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A comparative study between oral and vaginal sildenafil citrate in the treatment of IUGR and oligohydramnios

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Background: Intrauterine Growth Restriction (IUGR) is a challenging condition associated with adverse perinatal outcomes. Sildenafil Citrate, a phosphodiesterase type 5 inhibitor known for its vasodilatory effects, has been promising in improving uteroplacental perfusion. This prospective case-control study aims to investigate the impact of Sildenafil Citrate on IUGR, evaluating its potential as a therapeutic intervention.

Objective: The primary objective of this study is to determine whether the use of Sildenafil Citrate improves uteroplacental perfusion and fetal growth in pregnancies complicated byIUGR. This study also includes evaluating neonatal outcomes, and the overall feasibility of Sildenafil as a treatment option.

Methods: This study involves 50 pregnant women, gestational age between 25-37 weeks, diagnosed with IUGR, randomly assigned into two equal groups: a treatment group A administered orally with 50 mg Sildenafil Citrate per day and another treatment group B administered Sildenafil Citrate. Uteroplacental perfusion was assessed through Doppler ultrasound measurements, and fetal growth parameters were monitored using standard ultrasound techniques. Maternal and neonatal outcomes, including adverse effects, were also documented.

Results: The mean age of patients in group A was 29±5.2 years and group B was 28±4.5 years.Umbilical artery Doppler index significantly improved in sildenafil treated group compared to the control group. There was a significant difference in the mean gestational age at delivery in treatment group A compared to the group B (p value= 0.03). Birth weight in neonates of treatedparticipants was significantly higher as compared to the control group (p <0.001). A significant reduction in NICU admission was found in the new-borns in Sildenafil Citrate treated participant. There was no significant difference in the pregnancy outcomes related to oligohydramnios in both study groups.

Conclusion: Sildenafil Citrate is effective in extending the gestation to allow increased birth weight in patients diagnosed with IUGR. Administration of Sildenafil Citrate also reduces the admission of neonates to NICU.

Introduction:

Intrauterine Growth Restriction (IUGR) is a condition characterized by impaired fetal growth, resulting in a birth weight below the 10th percentile for gestational age [1]. The pathology of IUGR is multifactorial, and involves maternal, fetal, and placental factors. Placental insufficiency is a common contributor, affecting nutrient and oxygen exchange between the mother and fetus [2]**.** Inadequate oxygen availability in the placenta has been shown to be oneof the significant factors that leads to compromised fetal development [3]. Genetic factors, maternal malnutrition, hypertensive disorders, and infections also play significant roles in the etiology of IUGR [4].

Maternal factors that contribute significantly to IUGR include hypertension, malnutrition, and infections. Hypertensive disorders, especially preeclampsia is known to restrict blood flow to the placenta, thereby affecting fetal nutrition [5]. Maternal malnutrition due to inadequate dietary intake or underlying health conditions also limits the availability of essential nutrients for fetal growth. Antenatal infections such as intrauterine infections can directly impact fetal development [6].

Fetal factors associated with IUGR encompass elevated levels of urinary Protein S100B, genetic mutations of Insulin-like Growth Factor 1 (IGF1) or its receptor and SHOX, all of which are linked to growth-related impairments. IGF1 is essential for normal growth, development, and metabolism, while SHOX is involved in skeletal growth. Mutations in these genes can result in growth disorders and skeletal abnormalities [4].

The potential mechanism of action of Sildenafil citrate in the context of IUGR is attributed to its vasodilatory properties and the modulation of nitric oxide (NO) signalling [7]. As discussed previously IUGR there is usually impaired uteroplacental blood flow, contributing to inadequate nutrient and oxygen supply to the developing fetus. Sildenafil citrate, as a phosphodiesterase type 5 (PDE5) inhibitor, prevents the breakdown of cyclic guanosine monophosphate (cGMP), a signaling molecule involved in smooth muscle relaxation and vasodilation [8]. By inhibiting PDE5, Sildenafil citrate prolongs the action of cGMP, promoting vasodilation in the uterine arteries and potentially enhancing blood flow to the placenta. This vasodilatory effect may contribute to improved uteroplacental perfusion, addressing one of the underlying factors associated with IUGR [9].

Method:

This study recruited 50 pregnant women within the age group of 25- 30 years to maintain homogeneity in the study population. The population was randomly divided into two groups; one group (A) was treated with 50g Sildenafil citrate that was administered orally once in a day and the group B was also treated with 50mg Sildenafil citrate that was administered orally vaginally.

