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Article

STUDY OF THE COMPARISON OF EFFICACY OF GLIBENCLAMIDE AND INSULIN IN THE GESTATIONAL DIABETES MELLITUS TREATMENT

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Abstract:

Gestational diabetes mellitus is an important medical condition that is predisposing to treatment that greatly improves maternal and neonatal morbidities. The gold standard for the GDM management is Insulin, but it has many disadvantages in terms of patient acceptance and appropriateness. Oral hypoglycemic agents can revolutionize the treatment of GDM if they are proven safe.

Objective: *The aim of this study was to compare the glibenclamide and insulin efficacy in the management of GDM and to analyze neonatal and maternal outcomes.*

Study Design: *A prospective observational study.*

Place and Duration: *In the Obstetrics and Gynecology department of Holy Family Hospital, Rawalpindi for one year duration from October 2017 to October 2018.*

Methods: *We recruited 100 antenatal GDM diagnosed patients according to given criteria and were randomly assigned to 50 study groups. The insulin was given in Group A and glibenclamide in group B up to a maximum of 20 mg daily. In patients BSR were recorded and were monitored until birth and outcomes of neonates were also analyzed.*

Results: *After 7 days of treatment, in A 72% group and in 68% of group B the target blood glucose level was achieved and this variation was not different statistically. Prior to delivery, BSR in Group A improved in 88% and in Group B 86%. The decrease in fasting blood glucose levels was statistically significant in glibenclamide group before delivery. The neonatal and maternal morbidity incidence in both groups was comparable. 8% of patients failed with glibenclamide treatment and started using insulin.*

Conclusion: *In GDM, glibenclamide supposed to be an effective treatment agent with neonatal and maternal outcomes as compared to insulin. Further analysis is required before considered glibenclamide is granted as effective alternative to insulin.*

Key words: *Insulin, Target blood glucose levels, Glibenclamide, Gestational diabetes mellitus, neonatal and maternal morbidity.*

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INTRODUCTION:

Gestational diabetes mellitus (GDM) is a common disease among pregnant women in our country. Its incidence increases and effective control of blood glucose levels helps to reduce neonatal and maternal morbidities to a great extent[1-2]. For management of GDM Insulin was the gold standard due to its efficacy and safety as it did not pass through the placenta. Oral hypoglycemic agents have many advantages over insulin, given the acceptance and appropriateness of the patient[3]. Until recently, oral hypoglycemic agents have not been used during pregnancy in the treatment of GDM due to concerns about safety and efficacy in pregnancy[4]. A randomized controlled trial published in 2000 demonstrated that glibenclamide is a safe as compared to insulin in the GDM treatment[5]. Before the study of 404 patients of Langer, the glycburide did not show transplacental migration prior to the placenta perfusion study. Since 2000, numerous Level 1 and Level 2 evidence studies have shown similar results[6]. 80% of GDM patients were treated with glibenclamide, and glycemic control was provided without risk for mother and baby[7]. This is a big step forward for primary obstetric care providers. The option of treating GDM with oral medication is a wonderful development that makes a great contribution to optimizing the blood sugar levels of these patients even in low resource settings.

MATERIALS AND METHODS:

This prospective observational study was held in the Obstetrics and Gynecology department of Holy Family Hospital, Rawalpindi for one-year duration from October 2017 to October 2018.

