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COMPARATIVE STUDY OF SILDENAFIL CITRATE THERAPY VERSUS LOW DOSE ASPIRIN IN EARLY INTRAUTERINE GROWTH RESTRICTION

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ABSTRACT

Introduction: A complex and dynamic interaction of maternal, placental and fetal environment is involved in ensuring normal fetal growth. An imbalance or lack of coordination in this complex system may lead to intrauterine growth restriction(IUGR). In India, the prevalence of LBW has been reported as 26%. While the proportion of IUGR has been found to be 54%. Low dose aspirin is one of the most widely used drug for IUGR but sildenafil citrate is emerging drug for IUGR. The aim of study is to compare the effect of sildenafil citrate and low dose aspirin in intrauterine growth restriction. **Material and Method:** Study was conducted in tertiary care referral unit on 150 patients diagnosed with IUGR and were divided into three groups. Effect of drug was evaluated with improvement in ultrasonography parameter. **Result:** In present study there was increase in abdominal circumference of more than 10th percentile in 66% patient in sildenafil group, 58% in aspirin group and 38% in control group. Similarly there was increase in fetal weight of more than 10th percentile in 56% in sildenafil group, 50% in aspirin group and 20% in control group **Conclusion:** More improvement was seen with use of sildenafil citrate as compared to low dose aspirin in IUGR cases.

KEYWORD: IUGR, Sildenafil citrate, Aspirin.

INTRODUCTION

The primary endeavour of obstetrics is that every pregnancy should culminate in healthy mother in possession of healthy baby and prevention of perinatal and maternal morbidity and mortality. Identifying pregnancies and foetuses at risk will help to reduce perinatal morbidity

and mortality. A complex and dynamic interaction of maternal, placental and fetal environment is involved in ensuring normal fetal growth. An imbalance or lack of coordination in this complex system may lead to intrauterine growth restriction(IUGR).

Various definition of Intrauterine growth restriction has been suggested by different national and international societies till now. In spite of this there is no universally accepted diagnostic criteria for diagnosing IUGR. The American College of Obstetricians and Gynecologists (ACOG) defines IUGR as an estimated fetal weight less than the 10th centile.[1] The Royal College of Obstetricians and Gynaecologists (RCOG) uses fetal abdominal circumference (AC) or estimated fetal weight (EFW) less than 10th centile to diagnose a intrauterine growth restriction.[2]

Intrauterine growth restriction can be divided into early and late, according to gestational age at onset. The arbitrary cut off is at 32weeks.[3] The early and late onset IUGR not only differ from each other in terms of gestational age at onset but also differ in clinical manifestation, association with hypertensive disorder, pattern of fetal deterioration and placental dysfunction.

Early onset IUGR, comprised of 20-30% of all IUGR cases and is closely associated with hypertensive disorder. On other hand late onset IUGR comprise of large number of cases and is weakly associated with hypertensive disorder.[4] Early onset growth restricted fetuses carry one of the major risk factors for perinatal morbidity and mortality, either low birthweight or prematurity or both. Both early and late onset FGR are associated with poor short and long term neuro developmental outcome and also with cardiovascular and metabolic complications particularly in cases with birth weigth of less than 3rd percentile.[5]

IUGR is observed in about 24% of newborns; approximately 30 million infants suffer from IUGR every year.[6] The burden of IUGR is concentrated mainly in Asia which accounts for nearly 75% of all affected infants. Africa and Latin America account for 20% and 5% cases respectively. In India, the prevalence of LBW has been reported as 26%.[7] While the proportion of IUGR has been found to be 54%.[8,9]

Despite high incidence of IUGR, there is no specific treatment to reverse the course of intrauterine fetal growth restriction. Fetal growth restriction is probably among the obstetric

entities where there is the greatest variation in clinical practice, in terms of monitoring and recommended gestational age at delivery. Prenatal recognition of fetal growth restriction remains the main challenge in daily obstetric practice. Correct surveillance, antenatal management and timing of delivery can improve fetal and neonatal outcomes. So, there is a pressing need to develop new and effective treatments that can prevent or treat fetal growth restriction.

