

Premixed Insulin Aspart 30 (BIAsp 30) vs Premixed Human Insulin 30 (BHI 30) in Gestational Diabetes Mellitus – A Pilot Study

V Balaji¹, Madhuri S Balaji¹, Cynthia Alexander², S Ashalata³, R Sheela Suganthi³, S Suresh³, V Seshiah⁵

Abstract

Objective: The objective of the study was to compare premixed insulin aspart 30 (BIAsp 30) vs premixed human insulin 30 (BHI 30) on efficacy, safety, fetal and perinatal outcomes in pregnancies associated with gestational diabetes mellitus [GDM]. This was the first randomized study to use pre mixed insulin analogue [BIAsp] in GDM.

Methods: The study population consisted of 76 GDM women assigned to BIAsp 30 (group A) and an equal number to BHI 30 (group B).

Results: There was no statistically significant difference between the age, BMI, gestational weeks and glycemic level at entry between the group A and group B women ($p > 0.05$). There was no statistical difference between the two groups in glycemic control or insulin dose ($p > 0.05$) before confinement. The frequency of birth weight of new born above 90th percentile was 6.8% in Group 1 and 9.2% in Group 2. The proportion of macrosomia was higher in Group 2 when compared to Group 1, however the difference was not statistically significant ($P=0.819$).

Conclusion: BIAsp was safe during pregnancy and pregnant women found it convenient due to meal time dosing. Fetal outcome using BIAsp was also comparable with BHI 30.

Introduction

Gestational Diabetes Mellitus (GDM) is defined as carbohydrate intolerance developing or recognized during pregnancy. Women with the history of GDM are at the increased risk of future diabetes, predominantly type 2 diabetes as are their children.¹ The association of birth weight and diabetes appears to be U shaped, with the highest prevalence of diabetes occurring in both high and low-birth weight infants.² Hence, the goal in the management of GDM is to have newborn infants with birth weight appropriate for gestational age and this is possible by maintaining the mean plasma glucose of 95 ± 5 mg/dl, with range of 87-104 mg/dl.³ GDM women who fail to achieve acceptable glycemic control with Medical Nutrition Therapy (MNT) are advised human insulin. In many instances, short acting human insulin fails to control post prandial peak plasma glucose due to its pharmacokinetic profile of reaching peak concentration two to four hours after the subcutaneous injection. Whereas, the rapid acting analogue is able to blunt the peak post prandial glucose level due to its faster peak insulin concentration that occurs in about one hour after administration. But, the shortcoming with the rapid acting analogue is that it has to be administered with every meal along with basal insulin, resulting in a number of injections which a pregnant woman does not prefer. To overcome this barrier we tried to use the biphasic insulin aspart (BIAsp) which has 30% of rapid acting component aspart and 70% of

long acting component which is protamine crystallized insulin aspart. BIAsp given in the morning controls post breakfast and post lunch. Similarly administration in the evening is able to control post-dinner and fasting plasma glucose as well, with a lesser number of injections per day. This action profile prompted us to undertake a study to evaluate the efficacy, safety and fetal outcome in GDM women on BIAsp in comparison to premixed human insulin 30 (BHI 30) (30% short acting and 70% intermediate acting human insulin), which is predominantly used in our clinical practice.

Methods

We obtained the ethics committee clearance for recommending BIAsp to the pregnant women. Women with a history of pregestational diabetes were excluded from the study. After obtaining informed consent, a total of 1324 pregnant women in the gestational weeks of 20-24 weeks were given a 75 g of glucose load in the fasting state and intravenous blood sample was collected at 2 hrs. Diagnosis of GDM was made if the 2 hr post glucose (PG) was ≥ 140 mg/dl (WHO criteria).⁴ The plasma glucose was estimated by the Glucose oxidase peroxidase (GOD POD) method in the central laboratory using Hitachi auto-analyzer. A1c was estimated in all of them using High Pressure Liquid Chromatography (HPLC, Biorad). All of them underwent routine clinical examination. GDM was diagnosed in 195 pregnant women and they were advised MNT for two weeks. Among them, 152 GDM women who failed to respond to MNT by not maintaining a $FPG \leq 90$ mg/dl and $2hr PG \leq 120$ mg/dl were randomly assigned to receive either BIAsp 30 or BHI 30.

