)	1 (3)	
Hospitalization in NICU	Yes	10 (40)	5 (19)	5 (20)	16 (55)	0.001
	No	15 (60)	16 (81)	20 (80)	13 (45)	
Around the baby's head (cm)		33 (33-34.87)	33 (32.5-35)	33 (34-36)	33 (32-34)	0.33
Baby height (cm)		48 (45-49.75)	48 (48-48)	48 (48-50)	48 (43-49.5)	0.47

Abbreviation: NICU: Newborn Intensive Care Unit

4- DISCUSSION

IUGR is a complicated disorder causing significant perinatal morbidity and mortality, as well as neonatal and adult health problems (18). Preterm and term babies are at risk of a variety of metabolic disorders, polycythemia, pulmonary disorders, intraventricular hemorrhage, and cerebral palsy (19).

Despite various potential treatments for IUGR and the identification of high-risk patients, no definite cure or management program exists; therefore, efforts are continued to alleviate worries with appropriate therapeutic choices (20, 21).

Regarding the effect mechanism of these supplements, studies have declared that sildenafil is a vasodilator agent that prevents vasoconstriction and abnormal blood pressure (22). Studies have shown that sildenafil increases NO production, thereby preventing vasoconstriction. For this purpose, it was found that sildenafil increases cGMP production by inhibiting Phosphodiesterase type 5 (PDE5), which ultimately leads to NO production (23). Furthermore, it has been demonstrated that Melatonin, as a neuroendocrine hormone, promotes vasodilation and impacts cerebral arteries through myocyte BK_{Ca} channels (24). Furthermore, numerous studies have shown it to possess anti-inflammatory and antioxidant properties, making it suitable as an antioxidant treatment in IUGR to prevent fetal brain damage (25, 26). Melatonin also increases cord blood flow by increasing the bioavailability of NO due to its antioxidant effect (27, 28). So, given these properties of sildenafil and melatonin, and their positive synergetic effects research observations were interestingly promising.

Herein, we examined the effect of Melatonin and sildenafil separately and simultaneously in IUGR patients and

found a statistically significant difference in the S/D index of the middle cerebral artery after intervention which was lower in cases using sildenafil and Melatonin as compared to the other groups. Miller et al. also reported that melatonin supplements improved cerebral arteries and nerve activity (8). In another study, Eshraqi et al. evaluated the effects of sildenafil on the ultrasound indexes of patients with IUGR. They confirmed that PI/RI/SD indexes of cerebral artery umbilical cord in the intervention group were statistically lower than those in the control group (10). Yet another study by Maged et al., reported that the mean PI/RI/SD umbilical cord indexes, 4 weeks after sildenafil treatment, were significantly lower in the intervention group, compared to the control group (17). Therefore, though our results did not advocate improvements in PI/SD/RI indices of the umbilical artery and uterine artery (This contradictory finding could be due to the low sample size in the study groups as well as the different mechanisms of sildenafil and Melatonin in regulating blood flow), the positive effects of both studied medications in literature verify our reported improving booster effect of simultaneous consumption of sildenafil and melatonin on the S/D index of the middle cerebral artery. We also exhibited that Melatonin is more efficient than sildenafil when used as a single medication. McCarty et al. showed that Melatonin in the animal sample could improve umbilical and cerebral artery blood flow and prevent IUGR in patients (29). Also, in the study of Correa et al., it was found that improving uterine and cerebral artery blood flow can normalize Doppler ultrasound indices and prevent fetal growth disorders (30). In fact, Melatonin plays an important role in regulating inflammation and oxidative stress reactions; and since inflammatory reactions and oxidative stress are known as endothelial dysfunction and blood flow disorders, the use of Melatonin can improve the flow of blood uterine and cerebral arteries in IUGR patients.

Our results, further, revealed that neonatal hospitalization was lower in cases consuming both sildenafil and Melatonin. In the same line, a study by shehata et al., showed that, compared to controls, the number of patients receiving sildenafil admitted to the NICU was reduced. Also, their hospitalization time was reduced, but no significant relationship was observed between them (31). Furthermore, in Eshraqi et al. and Maged et al.'s studies, the mean hospitalization in the sildenafil intervention group was significantly lower than that the control group (10, 17), which agrees with our findings that NICU hospitalization in sildenafil and melatonin groups was significantly lower than that in placebo receivers. So, given the influential role of sildenafil in other studies and the lower rate of hospitalization in the melatonin group and combinatory sildenafil and melatonin group in our study, it could be concluded that the combination of sildenafil and Melatonin may be appropriate to reduce IUGR complications and finally reduce admission to NICU.