Various authors have prescribed various drugs for intrauterine growth restriction. Treatment option till now for IUGR were:-

- Aspirin
- Nitric oxide donar
- Sildenafil citrate

Aspirin

Intrauterine growth restriction is mainly due to imbalance between vasodilator and vasoconstriction substance mainly prostacyclin and thromboxane A2(TXA2). Low dose aspirin rectify this imbalance by shifting the balance towards inhibition of TXA2 synthesis and thereby improving uteroplacental blood flow. Leitich et al.[10] performed a meta analysis of low dose aspirin for the prevention of IUGR. The use of aspirin showed a significant reduction in intrauterine growth restriction and perinatal mortality.

Nitric oxide donar

L-Arginine improves Uteroplacental blood flow to overcome placental ischemia by increasing Nitric oxide. This results in vasodilation of uterine arteries. Neri et al.[11]

Evaluated the effects of L-arginine (ARG) infusion, the nitric oxide substrate on the uteroplacental circulation in the third trimester. They found that serum nitrites/nitrates as well as serum growth hormone levels were significantly raised by L-arginine. The authors also reported a significant decrease in resistance in the women where the IUGR was due to elevated resistance. They concluded that L-arginine infusion affects uteroplacental circulation in women with IUGR due to elevated resistance. Such an action is specific and appears to be mediated by a release of nitric oxide.

Sildenafil citrate

Sildenafil is emerging as a potential candidate for the treatment of intra-uterine growth restriction. Maharaj et al.[12] studied the effects and mechanisms of action of sildenafil citrate in human chorionic arteries. The authors concluded that sildenafil citrate vasodilated the feto-placental circulation via a cGMP dependant mechanism involving increased responsiveness to nitrous oxide.

As mentioned above no specific treatment is available for reversing intrauterine growth restriction inspite of it being a big challenge in obstetrics, this study is aimed at comparing the effect of sildenafil citrate and low dose aspirin in early intrauterine growth restriction.

MATERIAL AND METHOD

Study setting: Study was carried out in the department of Obstetrics and Gynecology AVBRH, SAWANGI(MEGHE) The study was approved by the ethical committee of Datta Meghe University of Medical Sciences.

Study design: Randomized control trial.

Study Population: A total of 150 antenatal women diagnosed with IUGR and fulfilled the inclusion criteria were included in the study from 2015 to 2017.

After taking informed consent they were randomly distributed into two groups by sealed envelope method into group A and group B, with 50 patients in each group and Group C with 50 patients as control.

Group A- treated with Sildenafil citrate

Group B- treated with low dose aspirin

Group C-Control group with tablet calcium along with empirical treatment.

Inclusion criteria

- Patients giving consent for the study
- Singleton pregnancy
- All primigravida and multigravida with IUGR from 28weeks to 32 weeks of gestation diagnosed by USG parameters like
  - Fetal abdominal circumference
  - Fetal weight

Exclusion criteria

- IUGR diagnosed before 28 weeks and after 32 weeks of gestation
- Symmetrical IUGR
- Fetus with chromosomal abnormality
- Congenital malformation
- Multiple pregnancies
- Wrong dates

Treatment protocol

Drug is to be given till 36weeks or delivery whichever occurs earlier.

GROUP A

To be treated with Tablet. sildenafil citrate 25mg, BD, orally as soon as patient is diagnosed (from 28 weeks to 32 weeks of gestation) till 36weeks.

GROUP B

Treated with Tab. low dose aspirin 75mg, HS, orally as soon as patient is diagnosed (from 28 weeks to 32 weeks of gestation) till 36 weeks.

GROUP C

Control group-tablet calcium OD along with empirical treatment(amino acid, micronutrients) was given as soon as patient is diagnosed (from 28 weeks to 32 weeks of gestation) till 36 weeks.

Ultrasonography was done in three groups every 4 weeks to see improvement in USG parameter of fetus(abdominal circumference and foetal weight).

OBSERVATION AND RESULT

150 women with singleton pregnancies were enrolled into the study, 50 were assigned to Group A (sildenafil citrate group) and 50 to Group B (low dose aspirin group) and 50 to Group C(control group) after randomization by sealed envelope method.

Following are the result of our study in tabular form.

Table I: Age wise distribution of cases.

Age Group(yrs)	Sildenafil Group n=50(%)	Aspirin group n=50(%)	Control group n=50(%)	Total	χ2-value
19-23 yrs	26(52%)	26(52%)	27(54%)	79(52.66%)	2.26 p=0.68,NS
24-28 yrs	20(40%)	18(36%)	21(42%)	59(39.99%)	
>28 yrs	4(8%)	6(12%)	2(4%)	12(8%)	
Total	50(100%)	50(100%)	50(100%)	150(100%)	
Mean ± SD	23.76±2.63	23.92±2.92	23.26±2.55	23.66±2.70	
Range	20-30	20-30	19-30		

In the present study, the patients were between 19-30 years of age. Maximum number of patients i.e 52% in sildenafil and aspirin group and 54% in control group were in between 19-23years of age.

