

Sildenafil Citrate Improves Ultrasound Doppler Velocimetry Indices in Foetal Growth Restriction – A Randomised Controlled Trial At A Tertiary Care Teaching Hospital in South India.

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Abstract:

Background: Foetal growth restriction is an undesirable and challenging diagnosis given the dire foetal and neonatal consequences it is associated with. Ultrasound doppler velocimetry is a surveillance tool in such pregnancies as it illustrates foetal perfusion and nutrient availability.

Materials & Methods: The study was conducted as a double blind placebo controlled randomized trial with 37 patients in study group who were administered Sildenafil 25mg TID and 56 patients in control group who were administered a similar placebo. Velocimetry indices in umbilical artery and middle cerebral artery were calculated at eligibility and one week post initiation of intervention. Differences in Sildenafil treated and Sildenafil naïve groups were analysed statistically. Secondary outcomes in terms of side effects were observed and analysed.

Results: 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.

Conclusions: Sildenafil appears to significantly normalize ultrasound doppler velocimetry indices in fetuses affected with late onset restriction.

Keywords: Foetal growth restriction, Sildenafil, Ultrasound doppler velocimetry

I. INTRODUCTION

Foetal Growth Restriction (FGR) refers to a pathological condition wherein the foetus in utero is unable to reach its genetic growth potential. The Royal College of Obstetricians & Gynaecologists (RCOG) operatively define small for gestational age (SGA) as a foetus with sonographically diagnosed abdominal circumference (AC) and / or estimated foetal weight (EFW) less than 10th centile [1]. 50 – 70% of all SGA babies show growth restriction [2]. Therefore FGR is operatively being described as AC or EFW less than 3rd centile or less than 10th centile with doppler changes and / or oligohydramnios [3,4].

FGR is an ominous diagnosis given the dire consequences associated with it. Perinatal mortality is increased in the FGR foetus and newborn [5]. Normal uteroplacental and foetoplacental circulation is essential to ensure nutrient and oxygen delivery at foetal tissues. FGR results from pathophysiological and environmental factors which operate to alter uteroplacental blood flow and placental function, therefore altering nutrient availability to the fetus [6].

Pregnancies with FGR are associated with elevated peripheral resistance in the maternal arterial system as seen in pregnancies with preeclampsia [7]. Chronic hypoxia has shown irresponsiveness of endothelial cells in umbilical vein which lead to foetoplacental vasoconstriction [8]. Placental insufficiency appears as the most common cause of FGR [9]

Studies have shown synthesis of Nitric Oxide (NO) in human myometrial and villous throphoblast cells throughout pregnancy [10]. NO is produced by NO synthetase, in endothelial cells and acts by paracrine route to cause smooth muscle relaxation in the walls of arterial and venous channels. This is achieved by increasing the concentration of cGMP locally within the cell by activation of guanylyl cyclase which converts GTP to cGMP. Animal studies have shown that FGR can be induced by blockage of NO synthesis [11]. Increased circulating

phosphodiesterase (PDE) activity, an enzyme responsible for physiological termination of NO activity, is seen in women with preeclampsia [12].

Reduction in blood flow assessed by ultrasound doppler velocimetry (UDV) in uterine artery (UA) and umbilical artery (UMA) is seen in FGR [13]. This manifests as an increase in UDV indices namely, RI (Resistance Index), PI (Pulsatility Index) and S/D (Systolic to Diastolic ratio). The RCOG prescribes UMA doppler as the primary surveillance tool in the growth restricted fetuses [1]. The 'brain sparing effect' causes centralization of blood at the cost of systemic circulation and manifests in the middle cerebral artery (MCA) as decrease in RI, PI and S/D on UDV.

Sildenafil citrate is a specific, 5- PDE inhibitor, approved by United States – Food & Drug Administration (US - FDA). It is classified as Pregnancy category – B drug. Inherently cGMP which is produced by NO is broken down to GMP by 5 – PDE leading to termination of its physiological action. Sildenafil inhibits the action of 5-PDE thereby leading to an increase in cGMP levels. Thus Sildenafil causes vasodilatation by potentiating the action of NO on smooth muscles of blood vessels [14].

