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Comparative Study between Acarbose and Insulin in the Treatment of GDM.

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ABSTRACT

Background: GDM is a condition with predominantly high post prandial blood sugar levels. If left untreated it causes adverse maternal and perinatal outcome. Moreover in the long term most of the GDM mothers become diabetics. Aim: To compare the effectiveness of acarbose and insulin in the treatment of GDM. **Methods:** A randomized controlled trial was conducted. All antenatal women attending antenatal OPD were screened for GDM using DIPSI guidelines. Medical nutritional therapy was initiated in all screen positive individuals. Glycemic profile was done after two weeks. The individuals with abnormal glycemic profile and who met the inclusion criteria were included in the study. **Results:** The subjects in both the groups were matched for age, parity and BMI. The average gestational age at which screening was positive was 26 weeks of pregnancy. It was found that that Acarbose is equally effective as insulin in controlling the maternal blood sugar and in turn HbA1C. Obstetric outcomes like mode of delivery, Amniotic Fluid index, fetal growth were comparable in both groups. Fetal outcomes like birth weight, cord blood insulin, Respiratory distress and hypoglycaemia were also comparable in both groups. **Conclusion:** Hence, acarbose is a drug with same maternal and neonatal outcomes as insulin but has a better compliance than insulin.

Keywords: Diabetes, Gestational diabetes mellitus, acarbose.

INTRODUCTION

Diabetes mellitus is a clinical syndrome characterized by hyperglycemia caused by absolute or relative insulin deficiency. Lack of insulin affects the metabolism of carbohydrate, protein and fat, and can cause significant disturbance in water and electrolyte homeostasis.[1] Normal pregnancy is described by mild fasting hypoglycemia, post prandial hyperglycemia and hyperinsulinemia.[2] This increased basal level of plasma insulin in normal pregnancy is associated with several unique responses to glucose ingestion. In a fed state there is prolonged hyperglycemia and hyperinsulinemia as well as greater suppression of glucagon.[3] This cannot be explained by decreased metabolism of insulin because its half-life during pregnancy is not changed.[4] Instead, this response is consistent with a pregnancy-induced state of peripheral insulin resistance the target of which is likely to assure a sustained postprandial supply of glucose to the fetus. Indeed insulin sensitivity in late normal pregnancy is 45-70% lower than that of nonpregnant women.[5] A woman who is unable to achieve adequate insulinogenic compensation develops Gestational Diabetes. Pregnancy unmasks the minor intolerance of carbohydrate metabolism in subjects with reduced pancreatic islet cell reserve.[6] Gestational Diabetes Mellitus is described as "carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy, whether or not insulin is used and regardless of whether diabetes persists after pregnancy".[7] Use of this term was encouraged in order to communicate the need for increased surveillance and to convince the woman of the need for further testing postpartum Gestational Diabetes is often asymptomatic and associated with increased fetal and neonatal morbidity and mortality. Good glycemic control reduces the risk of complication.8 Insulin has been the standard mode of treatment for GDM through the ages. But, of late there are increasing studies favoring the use of oral hypoglycemic agents (OHA's). OHA's like metformin, glyburide, Acarbose are being used increasingly for management of GDM management. In this study, we have analyzed the efficacy of Acarbose to Insulin in GDM patients. Acarbose has several advantages like low cost, storage at room temperature, oral administration and improved compliance when compared to insulin. Moreover, Acarbose is safer during (FDA category B) than insulin (FDA category C) in pregnancy.

