

**CORRELATION OF SILDENAFIL CITRATE SUPPLEMENTATION WITH UMBILICAL ARTERY DOPPLER INDICES AND PERINATAL OUTCOME IN PATIENTS OF FETAL GROWTH RESTRICTION**

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ABSTRACT **Background:** Intra uterine growth restriction is one of the major problems of developing country like India. FGR is one of the major culprits of perinatal mortality and morbidity. Sildenafil citrate, a phosphodiesterase inhibitor with vasodilatory properties, is a potential new therapy for FGR. **Materials and methods:** Present study was carried out in the Department of Obstetrics & Gynaecology in GSVM Medical College Kanpur from January 2020 to October 2021. Ninety-one cases with suspected intrauterine growth restriction were included. **Results:** We investigated the association of uteroplacental perfusion improvement after providing the sildenafil therapy and the found that PI decreased in a greater number of patients after therapy in study group rather than the control where the PI remained the same. The value of S/D also decreased in study group rather than control. APGAR scores, birth weight and NICU admissions were better in babies of patients treated with sildenafil. **Discussion:** The role of sildenafil in improvement of utero placental flow in the umbilical arteries was thus proved in our study. Sildenafil treatment also improved perinatal outcome in terms of NICU admissions and APGAR score at birth. **Conclusion:** In spite of its major burden on maternal and child health care, we are still in search of a definitive treatment. The empirical evidences of the current study indicate that Sildenafil citrate may offer a potential therapeutic strategy to improve perinatal outcomes. Sildenafil may represent a novel intervention for such pregnancies.

KEYWORDS : Pulsatility index; FGR; Systolic/diastolic ratio; Perinatal outcome

INTRODUCTION

FGR refers to a condition in which a foetus is unable to achieve its genetically determined potential size. 1-3 Factors causing or associated with impaired growth of foetus are traditionally divided into maternal, foetal or placental in origin. It is impossible to state the exact contribution that each pathology makes to the overall incidence of fetal Growth Restriction, as this varies with gestation and population studied. It is clear, however, that placental pathology underpins many deficits in growth, even in disease processes classified as 'maternal' or 'fetal'. For example chronic hypertension, maternal under nutrition, obesity and some congenital infections result in impaired placental development and function which are likely to cause or significantly contribute to the degree of growth restriction. 4-9 These impairments may be described collectively as 'placental insufficiency' - an umbrella term used to define conditions in which the placenta is unable to supply the foetus with the oxygen/nutrients required to support normal fetal growth. Abnormal uterine artery vascular adaption may lead to placental insufficiency and is an important cause of abnormal growth, as in the absence of foetal infection or chromosomal abnormalities, it accounts for the major proportion of FGR.

Sildenafil citrate induces vasodilation through inhibition of type 5 PDE. PDE is responsible for degradation of cGMP to GMP. Thus, in this manner it also causes vasodilation of myometrial arteries ultimately leading to an increase in the uteroplacental blood flow. 10 Phosphodiesterase is present in the foetoplacental circulation. Sildenafil vasodilates the foetoplacental circulation via a complete phosphodiesterase dependent mechanism involving increased responsiveness to nitric oxide. It also potentiates estrogen induced vasodilation.

As sildenafil has been shown to induce changes to flow in the umbilical and middle cerebral circulations, it is also likely to alter cardiac afterload, impacting cardiac development and consequently long-term cardiovascular function. Neurocognitive outcomes are important as the fetal brain undergoes massive growth and development in the second half of pregnancy so may be especially vulnerable to the direct effects of, or haemodynamic changes associated with, sildenafil citrate treatment.

MATERIALS AND METHODS

The study was conducted on the patients attending OPD with FGR in Department of Obstetrics and Gynaecology in GSVM Medical College Kanpur from January 2020 to September 2021. Patients with fetal growth restriction were taken and divided randomly into 2 groups. Study group (who were given the drug sildenafil citrate 25mg twice daily until 37 weeks or delivery whichever will be later) and control group (who were not given the drug). All the subjects that were given intervention were monitored for primary outcome variables before giving the treatment and after giving the treatment once in 15 days for out-patients and weekly for inpatients or more frequently depending on the severity of FGR with fetal Doppler and ultrasound techniques.