GDM women in Group A were initiated on 6 units of BIAsp before breakfast and similarly Group B women on the same dose of 6 units BHI 30. They were instructed on self monitoring of blood glucose (SMBG) using Accucheck active. A personal glucometer was dispensed to them and were asked to perform

¹Consultant Diabetologist, Dr. V. Seshiah Diabetes Research Institute, Dr Balaji Diabetes Care Centre, Chennai 600029, Tamilnadu, India;

²Prof. of Obstetrics and Gynecology, Madras Medical College and Director, Institute of Obstetrics and Gynecology, Chennai, Tamilnadu, India;

³Associate Consultant, Dr. V. Seshiah Diabetes Research Institute, Dr Balaji Diabetes Care Centre, Chennai 600029, Tamilnadu, India;

⁴Chairman, Dr. V. Seshiah Diabetes Research Institute, Dr Balaji Diabetes Care Centre, Chennai 600029, Tamilnadu, India

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Table 1 : Subject Demographics

	Group A Treated with BIAsp N = 76	Group B Treated with BHI 30 N = 76	P value
AGE (years)	28.92 ± 3.59	29.38 ± 4.64	> 0.05
BMI	27.18 ± 3.87	26.34 ± 4.02	> 0.05
Gestational Weeks At entry	22.75 ± 8.83	22.64 ± 9.23	> 0.05
FPG (mg/dl)	102.97 ± 18.67	103.58 ± 20.25	> 0.05
2 hr PG (mg/dl)	166.0 ± 36.81	163.83 ± 42.66	> 0.05
A1c (%)	6.10 ± 0.45	6.12 ± 0.72	> 0.05
Before Confinement			
A1c (%)	5.98 ± 0.52	6.04 ± 0.61	> 0.05
Insulin Requirement (IU/L)	17.20 ± 18.66	20.55 ± 20.92	> 0.05
Fetal Outcome			
Birth weight ≥ 90 th percentile	6.8%	9.2%	> 0.05

SMBG before and 2hr after each main meal. Subjects were contacted telephonically and based on their SMBG readings, insulin dose was titrated. In addition to SMBG, pregnant women visited the ante natal clinic every month for their routine check up. Ultimately all of them required twice a day administration of insulin to achieve FPG≤90mg/dl and 2hr PG≤120mg/dl.⁵

Subjects were asked to record hypoglycemic episodes if any. Maternal hypoglycemia is defined as an episode with symptoms consistent with hypoglycemia accompanied by plasma glucose measuring ≤70mg/dl and which was handled by the subject herself or any asymptomatic plasma glucose measurement ≤70mg/dl.⁶ Adverse events if any were recorded. At each clinic visit, vital signs and weight were recorded. All of them were followed throughout pregnancy till confinement. A1c was estimated before confinement and the pregnancy outcome details were recorded. Fetal macrosomia was defined as birth weight ≥90th percentile. The two groups were compared with regard to insulin requirement and the fetal outcome.

Statistical analysis: To compare the mean values between the groups, independent 't' test was used. Analysis was two tailed and p-value <0.05 was considered statistically significant. Statistical analysis was performed by using SPSS Version 10 package.

Results

Out of the total 152 women, who consented for the study, 76 GDM women were assigned to BIAsp 30 (group A) and an equal number on BHI 30 (group B) (Table 1). There was 100% compliance and follow up data was available for all of them. The mean age of the women in group A and group B were 28.92±3.59 and 29.38±4.64 years, respectively. The mean BMI of the group A women was 27.18±3.87 kg/m² whereas that of group B women was 26.34±4.02 kg/m². The mean gestational weeks at entry in group A and group B women were 22.75±8.83 and 22.64±9.23, respectively. There was no statistically significant difference between the age, BMI and gestational weeks of the group A and group B women (p>0.05).

The mean FPG and 2hr PG of group A women at entry were 102.97±18.67 mg/dl and 166.0±36.81 mg/dl, respectively. In group B, the mean FPG at entry was 103.58±20.25 mg/dl and 2hr PG was 163.83±42.66 mg/dl. The mean A1c at entry in group A and group B women were 6.10±0.45% and 6.12±0.72%,

respectively. There was no statistically significant difference in the glycemic level at entry between the two groups (p>0.05).

The A1c level of group A and group B women before confinement were 5.98±0.52% and 6.04±0.61%, respectively. The dosage of insulin required by the women in group A was 17.20±18.66 IU and that of group B was 20.55±20.92 IU. There was no statistical difference between the two groups in glycemic control or insulin dose (p>0.05). No maternal hypoglycemic episodes were observed. There were no adverse perinatal outcomes recorded.