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Comparison of efficacy of (maternal and perinatal outcome) Acarbose to Insulin in the treatment of GDM

MATERIALS AND METHODS

This Prospective Randomized controlled study was conducted in a tertiary care hospital. Inclusion criteria: All mothers diagnosed to have GDM attending OPD from 12 weeks to 32weeks of gestation; diagnosis is made by 75gm OGCT ≥ 140mg/dl, singleton pregnancy. Exclusion criteria: Gestational period <12 weeks and greater than 32 weeks, patients with pre existing liver disease, overt diabetes in pregnancy, multiple pregnancy, anomalous baby, abnormal LFT. Patients diagnosed as GDM with OGCT were first given diet counselling and kept on a meal plan for 2 weeks according to BMI and nature of work. Glycemic profile was done. If any of the pre -prandial glucose of greater 90mg/dl and Post prandial glucose level (2hrs) greater than 120 mg/dl, and if the inclusion criteria was met patients were included in the trial. Written informed consent was obtained and proforma was filled up. HbA1C levels were measured. Patients were randomly allotted into 2 groups, group 1 – acarbose and group 2 - insulin. Group 1 was started with Acarbose 25mg tid along with first bite of every meal. Repeat glycemic profile was done after two weeks. Dosage was adjusted according to the glycemic control in the subsequent follow ups up to a maximum dose of 200mg/dl tid. Insulin was started (both rapidly acting and intermediate acting as required by the patient) and dosage adjusted according to the glycemic control. Patients were followed up once in every 4 weeks up to 28 weeks followed by once in 15 days up to 32 weeks and then after once a week up to delivery and 6 weeks post delivery. Liver function tests were done after starting therapy every 6 weekly. Serial ultrasonograms were done to measure the growth and Amniotic Fluid Volume. At the time of delivery birth details were noted and cord blood insulin assay was done. Maternal HbA1C was measured. Babies were followed up for RDS and Hypoglycemia for the next 72 hours of life. The maternal outcomes like AFI, GHT, Mode of delivery, HBA1C both during screening and delivery were measured. Fetal outcomes like birth weight, RDS, hypoglycaemia and cord blood insulin were measured.

RESULTS

In this study 83 patients were included, 22 in Acarbose group and 61 in Insulin group. Both the groups were comparable in age wise distribution. Both the groups had similar obstetric scores.45.5% of women were primi gravid in acarbose group and 42.6 % women were primi gravidas in insulin group. 57.4 % of patients in the insulin group were multigravida and 54.4 % of women in the acarbose group were multigravida. Hence, there is an increased incidence of multi gravidas as compared to the primi. 35.25% of participants in the study had previous abortions. There were no intrauterine or intrapartum deaths in the previous pregnancies in the studied patients. It was observed that 13.6% of patients in acarbose group and 11.5 % patients in insulin group had Gestational Hypertension in the pregnancy studied. In our study there was 9.1% and 14.8 % hypothyroidism associated with GDM in acarbose group and insulin group respectively. 36.4 % of patients in acarbose group and 37.7 % of patients in insulin group had a positive family history of diabetes. 14% of patients in acarbose group and 7.4 % of patients in insulin group had GDM in the previous pregnancy. It was found that most of the individuals were overweight i.e; 63.6 % in acarbose group and 70.5% of patients in insulin group. P- Value is 0.647 (>0.05). Hence, the difference in BMI between the two groups was not statistically significant. Most of the patients were detected to have GDM only in late second trimester or in the third trimester only. Both the groups were comparable with regard to the period of gestation at which screening was positive. The average gestational age at which screening was positive was 26 weeks. The average OGCT value during screening was 158.32 in Acarbose group and 163.25 in the insulin group. The difference between the two groups is not statistically significant. (p value = 0.368) Though there are more number of cases in insulin group with HBA1C level >6 i.e; 47.5% when compared to acarbose group which had only 27.3% individuals with HBA1C level >6, the mean HBA1C level for acarbose group was 6.0227 and that of insulin group was 6.186. This difference is not statistically different. (p value – 0.335). The average period of gestation at which therapy was started is 28 weeks, which is 2 weeks after screening and medical nutrition therapy. In Group 1 – Acarbose, most of the individuals (81.81%) required only a minimal dose of acarbose i.e; 25 mg tid. However, the rest of the individuals required a increase in dosage according to their glycemic control. None of them required discontinuation of therapy due to deranged liver functions. In group 2 - Insulin, both short acting and intermediate acting insulin was given. 47.54 % required a dose of <10 U of insulin/day. 34.40% required 10-20 U of insulin/day and only 18.03% required >20 U of insulin. The average reduction in blood glucose levels in acarbose group was 23.6 mg/dL and in the insulin group was 23.9 mg/dL. The mean HBA1C levels at delivery was 5.1773 and 5.4016 for acarbose and insulin groups respectively. This difference is not statistically different. (p value 0.109). The mean reduction of HBA1C levels for acarbose group is 0.8454 and insulin group is 0.7853. 63.6% of individuals in the acarbose group had an amniotic fluid volume <10cm compared to 45.9% in insulin group. However, this