Table II: Gravida wise distribution of cases.

Gravida	Sildenafil group n=50(%)	Aspirin group n=50(%)	Control group n=50(%)	Total	χ2-value
Gravida 1	25(50%)	26(52%)	28(56%)	79(52.66%)	3.10 p=0.79,NS
Gravida 2	15(30%)	14(28%)	17(34%)	46(30.66%)	
Gravida 3	7(14%)	8(16%)	3(6%)	18(12%)	
>Gravida 3	3(6%)	2(4%)	2(4%)	7(4.66%)	
Total	50(100%)	50(100%)	50(100%)	150(100%)	

50% patients in sildenafil group, 52% patients in aspirin group and 56% patients in control group were primigravida.

Table III: Distribution of cases according to socio-economic status.

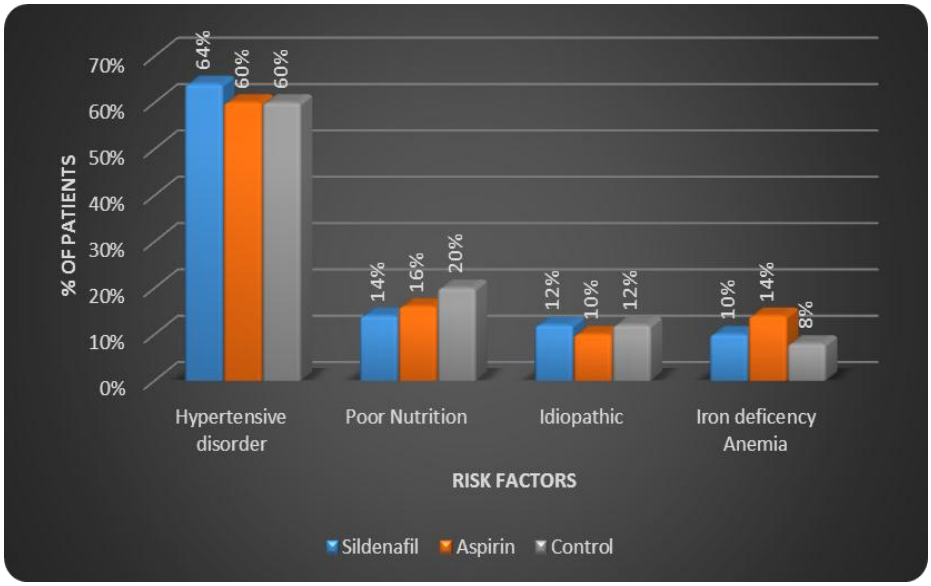
Socioeconomic status	Sildenafil group n=50(%)	Aspirin group n=50(%)	Control group n=50(%)	TOTAL	χ2-value
Upper Class(I)	0(0%)	0(0%)	0(0%)	0(0%)	1.37 p=0.96, NS
Upper Middle Class(II)	2(4%)	1(2%)	2(4%)	5(3.33%)	
Middle Class(III)	7(14%)	7(14%)	9(18%)	23(15.3%)	
Lower Middle Class(IV)	28(56%)	26(52%)	24(48%)	78(52%)	
Lower Class(V)	13(26%)	16(32%)	15(30%)	44(29.33%)	
Total	50(100%)	50(100%)	50(100%)	150(100%)	

Modified B.G. Prasad classification(2017) was used to classify patients on basis of socioeconomic status. Most of the patients in the present study (82% in sildenafil group, 84% in aspirin group and 78% in control group) are from a lower socioeconomic status. (Class IV +V).

Table IV: Distribution of cases according to risk factors for IUGR.

