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Prospective comparative study for analysing efficacy of L-Arginine against all essential aminoacids infusions in patients of oligohydramnios

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Abstract

Background: Oligohydramnios (reduced amniotic fluid) found to be responsible for many complications like Mal-presentations, Umbilical cord compression, Meconium aspiration syndrome and hence increased operative delivery. Maintenance of maternal hydration, supplementation of antioxidants and essential amino-acids is mainstay of treatment. Various modalities are available to treat oligohydramnios & reducing complications of oligohydramnios.

Objective: To compare efficacy of L- Arginine sachets versus All Essential Amino-Acids(EAA) infusions for treatment of oligohydramnios cases.

Study Design: Prospective comparative study.

Materials and Methods: A total of 100 women attending antenatal clinic diagnosed with oligohydramnios were included in our study. 50 patients received only L-Arginine sachets(5 gm twice a day). Another 50 received all EAA infusion(200 ml on alternate day preceded by 500 ml of 10% fructodex). Results of both the groups were obtained in view of -Mean increase in liquor, intervention delivery interval, and neonatal outcome.

Results: The Mean Gestational age at the time of recruitment was 32.3 and 31.6 weeks in study and control group respectively. The mean AFI at the time of enrollment was 6.13 ±0.53, 6.10 ±0.31 in both groups respectively. Patients were delivered at ≥ 37 weeks (in study group 80% in control group 78%). The Mean AFI at the end of therapeutic intervention was (8.63 ± 0.71 and 8.53 ± 0.70, in study group and control group respectively), so we got improvement in mean AFI by 2.50 ± 0.18 in study group and 2.43 ± 0.39 in control group. There was no significant neonatal morbidity in these patients. Significant improvement in liquor volume was obtained in both the groups.

Conclusion: Treatment with L-Arginine and All EAA infusion resulted in significant improvement in liquor and prolongation of duration of pregnancy. But L-Arginine sachets are more cost effective and without hospitalization. Also there is no significant difference between results of study and control groups.

Keywords: Oligohydramnios, L-Arginine sachets, All Essential amino-acids infusions.

Introduction

Amniotic fluid surrounds the foetus in uterus and protective cushion around it. The amniotic fluid increases about a litre between 32 to 36 weeks gestation but decreases thereafter till term up to 400 ml. Oligohydramnios is defined as AFI(amniotic fluid index) less than 8 on ultrasonography(USG). Between 5 and 7 considered as moderate oligohydramnios.[1,2] And less than 5 is considered as severe Oligohydramnios[3] which carries an increased risk of operative interference and perinatal mortality and morbidity. Identification and proper management of oligohydramnios can result in a favourable outcome.

Amniotic fluid is one of the essential requirements for appropriate fetal growth and good fetal outcome. Decreased amniotic fluid (oligohydramnios) leads to increase in danger of caesarean/operative delivery because of fetal distress. Oligohydramnios is closely associated with,

- Chronic placental insufficiency
- Fetal hypoxia due to umbilical cord prolapse and cord compression which is consequence of rupture of membranes
- Impaired lung development
- Restricted space for the fetus to grow
- Non reassuring fetal heart rate in labour.
- Meconium aspiration syndrome
- Danger of preterm labour
- Decreased in APGAR score lower than 7 in the 5th minute
- Admissions to NICU
- Still birth.

In chronic placental insufficiency, the fetus becomes hypoxic and autonomic nervous reflexes that consequently get activated. So it results in to redirecting blood flow to vital organs such as brain and heart at the cost of renal circulation. There is significant reduction in urine output leads to oligohydramnios, which results in reduction of available intrauterine space for adequate fetal growth. Because of pressure symptoms, fetus may develop musculoskeletal deformities like club foot, talipes with or without wry neck. Sometimes fetal skin becomes dry and wrinkled giving old man's look. Pulmonary hyperplasia is also known complication due to decreased amniotic fluid flow in tracheobronchial tree.

Nitric oxide, A free radical compound relaxes smooth muscle and hence blood vessels. L-Arginine is

essentially used to make this free radical. L- Arginine is also helpful to get rid of a waste product like amonia. It can be converted to glucose and glycogen by transferring to L-glutamet and L-proline.[4]

Maternal blood volume, hydration status, maternal osmolality plays an important role in maintaining amniotic fluid volume. Intravenous infusions containing all essential amino acids increases osmolality & blood volume, ultimately leads to increase in amniotic fluid volume. This increase could have been due to increase in the utero-placental perfusion also.

