

Oral Hypoglycemic Glibenclamide: Can it be a Substitute to Insulin in the Management of Gestational Diabetes Mellitus? A Comparative Study

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ABSTRACT

Introduction: Gestational diabetes is a common medical disorder in pregnancy. So long, it has been usually treated by insulin. Now it has been found that oral glibenclamide can be used instead of insulin with similar glycemic control and without any adverse maternal and fetal effect.

Methods: A comparative study between oral glibenclamide and insulin for the management of gestational diabetes mellitus (GDM) was conducted. It was a prospective randomized study and patients attending the antenatal clinic were screened with 75 gm oral glucose between 20 to 28 weeks and GDM was diagnosed based on WHO criteria of 2 hours blood glucose ≥ 140 mg/dl. Women with gestational diabetes were given medical nutritional therapy (MNT) for 2 weeks. Out of this, 60 women did not achieve the target blood glucose. The goal of treatment was maintenance of mean plasma glucose (MPG) of about 105 mg%. For this the fasting plasma glucose should be around 90 mg/dl and postprandial peaks around 120 mg/dl. Patients were randomly assigned to receive glibenclamide (group A, n = 30) or insulin (group B, n = 30). In group A, glibenclamide was given 2.5 mg orally in morning and doses were increased weekly by 2.5 mg up to a maximum of 20 mg and doses >7.5 mg were given in two divided doses. In group B, insulin 0.7 units per kilogram of body weight at admission was given subcutaneously three times daily and increased weekly as necessary. Self monitoring of blood glucose with glucometer was done. Blood glucose was also measured from the laboratory every week. Glycosylated hemoglobin (HbA1c) was measured before initiation of therapy and repeated in the third trimester before confinement. Terminations of pregnancy in both the groups were done between 37 and 38 weeks. The infant birth weight, blood glucose and serum bilirubin were also recorded in all cases.

Results: The present study showed that the two groups had similar glycemic status (fasting blood sugar in group A was 103.5 ± 14.62 mg/dl and postprandial blood sugar was 184.1 ± 20.46 mg/dl whereas in group B it was 109.3 ± 19.63 mg/dl and 194.3 ± 18.47 mg/dl) at the time of entry into the study. The two groups also showed similar levels of glycemic control just before confinement (fasting blood sugar in group A was 88.23 ± 6.55 mg/dl and postprandial blood sugar was 122.7 ± 10.3 mg/dl whereas in group B it was $88.17 \pm$ mg/dl and 128 ± 12.38 mg/dl) and there was no significant statistical difference in the two groups ($p > 0.05$). The perinatal outcomes in both the groups were also nearly same. There was no significant difference in birth weight, blood sugar level of neonates and complications between the two groups. There was no case of macrosomia in the two groups and the number of infants large for gestational age (LGA) was four in group A and two in group B. Hypoglycemia in newborn was slightly higher in the group A compared to group B (4 and 3 respectively).

Conclusion: From our study, it is evident that the use of oral agents is a pragmatic alternative to insulin therapy in cases of

gestational diabetes because of similar glycemic control, ease of administration and better patient compliance due to noninvasive treatment.

Keywords: Gestational diabetes mellitus (GDM), Glibenclamide, Insulin, Glycemic, Hypoglycemia, Macrosomia.

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INTRODUCTION

Gestational diabetes mellitus is one of the most common medical complications of pregnancy and is associated with adverse maternal and fetal outcome. Gestational diabetes is increasing globally and India is not an exception. Study conducted by V Seshiah et al in 2004 concluded that there is an overall prevalence of 17.7% of gestational diabetes mellitus (GDM) in our country.¹ They also concluded that this high prevalence of GDM necessitates a universal screening for glucose intolerance in pregnancy in Indian women.² The principal approach to treatment of GDM is diet control with addition of insulin when diet alone is not sufficient. Over the years, insulin was the only option and oral hypoglycemic agents were avoided due to the fear of teratogenicity as well as fetal hyperinsulinemia and hypoglycemia. Insulin therapy is effective in achieving appropriate levels of glycemia, but it involves multiple daily injections and patient compliance is often suboptimal as women prefer to take tablets rather than multiple injections. The use of oral agents is a pragmatic alternative to insulin therapy because of easy administration and patient satisfaction due to noninvasive treatment. Glyburide (micronized form of glibenclamide) belonging to sulfonylurea group has been studied in many randomized control trials and has shown to achieve similar levels of glycemic control as insulin.³⁻⁵ It was also shown that this drug does not cross the placenta and hence can be safely administered in the second trimester of pregnancy as an alternative to insulin.⁶ Hence, we undertook a study to compare insulin and glibenclamide for treatment of GDM.

