



STUDY IN EFFECT OF SILDENAFIL IN MANAGEMENT OF INTRAUTERINE GROWTH RESTRICTION IN MGM MEDICAL COLLEGE & L.S.K HOSPITAL, KISHANGANJ

Medical Science

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ABSTRACT

Introduction: IUGR is one of the most common complications of pregnancy and major cause of iatrogenic prematurity.

Amis and objectives: To study effect of sildenafil on pregnancy complicated with IUGR and to see its effect on fetal outcome and perinatal outcome by seeing parameters like increased AC, AFI and liquor, improvement in fetal Doppler parameters and birth weight ,APGAR scoring ,no. of NICU admission.

Material and methods: MGM MEDICAL COLLEGE & L.S.K HOSPITAL, KISHANGANJ. Observational, prospective and descriptive study.

Conclusion: We found that the mean PRE T/t MCA S/D in Control group was greater than case group which was statistically significant. It was found that mean PRE T/t MCA PI at Case group was greater than control group which was statistically significant. It was found that mean POST T/t MCA S/D at Control group was greater than case group which was statistically significant. We found that mean POST T/t MCA PI at Case group was greater than control group which was statistically significant. We found that the mean PRE T/t UA PI in case group was greater than control group which was statistically significant. It was found that mean PRE T/t UA RI at Case group was greater than control group which was statistically significant. It was found that mean POST T/t UA RI at Control group was greater than case group which was statistically significant.

KEYWORDS

Intrauterine, sildenafil, Iatrogenic prematurity and vasodilation

INTRODUCTION

Intrauterine growth restriction (IUGR) is one of the most common complications of pregnancy and major cause of iatrogenic prematurity. Most frequent etiology of IUGR is abnormal placentation which is frequently associated with impaired/compromised utero placental blood flow due to increased vasoconstriction. Sildenafil, being a phosphodiesterase inhibitor acts as a vasodilator and has shown a promising outcome in treatment of IUGR. Fetal growth restriction (FGR) is a major cause of perinatal mortality and morbidity. FGR is a wide-ranging pregnancy problem with a number of possible mechanisms leading to reduced fetal growth. Only a proportion of pregnancies with FGR show altered maternal peripheral vascular resistance. Some pregnancies with fetal growth restriction have elevated peripheral maternal vascular resistance in uterine arteries and hence poor perinatal outcome. Such pregnancies, if resistance values are normalized in later trimesters have a significantly better outcome¹. Sildenafil citrate increases uterine blood flow and potentiates estrogen-induced vasodilation². In this paper, a case of early onset fetal growth restriction was reported where administration of Sildenafil citrate could normalize the uteroplacental insufficiency with a favorable fetal outcome.

Hemodynamic changes involve maternal uterine, fetal umbilical, and middle cerebral arteries and precordial veins for cardiac effects of placental dysfunction³. The circulatory adaptation consists in an increased umbilical artery and decreased middle cerebral artery blood-flow resistance⁴.

Despite the significant risks associated with IUGR-affected pregnancies, there remains no treatment. The only option currently available to clinicians is early delivery of the baby which is itself associated with increased morbidity and/or mortality.

Furthermore, there are still no drugs developed specifically for obstetric conditions currently in clinical trials. This has led to the assessment of drugs currently used in clinical practice for other diseases, to be assessed on a re-purpose basis as potential therapeutics in the treatment of IUGR.

Sildenafil citrate significantly enhances vasodilation of myometrial small arteries and is also associated with fetal weight gain which offers a potential therapeutic possibility for IUGR.

To study effect of sildenafil on pregnancy complicated with IUGR and to see its effect on fetal outcome and perinatal outcome by seeing parameters like increased AC, AFI and liquor, improvement in fetal

Doppler parameters and birth weight ,APGAR scoring , no. of NICU admission

MATERIAL AND METHODS

Antenatal women attending antenatal OPD at MGM MEDICAL COLLEGE & L.S.K HOSPITAL, KISHANGANJ over a period of 12 months. 60 such females of 26 to 34 wks of gestation were selected who are suspected to have IUGR by following criteria

Study group: 60 Patients

Data Collection Forms:

A well designed proforma containing various parameters under study was used for data collection. The data was maintained on computer. After obtaining the approval from permission from IEC the study tools were developed. All patients were admitted in our hospital. Data collection was started after explaining the purpose of the study and obtaining informed consent of the husbands or legal guardian. Baseline information was collected via structured interview using predesigned questionnaire.