Aims & Objective

- To evaluate the efficacy of L-Arginine against all EAA infusion in management for Oligohydramnios.
- To compare the two treatment modalities for oligohydramnios patients which are widely used.
- To achieve great fetal growth and good fetal outcome in oligohydramnios cases.
- To reduce early operative interference and maternal as well as foetal morbidity and mortality.

Materials and Methods

In a prospective study conducted in the Department of Obstetrics and Gynaecology, A.C.P.M Medical College, Dhule, total of 100 women attending antenatal clinic diagnosed with oligohydramnios were included following written informed consent. Study group of 50 patients from first unit of department of OBGY received L-Arginine sachets (5 gm twice a day with full glass for four weeks). And 50 patients of second unit(control group) received All essential amino acids infusion of 200 ml on alternate day preceded by 500 ml of 10% fructodex. Follow up of the patients was done by assessing:

1. AFI on USG: AFI was measured with four quadrants technique which consists of measuring the largest pool of fluid found in each of the four quadrants of the uterus. follow-up scan done every fortnightly.
2. Prolongation of labour till term.
3. Maternal & foetal outcome after labour: assesed with respect to
   - Incidence of meconium stained liquor
   - Intra-partum foetal distress
   - Mode of delivery
   - Indication of L.S.C.S
   - Foetal outcome was studied with regards to birth weight & APGAR.

A detailed obstetric, menstrual, past, personal and family history was taken, general, systemic examinations and obstetrics examinations were conducted. Abdominal girth and fundal height was measured and recorded in cms. weekly. A record of foetal movements and FHR was maintained.

All blood & urine investigation related to ANC profile were done. Oral iron, multi-vitamins, calcium therapy was continued as before.

Inclusion criteria

- oligohydramnios cases with AFI <8.
- gestational age between 24 and 36 weeks,
- singleton pregnancy
- presence of intact membranes.
- oligohydramnios with pre-eclampsia.
- oligohydramnios with IUGR.

Exclusion criteria:

- Pregnancies with congenital anomalies in fetus.
- Pregnancies with diabetes mellitus
- Pregnancies with renal ,cardiovascular ,abdominal ,pulmonary disease
- Prelabor preterm rupture of membranes (PROM)
- Very severe preeclampsia
- History of having received treatment for oligohydramnios.
- Patients not giving consent.

Results

Table 1: Most of the cases were primigravidae (70% in study group, 74% in control group). They were diagnosed to have low AFI during their third trimester (range 29-35 weeks) scan for fetal growth and amniotic fluid estimation. Mean increase in AFI after intervention 2.50±18 (study group) & 2.43±39(control group) obtained.

Table 1: Comparative Data

Maternal characteristics	Number of patients (total 100)	
	50 (study group)	50 (control group)
Age(mean ±SD)	28 ± 3.9	27.6 ± 4.1
Parity	35- primigravida (70%) 15-multigravida (30%)	37- primigravida (74%) 15-multigravida (30%)
Mean gestational age	32.3 (range 24 to 36 weeks)	31.6(range 24 to 36 weeks)
Mean AFI before intervention	6.13 ±0.53	6.1 ± 0.31
Mean AFI After intervention	8.63 ± 0.71	8.53 ± 0.70
Mean Increase in AFI	2.50 ± 0.18	2.43 ±0.39

Table 2: Shows two types of interventions, one is L-Arginine sachets for the study group. And All EAA infusions for the control group and their results.

Table 2: Comparison of study and control group in terms of AFI

Type of Intervention	L-Arginine sachets	24-28 weeks (n=14)		28-32 weeks(n=16)		32-36 weeks(n=20)		P- value
		Pre Rx AFI mean±SD	**post Rx AFI mean±SD**	**Pre Rx AFI mean±SD**	**post Rx AFI mean±SD**	**Pre Rx AFI mean±SD**	**post Rx AFI mean±SD**	
		6.2±0.28	8.4±0.44	6.4±0.56	8.9±0.43	5.8±0.24	8.6±0.27	9.11776E-27 HS*
	All essential amino acids infusion	24-28 weeks(n=12)		28-32 weeks(n=16)		32-36 weeks(n=22)		
		Pre Rx AFI mean±SD	**post Rx AFI mean±SD**	**Pre Rx AFI mean±SD**	**post Rx AFI mean±SD**	**Pre Rx AFI mean±SD**	**post Rx AFI mean±SD**	**P- value**
		6.0±0.49	8.3±0.56	6.2±0.88	8.8±0.46	6.1±0.59	8.5±0.85	1.79055E-28 HS*

* HS: Highly significant.