RESULTS

Table 1. Distribution of patients according to socio demographic profile.

	Study group% (n=45)	Control group% (n=46)
DEMOGRAPHIC STATUS		
RURAL	68	75
URBAN	32	24
SOCIOECONOMIC STATUS		
Lower	56	54
Middle	26	27
Upper	18	19
EDUCATIONAL STATUS		
Primary	29	28
Secondary	56	54
Senior Secondary	17	18

Table 2. Baseline characteristics.

	Study group (n=45)	Control group (n=46)
Maternal age	24.4±1.9	25.64±1.5
Gestational age	31.3±1.8	30.8±1.19
Parity	0.52±1	0.64±1

Table 3. Umbilical artery doppler indices with pulsatility index.

Umbilical artery doppler indices	Study group P.I. +S.D. (n=45)	Control group P.I.+S.D. (n=46)
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Before therapy	1.13±0.10	1.04±0.35
After therapy (2 weeks)	1.01±0.13	1.02±0.31
CI 95%	0.12(0.02-0.21)	0.01(0.05-0.09)
P value	0.019	0.60

Table 4. Umbilical artery doppler indices with S/D Ratio.

Umbilical artery doppler indices	Study group S/D Ratio+ S.D. (n=45)	Control group S/D Ratio+ S.D. (n=46)
Before therapy	3.26±0.54	2.95±0.16
After therapy	2.66±0.33	2.81±1.3
CI 95%	0.60(0.36-0.83)	0.14(0.09-0.37)
P value	0.01	0.22

Table 5. Prolongation of pregnancy in study group (n=45).

Gestational age at time of admission	Gestation age at time of delivery (in weeks)					
	Early premature (32-34 weeks)			Late premature (34-37 weeks)		
	N	%	P value	N	%	P value
27-30 weeks (n=29)	5	17	0.12	24	82.7	0.003
30-32 weeks (n=9)	3	33	0.18	6	66.67	0.001
32-34 weeks (n=6)	0	0	-	6	100	0.000
34-36 weeks (n=1)	0	0	-	1	100	-

Table 6. Prolongation of pregnancy in control group (n=46)

Gestational age at time of admission	Gestation age at time of delivery (in weeks)					
	Early premature (32-34 weeks)			Late premature (34-37 weeks)		
	N	%	P value	N	%	P value
27-30 weeks (n=29)	20	76	0.001	9	31	0.12
30-32 weeks (n=9)	7	77.7	0.003	2	22.2	0.15
32-34 weeks (n=6)	4	66.6	0.002	2	33.33	0.13
34-36 weeks (n=2)	0	0	0	2	100	0.000

EFFECT ON FETAL OUTCOME**Table 7.** Distribution of patients according to APGAR score in each group.

Apgar Score		Study (n=45)		Control (n= 46)	
		No.	%	No.	%
1 min	6-8	29	64	13	28
	8-10	17	35	32	71
5 min	6-8	27	60	15	33
	8-10	19	40	30	66
10 min	6-8	30	65.21	12	26.6
	8-10	16	34.7	33	73.3
P value = 0.001					

Table 8. Distribution of patients according to NICU admission in each group.

NICU admission	Study (n=45)		Control (n=46)	
	No.	No.	%	%
Yes	12	24	53	26
No	33	21	46	73
P value = 0.021				

Table 9. Evaluation of side effect of Sildenafil citrate in study and its correlation with continuation of treatment (n=45).

Side effect	Number	Percentage
Nausea / Vomiting	3	7
Headache	17	38
Flushing	0	0
Vaginal throbbing pain	4	9
Palpitation	1	2
No side effect	20	44

The total number of patients of all types of FGR (mild and severe) were 120 of which 46 patients were followed in control group and 4 could not be followed up in study group similarly 5 patients could not be followed up in study group, so total 91 patients were taken. All the socio demographic parameters in both groups were found to be comparable and there was no confounding factor regarding socio demographic profile.