RESULT AND DISCUSSION

Our study showed that in Case Group, the mean GA at DELIVERY (mean± s.d.) of patients was 36.9767± 1.8975. In Control Group, the mean GA at DELIVERY (mean± s.d.) of patients was 35.3833± 1.8063. Difference of mean GA at DELIVERY in both Group was statistically significant (p=0.0015). In Case Group, 12(40.0%) patients had PRETERM deliveries and 18(60.0%) patients had TERM deliveries. In Control Group, 21(70.0%) patients had PRETERM deliveries and 9(30.0%) patients had TERM deliveries. Association of PRETERM/TERM deliveries in both group was statistically significant (p=0.0195). In Case Group, 14(46.7%) patients had LSCS and 16(53.3%) patients had VD. In Control Group, 17(56.7%) patients had LSCS and 13(43.3%) patients had VD. Association of MODE OF DELIVERY in both group was not statistically significant (p=0.4383). In Case Group, 28(50.0%) patients were Live Birth. In Control Group, 28(50.0%) patients were Live Birth. Association of Live Birth in both group was not statistically significant (p=1.0000).

Premalatha HL et al⁵(2016) found that intervention included the administration of Sildenafil citrate 25mg three times daily until delivery and the major outcome variables were Doppler studies of Uterine artery, umbilical artery, MCA and ductus venosus, Amniotic fluid volume and gestational age. Pregnant women were in the age group of 18-36 years and between 22 -34 weeks of gestational age at the time of recruitment into the study. All the subjects were given intervention and monitored for primary outcome variables once in

fifteen days with fetal Doppler and ultrasound techniques. Among the subjects students 2% resulted in stillbirths, 98% retained in the study up to delivery and 80% followed up to three years following delivery. Majority of the women (60%) in the 30 weeks of gestational age and 10% among 22 weeks and 30% between 32-36 weeks of gestation age showed USG abnormalities respectively. Among the USG abnormalities IUGR was found among 70% of women and 30% were found with oligohydramnios before intervention and became 0% and 10% after intervention respectively ($p < 0.005$). Study concludes that Sildenafil citrate would be useful to improve perinatal outcome in women with IUGR both early onset and late onset and Oligomnios.

It was found that in Case Group, the mean PRE T/t fetal AC (mm) (mean $\pm$ s.d.) was 225.2100 $\pm$ 14.9134. In Control Group, the mean PRE T/t fetal AC (mm) (mean $\pm$ s.d.) was 221.7667 $\pm$ 17.0914. Difference of mean PRE T/t fetal AC (mm) in both Group was not statistically significant ($p=0.4091$). In Case Group, the mean post-treatment fetal AC (mm) (mean $\pm$ s.d.) was 260.0533 $\pm$ 14.6982. In Control Group, the mean Post -treatment fetal AC (mm) (mean $\pm$ s.d.) was 252.8667 $\pm$ 17.3319. Difference of mean Post -treatment fetal AC (mm) in both group was not statistically significant ($p=0.0886$). In Case Group, the mean fetal AC gain (mm) (mean $\pm$ s.d.) was 34.7700 $\pm$ 2.3246. In Control Group, the mean fetal AC gain (mm) (mean $\pm$ s.d.) was 31.1000 $\pm$ 2.2338. Difference of mean fetal AC gain (mm) in both group was statistically significant ($p < 0.0001$). After 4 weeks of treatment, In Case Group, 22(73.3%) patients had fetal AC reaching >5th percentile for that GA. In Control Group, 10(33.3%) patients had fetal AC >5th percentile for that GA. Association of post treatment fetal AC reaching >5th percentile for that GA in both group was statistically significant ($p=0.0019$).

