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Research Article

COMPARATIVE STUDY OF ORAL L-ARGININE THERAPY VERSUS NON-AMBULATORY TREATMENT IN PREGNANCY WITH ASYMMETRICAL FETAL GROWTH RESTRICTION

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ABSTRACT

L-arginine is a unique molecule that produces nitric oxide in body and plays a crucial role in physiological hemodynamic modification in pregnancy. A randomised comparative prospective study was carried out in a maternity hospital in Kolkata over one year. The study involved a study group of fifty antenatal mothers with asymmetrical fetal growth restriction detected ultrasonographically around 30-32 weeks of gestation and treated with 5 grams of L-arginine per day over a period of 28 days and a historical control group of fifty patients of same parameters with non- ambulatory treatment in home atmosphere. The aim of our study was to compare the fetal growth and pregnancy outcomes in pregnant mothers supplemented with L-arginine with that in the control group with non-ambulatory treatment in home atmosphere. L-arginine was found to accelerate fetal growth. Fetal growth restriction at delivery in L-arginine group was 42% compared to 46% in control group (p=0.84). Moreover, neonates of treatment group revealed higher Apgar score, lower incidence of respiratory distress syndrome (16% versus 42%, p=0.0076) and intraventricular haemorrhage (2% versus 20%, p=0.007) and lower admission to neonatal intensive care unit (10% versus 44%, p=0.000225). Caesarean section rate was higher in control group than in arginine group (80% versus 72%, p=0.48). Hence, oral treatment with L-arginine seemed promising in improving fetal outcome.

Keywords: L-arginine, asymmetrical fetal growth restriction, respiratory distress syndrome, intraventricular haemorrhage, Apgar score

INTRODUCTION

Arginine is an alpha-amino acid (chemically 2-amino-5-guanidino-pentanoic acid)[1]. The L-form of arginine is one of the 20 most common natural amino acids. In our body a chemical called nitric oxide (NO) is produced enzymatically from L-arginine by inducible enzyme nitric oxide synthase (iNOS)[2]. L-arginine is a precursor of NO and may play a role in placental vascular mediation or local vasodilation[3]. Nitric oxide diffuses into underlying vascular smooth muscle cell and mediates vasodilatation and platelet stabilisation by a cyclic –GMP dependant process. In pregnancy the primary step in the physiological hemodynamic modification is blood volume expansion preceded by arterial tonicity.

Poor placentation is indicated by persistence of high impedance in the uteroplacental circulation assessed by the second trimester Doppler study of uterine vessels. It represents a powerful predisposing factor to asymmetrical intrauterine growth restriction (IUGR) and preeclampsia[4].

MATERIALS AND METHODS

This is a hospital based comparative prospective study conducted in a charitable maternity hospital in Eastern India between February 2014 and January 2015.

The objective of our study is to investigate the effect of dietary intake of nitric oxide donor L-arginine on fetal and neonatal outcomes in asymmetrical fetal growth restriction (FGR).

Fifty antenatal mothers with singleton pregnancy with asymmetrical FGR detected ultrasonographically between 30-32 weeks of gestation were selected as the study group. They were treated with 5 gram of L-arginine (additionally 2.5 mg folic acid and 10 mg zinc sulphate monohydrate) administered daily along with bed rest. A historical control group of age and parity matched fifty antenatal women with singleton pregnancy was chosen from the case records of the hospital between February 2009 and January 2010 who were diagnosed with asymmetrical FGR by ultrasound between 30-32 weeks of gestation and treated with bed rest in home atmosphere as per standard practice then. The total duration of treatment was 28 days for the arginine group. The monitoring was done according to standard protocol of antenatal check up and ultrasonography with Doppler velocimetry every two weeks and non-stress test weekly. The time and mode of delivery in each case was decided depending on the condition of mother and fetus.

Patients with history of smoking, essential hypertension, coronary heart diseases, renal diseases, diabetes mellitus and diagnosed fetal malformation were excluded from the study.

The protocol for use of L-arginine was approved by the Ethical Committee of the hospital and written informed consent was taken from the patients entering the study group. For the historical control, permission was taken from hospital records section. The Ethical clearance number is MB/2009-2010/1/1205.

After delivery the parameters assessed were gestational age at delivery, birth weight, mode of delivery, Apgar score at 1 minute and 5 minutes, signs of infection by sepsis screening, respiratory distress syndrome and admission to neonatal intensive care unit (NICU). Side effect of current therapy if any was noted.

Statistical analysis was done using Student t-test and Chi square test wherever applicable using Graphpad. A value of $p<0.05$ was considered as statistically significant.