We intended to administer Sildenafil citrate and evaluate its effects on UDV indices in UMA and MCA. Hypothetically Sildenafil should cause vasodilatation and improve blood flow in UMA and normalize blood flow in MCA and the same was planned to be tested statistically.

II. MATERIALS AND METHODS

The study was conducted as a double blinded placebo controlled randomized trial at ESIC Medical College Hospital, which is a tertiary care teaching hospital with referrals from 35 ESIC hospitals and dispensaries in addition to its own patients. The study was conducted on consenting patients over a period of one year from 2016 to 2017 after approval from the Institutional Ethics Committee.

Patients fulfilling the selection criteria were included in the study. The investigating physician and the radiologists who performed the scan were blinded. 93 patients were included in the study after obtaining informed consent. They were randomly distributed into study and control group. 37 patients were administered Sildenafil and were termed '*Sildenafil Treated*' and 56 were administered a placebo and were termed '*Sildenafil Naïve*'.

Initially the treatment started with Sildenafil (Viagra[®] - Pfizer) 25mg TID for a week and later increased to 50mg TID till delivery. A UDV scan was done at eligibility for all patients. Those with absent or reduced end diastolic velocity (AREDV) at eligibility were not included in the study. Frequency of antenatal surveillance was determined in accordance with RCOG Greentop Guideline – 31 [a]. UMA and MCA UDV indices, namely RI, PI and S/D were assessed at every surveillance scan. These scans were performed not less than 2 hours and not more than 4 hours after ingesting the tablet. Scans with one week interval after initiation of the drug were considered for analysis. Patients who delivered or were needed to be terminated before the first surveillance scan were not considered for further involvement in the study.

The UDV was performed by LOGIQ C5 Premium equipment (GE Healthcare India), using a 3.5MHz concex transducer and a 100Hz high pass filter. A regular obstetric scan was performed and the umbilical cord was traced at its placental end. Using colour flow imaging, the UMA was identified and the pulsed doppler sample gate was placed on the vessel to obtain waveforms. The MCA UDV was performed by obtaining a transverse view of the foetal brain at the level of the biparietal diameter and then moving the transducer towards the base of the skull till the level of the lesser wing of the sphenoid bone. Using color flow imaging, the middle cerebral artery could be visualised as a major lateral branch of the circle of Willis, running anterolaterally at the borderline between the anterior and the middle cerebral fossae. The pulsed doppler sample gate was then placed at the origin of this vessel to obtain flow velocity waveforms. The UDV parameters assessed by a single radiologist were considered to eliminate inter observer variation errors. PI, RI and S/D were calculated using UDV waveforms. An average of two readings for each vessel was considered for the study.

The primary outcome of the study was a statistical comparison of change in UDV indices between study and control groups. The secondary outcomes included percentage change in UDV indices with Sildenafil administration and adverse effects noted with drug administration. Data was statistically analysed using GraphPad software (www.graphpad.com) and social science statistics (www.socscistatistics.com). Percentage change in UDV indices was calculated by using specific UDV index values (IV) before and after intervention in both the groups using the formula $\Delta\% = \left(\frac{IV \text{ after intervention} - IV \text{ before intervention}}{IV \text{ before intervention}} \right) * 100$

Inclusion criteria:

1. Age 18 – 40 years.
2. AC and / or EFW < 10th centile.
3. Third trimester of pregnancy.
4. Late onset FGR.
5. Booked cases.

Exclusion Criteria:

1. Cardiovascular morbidity in mother.
2. AREDV in UMA at eligibility.
3. Diastolic BP more than 110mmHg and / or mother on anti-hypertensive at eligibility.
4. Foetal anomalies or chromosomal abnormalities.
5. Early onset FGR (Diagnosed before third trimester).
6. Intra uterine foetal death at eligibility.
7. Twin gestation.