We also reported a higher weight at birth in cases who consumed both sildenafil and Melatonin. In studies by Darwish et al. and Eshraqi et al., the weight at birth was found to be seemingly higher in the sildenafil group than in the control groups, but the difference was not statistically significant (10, 32). In contrast, in the present study, weight at birth in both sildenafil and placebo groups were similar and significantly lower than those in the groups treated with Melatonin and Melatonin with sildenafil, which indicates the stronger effect of Melatonin compared to sildenafil in increasing infant's weight. Similarly, Andrew Sharp et al. demonstrated that sildenafil alone was not beneficial in inducing fetal growth and delayed delivery to increase birth weight

(9).

In addition, our results revealed no statistically significant difference in terms of Apgar score of the first and fifth minutes between groups. However, in the study by Eshraqi et al., there was a significant relationship between the first- and fifth-minute Apgar scores (10) and Maged et al., demonstrated that the mean Apgar score of the fifth minute was higher in the sildenafil group compared to the control group (17). It is assumed that these contradictions between studies may be due to the sample sizes, study designs, different methodologies, and medication dosage, but it demands further investigations to obtain absolute results.

On the other hand, studies have proven that melatonin measures reduce in the umbilical cord of intrauterine growth restriction cases (33), and Melatonin and sildenafil are used as effective supplements in many diseases (34). So, it seems that melatonin exposure is an effective treatment option in IUGR cases. Lemley, et al., for instance, illustrated that Melatonin expanded blood flow after 10 days of consumption, and Doppler ultrasonography is valuable to follow-up umbilical blood flow (28). Hence, they concluded that Melatonin could prevent the IUGR complications resulting from umbilical blood flow abnormalities. In contrast to our findings, Alejandro González-Candia et al.'s study did not support the effectiveness of Melatonin to improve fetus status in IUGR (35); their study was conducted on animal models, which is entirely different from those of human biology, and this may have led to the reported inconsistency. Anyhow, despite all discussed advantages, we found no improvement in infants' height and head circumference outcomes after the intervention, indicating that the studied medications cannot influence these factors.

Another variable that prevented Melatonin and sildenafil in IUGR patients was Meconium aspiration. For this purpose, in the study by Turner et al., it was shown that the incidence risk was lower in patients receiving sildenafil, compared with patients receiving placebo (36). The study by Bulani et al. also showed that the incidence of Meconium aspiration was lower in patients receiving sildenafil and aspirin, compared with controls (37). The present study showed that Meconium aspiration did not occur in any of the patients receiving Melatonin and sildenafil.

4-1. Limitations of the study

The study was limited by the small sample size, which was taken from pregnant women living in Yasuj city. To the best of our knowledge, the valuable strength in this current clinical trial is that it is the first study to evaluate both Melatonin and Sildenafil simultaneously and compare their use to the single use of either prescription as a novel treatment for IUGR.

5- CONCLUSION

Altogether it was presented that Melatonin is stronger and more effective than sildenafil in IUGR treatment, and its application either separately or simultaneously with sildenafil can enhance outcome improvement and therapeutic properties of current approaches in this abnormality.

6- ETHICAL CONSIDERATIONS

The Medical Ethics Committee of Yasuj University of Medical Sciences approved this study (IR.YUMS.REC.1398.129). All the procedures performed in the study involving human participants were in accordance with ethical standards of the local ethics committee of Yasuj University of Medical Sciences, as well as 1964 Helsinki declaration. Written informed consent was obtained from all participants. The study has been submitted to the

Iranian clinical trials registration Website (IRCT20160524028038N6).

7- CLINICAL TRIAL REGISTRATION

The study has been submitted to the Iranian clinical trials registration Website. (https://trialsearch.who.int/Trial2.aspx?TrialID=IRCT20160524028038N6).

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