Table 1: Baseline characteristics of the compared groups

	Arginine group (n=50)	Control group (n=50)	P value
Maternal age (years)	28.5±2.8	28.5±2.1	NS (0.84)
Nulliparity (%)	86	82	NS
Gestational age at entry (weeks)	31.2±1.1	31.1±1.4	NS(0.42)
Effective fetal weight (grams)	1280±440.5	1240.2±447.3	NS(0.65)

NS-not significant

Table 2: Post delivery assessment of neonates in the compared groups

	Arginine group (n=50)	Control group (n=50)	P value
Birth weight (Grams)	2524.2±643.71	1980±817.6	0.0004
Gestational age at delivery (weeks)	36.4±2.6	34.2±3.4	0.0004
Apgar score at 1 minute			
8-10	34.68%	16.32%	0.0006
5-7	9.18%	18.36%	0.0705
0-4	7.14%	9.18%	0.7858
Apgar Score at 5 minutes			
8-10	45.90%	24.48%	0.0001
5-7	4.8%	18.36%	0.0013
0-4	1.2%	8.16%	0.0309

Table 3: Pregnancy and neonatal outcomes in the compared groups

	Arginine group (n=50)	Control group (n=50)	P value
Caesarean section (%)	72	80	NS (0.48%)
Neonatal infection (%)	14	16	NS (1.00)
Respiratory distress syndrome (%)	16	42	0.0076
Intracranial haemorrhage (%)	2	20	0.007
FGR at delivery (%)	42	46	NS (1.00)
NICU admission (%)	10	44	0.000225

NS- not significant, FGR- fetal growth restriction, NICU- neonatal intensive care unit

RESULTS

The number of patients in both study group and control group was 50 each. There were no significant differences in mean maternal age (28.5± 2.8 years versus 28.6± 2.1 years), nulliparity (43 out of 50 versus 41 out of 50), estimated fetal weight at entry (1280±440.5 gram versus 1240.2±447.3 grams) and gestational age at enrolment (31.2±1.1 weeks versus 31.0±1.1 weeks). [Table 1]

Comparing L-arginine and control group, there were significant differences in birth weight (2524.2±643.71 grams versus 1980±817.6 grams) as well as gestational age at delivery (36.4±2.6 weeks versus 34.2±3.4 weeks). Post natal assessment showed that median values of Apgar score at 1 minute (9 vs. 6) and 5 minute (10 vs. 7) in L-arginine group were higher than in the control group. [Table 2]

There was higher incidence of caesarean section in the control group (72% vs. 80%) but the difference was not statistically significant. Interestingly, in the L-arginine group, significant decrease in intracranial haemorrhage (2% vs. 20%, p=0.007) and respiratory distress syndrome (16% vs. 42%, p=0.0076) among the neonates was noticed. In the study group, the percentage of FGR at delivery was 42 compared to 46 in control group, p value being non significant (p=1.00). The incidence of neonatal infection was 14% (7 out of 50) in study group and 16% (8 out of 50) in the control group, the p value also being non-significant (1.00). However, there was a significant difference in admission to NICU (10% vs. 44%). [Table 3]

DISCUSSION

Our study showed promising results among the study group treated with L-arginine. There were statistically significant increased birth weight and gestational age at delivery. There were greater proportion of neonates with Apgar score 8 to 10 and statistically significant decreased incidence of respiratory distress syndrome, intracranial haemorrhage and NICU admission.

There are studies reporting that L-arginine substrate for nitric oxide improves the feto-maternal circulation in two ways. Firstly it causes vasodilatation. Secondly it has anti-aggregating effect on platelets. The facts may increase the volume and viscosity of blood in the feto-maternal circulation. The facts may influence the growth retarded foetuses stimulating fetal growth[5].

The study by P.Sieroszewski et al showed detectable changes in uterine Doppler measurements and other Doppler indices in women with IUGR suggesting L-arginine may affect uteroplacental circulation in patient with fetal growth restriction[6].

Di Iorio et al concluded that placental nitric oxide is significantly associated with maintenance of adequate uteroplacental perfusion in growth restricted fetuses[7].

P.J.Thureen et al measured plasma concentration of L-arginine and insulin in the uterine, umbilical and fetal arteries of twelve pregnant ewes[8].They noticed that a rise in maternal plasma L-arginine concentration increases the net uptake of maternal, uteroplacental and fetal arginine. It accelerates the secretion of insulin in fetus as

well as in the mother. In regards to our results of pregnancy outcome, similar effects of L-arginine on pregnancy outcome have been found by Xiao et al[9].

Our study has demonstrated that the supplementation of L-arginine in pregnancies complicated by fetal growth restriction has added advantage over only bed rest in improving the fetal and maternal outcomes. The treatment duration is only of 28 days and without any adverse side effects. Hence, in respect to Indian scenario the treatment seems to be cost effective. A large trial is required to assess the cost benefit ratio of the treatment.

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