Research Involving Human Participants:

- All procedures performed on the patient were in accordance with the ethical standards of the institutional and national research committee and with the 1975 Helsinki declaration and its latest amendment in 2000 and other comparable ethical standards.
- All treatment protocols followed are in accordance with the latest accepted Evidence Based Medicine Norms of the RCOG
- Foetal sex was neither detected nor revealed, in accordance with the PNDT Act 1994.

III. Results

We had 4163 deliveries in the past year, out of these 732 were SGA babies, which brings the incidence to 17.58%. Of these, 93 consenting patients fulfilling our criteria were considered for study. Over the study period 26 patients had pregnancy induced hypertension and 39 were diagnosed with oligohydramnios, but the same was neither considered nor evaluated as it was not included in our operational definition. Maternal characteristics in study and control groups at eligibility are as shown in Table – 1. None of the differences between them are found significant, hence the groups are comparable.

Table – 1: Demographic Characteristics

S.No.	Maternal Characteristic	Sildenafil Treated N = 37 (Mean ± SD)	Sildenafil Naïve N = 56 (Mean ± SD)	P - value
1.	Maternal Age	26±4.65 years	27±3.43 years	P [†] 0.23*
2.	Gestational Age	32±2.37 weeks	32±1.94 weeks	P [†] 1*
3.	BMI	24.3±1.2kg/m ²	23.4±1.7kg/m ²	P [†] 0.12*
4.	Parity n(%)	Primi	19(51.35%)	P [‡] 0.91*
		G2 – G4	13(35.13%)	
		Grand multi	5(13.51%)	

P[†] - calculated by unpaired t test (two tailed) | P[‡] - calculated by chi square test
* - Statistically insignificant

Table – 2 illustrates the UDV characteristics in UMA and MCA in study and control groups at eligibility. Both the groups are comparable as the differences are not significant.

Table -2: UDV characteristics at eligibility

S.No.	UDV characteristic	Sildenafil Treated Group (M±SD)	Sildenafil Naïve Group (M±SD)	P [†]
1.	UMA-RI	0.655±0.06	0.626±0.09	0.08*
2.	UMA-PI	1.122±0.12	1.136±0.1	0.54*
3.	UMA-S/D	3.41±0.36	3.26±0.41	0.07*
4.	MCA-RI	0.651±0.06	0.639±0.08	0.43*
5.	MCA-PI	1.52±0.46	1.43±0.57	0.42*
6.	MCA-S/D	5.19±2.63	5.07±3.02	0.82*

P[†] - calculated by unpaired t test (two tailed) | * - Statistically insignificant

Sildenafil administration in study group was associated with a statistically significant decrease in UDV indices (RI, PI & S/D) in UMA compared to control group (P values 0.0003, 0.04 and 0.008 respectively). Similarly a significant increase in UDV indices (RI, PI & S/D) was observed in MCA upon drug administration when compared with Sildenafil Naïve group with P values 0.0002, 0.009 and 0.04 respectively. The same is tabulated in Table –3

Table – 3: UDV characteristics in study and control groups

S.No.	UDV characteristic	Sildenafil Treated Group (M±SD)	Sildenafil Naïve Group (M±SD)	95% CI	P [†]
1.	UMA-RI	0.556±0.08	0.615±0.07	-0.059	0.0003**

				(-0.09 to -0.027)	
2.	UMA-PI	1.06±0.16	1.124±0.14	-0.064 (-0.126 to -0.001)	0.04**
3.	UMA-S/D	2.83±0.58	3.06±0.23	-0.23 (-0.401 to -0.059)	0.008**
4.	MCA-RI	0.763±0.08	0.686±0.1	0.077 (0.038 to 0.115)	0.0002**
5.	MCA-PI	1.91±0.78	1.51±0.66	0.40 (0.101 to 0.698)	0.009**
6.	MCA-S/D	6.63±2.79	5.24±3.46	1.39 (0.038 to 2.741)	0.04**

P[†] - calculated by unpaired t test (two tailed) | ** - Statistically insignificant

Percentage changes in UMA and MCA, UDV indices from eligibility to the point of determination of effect, in study group are represented in Figure 1 and Figure 2 respectively. Figure 3 represents percentage changes in UDV indices in control group.