Oyston C et al ⁶ (2016) found that Intrauterine growth restriction (IUGR) causes short- and long-term morbidity. Reduced placental perfusion is an important pathogenic component of IUGR; substances that enhance vasodilation in the uterine circulation, such as sildenafil citrate (sildenafil), may improve placental blood flow and fetal growth. This study aimed to examine the effects of sildenafil in the growth-restricted ovine fetus. Ewes carrying singleton pregnancies underwent insertion of vascular catheters, and then, they were randomized to receive uterine artery embolization (IUGR) or to a control group. Ewes in the IUGR group received a daily infusion of sildenafil (IUGR+SC; $n=10$) or vehicle (IUGR+V; $n=8$) for 21 days. The control group received no treatment ($n=9$). Umbilical artery blood flow was measured using Doppler ultrasound and the resistive index (RI) calculated. Fetal weight, biometry, and placental weight were obtained at postmortem after treatment completion. Umbilical artery RI in IUGR+V fell less than in controls; the RI of IUGR+SC was intermediate to that of the other 2 groups (mean $\pm$ SEM for control versus IUGR+V versus IUGR+SC: Δ RI, 0.09 $\pm$ 0.03 versus -0.01 $\pm$ 0.02 versus 0.03 $\pm$ 0.02; $F(2, 22)=4.21$; $P=0.03$). Compared with controls, lamb and placental weights were reduced in IUGR+V but not in IUGR+SC (control versus IUGR+V versus IUGR+SC: fetal weight, 4381 $\pm$ 247 versus 3447 $\pm$ 235 versus 3687 $\pm$ 129 g; $F(2, 24)=5.49$; $P=0.01$ and placental weight: 559.7 $\pm$ 35.0 versus 376.2 $\pm$ 32.5 versus 475.2 $\pm$ 42.5g; $F(2, 24)=4.64$; $P=0.01$). Sildenafil may be a useful adjunct in the management of IUGR. An increase in placental weight and fall in fetal-placental resistance suggests that changes to growth are at least partly mediated by changes to placental growth rather than alterations in placental efficiency.

We found that it was found that in Case Group, 4(14.3%) patients had APGAR (4-6) and 24(85.7%) patients had APGAR (7-10). In Control Group, 8(26.7%) patients had APGAR (4-6) and 20(71.4%) patients had APGAR (7-10). Association of APGAR 1m vs group was not statistically significant ($p=0.1926$). In Case Group, 1(3.6%) patients had APGAR (4-6) and 27(96.4%) patients had APGAR (7-10). In Control Group, 4(14.3%) patients had APGAR (4-6) and 24(85.7%) patients had APGAR (7-10). Association of APGAR 5m vs group was not statistically significant ($p=0.1597$).

Chen J et al ⁷ (2016) found that nine trials (576 patients) compared L-arginine with either placebo or no intervention. In the L-arginine treatment groups of the L-arginine trials, there was a significant increase in fetal birth weight (SMD 0.41, 95% CI [0.24, 0.58]), gestational age (SMD 0.30, 95% CI [0.07, 0.54]); L-arginine treatment group have a significant reduction in the ratio of neonatal respiratory distress syndrome ($P = 0.009$), intracranial hemorrhage of fetuses ($P = 0.002$), but the number of included studies and people on these

outcomes are small. As only one trial (41 patients) compared sildenafil citrate with placebo, it was too small for reliable conclusions about possible differential effects could be drawn. The results of this meta-analysis showed that L-arginine increased birth weight and prolonged gestational age at labor of IUGR fetuses. However, further large-scale RCTs are needed to adequately assess the effect of L-arginine and Sildenafil citrate on clinical outcomes, because the number of study may be small.