Women included between 20 and 40 years of age and had a single pregnancy between 24 and 34 weeks of age. We have excluded women with diabetes or other medical disorders before pregnancy. Women included who were meeting the inclusion criteria i.e 24-28 years age. For gestational weeks, a 1-hour 50 gm oral glucose test was used for GDM. After glucose testing, women with plasma glucose concentrations between 140 and 200 mg / dl were subjected to a 100 g oral glucose tolerance test. 1 hour after plasma glucose concentration, 50 g oral glucose loading test greater than 200 mg / dl or 100 g tolerance test value of two or more were diagnosed in GDM Carpenter and Coustan1 in oral glucose (fasting 95 mg / dl, 1 hour 180 mg / dl, 2 hours at 155 mg / dl and 3 hours at 140 mg / dl were abnormal. At the time of diagnosis, women were offered three meals a day and four meals a day, suggesting 40 to 45% of calories containing carbohydrates. They were also recommended to take a 20-minute walk a day. After 2 weeks of dietary treatment, capillary glucose monitoring was obtained. The failure of dietary therapy was defined as FBS greater than 90 mg / dl and 2 h PPBS higher than 120 mg / dl. These patients were exposed to two arms. Women in the insulin arm were identified as Group A and glibenclamide groups as Group B. Glibenclamide started with a daily dose of 2.5 mg and was then increased to a maximum of 20 mg per day at a dose of 10 mg. An increase in the glibenclamide dose was recommended when capillary blood glucose levels increased above the desired levels (FBS> 90 mg / dL and RBS> 120 mg / dL). Glibenclamide insufficiency was defined as capillary blood glucose levels above the desired range at the maximum dose for 1 week. If glibenclamide insufficiency was detected, treatment was discontinued and patients were switched to insulin. Demographic data, relevant medical and obstetric history, weekly glucose values, and birth and neonatal outcomes were recorded in a data sheet. Fetal monitoring started with the number of fetal movements per week at 28 weeks. No stress test or amniotic fluid index was applied in 34 weeks. All patients were routinely examined for 30 to 32 weeks of gestation and again for 36 to 38 weeks of gestation, mostly with an ultrasound to evaluate macrosomia and polyhydramnios. When blood glucose levels were taken under control, patients were allowed to give birth sooner or 40 weeks if there were any complications. Newborn results were analyzed; macrosomia (birth weight> 4 kg) was defined as positive pressure ventilation for the first time, which required ventilatory support for at least 4 hours with respiratory distress (supplemental oxygen or sustained positive airway pressure.) 24 hours after birth, neonatal hypoglycemia (blood glucose level <40 mg / dl), hyperbilirubinemia (serum bilirubini> 12 mg / dl), preterm delivery (<37 weeks of gestation), hypocalcemia (serum calcium <7 mg / dl and hypomagnesemia (serum magnesium level <1.5 mg / dl) Data were summarized as frequencies or percentages for categorical variables, tools for continuous variables and standard deviations and interquartile values for distributions using c-square variables for categorical variables and using t-test for two samples for variables. SPSS was used to exclude a significant difference in both groups.

RESULTS:

Table 1 shows the age distribution of the opposition in the study in both groups. The mean age in Group A was 27.86 (SD +/- 3.58), while in Group B it was 28.22 (SD +/- 3.12).

Table 1

Age Distribution		
Age (Yrs)	Group A N=50 # of patients (%)	Group B N=50 # of patients (%)
<25	9 (18)	14(28)
25-30	33 (66)	29(58)
>30	8 (16)	7(14)

Table 2

BMI	GROUP A N = 50 # OF PATIENTS (%)	GROUP B N = 50 #OF PATIENTS (%)
18-24	12 (24)	8 (16)
25-30	23 (46)	30 (60)
> 30	15 (30)	12 (24)

Table 2 shows the BMI distribution of the population studied. The mean BMI was 28.04 +/- SD (3.34). The mean BMI was 28.28 (SD +/- 3.76) in Group A and 27.76 (SD +/- 3.99) in Group B. Table 3 shows the prevalence of Diabetes Mellitus in both groups in the family history (46% in Group A and 36% in Group B).

Table 3

FAMILY HISTORY of DM		
FAMILY HISTORY	GROUP A	GROUP B
	N =50	N =50
PRESENT	23 (46)	18 (36)
ABSENT	27 (54)	32 (64)

Table 4

HbA1c at recruitment		
HbA1c	Gp A N =50 # of pts	Gp B N =50 # of pts
<6	19 (38)	25 (50)
6.1-7	26 (52)	23 (46)
>7	5 (10)	2 (4)

Table 4 shows the HbA1C value at the time of recruitment. The mean HbA1C value in the study was 6.23 SD +/- (3.97). The mean HbA1C in Group A was 6.6 (SD +/- 5.57) and in Group B 6.1 (SD +/- 0.66). There was no statistical data. Significant difference between two groups found (p value 0.28)> 0.05.
Table 5 shows the number of patients who achieved controlled blood glucose levels in the first week of treatment. In Group A, control was 72% per week and 68% in Group B.