Figure 1: Percentage change (Δ%) ‘decrease’ in UMA-UDV indices after intervention.

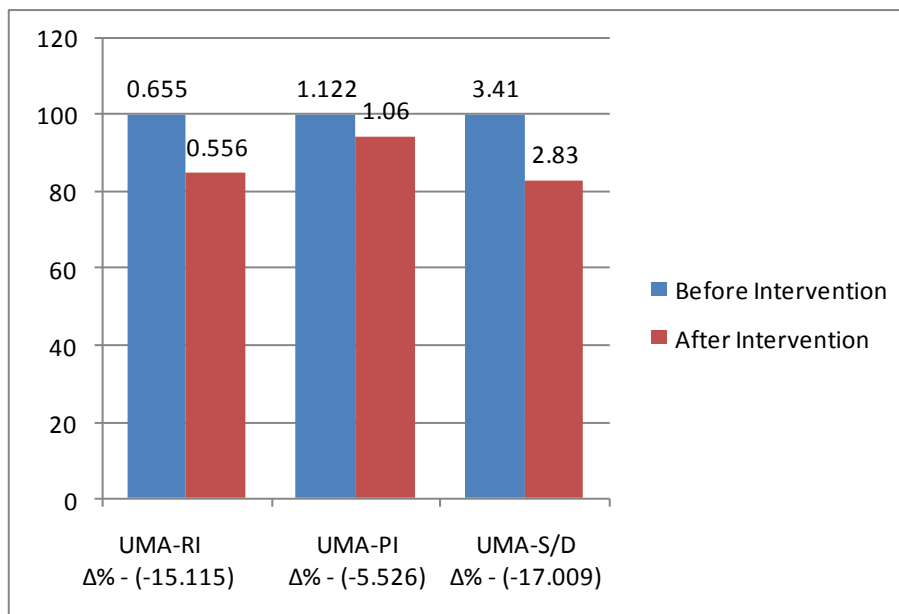


Figure 2: Percentage change (Δ%) ‘increase’ in MCA-UDV indices after intervention.

