



ROLE OF SILDENAFIL CITRATE IN FGR AND OLIGOHYDRAMNIOS COMPLICATED PREGNANCY: A RANDOMISED CONTROLLED TRIAL

Gynaecology

Dr Ayesha Ansari	Senior resident , LTMMC & GH Department Of Obstetrics And Gynaecology Lokmanya Tilak Municipal Medical College And General Hospital
Dr Archana Bhosale *	Asst Prof , LTMMC & GH Department Of Obstetrics And Gynaecology Lokmanya Tilak Municipal Medical College And General Hospital *Corresponding Author
Dr Kavya HS	senior resident , LTMMC & GH Department Of Obstetrics And Gynaecology Lokmanya Tilak Municipal Medical College And General Hospital

ABSTRACT

BACKGROUND: Fetal growth restriction and oligohydramnios complicate around 7-10% of all pregnancies. Sildenafil citrate a PDE5 inhibitor, being a vasodilator helps in improvement of placental blood flow increasing nutrient and blood supply to the fetus.

MATERIALS: A randomized controlled trial was undertaken at a tertiary care institute at Mumbai to evaluate the effect of sildenafil citrate in improving neonatal outcome in cases of FGR and oligohydramnios. Patients in the placebo group and treatment group were followed up with serial USG scan and doppler indices.

RESULTS: Patients treated with Sildenafil citrate showed a statistically significant improvement in Doppler indices. This result correlated with increased gestational age at delivery, improved birth weight and better APGAR scores.

CONCLUSION: FGR and oligohydramnios, though one of the most common pregnancy issues had a limited treatment approach. The use of sildenafil has revolutionized the management of this condition.

KEYWORDS

FGR, Oligohydramnios, Sildenafil citrate.

INTRODUCTION

Fetal growth restriction (FGR-defined as abdominal circumference AC<10th percentile) and oligohydramnios (amniotic fluid index AFI<5) is a consequence of change in placental blood flow dynamics secondary to multiple causes like preeclampsia, anemia, nutritional, abruption, etc, and has been implicated in more than 50% of iatrogenic premature births. It affects 7-8% of all pregnancies. The incidence of oligohydramnios in the literature varies from less than 0.5% to above 5%, depending on the study population and definition of oligohydramnios. Oligohydramnios, often due to impaired placental function, has been associated with an increased risk of caesarean delivery for fetal distress, as well as low Apgar score, postmaturity, meconium aspiration syndrome and perinatal mortality and morbidity. There is evidence from ex-vivo and animal models of growth restriction that the phosphodiesterase (PDE) 5 inhibitor sildenafil citrate increases average pup birth weight, improves uteroplacental blood flow and potentiates estrogen induced vasodilatation. Its use during pregnancy have reported no deleterious effects on either the mother or offspring in animal models or human beings. An attempt was made to study the effect of sildenafil citrate to improve the placental blood flow in the treatment of oligohydramnios and FGR.

METHODS

A randomized controlled trial was undertaken at a tertiary care centre in Mumbai, India over a period of 3 years. The aim of the study was to decipher the effect of sildenafil in the treatment of oligohydramnios and FGR.

The primary objectives were

- to evaluate the increase in AFI in patients with oligohydramnios (AFI<5)
- to evaluate its use in reversing USG doppler changes (Doppler flow velocimetry in uterine, umbilical, middle cerebral artery) in FGR cases and %increase in the Abdominal circumference of fetus on USG.

The secondary objectives include

- gestational age and birth weight at delivery
- APGAR score at birth
- need for NICU admission post delivery and its duration
- Perinatal mortality rate.
- % increase in birth weight post treatment.

A total of 200 patients of oligohydramnios and FGR were included in the study and randomized into treatment (100pts) arm and placebo (100pts) arm after complying to institutional ethics norms and obtaining written Informed Valid Consent from the patients.

After ensuring complete history and physical examination, Investigations done include complete blood picture, random blood sugar, liver function tests, S.creatinine, albumin, urine analysis. Fetal Doppler indices measurement- For Umbilical vessels the following indices were measured:

- The Systolic/Diastolic (S/D) ratio.
- Resistance index (RI).
- Pulsatility index (PI).

All three indices are highly correlated. PI shows a linear correlation with vascular resistance as opposed to both S/D ratio and RI, which show a parabolic relationship with increasing vascular resistance. Abnormal umbilical artery Doppler indices were defined as S/D ratio greater than 2 and RI greater than 0.7, so all these pregnancies were the candidates of our study.

INCLUSION CRITERIA:

- From 26 weeks to term gestation
- Singleton pregnancy
- AFI<5,
- FGR babies diagnosed by AC<10th percentile and effective fetal weight<10th percentile and reduced umbilical artery blood flow velocimetry.

EXCLUSION CRITERIA:

- <26weeks and >37 weeks
- Multiple gestation
- Reversed diastolic flows in umbilical artery
- TORCH infections
- Congenital anomalies

After complying to criteria and consent from the patients, they were randomized into treatment arm and control arm-100 patients in each arm. Patients with either or both oligohydramnios and FGR were treated with Tab sildenafil citrate 25mg BD per vaginal. All patients were followed up by weekly growth scans to check improvement in AFI and Abdominal circumference and

fortnightly Doppler scans to evaluate uterine, umbilical, middle cerebral artery and ductus venosus flows before and after sildenafil administration. Gestational age at delivery, mode of delivery, need for iatrogenic induction of labour, meconium stained liquor, APGAR score and weight at birth, need for NICU admission, causes of NICU admission duration of stay in NICU were studied.