MATERIALS AND METHODS

The study was conducted at Department of Gynecology and Obstetrics, Medical College and Hospital, Kolkata, from 1st January 2010 to 31st December 2010, after taking clearance

from ethical committee. It was a prospective randomized study. Patients attending the antenatal clinic were screened with 75 gm oral glucose between 20 and 28 weeks and GDM was diagnosed based on WHO criteria of 2 hours blood glucose ≥ 140 mg/dl.⁷ In all cases, written informed consent was taken and a thorough history, clinical and sonological examinations were done. Women with pregestational diabetes, severe anemia, heart diseases, renal disorders and women on steroids were excluded from the study. Glycosylated hemoglobin (HbA1c) was measured before initiation of therapy and repeated in the third trimester before confinement. The prepregnancy body mass index (BMI) was also calculated. Women with singleton pregnancy and gestational diabetes (based on above criteria) were enrolled in the study. They were then given medical nutritional therapy (MNT) for 2 weeks. All women were provided standard nutritional instructions for three meals and three snacks. The diets were designed to provide 25 kcal per kilogram of body weight for the obese women and 35 kcal per kilogram for the nonobese women, with 40 to 45 percent of the calories from carbohydrates.⁸ Out of this, 60 women did not achieve the target blood glucose. The goal of treatment was maintenance of mean plasma glucose (MPG) level of about 105 mg%. For this the fasting plasma glucose should be around 90 mg/dl and postprandial peaks around 120 mg/dl. Patients were randomly assigned to receive glibenclamide (group A, n = 30) or insulin (group B, n = 30). Randomization was done using a table of random numbers. In group A, the starting dose of glibenclamide was 2.5 mg orally in the morning and when indicated doses were increased weekly by 2.5 mg up to a maximum of 20 mg and doses >7.5 mg were given in two divided doses. It was proposed that if the blood glucose values of a woman treated with the maximal dose of glibenclamide did not meet the goals for a two-week period, her treatment would be switched on to insulin therapy. In group B, the starting dose of insulin was 0.7 units per kilogram of actual body weight at admission, given subcutaneously three times daily and increased weekly as necessary. The women were instructed to measure blood glucose with a glucometer seven times daily: after an overnight fast, before meals, two hours after meals and at bedtime. Blood glucose was also measured from the laboratory every week. Terminations of pregnancy in both the groups were done between 37 and 38 weeks. The infant's birth weight (weight more than 90th percentile was considered large for gestational age while those more than 4 kg was considered macrosomia), blood glucose (capillary blood by glucometer) immediately after delivery and 1 hour after birth (a cut-off of 44 mg/dl was taken to define neonatal hypoglycemia) and serum bilirubin (when baby developed clinical jaundice) were recorded in all cases. All babies were followed by the neonatal team for development of any complications for 7 days. Data collected were analyzed using standard statistical protocol (the student's t-test was used to compare the numerical data between the two groups).

OBSERVATIONS

A total of 60 women with GDM were randomly divided into two groups: Group A (n = 30, received glibenclamide) and

Table 1: Characteristics of the patients selected

Demographics	Group A (n = 30)	Group B (n = 30)
Age (years)	26.3 \pm 4.6	26 \pm 4.3
BMI (kg/m ²)	23.7 \pm 2.7	23 \pm 2.9
Gestational age at entry (weeks)	28.3 \pm 2.2	27.4 \pm 2.7

Group A: Glibenclamide group; Group B: Insulin group

group B (n = 30, received insulin). The two groups were similar in terms of mean age, BMI and gestational age at the initiation of treatment (Table 1). The present study showed that the two groups had similar glycemic status (fasting blood sugar in group A was 103.5 \pm 14.62 mg/dl and postprandial blood sugar was 184.1 \pm 20.46 mg/dl whereas in group B it was 109.3 \pm 19.63 mg/dl and 194.3 \pm 18.47 mg/dl) at the time of entry into the study (Table 2). There was no statistical difference in the two groups in their screening blood glucose ($p > 0.05$). The two groups also showed similar levels of glycemic control (fasting blood sugar in group A was 88.23 \pm 6.55 mg/dl and postprandial blood sugar was 122.7 \pm 10.3 mg/dl whereas in group B it was 88.17 mg/dl and 128 \pm 12.38 mg/dl) before confinement (Table 3). Glycosylated hemoglobin at the time of entry into the study (HbA1c in group A was 6.25 \pm 0.60% and in group B was 6.46 \pm 0.77%) and before confinement (HbA1c in group A was 6.08 \pm 0.55% and in group B was 6.24 \pm 0.57%) was also similar in both groups with no significant statistical difference ($p > 0.05$) between the two groups. Group B receiving insulin required more frequent dose titration compared to group A receiving glibenclamide. There were no documented episodes of hypoglycemia in the two groups; however, two patients in the glibenclamide group had occasional symptoms suggestive of hypoglycemia in the morning before breakfast. The majority of the patients in the two groups had delivered by elective cesarian section at 37 to 38 weeks. The perinatal outcomes in both the groups were also nearly same. There was no significant difference in birth weight, blood sugar and complications between the two groups (Table 4). There was no case of macrosomia in both groups and the number of infants large for gestational age (LGA) was four in group A and two in group B. It was found that these LGA infants were born to those women who initiated their treatment late at 30 to 33 weeks. Hypoglycemia in newborn was slightly higher in the group A compared to group B (4 and 3 respectively, Table 4). Two infants in the group A had hyperbilirubinemia requiring phototherapy. One infant in the group A had congenital anomaly in the form of spina bifida occulta. There was one incident of sudden intrauterine fetal death in the group B. One infant in group B was admitted in NICU due to acute respiratory distress syndrome (ARDS).