Risk Factors	Sildenafil group n=50(%)	Aspirin group n=50(%)	Control group n=50(%)	TOTAL	χ2-value
Hypertensive disorder	32(64%)	30(60%)	30(60%)	92(61.33%)	0.44.p=0.79,NS
Poor Nutrition	7(14%)	8(16%)	10(20%)	25(16.66%)	1.34,p=0.51,NS
Idiopathic	6(12%)	5(10%)	6(12%)	17(11.33%)	0.26,p=0.87,NS
Iron deficiency Anaemia	5(10%)	7(14%)	4(8%)	16(10.66%)	1.95,p=0.37,NS
Total	50(100%)	50(100%)	50(100%)	150(100%)	

In present study most common risk factor for IUGR is hypertension(64% in sildenafil group, 60% in aspirin group and 60% in control group) followed by poor nutrition (14% in sildenafil group, 16% in aspirin group and 20% in control group). Idiopathic and anaemia are other risk factor(12% & 10% in sildenafil group, 10% & 14% in aspirin group, 12% & 8% in control group).



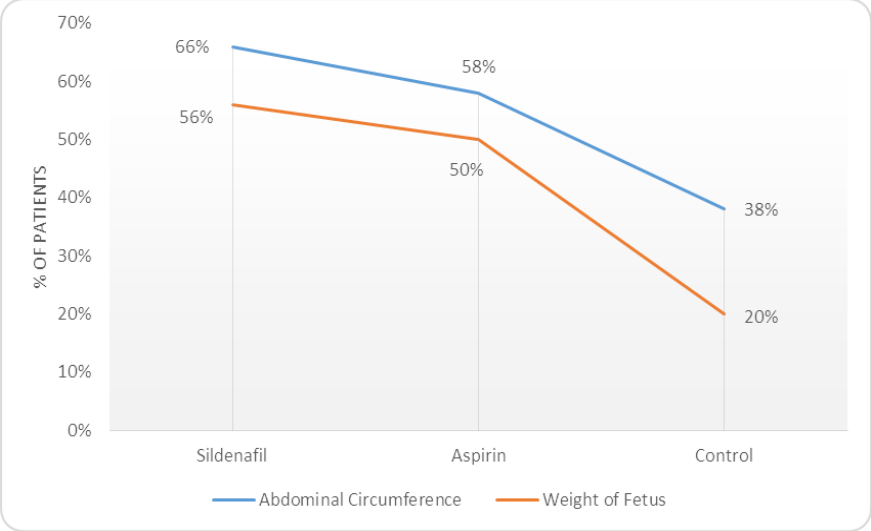
Graph IV: Distribution of cases according to risk factors for IUGR.

Table V: Table showing increase in percentile more than 10th percentile of USG parameter in all three groups.

USG PARAMETER	SILDENAFIL GROUP N=50(%)	ASPIRIN GROUP N=50(%)	CONTROL GROUP N=50(%)	χ2-value
ABDOMINAL CIRCUMFERENCE(>10th PERCENTILE)	33(66%)	29(58%)	19(38%)	16.75 p=0.0002,S
WEIGHT OF FETUS(>10th PERCENTILE)	28(56%)	25(50%)	10(20%)	30.54 p=0.0001,S

In present study there was increase in abdominal circumference of more than 10th percentile in 66% patient in sildenafil group, 58% in aspirin group and 38% in control group.

Similarly there was increase in fetal weight of more than 10th percentile in 56% in sildenafil group, 50% in aspirin group and 20% in control group. By using chisquare test statistically significant difference was found in increase in abdominal circumference and foetal weight (>10th percentile) in patients of three groups(χ2-value=30.54,p-value=0.0001).



Graph V: Graph showing increase in percentile more than 10th percentile of USG parameter in study group.

Table VI: Table showing gestational age at delivery in weeks.

Gestational Age at delivery	Sildenafil group n=50(%)	Aspirin group n=50(%)	Control group n=50(%)	χ2-value
<37 weeks	10(20%)	12(24%)	23(46%)	9.33 p=0.009, S
≥37 weeks	40(80%)	38(76%)	27(54%)	
Total	50(100%)	50(100%)	50(100%)	

In the present study the period of gestation at delivery was less than 37 weeks in 20% patient in the sildenafil group, 24% patient in the aspirin group and 46% in control group.

Table VII: Table showing fetal outcome in terms of apgar score.