STATISTICS: The continuous data was analyzed using unpaired or paired T test, while the qualitative data was analyzed using Fischer's exact test or chi square test.

RESULTS : All the patients included in the study were standardized for age(18-35 years), parity(primigravida to 3rd gestation), inter-pregnancy interval(2-5yrs) and the socioeconomic status(Kuppuswamy scale- lower middle). The gestational age on admission into the study ranges from 26-37weeks while the estimated fetal weight on the initial ultrasound ranges from 850gm to 1650gm.

Table - 1

	SILDENAFIL GROUP(N=100)	PLACEBO GROUP(N=100)	TEST OF SIGNIFICANCE	P VALUE
GESTATIONAL AGE ON ENTRY IN STUDY RANGE MEAN+/- SD	26-37 31.5+/-4.5	26-37 32.4+/-5.2	Unpaired t test 1.30	0.192 (NOT SIGNIFICANT)
ESTIMATED FETAL WEIGHT AT START(GMS) RANGE MEAN+/- SD	850-1650 1242+/-328	900-1450 1198+/-422	Unpaired t test 0.8232	0.4114 (not significant)

When comparing the 2 arms, patients receiving sildenafil treatment had a statistically significant outcome in terms of increase in AFI, gestational age of delivery and newborn outcome. The birth weight improved drastically from very low birth weight to normal/low birth weight giving a better post natal course.

Table 2

	Sildenafil treatment N=100	Placebo treatment N=100	Test of significance (T TEST)	P VALUE
AFI MEAN SD SEM	8 1.4 0.142	3.7 0.2 0.027	28.95	<0.0001 (STATISTICALLY SIGNIFICANT)
GESTATIONAL AGE AT DELIVERY MEAN SD SEM	38 1.5 0.15	34.5 2 0.2	14.0098	<0.0001 (STATISTICALLY SIGNIFICANT)
BIRTH WEIGHT AT DELIVERY MEAN SD SEM % increase in birth weight post treatment	2300 220 22 15-20-%	1850 175 17.5 2-5%	16.0077 14.76	<0.002 (STATISTICALLY SIGNIFICANT)
APGAR SCORE MEAN SD SEM	9 1 0.1	7 1 0.1	14.14	<0.001 (STATISTICALLY SIGNIFICANT)

MECONIUM STAINED LIQUOR MEAN SD SEM	8 5 0.5	8.5 3 0.3	0.8575	0.3922 (STATISTICALLY NOT SIGNIFICANT)
NICU ADMISSION MEAN SD SEM	5 3 0.3	16 5 0.5	18.86	<0.001 (STATISTICALLY SIGNIFICANT)
DURATION OF STAY OF BABY IN NICU MEAN SD SEM	1 1 0.1	4 1 0.1	21.21	<0.001 (STATISTICALLY SIGNIFICANT)

Table
SILDENAFIL GROUP3

	Before treatment	After treatment	Chi square test	"p" value
Uterine artery notching	59%	23%	26.78	<0.001 (highly significant)
Brain sparing effect	18%	4%	8.63	0.0033 (highly significant)

The uterine artery notching and brain sparing effect also showed a statistically significant reversal which increased the avg gestational age at delivery of these patients.

DISCUSSION:

An intact uteroplacental and fetoplacental circulation ensures adequate blood, oxygen and nutrient supply to the fetus. Fetal growth restriction has a multifactorial causation, the main pathophysiological mechanism being alteration in uteroplacental blood flow, placental function and hence decreased growth factors reaching the baby. Vasoconstriction in the placental circulation can be overcome by phosphodiesterase 5 inhibitors(sildenafil citrate). Several studies have shown that sildenafil improves uteroplacental blood flow and thus improves fetal weight . According to Amr El-Shalakany et al. Tab sildenafil 25mg tds improved fetal birth weight, increased mean gestational age at delivery and reduced NICU admissions.They also concluded that sildenafil increased the amniotic fluid index and improves doppler flows.El-Sayed et al. in a randomized controlled trial of 54 patients at 24 weeks or more complicated by FGR and abnormal Doppler indices were randomly allocated 1:1 into an intervention arm (receive sildenafil citrate, 50 mg) or a control arm (receive placebo).There was a significant pregnancy prolongation in sildenafil group, increased GA at delivery, improved neonatal weight (p=.0001), and found less admission to neonatal intensive care unit . These findings were not consistent with Miller et al. who found in an experimental animal study that Sildenafil reduced uterine blood flow and this was associated with significant deterioration in fetal wellbeing.They explained their findings by the action of Sildenafil on maternal systemic circulation, altering it and resulting in blood flow "steal" from the uteroplacental circulation to the systemic vascular circulation that has lowered its resistance due to widespread systemic vasodilatation.They also provided an alternative explanation for the decrease in UBF which is the extensive cellular and tissue distribution of the PDE-5 enzyme throughout the body and therefore lack of relative specificity within the uteroplacental circulation. These findings of Miller et al. in the animal study couldn't be confirmed in human.(12) By improving placental circulation sildenafil treatment may also help in treatment of suspected or proven preeclampsia where the pathophysiology remains the same.

CONCLUSION:

Thus from the results obtained, it can be deduced that sildenafil citrate definitely has an important role to play in the management of fetal growth restriction and oligohydramnios. Its role also opens new avenues for its use in early onset FGR as well as Preeclampsia.

DISCLOSURES:

There are no conflicts of interest.

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