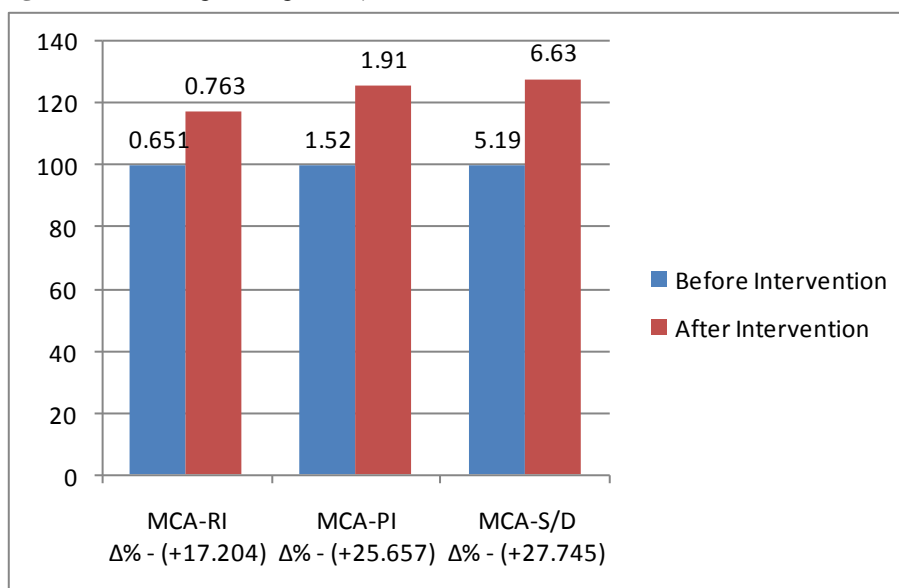


Figure 3: Percentage change ($\Delta\%$) in UDV indices in control group

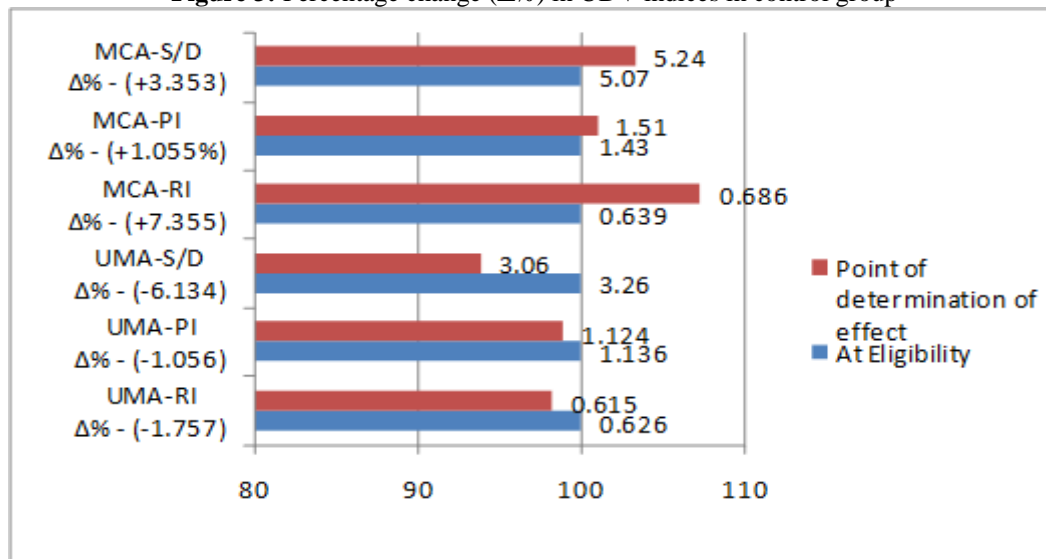


Table 4 compares the proportion of patients in each group with $\geq 10\%$ change ($\Delta_{10\%}$) in UDV indices. Change in beneficial direction was alone considered in both groups. The results seem significant statistically in that patients administered with Sildenafil showed higher proportions with desirable changes in doppler indices.

Table 4: Proportion of patients with $\geq 10\%$ change in UDV indices in study and control groups

S.No.	Udv Characteristic	Sildenafil Treated Group (N) (N = 37)	Sildenafil Naïve Group (N) (N = 56)	P [‡]
1.	$\downarrow \geq \Delta_{10\%}$ Ri-Uma	12(32.43%)	5(8.92%)	0.004**
2.	$\downarrow \geq \Delta_{10\%}$ Pi-Uma	14(37.83%)	6(10.71%)	0.001**
3.	$\downarrow \geq \Delta_{10\%}$ S/D-Uma	16(43.24%)	9(16.07%)	0.003**
4.	$\uparrow \geq \Delta_{10\%}$ Ri-Mca	10(27.02%)	5(8.92%)	0.02**
5.	$\uparrow \geq \Delta_{10\%}$ Pi-Mca	13(35.13%)	8(14.28%)	0.01**
6.	$\uparrow \geq \Delta_{10\%}$ S/D-Mca	18(48.64%)	11(19.64%)	0.03**

P[‡] - calculated by chi square test | ** - Statistically Significant

The adverse drug effects hence observed during the study period have been tabulated below in Table 5, which shows a poor tolerance to orally administered drug. Headache (P-0.0001), Dizziness (P<0.0001) and gastro intestinal (GI) disorders(P-0.04) appear to be significantly high in the study group. Flushing (P-0.28) and Blurring of vision (P-0.78) are apparently more in study group but the difference is not significant. 83.92% patients in control group were free from side effects compared to 37.83% in study group which appears statistically significant with a P value of 0.0003.