Apgar Score	Sildenafil group n=50(%)	Aspirin group n=50(%)	Control group n=50(%)	χ2-value
<7	3(6%)	5(10%)	10(20%)	4.92 p=0.08, NS
≥7	47(94%)	45(90%)	40(80%)	
Total	50(100%)	50(100%)	50(100%)	

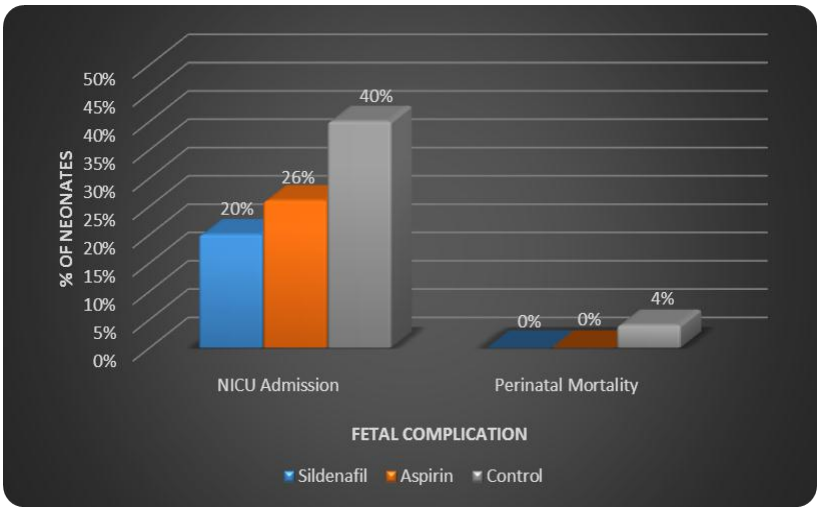
The Apgar scores of more than or equal to 7 is seen in 94% newborn babies in the sildenafil group 90% in aspirin group and 80% in control group.

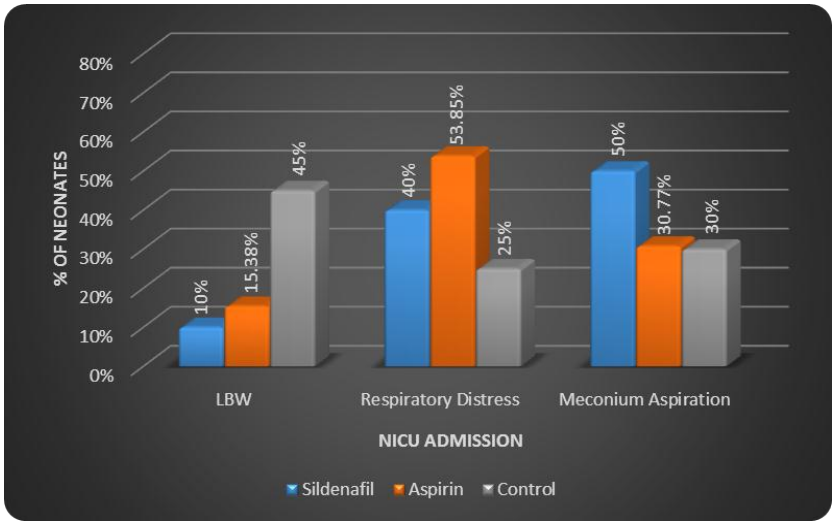
Table VIII: Table showing effect on neonate.

FETAL COMPLICATION	SILDENAFIL GROUP n=50(%)	ASPIRIN GROUP n=50(%)	CONTROL GROUP n=50(%)	χ2-value
NICU ADMISSION	10(20%)	13(26%)	20(40%)	7.74 p=0.25, NS
a) LOW BIRTH WEIGHT	1(10%)	2(15.38%)	9(45%)	
b) RESPIRATORY DISTRESS	4(40%)	7(53.84%)	5(25%)	
c) MECONIUM ASPIRATION	5(50%)	4(30.77%)	6(30%)	
Perinatal mortality	0(0%)	0(0%)	2(4%)	

In the present study 20% neonate were admitted to NICU in sildenafil group, 26% in aspirin group, 40% in control group due to low birth weight, respiratory distress, meconium aspiration. There was highest percentage of NICU admission in control group due to low birth weight(45%). Whereas NICU admission due to low birth weight was 10% in sildenafil group and 15.38% in aspirin group. Other causes of NICU admission were respiratory distress 40% in sildenafil group, 53.84% in aspirin, 25% in control group. Meconium aspiration was present in 50% in sildenafil group, 30.77% in aspirin group and 30% in control group.

There were 2 perinatal mortality in control group, one was due to very low birth weight with respiratory distress and other was due to low birth weight along with doppler changes.





Graph VIII: Graph showing effect on neonate.

DISCUSSION

Intrauterine growth restriction (IUGR) is a major problem in obstetrics and carries an increased risk of perinatal mortality and morbidity. Identification of intra uterine growth restriction is crucial because if diagnosed early and properly managed it can result in a favourable outcome. Certain pregnancies are at high risk for growth restriction but a large percentage of cases occur in the general obstetric population.