Table 3 shows the obstetric outcome of the fetuses after intervention in mothers. Out of 100 patients from study and control groups, 64 fetuses delivered vaginally, among them 33 from study and 31 from control group. And 36 required L.S.C.S(17 from study and 19 from control) Among the different indications of L.S.C.S. foetal distress[Total 11, 5(study), 6(control)] accounts for 30.55%. This can be due to the fact that fetuses with oligohydramnios are likely to experience variable deceleration and cord compression. Out of 36 patients of L.S.C.S Malpresentation cases were 8(4 from each group), Previous L.S.C.S were 8(4 from each group), failed induction were 6(3 from each group), severe oligohydramnios were 3(1from study & 2 from control group).

Table 3: Comparison of Mode of delivery

Mode of delivery	Study group (50 patients)		Control group (50 patients)	
	Vaginal	**Caesarean**	**Vaginal**	**Caesarean**
	33	17	31	19
Indications for caesarean delivery				
Fetal distress		5		6
Malpresentations		4		4
Previous lscs		4		4
Failed induction		3		3
Severe oligohydramnios		1		2
		17		19

Table 4 is showing the comparison between the studies conducted in past and present study. In those studies improvement in AFI after giving intervention is compared with the present study. And it clearly states that the significant improvement is there after intervention in study and control groups.

Table 4: Comparison of results of the present study and previous studies

Amniotic fluid index	Dois et al. (1998)	Magnan et al. (2003)	Malhotra et al. (2004)	Shripad et al(2013)	Present study (2016)
pre treatment	7.1	8.6	6.8	6.9	6.13
Post treatment	9.9	10.1	10.1	9.3	8.63
Improvement in AFI	2.8	1.5	1.5	2.4	2.5

Table 5 shows the neonatal outcome in these study group (n=50) and control group (n=50) There were no still birth/neonatal or perinatal death. Small for gestational age fetuses were 4 in study group and 5 in control group. 3 from study, And 4 from control group required resuscitation of fetuses. 6 fetuses from study group And 5 fetuses from control group needed NICU admission and they were well managed by the pediatrician. There was no incidence of necrotizing enterocolitis, hypoxic ischemic encephalopathy, or sepsis in any of the babies.

Table 5: Neonatal outcome

	Study group	Control group
Small for gestational age fetuses	4	5
Average birth weight fetuses.	46	45
Resuscitation required for number of fetuses	3	4
Still birth/neonatal death	0	0
NICU admissions	6	5

Table 6 shows the gestational age of the fetus in weeks at time of delivery after giving intervention in both the groups. Prolongation of pregnancy till term (≥37 weeks) is 80% in study group, 78% in control group.

Table 6: Status of Prolongation of pregnancy

GA at the time of delivery in weeks	Study group	Control group
≤32	0	1
32-34	4	5
34-36	6	5
≥37	40	39

Discussion

Amniotic fluid has different functions. It plays role in fetal lung development by two-way movement of fluid into fetal bronchioles, thus prevents fetal lung hypoplasia. When Amniotic fluid is adequate, prevents contractures of limbs. Amniotic fluid protects the fetus from mechanical injury by preventing adhesions between fetus and amnion. Oligohydramnios during labour is known to cause variable amount of umbilical cord compression and fetal hypoxia.

Now a days due to easy availability of USG, more and more cases of oligohydramnios are being identified. So we can anticipate the problems which are going to occur during labour, and also helps in taking necessary preventive steps. It is utmost important to find out effective, economical, easily available treatment modality for the cases of oligohydramnios.

Different treatment modalities are L-Arginine amino acid with oral hydration, all aminoacids orally with hydration, all amino-acids intravenous infusion, Amnio-infusion.

Amnioinfusions guided by serial ultrasound have been tried recently but with varying success rates. It carries the danger of fetal loss as it is an invasive procedure. It is not easily available in India. So not considered as treatment of choice for the oligohydramnios cases.