For inclusion into the study, participant should have a confirmed diagnosis of Intrauterine Growth Restriction based on standardized criteria, such as fetal biometry, Doppler ultrasound, and growth percentiles. Gestational age should be between 25-37 weeks and should be able to provide written informed consent and should agree for regular follow up. To control forpotential factors affecting the outcome of study, only singleton pregnancies were included to avoid the influence of multifetal gestations on IUGR.

Exclusion of participants was done if severe maternal medical conditions such as severe hypertension, pre-eclampsia, diabetes, or other conditions were present as they might independently impact fetal growth. Presence of structural or chromosomal abnormalities in the fetus excluded the participant from this study. Participants with known allergies to Sildenafil or medical contradictions, such as concurrent use of nitrate medications, were excluded. Cases where immediate delivery was indicated due to severe fetal distress were also excluded. Patients with history of substance abuse were excluded as this may impact fetal growth and complicate the assessment of the intervention.

Data was analysed using GraphPad Prism 10. Umbilical Doppler index was compared using Paired t test while as the gestational age at delivery and birthweight was analysed usingunpaired t test. P value <0.05 was considered significant.

Results:

To ensure a homogeneous study population and control for age-related factors, we restricted participants to age group of 25 to 30 years with average age of the population in group A being 27±4.5 years and 28±5 years in group B. Gestation was decided based on reports showing intervention being most effective. The mean gestational age of patients at recruitment was 29.4±2.3 weeks in group A and 28±2.1 weeks in group B (Table 1).

	Group A	Group B
Mean Age (years)	28±5	27±4.5
Mean Gestational age at admission (weeks)	29.4±2.3	28±2.1

Table 1: Demographic data

We analysed whether the treatment with sildenafil citrate resulted in improvement in the uteroplacental perfusion by quantifying the S/D ratio = (systolic / diastolic ratio). Resistance index (RI) = (systolic velocity - diastolic velocity / systolic velocity). Pulsatility index (PI) as

described previously [10, 11]. We found a significant decrease in the S/D, RI and PI after administration of sildenafil citrate vaginally. There was no significant difference in the parameters in oral administered group of patients (Table 2).

	Umbilical artery Doppler index (Vaginal Route) N=25		**P Value**	**Umbilical artery Doppler index (Oral Route) N=25**		**P Value**
	Before Treatment	**After Treatment**		**Before Treatment**	**After Treatment**	
S/D	4.3 ± 0.2	4.1 ± 0.3	< 0.05	4.6 ± 0.1	4.5± 0.4	0.2312
RI	0.79 ± 0.01	0.73 ± 0.02	< 0.0001	0.78 ± 0.04	0.77 ± 0.02	0.2691
PI	1.92 ± 0.02	1.88 ± 0.02	< 0.0001	1.93 ± 0.03	1.94 ± 0.01	0.1204

Table 2: Umbilical artery Doppler index

We further looked at the gestational age at delivery to assess whether there was any prolongation of gestation after treatment. We found that, in vaginal administered group gestational age at delivery was significantly higher when compared to the oral administered group (p= 0.03). We also found that birthweight in the babies born from vaginal administered group was significantly higher compared to oral administered group (p <0.001) (Table 3).

	Vaginal Route	Oral Route	P- Value
Mean Gestational Age at delivery (weeks)	35.92 ± 1.4	35.6± 1.52	0.03
Birth weight (gram)	2075.48 ± 250.1	18341.2 ± 289.82	<0.001

Table 3: Comparison of gestational age and birthweight.

We also analysed the neonatal outcomes in both the study groups. We found that 84% new- borns delivered in vaginal administered group were alive while as in oral administered group 72% were born alive. 44% of neonates in group B were admitted to NICU while 60% of neonates in group A were admitted to NICU.