Maternal age

In present study maximum number of patient were in age group of 19-23 years(52.66%) as shown in table I. This is comparable with study done by Kumar M et al[13] in which maximum number of patient were in age group of 21-25 years(65.9%).

The study done by Kandhasamy K et al[14] found maximum number of patients were in 20-25 years(72.1%) of age group which is in accordance with our study.

Gravida

In our study as shown in table no. II we observed intrauterine growth restriction was more common with primigravida patients(52.66%) which is similar with study done by Bassetty KC et al[15] in which 73% of patients were Primigravida. In study done by Motghare DD et al[16] majority of patients having IUGR were Primigravida(57.14%) which is similar to our study.

Similarly, study done by Negi KS et al[17] maximum patients(40.69%) were Primigravida and study done by Choudhary AK et al[18] in 2013 also showed similar result as our study.

Socioeconomic status

As shown in table no. III we divided the patients in our study according to socioeconomic status by using modified B.G. Prasad classification. It was observed in our study that most of patients having IUGR belong to low socioeconomic status. The reason of this correlation predominantly can be because of under nutrition of the mother prior to and during pregnancy. Another factors contributing to this relation can be lack of approach to health system and maternal education.

Our finding is in accordance with study done by Ashwani N et al[19] in which also majority of patient were in low socioeconomic group. Study done by Rajashree K et al[20] in 2015 on 131 patients, showed 46.57% belong to class IV and 33.59% belong to class V which is similar to our study(52% in class IV and 29.33% in class V).

In study done by Gagan A et al[21] 47.62% of cases belong to class IV which is similar to present study. Study done by S Muthayya et al[22] in 2009 observed that IUGR is mostly associated with low socioeconomic group.

Risk factor of iugr

In our study we observed close relation of IUGR with hypertensive disorder. As shown in table no.IV majority of patients developing IUGR were associated with hypertensive disorder.(61.33%).

Pathogenesis of pregnancy induced hypertension and intrauterine growth restriction is strictly connected with poor supply of the fetomaternal unit with well oxygenated blood rich in all nutritional substances.[23] Similarly, the theory of abnormal placental implantation or reduced trophoblast invasion continues to link preeclampsia and intrauterine growth restriction (IUGR) as pregnancy disorders with a common pathogenesis.[24]

Our observation is comparable with study done by Thekkedathu VCA et al[25] which showed 53.3% of cases in their study had pre eclampsia.

In study done by Domple VK et al[26] showed most common risk factor of IUGR is, pregnancy induced hypertension. Similarly, study done by Singh G et al[27] in 2006, observed women with preeclampsia have six times more chances of developing IUGR. The number of cases in this study having preeclampsia were 32.5%. Study done by Muhammad T et al[28]

suggested that pregnancy induced hypertension significantly and strongly contribute to intrauterine growth restriction.

Analysis of improvement in abdominal circumference and foetal weight in all three groups after completion of treatment.

In the present study it is seen that 66% of cases had improvement in abdominal circumference (more than 10th percentile) in sildenafil group, 58% had improvement in aspirin group and 38% had improvement in control group as shown in table no. V. This finding is in accordance with study done by Singh A et al[29] in 2016 on effect of sildenafil on IUGR, on 100 patients, which showed improvement in abdominal circumference of 70% of cases in sildenafil group compared to 34% in non-treated group. Similarly, study done by Premlatha HL et al[30] in 2015 also concluded that sildenafil showed 70% increase in abdominal circumference in sildenafil group. Study done by Kalinka J et al[31] showed improvement in abdominal circumference in patient of IUGR treated with low dose aspirin.

Improvement in foetal weight (more than 10th percentile) seen in 56% of cases in sildenafil group, 50% of cases in aspirin group and 20% of cases in control group. This finding is in accordance with study done by Singh A et al[29] in 2016 on effect of sildenafil on IUGR, which showed improvement in foetal weight of 63% of cases in sildenafil group compared to 20% of cases in non-treated group. Study done by Ali MK et al[32] and Kalinka J et al[31] showed improvement in foetal weight after treatment with low dose aspirin.

From table no. V it can be seen that though both drugs are improving foetal weight and abdominal circumference but it can be seen that sildenafil citrate has more percentage of improvement than low dose aspirin in our study.