Table 5: Adverse Effects of the drug in study and control groups

S.No.	Adverse Effects	Sildenafil Treated Group (n)	Sildenafil Naïve group (n)	P [‡]
1.	Headache	16(43.24%)	5(8.92%)	0.0001**
2.	Dizziness	18(48.64%)	6(10.7%)	<0.0001**
3.	Flushing	6(16.21%)	5(8.92%)	0.28*
4.	Blurring of Vision	2(5.4%)	0	0.78*
5.	GIT disorders	8(21.62%)	4(7.14%)	0.04**
6.	No adverse effects	14(37.83%)	47(83.92%)	0.0003**

P[‡] - calculated by chi square test | ** - Statistically Significant | * - Statistically insignificant

IV. Discussion

To our knowledge this is the first RCT on Indian patients to assess the effect of Sildenafil Citrate on UDV indices in FGR. We report statistically significant improvements in UMA and MCA, UDV indices in fetuses affected with FGR. Hence it is implied that Sildenafil significantly improves uteroplacental circulation and normalizes blood flow in foetus, when used in late onset FGR.

Ruling out congenital anomalies, the most commonly implicated cause of FGR is placental in origin due to vasoconstriction of blood vessels. This causes reduced substrate availability and oxygen delivery at foetal tissues[15] which jeopardises foetal growth and development, leading to a lag in observed growth and expected

genetic growth potential. Bower et. al. in 1998 documented UDV changes in UMA in pregnancies diagnosed with FGR [13].

UDV indices in UMA are indicators of placental circulation and an increase in them implies foetal hypoperfusion. Our study shows a significant decrease in these indices with Sildenafil use which indicates improvement of perfusion with drug use. This is in agreement with the findings of Marzieh et. al. who reported improvement in UMA-UDV with the use of Sildenafil [16].

UDV indices in MCA are indicators of 'blood flow centralisation' or 'brain sparing effect' and a decrease in them implicates compromised systemic perfusion. We report a significant beneficial change in MCA-UDV indices with Sildenafil use. This is in agreement with the results of a RCT by Marzieh et. al. who reported significant normalization of MCA UDV indices with use of Sildenafil [16].

We also report a significantly higher proportion of patients in study group showing desirable UDV changes when administered Sildenafil compared to those who were in control group which rules out the effect of advancing gestational age which appears to confound the outcomes. Soregaroli et. al. have documented that normalization of UDV indices is associated with significant improvement of pregnancy outcomes [17].

Dadelszen et. al. in their RCT report a significant increase in growth velocity and improvement in pregnancy outcomes with Sildenafil use in FGR [18]. In a prospective observational study on Indian patients a significant improvement of outcomes was documented by Premalatha et. al. [19]. These effects could be explained with improvement of foetal perfusion and the resultant nutrient availability. Data from randomised controlled studies on the efficiency of Sildenafil in treatment of FGR is limited. Cases reported by Panda et. al.[20] and Rana et. al. [21] on Indian patients reported improvement of doppler blood flow indices and improvement of pregnancy outcomes following Sildenafil administration post diagnosis.

The beneficial effects of Sildenafil are more reinforcing as the drug has a good safety profile. Samangaya et. al. ruled out any teratogenic effect implicated with Sildenafil use[22]. Similarly reassuring data comes from studies where Sildenafil was used as an adjunct to infertility treatment [14,23]. Furthermore the adverse effects appear to be the extended side effects of the drug and are not potentially threatening, but are sufficient enough to reduce drug acceptability. Vaginal route of administration could possibly be a better route of administration and would reduce such effects to some extent. Further studies to correlate changes in UDV indices and foetal/neonatal outcomes with the use of Sildenafil in FGR are required.

V. Conclusions

There is emerging new evidence which hypothesizes aetiological relationship between diseases of adulthood and FGR [24]. This is disturbing as Barkers hypothesis adds 'onset of adult disease' to the already existing adverse spectrum of foetal and neonatal jeopardy, and childhood and adult sequelae associated with FGR. The disease is more so challenging to the obstetrician in that it lacks a specific pharmacotherapy backed with evidence. In such a helpless situation Sildenafil appears to emerge as a possible intervention in foetal interest.

Declarations

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee of ESIC Medical College.

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