We found that in Case Group, the mean PRE T/t UA PI (mean $\pm$ s.d.) of patients was 1.0073 $\pm$.1307. In Control Group, the mean PRE T/t UA PI (mean $\pm$ s.d.) of patients was .9133 $\pm$.0730. Difference of mean PRE T/t UA PI with both Group was statistically significant ($p=0.0011$). In Case Group, the mean PRE T/t UA RI (mean $\pm$ s.d.) of patients was .8313 $\pm$.0742. In Control Group, the mean PRE T/t UA RI (mean $\pm$ s.d.) of patients was .8020 $\pm$.0433. Difference of mean PRE T/t UA RI with both Group was not statistically significant ($p=0.0665$). In Case Group, the mean POST T/t UA PI (mean $\pm$ s.d.) of patients was .8590 $\pm$.1300. In Control Group, the mean POST T/t UA PI (mean $\pm$ s.d.) of patients was .9240 $\pm$.1701. Difference of mean POST T/t UA PI in both Group was not statistically significant ($p=0.1017$). In Case Group, the mean POST T/t UA RI (mean $\pm$ s.d.) of patients was 7200 $\pm$.1040. In Control Group, the mean POST T/t UA RI (mean $\pm$ s.d.) of patients was .7807 $\pm$.0996. Difference of mean POST T/t UA RI in both Group was statistically significant ($p=0.0246$). In Case Group, the mean PRE T/t MCA PI (mean $\pm$ s.d.) of patients was 1.9593 $\pm$.2466. In Control Group, the mean PRE T/t MCA PI (mean $\pm$ s.d.) of patients was 1.7147 $\pm$.1143. Difference of mean PRE T/t MCA PI in both Group was statistically significant ($p < 0.0001$). In Case Group, the mean PRE T/t MCA RI (mean $\pm$ s.d.) of patients was .7947 $\pm$.0218. In Control Group, the mean PRE T/t MCA RI (mean $\pm$ s.d.) of patients was .7883 $\pm$.0374. Difference of mean PRE T/t MCA RI in both Group was not statistically significant ($p=0.4263$). In Case Group, the mean POST T/t MCA PI (mean $\pm$ s.d.) of patients was 1.6920 $\pm$.2681. In Control Group, the mean POST T/t MCA PI (mean $\pm$ s.d.) of patients was 1.5410 $\pm$.1648. Difference of mean POST T/t MCA PI in both Group was statistically significant ($p=0.0110$). In Case Group, the mean POST T/t MCA RI (mean $\pm$ s.d.) of patients was .7367 $\pm$.0442. In Control Group, the mean POST T/t MCA RI (mean $\pm$ s.d.) of patients was .7450 $\pm$.0446. Difference of mean POST T/t MCA RI with in Group was not statistically significant ($p=0.4704$).

Khan MI et al ⁸ (2017) found that differences in Sildenafil treated and Sildenafil naïve groups were analysed statistically. Secondary outcomes in terms of side effects were observed and analysed. Sildenafil treated fetuses showed significantly higher decrease in RI ($P=0.0003$), PI ($P=0.04$) and S/D ($P=0.008$) in umbilical artery compared to control group. They also showed -15.115%, -5.526% and -17.009% decrease in RI, PI and S/D respectively post eligibility in study group compared to -1.175%, -1.056% and -6.134% decrease in control group. Middle cerebral artery velocimetry showed a higher increase in RI (+17.204% vs. +7.355%), PI (+25.657% vs. +1.055%), S/D (+27.745% vs. +3.353%) in study vs. control group from eligibility to determination of effect. A significantly higher increase was also seen at determination in study group compared to control group with P values of 0.0002, 0.009 and 0.04 respectively for RI, PI and S/D. Sildenafil appears to significantly normalize ultrasound doppler velocimetry indices in fetuses affected with late onset restriction.

Our study showed that in Case Group, the mean BMI (kg/m²) (mean $\pm$ s.d.) of patients was 24.1600 $\pm$ 3.4452. In Control Group, the mean BMI (kg/m²) (mean $\pm$ s.d.) of patients was 24.0633 $\pm$ 2.8181. Difference of mean BMI (kg/m²) in both Group was not statistically significant ($p=0.9057$).