Analysis of gestational age at delivery

Table no. VI shows distribution of patients according to gestational age at delivery. In present study 20% of patients in sildenafil group and 46% of patients in control group had delivery before 37 weeks. This observation is in accordance with the study done by Singh A et al[29] in 2016, in which 16% of patients had delivery before 37 weeks in sildenafil group and 38% of patients in control group.

Similarly in aspirin group patients delivered before 37 weeks were less than that in control group. This is in accordance with study done by Ali MK et al[32], in which they also observed

more number of delivery before 37 weeks in control group and this data was statistically significant in both study.

So, it can be said that patients having delivery before 37 weeks of gestation were maximum in control group, the reason for this in our study was that most of pregnancies in control group were having severe IUGR, doppler changes and severe oligohydrominos which led to early termination of pregnancy. When both drugs are compared more number of delivery before 37 weeks were seen in aspirin group than in sildenafil group(24% and 20%).

Foetal outcome in terms of apgar score

Table no. VII shows APGAR score at birth in sildenafil group was more than or equal to 7 in 94% of patients and in control group in 80% of patients. This is in comparison with study done by Kubo M et al[33] in 2016, they observed 81% of patients in study group had APGAR score more than or equal to 7 and 57% in control group had APGAR score more than or equal to 7. Similarly, study done by Dunn L et al[34] observed that APGAR score less than 7 was present in 7.1% of patients in sildenafil group, in the present study APGAR less than 7 was present in 6% of neonate.

In aspirin group and control group 90% and 80% of patients respectively had APGAR score more than or equal to 7 and 10% and 20% of patients respectively had APGAR score less than 7. This is similar with study done by Ali MK et al[32] in which they also observed 72% and 40% of patients in aspirin and control had APGAR score more than or equal to 7 and 28% and 60% had APGAR score less than 7 respectively.

From above observation it can be seen that of APGAR score at birth was more satisfactory in sildenafil group(94%) than in aspirin group(90%) than in control group(80%). The reason for this variation may be because of higher percentage of deliveries in control group were terminated before 37 weeks and were accompanied with doppler changes or severe oligohydrominos or severe IUGR. The difference between sildenafil and aspirin group can be due to more number of low birth weight babies were present in aspirin group than in sildenafil group in our study which was associated with more chances of neonates requiring NICU admission.

Analysis of foetal complication

As shown in table no. VIII NICU admission in sildenafil group were 20% and in control group was 40%. This is in comparison with study done by Singh A et al[29] in which NICU admission in sildenafil group was 28% and in control group was 40%.

Most common cause of NICU admission in sildenafil group was meconium aspiration which is also seen in study done by Singh A et al.[29] Another cause of NICU admission was respiratory distress which was found to be similar with study done by Kubo M et al.[33] Maximum number of admissions in NICU in control group were due to low birth weight(45%).

In aspirin group 26% neonate were admitted to NICU and 40% in control group had NICU admission. This is in accordance with study done by Ali MK et al[32] in which NICU admission were 32% in aspirin group and 65% in control group. Study done by McCowan et al[35] observed 71% neonate were admitted to NICU in aspirin group and 74% in control group were admitted to NICU.

There were no perinatal death in our study in sildenafil and aspirin group. Similarly, study done by Kubo M et al[33] also did not have any neonatal death Study done by Singh A et al[29] on 100 cases, had 6% neonatal death in sildenafil group and 10% in control, causes of neonatal death are not specified. Study done by McCowan et al[35] also did not have any neonatal death in their study in aspirin group. In our study there were two perinatal death in control group out of which one was due to very low birth weight along with respiratory distress and other was due to low birth weight along with unfavourable doppler changes.

Number of NICU admissions were maximum in control group(40%) due to higher percentage of low birth weight(45%). When sildenafil and aspirin group were compared more number of NICU admission were seen in aspirin group(26%) than in sildenafil group(20%). This difference was probably due to more number of low birth weight babies born in aspirin group(15.38%) than in sildenafil group(10%) which was associated with respiratory distress and meconium aspiration.

CONCLUSION

Our study showed that though low dose aspirin and empirical treatment (micronutrients and amino acid) had improvement in Ultrasonography parameters but more improvement was

seen in sildenafil citrate group and it was statistically significant along with that sildenafil citrate had shown better neonatal outcome as compared to low dose aspirin and empirical treatment. Further studies are required incorporating doppler use to confirm the therapeutic potential of sildenafil citrate in IUGR.

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