Table 5

Plasma glucose levels after starting treatment		
	Group A N=50 # of patients (%)	Group B N=50 # of patients (%)
Controlled	36(72)	34(68)
Uncontrolled	14(28)	16(32)

Table 6

Plasma glucose levels after start of treatment			
	GROUP A N=50 Mean (+/-SD)	GROUP B N=50 Mean (+/-SD)	p value
FBS	95.80 (17.48)	90.28 (13.21)	0.07
PPBS	123.1 (29.78)	122.52 (26.29)	0.91

Table 6 shows the mean fasting and postprandial blood glucose levels for 2 hours in both groups 1 week after starting treatment. The difference was not statistically significant. In both groups, the number of patients who can reach the pre-target target blood glucose levels is as follows (88% in Group A and 86% in Group B).
Table 7 shows the fasting before birth and the postpartum blood glucose level. The difference between the two groups was statistically significant in fasting blood glucose levels (p 0.002 value).

Table 7

Mean Blood Levels Before Delivery			
	GROUP A MEAN (+/-)	GROUP B MEAN(+/-)	P VALUE
FBS	89.26 (12.1)	82.58 (8.19)	0.002
PPBS	111.48 (12.1)	107.3 (13.90)	0.115

Table 8 compares the plasma glucose levels between the two groups. The difference between the two groups in decreasing the fasting blood glucose levels was only statistically significant.

Table 8

COMPARISON OF BLOOD LEVELS BTWN THE TWO GROUPS

Mean	Plasma Levels Before Treatment		P VALUE
	GROUP A	GROUP B	
FBS	106	105	0.65
PPBS	140	141	0.67

Table 8

Plasma Levels 1 Wk After Rx		P value
GROUP A	GROUP B	
95	90	0.078
123	122	0.918

Table 8

Plasma Levels Before Delivery		P VALUE
GROUP A	GROUP B	
89	82	0.002
111	107	0.115

Table 9 compares the gestational age at birth. There was no statistically significant difference between the two groups in terms of gestational age at the end of pregnancy (p value 0.73). 80% of the patients ended the pregnancy. 30% of the study population had a spontaneous study onset and 70% had labor induction.

Table 9

AGE AT DELIVERY		
GA IN WKS	GROUP A N =50	GROUP B
<34	2 (4)	1 (2)
34-37	7 (14)	9 (18)
>37	41(82)	40 (80)

Table 10

MATERNAL MORBIDITY		
OUTCOME	GROUP A	GROUP B
INFECTION	16(32)	12 (24)
PIH	4 (8)	2 (4)
OPER.DEL	21 (42)	16 (24)
PRETERM D	7 (14)	8 (16)
POLYHYDR	6(12)	2 (4)

Table 10 compares the different maternal morbidities between the two groups. Operational delivery is at the top of the list. Table 11 shows the mode of delivery between patients in two groups. 63% had vaginal delivery and 37% had surgical delivery.

Table 11

MODE OF DELIVERY	GROUP A # (%)	GROUP B # (%)
SVD	26 (52)	28 (56)
AVD	3 (6)	6 (12)
EL.LSCS	12(24)	9 (18)
EMER.LSCS	9 (18)	7(14)

Table 12

INDN. FOR LSCS	GROUP A # (%)	GROUP B # (%)
CPD	3 (6)	1 (2)
PREV.LSCS	10 (20)	8 (16)
FOETAL DISTRESS	4 (8)	5 (10)
PRECIOUS PREGNANCY	1 (2)	1 (2)
FAILED INDUCTION	2 (4)	0 (0)
MALPRESENTATION	1 (2)	0 (0)
OTHERS	0 (0)	1 (2)

Table 12 shows the indications of LSCS in both groups.

Table 13 compares the newborn results between the two groups. Hyperbilirubinemia, prematurity, and hypoglycemia were common morbidities. There was no statistically significant difference between the two groups according to the newborn results.