DISCUSSION

The present clinical study was done to compare insulin and glibenclamide for treatment of GDM. In our study 60 women with GDM were divided into two groups—group A (n = 30,

Table 2: Glycemic status at the time of entry

Variables	Group A (n = 30)	Group B (n = 30)	p-value
Fasting blood sugar	103.5 ± 14.62	109.3 ± 19.63	0.199
Postprandial blood sugar after 75 gm glucose	184.1 ± 20.46	194.3 ± 18.47	0.048
Glycosylated hemoglobin (%)	6.25 ± 0.60	6.46 ± 0.77	0.2435

Group A: Glibenclamide group; Group B: Insulin group

Table 3: Glycemic status before confinement

Variables	Group A (n = 30)	Group B (n = 30)	p-value
Fasting blood sugar	88.23 ± 6.55	88.17 ± 8.44	0.97
Postprandial blood sugar after 75 gm glucose	122.7 ± 10.3	128. ± 12.38	0.07
Glycosylated hemoglobin (%)	6.08 ± 0.55	6.24 ± 0.57	0.26

Group A: Glibenclamide group; Group B: Insulin group

Table 4: Neonatal outcome

Variables	Group A (n = 30)	Group B (n = 30)	p-value
Gestational age at birth (weeks)	37.05 ± 1.1	37.2 ± 1.38	0.60
Birth weight (kg)	3.01 ± 0.40	2.98 ± 0.39	0.76
Neonatal blood glucose (mg/dl)	74 ± 20	69.8 ± 14.8	0.19
Large for gestational age	4	2	
Hypoglycemia	4	3	

Group A: Glibenclamide group; Group B: Insulin group

received glibenclamide) and group B (n = 30, received insulin). The two groups had similar glycemic status (fasting blood sugar in group A was 103.5 ± 14.62 mg/dl and postprandial blood sugar was 184.1 ± 20.46 mg/dl, whereas in group B, it was 109.3 ± 19.63 mg/dl and 194.3 ± 18.47 mg/dl) at the time of entry into the study. The fasting blood sugar (FBS) in group A (treated with glibenclamide) just before confinement was 88.23 ± 6.55 mg/dl and postprandial blood sugar (PPBS) after 75 gm oral glucose was 122.7 ± 10.3 mg/dl whereas in group B (treated with insulin) it was 88.17 ± 8.44 mg/dl and 128 ± 12.38 mg/dl. Therefore, the two groups showed similar levels of glycemic control before confinement with no significant statistical difference (p > 0.05) between the two groups. This study showed that the glycemic control in GDM treated with insulin and glibenclamide was essentially the same. Similar findings were also reported by Langer O et al 2004.³ Glyburide (micronized form of glibenclamide) has been studied in many randomized control trials and has shown to achieve similar levels of glycemic control as insulin.³⁻⁵ The perinatal outcomes in both the groups were also nearly same. There was no significant difference in birth weight, blood sugar and complications between the two groups. There was no case of macrosomia in the two groups and the number of infants large for gestational age (LGA) was four in group A and two in group B. Hypoglycemia in newborn was slightly higher in the group A compared to group B (4 and 3 respectively). A cost analytic study conducted by L Goetzl et al, comparing glyburide and insulin in treatment of GDM showed an average cost saving per pregnant women of US\$ 165.84 in favor of glyburide.⁹ A cost analysis was not done in our study as both the drugs were freely available through government supply.

CONCLUSION

From our study, it is evident that the use of oral glibenclamide for the treatment of gestational diabetes is an alternative to insulin therapy because of similar glycemic control, ease of administration and better patient compliance due to noninvasive treatment.

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