Neonatal Outcomes	Vaginal Route (frequency)	Percentage	Oral Route (Frequency)	Percentage
Live birth	21	84	18	72
Admission to NICU	11	44	15	60

Table 4: Neonatal outcomes

We also evaluated the impact of oral and vaginal administration on the Amniotic Fluid Index (AFI) at three different time points: before administration, after 1 week, and after 2 weeks. Initially, the AFI was

similar between the two groups, with the oral administration group having an AFI of 5.84 ± 0.64 cm and the vaginal administration group having an AFI of 5.92 ± 0.72 cm (p = 0.66). After one week, the AFI increased to 7.1 ± 0.22 cm in the oral administration group and to 6.93 ± 0.14 cm in the vaginal administration group, however the difference in the two groups was not statistically significant (p = 0.26). After two weeks, the AFI further increased to 9.22 ± 0.32 cm for oral administration and to 9.15 ± 0.1 cm for vaginal administration (p = 0.30). The p-values at each time point indicate that the differences in AFI between the two administration methods were not statistically significant.

	Oral administration AFI (cm)	Vaginal administration AFI (cm)	p-Value
Before administration	5.84±0.64	5.92±0.72	0.66
After 1 week	7.1±0.22	6.93±0.14	0.26
After 2 weeks	9.22±0.32	9.15±0.1	0.30

- AFI: Amniotic Fluid Index
- Values are presented as mean ± standard deviation.
- p-Value indicates the statistical significance of differences between oral and vaginal administration methods at each time point.

Discussion:

The use of Sildenafil citrate in Intrauterine Growth Restriction (IUGR) has generated keen interest within the field, as it has been shown to address the vascular aspects associated with IUGR. Although limited, the current literature presents concurring and interesting findings. The pioneering report which delves into the effect of Sildenafil citrate in treating IUGR in the context of vascular perfusion was done by Dadelszen et al. 2011. They show that Sildenafil Citrate was effective in late second trimester and was able to treat IUGR significantly [7].

Oral sildenafil has been more extensively studied in the management of IUGR. Several clinical trials and observational studies have evaluated its efficacy and safety in pregnant women with IUGR, demonstrating promising results in improving fetal growth parameters and reducing the incidence of adverse perinatal outcomes [13-15]. In contrast, vaginal sildenafil as a treatment for IUGR is a relatively newer approach that has gained interest among clinicians due to its potential advantages, including targeted delivery to the uterine vasculature and avoidance of systemic side effects associated with oral administration. However, the data regarding itsefficacy, safety, and optimal dosing regimen is limited.

In this study we show that vaginal administration of sildenafil citrate was able significantly improve the Umbilical artery Doppler indices that include S/D, RI and PI when compared to the oral administered group. Our study was consistent with previous report by Dastjerdi et al. 2012 that shows sildenifal citrate treatment leads to a significant decrease in umbilical artery Doppler

index [12]. Another study by Maged et al. 2018 also shows that sildenafil citrate treatment was able to reduce the Umbilical artery Doppler index significantly [13].

Sildenafil citrate has also been reported to prolong gestation [14, 15]. Abdelshafy et al. 2019 and Eshraghi et al. 2021 have also reported that Sildenafil citrate administration in pregnant women diagnosed with IUGR leads to an increase in gestation age at delivery and also improves the birth weight of new-born. We also found that the gestation age at delivery was significantly increased in the treatment group in companion to the control group. In our studythe birth weight of new-born was also significantly increased in treatment group compared to control group. In concurrence with our study, these studies also show that the treatment group had more live births and reduced NICU admissions. In contrast with this data, a recent meta- analysis by Rakhanova et al. 2023 has shown that gestational age and neonatal death rate donot differ in the sildenafil citrate treated group compared to the control group. However, the birthweight in the treatment group increases significantly [16].

We further show that there is no statistically significant difference on the changes in Amniotic Fluid Index (AFI) when sildenafil citrate is administered orally or vaginally. This study correlates with several previous studies which have shown that sildenafil doesn't not have a significant impact on the pregnancy outcomes in patients with oligohydramnios [17-19].

Conclusion:

IUGR is a multifaceted condition with adverse perinatal outcomes if left untreated. Therefore, understanding the complex interplay of these factors is crucial for early identification and effective management of IUGR. There are certain contrasting research outcomes from various reports regarding the neonatal outcomes in terms of live births and NICU admissions, however the majority of literature concurs on the effectiveness of sildenafil citrate in improving the umbilical artery index and birthweight of the new-born. Our study also contributes to the literature to understand the safety and effectiveness of the drug in treating IUGR. However, the certain limitation including less population size and limited parameters creates a scope for a follow up study. Further research is needed to fully elucidate the specific mechanisms and assess the safety and efficacy of Sildenafil citrate in managing IUGR.

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