Singh A et al ⁹ (2016) found that according to treatment with Sildenafil women were divided in two groups. Both groups were followed up till delivery and their outcome including birth weight, AC and complications related to IUGR were compared. IUGR was found to be more prevalent in primi gravidas and women of lower socioeconomic and educational status with low BMI. They found Hypertension in pregnancy as significant causative factor precipitating the IUGR [68%]. In sildenafil treated group significant 63% mothers had baby with birth weight >10 percentile whereas in sildenafil non treated group only 20% had > 10 percentile birth weight. The mean birth weight of Sildenafil treated group was 2594gm whereas in non-treated group it was 2200gm. In their study, they observed improved AC in

70% whereas in control group improvement was only in 34% which was significant. Sildenafil was found to improves birth weight, abdominal circumference, and reduce the complications related to IUGR.

Table: Distribution of mean PRE T/t MCA S/D, PRE T/t MCA PI, PRE T/t MCA RI, POST T/ t MCA S/D, POST T/ t MCA PI and POST T/t MCARI

		Num ber	Mean	SD	Minimu m	Maxim um	Media n	p- value
PRE T/t MCA S/D	Case	30	6.2093	.3392	5.8000	7.0000	6.1000	0.0115
	Control	30	6.4957	.4957	5.6000	7.5000	6.4000	
PRE T/t MCA PI	Case	30	1.9593	.2466	1.6000	2.7000	1.9000	<0.0001
	Control	30	1.7147	.1143	1.4000	1.8500	1.7300	
PRE T/t MCA RI	Case	30	.7947	.0218	0.7000	0.8200	0.8000	0.4263
	Control	30	.7883	.0374	0.7000	0.8200	0.8000	
POST T/ t MCA S/D	Case	30	5.5707	.4349	5.1000	6.5000	5.4000	0.0200
	Control	30	5.8723	.5368	5.1000	6.9000	5.8000	
POST T/ t MCA PI	Case	30	1.6920	.2681	1.0100	2.4000	1.6850	0.0110
	Control	30	1.5410	.1648	1.0200	1.7000	1.5800	
POST T/ t MCA RI	Case	30	.7367	.0442	0.7000	0.8000	0.7000	0.4704
	Control	30	.7450	.0446	0.6800	0.8000	0.7400	

Table: Distribution of mean pre and post T/t UA S/D, PI and RI: Group

		Num ber	Mean	SD	Minim um	Maxim um	Median	p- value
PRE T/t UA S/D	Case	30	3.5600	.2943	3.2000	4.3000	3.5000	0.3717
	Control	30	3.4933	.2791	3.2000	4.5000	3.4000	
PRE T/t UA PI	Case	30	1.0073	.1307	0.8000	1.3000	1.0000	0.0011
	Control	30	.9133	.0730	0.8000	1.2000	0.9000	
PRE T/t UA RI	Case	30	.8313	.0742	0.7000	0.9000	0.8350	0.0665
	Control	30	.8020	.0433	0.7000	0.9000	0.8000	
POST T/t UA S/D	Case	30	3.1867	.5667	2.5000	5.4000	3.0000	0.1176
	Control	30	3.3967	.4507	2.9000	4.4000	3.2000	
POST T/t UA PI	Case	30	.8590	.1300	0.7000	1.2000	0.8000	0.1017
	Control	30	.9240	.1701	0.7000	1.3000	0.8600	
POST T/t UA RI	Case	30	.7200	.1040	0.6000	0.9000	0.7000	0.0246
	Control	30	.7807	.0996	0.6000	0.9000	0.7700	

CONCLUSION

We found that the mean PRE T/t MCA S/D in Control group was greater than case group which was statistically significant. It was found that mean PRE T/t MCA PI at Case group was greater than control group which was statistically significant.

It was found that mean POST T/ t MCA S/D at Control group was greater than case group which was statistically significant. We found that mean POST T/ t MCA PI at Case group was greater than control group which was statistically significant.

We found that the mean PRE T/t UA PI in case group was greater than control group which was statistically significant. It was found that mean PRE T/t UA RI at Case group was greater than control group which was statistically significant.

It was found that mean POST T/t UA RI at Control group was greater than case group which was statistically significant.

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