The means (95% CI) of the umbilical artery pulsatility index (PI) and

systolic/diastolic ratio(S/D) significantly decreased 2 weeks after sildenafil ingestion as compared to control group. Mean umbilical artery systolic/diastolic (S/D) significantly decreased in Sildenafil group as compared to the control group. [95% CI 0.37-0.84], p value=0.002. Mean umbilical artery pulsatility index significantly decreased in the study group in comparison with the control group. [95% CI 0.02-0.22], p value=0.019.

In the study group sildenafil citrate supplementation led to more prolongation of pregnancy outcome as compared to the control group. APGAR score at 1 minute, 5 minutes and 10 minutes were in 8-10 range in 71% and 66% and 73% of study group and in 6-8 range in 64%, 60% and 65% in control group p value of these results was 0.001 i.e. statistically significant because of which more number of NICU admissions were also in the control group as compared to study group whose p value was 0.021 that was statistically significant.

APGAR score in study were significantly better than in control group therefore more NICU admissions were observed in control group which was found to be significant.

In our study 51% patients who were given sildenafil reported no side effect and the most common side effect reported was headache 31% but not significant enough so as to cause discontinuation of treatment.

DISCUSSION

In our study, significant improvements found in the doppler indices were similar to the results found in a study conducted in which 60 FGR patients over a time period of 4 years comparing sildenafil citrate therapy for severe early onset growth restriction and found out a significant decrease in the umbilical artery parameters in the study population.¹¹

Similarly, in other study done has shown the improvement of doppler parameters were found in 30 cases with FGR by giving sildenafil citrate therapy over a period of 2 weeks in different age groups.¹²

Similar results were also observed in a study conducted at Tehran where 59 pregnant women with FGR were taken and demonstrated a significant decrease in systolic/diastolic ratios and pulsatility index for umbilical artery and a significant increase in MCA PI (p=0.008) after giving sildenafil therapy.¹³

Wareing M and Myers JE were conducted a study demonstrating the effect of sildenafil citrate on uterine blood vessels in isolated myometrial arteries demonstrating enhanced vasodilatation in arteries run with sildenafil.¹⁴

Significant, improvement of utero placental flow in the uterine arteries and umbilical arteries was also observed in a study conducted by Premalatha et al showed significant improvement in women with FGR.¹⁵

El Sayed MA et al also assessed doppler indices in growth restricted fetus and demonstrated their effect after administration of sildenafil citrate found much improvement in uteroplacental perfusion after providing sildenafil.¹⁶

In the study in terms of perinatal outcome findings correlated with study conducted by Premalatha et al where 100 pregnant women with fetal growth restriction were taken and sildenafil treatment improved perinatal outcome in terms of NICU admissions and APGAR score at birth.¹⁵

Similar results were also obtained by a study conducted by Singh A et al where the mean birth weight of sildenafil treated group was 2594gm whereas in non-treated group it was 2200gm. Also, they reported that in sildenafil treated group 63% mothers had baby with birth weight >10 th percentile while in non-treated group only 20% had >10 th percentile birth weight.¹⁷

Also, similar findings were corroborated in a study conducted to demonstrate the role of sildenafil in FGR pregnancies in northern India and took a total of 100 subjects in which they and 86% of cases showed improvements in terms of fetal outcome and long-term fetal effects.¹⁸ Similarly, in a case study conducted by Choudhary R et al in women with early-onset FGR at 26 weeks of gestation, after treatment with sildenafil citrate, showed improvement in amniotic fluid index and

fetal weight, finally resulting in delivery of a full-term healthy baby with uneventful neonatal course.¹⁹

In our study where sildenafil was given in a dose of 25mg BD 51% patients who were given sildenafil reported no side effect and of the patients in whom side effects were reported the most common side effect reported was headache 31%.

This was in correlation with a study conducted by Dunn L Greer et al²⁰ where the maximum tolerable dose at which side effects were reported was 50mg BD and the incidence of headache and vaginal dryness and throbbing pain was found out to be the main cause for discontinuation of treatment. Also, over 100 pregnant women with FGR reported negligible side effects in the study group and those who reported side effects were mostly in the form of headache and palpitations.¹⁵

CONFLICT OF INTEREST: None

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