reduction in AFI in the Acarbose is not statistically significant. (p value = 0.154)

Table 1: Mean maternal HbA1C levels at delivery.

Groups	N	Mean	SD	Unpaired t Test	P Value
Acarbose	22	5.1773	0.54242	1.618	0.109
Insulin	61	5.4016	0.56258		

Table 2: Mean AFI levels before delivery.

AFI						
	< 10 cm		> 10 cm		Chi Square Test	P Value
	N	%	N	%		
Acarbose	14	63.6	8	36.4	2.034 1 df	0.154
Insulin	28	45.9	33	54.1		

There is an increased incidence of caesarean rates in both the groups. 72.7% and 82 % in acarbose and insulin groups respectively. All caesareans were lower segment caesarean sections only. 4.5% and 3.3% of women in acarbose and insulin groups respectively, required an instrumental delivery (vacuum or low forceps). Normal vaginal delivery was possible in 22.7% and 14.8% women in acarbose and insulin groups respectively.

The indications for caesarean sections was only obstetric cause. CPD was the leading cause of caesarean section in acarbose group (36.4%) whereas in the insulin group both previous caesarean section and fetal distress were the leading causes (23% each). In our institution VBAC was not done for patients with GDM or any other co morbidities. Moreover, cases were assessed for CPD and induced with PGE2 gel intra-cervical after completion of 38 weeks of gestation if the woman does not deliver before that. Only one dose of gel was instilled because GDM is a high risk pregnancy. Failed induction was the cause of caesarean section in 18.2% AND 11.5% of women in the acarbose group and insulin groups respectively. Breech presentation was taken up for elective LSCS at 38 completed weeks or as an emergency if the women get into labour before that. 9.1 % and 3.3% of women in acarbose and insulin groups respectively were operated for breech presentation.

31.8% and 32.8% of women in acarbose and insulin groups respectively had premature babies. This difference is not statistically significant (p value = 0.934). 31.8% and 32.8% of women in acarbose and insulin groups respectively had premature babies. This difference is not statistically significant (p value = 0.934)

Table 3: Average birth weight between groups.

	Groups	N	Mean	SD	Unpaired t Test	P Value
Birth Weight	Acarbose	22	3.06	0.438	0.972	0.334
	Insulin	61	2.95	0.463		

Table 4: Statistical analysis of fetal maturity.

Period Of Gestation During Delivery						
	< 37		> 37		Chi Square Test	P Value
	N	%	N	%		
Acarbose	7	31.8	15	68.2	0.007 1 df	0.934
Insulin	20	32.8	41	67.2		

Table 5: Cord Blood Insulin.

	Groups	N	Mean (µU/ml)	SD	Unpaired t Test	P Value
Cord Blood Insulin	Acarbose	22	5.9227	1.68973	1.669	0.099
	Insulin	61	6.6590	1.80263		

The mean cord blood insulin in acarbose group was 5.9 µU/ml and for insulin was 6.6 µU/ml. This difference is not statistically significant. (p value = 0.099). Hypoglycaemia in neonates is defined as blood sugar value <40 mg/dl. No babies in the acarbose group developed hypoglycaemia. But, 21.3 % of babies in the insulin group developed hypoglycaemia. Respiratory distress was found in 5% and 23 % of babies in acarbose and insulin groups respectively. Most of them had only a transient tachypnea of newborn and none of them required surfactant therapy.