Table 13

NEONATAL OUTCOME	GROUP A	GROUP B	P VALUE
Preterm	9 (18)	10(20)	NIL
Macrosomia	4 (8)	1(2)	0.37
Hyperbilirubinemia	10 (20)	14(28)	1
Respiratory distress	2 (4)	3 (6)	1
Hypoglycemia	6 (12)	4 (8)	0.74
Hypocalcemia	1 (2)	0 (0)	NIL

Table 14

Birth Weight Distribution in two Groups		
Weight In KGS	Group A	Group B
<2.5	5 (10)	9(18)
2.6-3.5	31 (62)	32(64)
3.6-3.9	10 (20)	8(16)

Table 14 shows the distribution of birth weight between two groups in newborns. The mean birth weight was 3.1 kg in Group A and 2.9 kg in Group B. The difference in birth weight was not statistically significant (p value 0.35). The minimum and maximum insulin dose requirements in Group A were 4 IU / day and 30 IU / day, respectively, in glibenclamide 2.5 mg / day and 20 mg / day, respectively. The dose in Group B was as follows (2.5 mg-8%, 5 mg-6%, 7.5 mg-6%, 10 mg-44%, 15 mg-20%, 20 mg-16).

DISCUSSION:

Glucose intolerance during pregnancy can be variable. Early diagnosis, adequate treatment and follow-up are vital for the successful management of these patients[8-10]. The mean age of the population studied was 28.42 ± 4.48 years. When maternal age is more than 30 years old, there is an increase in the incidence of GDM[11]. It is associated with an increase in the incidence of GDM for more than 30 years. Multiparous women were more affected than primigravida in the study, but the association was not statistically significant. Family history of diabetes mellitus was present in 41% of patients. There was a significant relationship between the family history of diabetes and the onset of glucose intolerance in the current pregnancy. In a study by Abha et al[12]. the past history of GDM in previous pregnancies was the most common factor associated with glucose intolerance in subsequent pregnancies. In this study, both arms of the study population were similarly matched with age, parity, BMI, family history of DM, and gestational age at delivery[13]. Glibenclamide is a common oral hypoglycemic agent that is absorbed within 1 hour and peaks in about 4 hours. It has a half-life of 10 hours and is removed from the plasma in about 24 hours with continued anti-glycemic effects 24 hours after administration of a single dose. Glibenclamide does not significantly exceed placental barriers. There are several randomized controlled trials comparing insulin and glibenclamide. They were made in different countries and communities. Langer et al performed the study in the USA in 2000, after a 3-hour OGTT with 404 participants. In 2005, Bertini et al. Worked with 70 patients after 75 g WHO OGTT in Brazil. Anjalakshi et al performed the study in 2006 with 75 g WHO OGTT in India with 26 participants[14]. The trials also compared different treatment interventions. Langer et al., 404 patients with the largest RCT, fasting BSR between insulin or glibenclamide users or two hours of postprandial blood glucose levels reported that there was no statistically significant difference. A smaller RCT of Anjalakshi et al. Reported similar findings. Among the studies, there were differences in the age at the time of recruitment. In this study, 8% of patients had to switch to insulin to achieve blood glucose levels[15]. This was 4% of the study by Langer et al. Patients who started taking glibenclamide retained their desired blood sugar levels during their time. Those who failed with Glibenclamide treatment stated that fasting and postprandial blood glucose levels were significantly higher for 2 hours and

remained outside the desired levels during treatment. The mean duration of glibenclamide treatment was 6 to 8 weeks. This study also showed that glibenclamide treatment was much lower cost than insulin treatment. Glibenclamide is also better accepted by the patient because it is administered orally via insulin compared to parenteral administration.

CONCLUSION:

In GDM patients, an effective drug in the treatment is Glibenclamide with less neonatal and maternal morbidity and mortality comparable to insulin. However, in order to know the importance of glibenclamide as an insulin alternative in the treatment of women with Diabetes Mellitus, there is still a strong need for randomized clinical trials to address various problems, including long-term follow-up of gestational diabetes.

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