The frequency of birth weight of new born above 90th percentile was 6.8% in group A and 9.2% in group B. The proportion of macrosomia was higher in group B when compared to group A, however the difference was not statistically significant (p=0.819)

Discussion

The risk of macrosomia increases as maternal glycemia rises, particularly with elevated post prandial glucose concentration.⁷ During normal pregnancy, the peak plasma glucose occurs one hour after a meal and never crosses 120mg/dl and as such the therapy has to be tailored to meet this criterion.⁸ The short acting human insulin fails to achieve the acceptable level of glycemic control due to its pharmacokinetic property. Soluble human insulin which is in hexamer form takes more than one hour to dissociate into monomeric form and the peak insulin action is delayed. Due to this insulin kinetics, early post prandial hyperglycemia and the risk of hypoglycemia before the next meal occurs. Pregnant women can overcome this discrepancy of "food and insulin mismatch" by taking the insulin 30-40 minutes before a meal. This recommendation may pose a problem in a few of them who have unpredictable timing, size and content of the meal. Pregnant women at times may not consume adequate food after taking the insulin dose. This could result in hypoglycemia before the next meal which is hazardous to pregnant women. The rapid acting insulin analogues are ideal for pregnant women who may have erratic eating habits. Rapid acting analogue allows more flexible meal-time dosing but results in a number of injections with meals and also the need for basal insulin. This multiple dosing can be obviated possibly by biphasic insulin preparations, either BHI or BIAsp.

BHI's may reduce the number of injections per day, but soluble insulin and isophane insulin components of BHI fail to recreate physiological insulin profile resulting in unacceptable glycemic excursions due to their pharmacokinetic actions. Whereas the BIAsp which has 30% rapid acting insulin analogue with 70% protamine crystallized insulin aspart provides physiological replacement by both meal related and basal insulin release. Though we expected BIAsp group to fare better in terms of glycemic control, this was not evident from this study as there was no statistically significant difference between the two groups in the A1c levels.

The risk of macrosomia increases with increased maternal post prandial glucose levels.⁸ We anticipated that the rate of macrosomia would be less with analogues than with human insulin, but we didn't observe in this study any statistical significance in the birth weight between these two groups. Hod et al also observed that the fetal outcome with insulin aspart was comparable with human insulin.⁹

Conclusions

A significant clinical observation in this study was, the pregnant women found BIAsp convenient as this preparation

allows flexibility in the meal time insulin dosing and did not disturb their routine life pattern. Most importantly, BIAsp was found to be safe during pregnancy. Possibly, ours is the first study to use BIAsp in GDM. We suggest further studies may be performed using BIAsp during pregnancy.

Competing Interests: "None to declare"

References

1. Dornhorst A, Rossi M. Risk and prevention of type 2 diabetes in women with gestational diabetes. *Diabetes Care* 1998; 21 Suppl 2: B43-9
2. McCance DR, Pettitt DJ, Hanson RL, Jacobsson LT, Knowler WC, Bennett PH. Birth weight and non-insulin dependent diabetes: thrifty genotype, thrifty phenotype, or surviving small baby genotype? *BMJ* 1994; 308: 942-5.
3. Langer O, Levy J, Brustman L, Anyaegbunam A, Merkatz R, Divon MY. Glycemic control in gestational diabetic mellitus: how tight is tight enough: small for gestational age versus large for gestational age? *Am J Obstet Gynecol* 1989; 161: 646-653.
4. WHO study group prevention of diabetes mellitus - Geneva. World health Org (Tech Report Series 844), 1994.
5. Schaefer-Graf UM, Kjos SL, Kilavuz O, Plagemann A, Brauer M, Dudenhausen JW et al. Determinants of fetal growth at different periods of pregnancies complicated by gestational diabetes mellitus or impaired glucose tolerance. *Diabetes Care* 2003; 26: 193-8.
6. American Diabetes Association, Workgroup on hypoglycemia: Defining and reporting hypoglycemia in diabetes. A report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care* 2005; 28: 1245-1249.
7. Jovanovic-Peterson L, Peterson CM, Reed GF, Metzger BE, Mills JL, Knopp RH, et al. Maternal postprandial glucose levels and infant birth weight: the Diabetes in Early Pregnancy Study. The National Institute of Child Health and Human Development-Diabetes in Early Pregnancy Study. *Am J Obstet Gynecol* 1991; 1213 164(1 Pt 1): 103-11.
8. Jovanovic L. What is so bad about a big baby? *Diabetes Care* 2001; 24: 1317-8.
9. Hod M, Damm P, Kaaja R, Visser G, Dunne F, Demidova I et al. Insulin Aspart Pregnancy Study Group. Fetal and perinatal outcomes in type 1 diabetes pregnancy: a 24 randomized study comparing insulin aspart with human insulin in 322 subjects. *Am J Obstet Gynecol* 2008; 198: 186.e1-7. 29.