DISCUSSION

A study was done by Seshiah et al for detection of GDM in the three trimesters of pregnancy. Among the studied patients 16.3% were within 16 weeks of gestation, 23.1% were between 17-23 weeks of gestation,60.6% were more than 24 weeks. In our

study, the mean gestational age at screening was 26 weeks and at delivery was 37 weeks. Prevalence of gestational diabetes increases with gravidity from 16-3% in primis to 25-8% in gravida > 4 in a study by Seshiah et al.[9,10] Serirat et al in 1992 have shown that family history of diabetes is present in 23.1% of patients with abnormal glucose tolerance.[11] Moses et al has shown that family history of diabetes is present in 11.6% of patients with GDM. In our study, positive family history was present in 37.05% of cases of GDM.[12] Serirat et al in 1992, in a study found that obesity was present in 26.5% of patients with GDM. In a study by Seshiah et al the incidence of GDM was 33.3% in patients with BMI > 30. In our study 22.65% of cases of GDM fell in the normal BMI group, 67.05% had BMI between 25 - 30 (overweight) and 10.3% had BMI > 30 (obese) this shows an increased incidence of GDM in overweight and obese individuals.[9,10] Maternal mortality has become rare in women with diabetes a emphasized by Cousins who stated that mortality is increased 10 fold, most often as a result if ketoacidosis, hypertension, preeclampsia, pyelonephritis and patients with coronary artery disease. In our study there was no morality.[13] Suhoven and Terano et al in 1993 reported the incidence of GHT and preeclampsia to be 2 times more common among GDM patients than controls (19.8% vs. 10%).[14] In our study, GHT in the present pregnancy was 13.6% in acarbose group and 11.5% in insulin group. In the study group 8 patients had previous early pregnancy losses,1 of whom had 2 previous abortions,1 patient had an IUFD and 1 patient lost the previous baby to perinatal jaundice. Thus the incidence of fetal wastage was 33.3%. After treatment with Acarbose all the present pregnancies were carried to term with no fetal wastage.96.7% of the babies had a good Apgar score of >7. In our study there were no fetal wastage during the study period. Bertini et al, J.Perinatal medicine, 2005 studied the perinatal outcome in GDM cases managed with insulin, glyburide and Acarbose. The rate of large for gestational age fetuses in each group was 3.7%, 25% and 10.5% respectively.[15] At term, in our study, there was 9.1% and 13.1% of babies in acarbose group and insulin groups respectively with birth weight >3.5 kg. Hypoglycaemia was not there in any of the babies from acarbose group while 21.3% of babies had hypoglycemia in the insulin group. 4.5% of babies in acarbose group and 23% of babies in insulin group had respiratory distress. Most of them had only transient tachypnea and none required surfactants. Bertini AM et al found that glucose control was not achieved in 42.1% of patients using Acarbose.[15] Spellacy, WN Miller, S Winegar found that Macrosomia was present in 50% of pregnancies with GDM.[16] Langer et al also found 50% of pregnant patients with GDM to have macrosomia. In our study The average birth weight in acarbose and insulin groups were 3.06 kgs and 2.95 kgs respectively.17 2 babies (9.1%) in acarbose group and 8 babies (13.1%) in insulin group were >3.5 kgs. This is not a statistically significant difference (p value = 0.619) In our study, The mean cord blood insulin in acarbose group was 5.9 µU/ml and for insulin was 6.6 µU/ml. This difference is not statistically significant. (p value = 0.099).

CONCLUSION

GDM patients treated with Acarbose had good glycemic control which was equivalent to insulin during the antenatal period and delivery. It was equally effective in preventing the maternal complications due to hyperglycemia, as well as complications for the fetus like macrosomia, anomalies, growth restriction, hyperinsulinism, hypoglycemia, etc. The fetal outcome after treatment of GDM with Acarbose was good. There were no adverse effects of the drug. It is hence equally effective compared to insulin in achieving good glycemic control and preventing maternal and fetal complications of GDM. Thus Acarbose is a safe and effective oral drug in the management of GDM. Moreover, its advantage of oral administration and local action on the intestines make it an attractive alternative to insulin in the treatment of GDM.

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