All EAA infusion preceded by 10% of fructodex solution is one of the treatment modality. In which amniotic fluid volume seems to get improve because of maintenance of hydration and balance of required nutritional agents.[5] Adequate hydration of mother is therapeutic intervention to improve the placental fluid transfer. According to physiological principles, osmotic forces regulates water transfer between mother and fetus, in which electrolyte gradients determine net transplacental water exchange. In an ovine study with maternal fluid overloading, it was reported that a reduction of maternal fetal osmotic gradient facilitated water transfer to the fetus, leading to an increase in fetal urine production, and thereby increase the liquor. Fructodex solution is a combination of dextrose 5% and fructose 5%. Dextrose and fructose molecules readily pass the placental barrier and act as an energy source for the growing fetus and, hence, may be useful in growth-restricted fetuses. They are also readily oxidized to carbon dioxide and water at the end of energy production. Carbon dioxide is readily excreted by maternal lungs and the remaining of intravenous fluid acts like hypotonic solution which induces osmotic diuresis in even otherwise normal fetus and improves liquor.

L-Arginine is a versatile amino acid which serves several biological functions. It serves as a precursor for proteins and also for Nitric oxide(NO). Nitric oxide is an important regulator of placental perfusion, As it is identified as endothelium-derived relaxing factor.[6] NO is synthesized by the stereospecific enzyme, NO synthase through the L-Arginine/NO pathway, in which L-Arginine is the only substrate for the production of NO.[7] NO also causes vasodilatation in renal vessels thereby increasing glomerular filtration rate (GFR) and ultimately enhance fetal urine production. L-Arginine causes increase in utero-placental blood flow by nitric oxide mediated dilatation of vessels and platelet stabilization by cyclic GMP-dependent process.[8] Thereby increasing the supply of nutrients to the fetus, helps in growth of fetus. L- Arginine is an essential amino acid which plays a role in lowering blood pressure because a major cause of high blood pressure is narrowing of the arteries. One study by Ropacka et al, L-Arginine was found to be effective in cases of Intrauterine growth restriction.[9] Similarly in another study in growth restricted and pre-eclamptic patients by Dera et al, use of L-Arginine was associated with lower rate of operative deliveries and higher Apgar scores at both 1 and 5 minutes.[10] It is available as 5-8 gm powder or granules in sachet. It was given with one full glass of water two times in a day at least for four weeks. So hydration is also improved along with above benefits of L-Arginine ultimately leads to significant rise in AFI and also prolongation of pregnancy till term. That is also with good fetal outcome without life threatening complications.

Abida Ahmad studied the effect of intravenous infusion of 200 ml of aminoacids and 500 ml of 10% fructodex on alternate day basis in 20 clinically and sonographically proven cases of oligohydraamnios.

Significant improvement in amniotic index was observed at the time of delivery.[11]

Sreedharan et al studied the effect of L-Arginine in 100 women diagnosed to have oligohydramnios between 28 and 36 weeks of gestation.[12] The expectant mothers were prescribed sachets of L-Arginine containing 3 g of the active ingredient for periods varying between 1 and 4 weeks. There was significant improvement in AFI (by 2.03 ± 0.39 cm), and they opined that L-Arginine can be used as a cheaper alternative to ultrasound-guided amnioinfusion in pregnancy complicated by low liquor remote from term.

Here in this study we have compared efficacy of L-Arginine sachets and all amino-acids infusion for improving AFI for the oligohydramnios cases. There was no significant difference when rise of Mean AFI after intervention in study(2.50±0.18) and control group(2.43±0.39) was compared. Good fetal growth, Prolongation of pregnancy till term, outcome of the fetus, operative interference, were also similar in both groups. Conditions associated with fetal outcome in cases of oligohydramnios like Small for gestational age fetuses, Resuscitation required, NICU admissions, those counts were also similar in both group. There were no still birth or neonatal death in any of the group. Now we have compared efficacy of L-Arginine sachets against all EAA infusions, it turns out to be similar. While L-Arginine sachets got advantage of No Hospitalization, Also overall cost in comparison with all EAA is much more less. So compliance of the patients are better in study group. here best treatment option for oligohydramnios cases turns out to be L-Arginine sachets twice a day with full glass of water that can maintain maternal hydration.

Conclusion

Management of Oligohydramnios cases is a challenging Job. Management of hydration; Correction of growth restriction & Prolongation of pregnancy till term are main objective of the treatment. Treatment with L-Arginine and All EAA infusion resulted in significant improvement in liquor and prolongation of duration of pregnancy, but cheap and feasible method with same results is L-Arginine sachets with Maternal hydration in resource-poor countries.

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