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Original Research

A randomized controlled trial comparing acarbose *vs.* insulin therapy for gestational diabetes in individuals with inadequate glycemic control by diet alone

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Summary

Introduction: Gestational diabetes (GD) is one of the most common medical complications of pregnancy, associated with increased incidence of pre-eclampsia, macrosomia, and cesarean delivery. Insulin therapy is the cornerstone treatment in those individuals with inadequate glycemic control by diet alone. The burden of insulin treatment includes the need for multiple injections, intensive blood glucose monitoring, risk of hypoglycemia, and emotional distress. Alternatives to insulin treatment have been studied in the past but there is limited previous experience with acarbose. *Objective:* To compare acarbose to insulin therapy and evaluate the proportion of subjects requiring rescue therapy with insulin due to inadequate glycemic control; as a secondary objective, pregnancy outcomes were assessed. *Materials and Methods:* Pregnant patients diagnosed with GD who failed glycemic control on dietetic treatment, were randomized to receive standard insulin therapy or acarbose. If the oral drug was not tolerated or glycemic goals were not met, standard insulin therapy was initiated. *Results:* A total of 104 patients were randomized (acarbose n = 40). Two patients in the acarbose group and six in the insulin group withdrew their consent before any study intervention due to personal preferences. In the acarbose group, 27/38 subjects (71%) achieved and maintained glycemic targets until delivery, while 11/38 (29%) received rescue insulin therapy and discontinued the study drug. No differences were found in birth weight, gestational age at birth, or Apgar score. Three patients in the acarbose and five in the insulin group presented perinatal complications. *Conclusion:* In this study, acarbose was found to be a safe and effective alternative to insulin therapy. Insulin therapy and its burden were avoided in over 70% of the GD patients failing nutritional therapy. Studies with a larger sample size and long-term follow-up are needed.

Key words: Gestational diabetes; Insulin treatment; Acarbose; Pregnancy outcomes.

Introduction

Gestational diabetes (GD) is one of the most common medical complications of pregnancy and it can increase the incidence of pre-eclampsia, macrosomia, and cesarean delivery [1, 2]. Depending on the criteria used to define GD and the population studied, its prevalence varies widely [3, 4]. It has been estimated that 75% to 90% of cases of hyperglycemia during pregnancy are due to GD [5]. Infants born to mothers with GD are at increased risk of fetal macrosomia, hypoglycemia, and hyperinsulinemia at birth, and shoulder dystocia associated with obstructed labor [6], while mothers are at increased risk of pre-eclampsia, gestational hypertension, cesarean section, and hydramnios [7].

Lifestyle changes are an essential component of GD treatment; when glycemic targets are not reached then conservative management pharmacotherapy is used. Insulin is the preferred medication for treating hyperglycemia in GD since it does not cross the placenta, and while metformin and glyburide, both agents crossing the placental barrier, have some safety data in GD, they lack long-term studies [8]. Acarbose, which reversibly inhibits α-glucosidases present in the brush-border of the small intestinal mucosae and is not significantly absorbed, may be an alternative to other oral agents since it can effectively treat postprandial hyperglycemia [9]. Limited evidence of its use in GD has been reported in a small study by Zarate *et al.* [10] in which six patients were treated in an open label, non-randomized, single arm trial, and despite its methodological flaws, subjects included in the study avoided the need for insulin therapy and had no major side effects, other than poor gastrointestinal tolerance, as described in non-pregnant patients treated with acarbose.

Accordingly, the present authors designed a randomized controlled trial comparing acarbose to insulin therapy in GD patients failing a two-week lifestyle intervention and aimed to evaluate the proportion of subjects requiring rescue therapy with insulin due to inadequate glycemic control while

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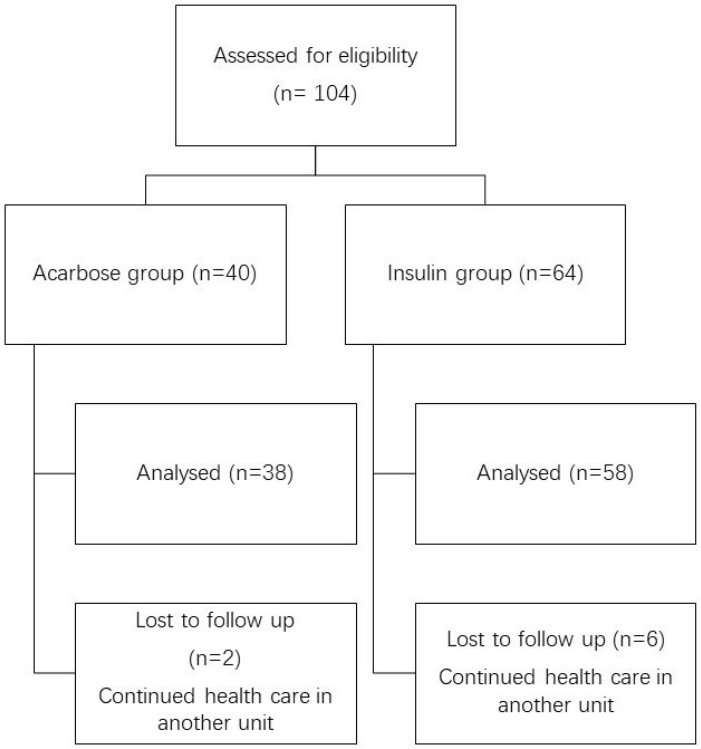

Figure 1. — Patient disposition.

exploring pregnancy outcomes as a secondary objective.

Materials and Methods

Ninety-six pregnant patients diagnosed with GD using the ADA protocol [11] and who failed a dietary intervention participated in this open-label, randomized control study. The diagnosis of GD was made if Carpenter and Coustan criteria were met (Figure 1) [12]. Patients with any concomitant chronic disease were not eligible to participate. The study protocol was approved by the institutional Research and Ethics Committees and each subject consented to participate in the study. Eligible patients were attending prenatal care at the outpatient obstetrics clinic in this University Hospital and were invited to participate once glycemic targets were not met (fasting glucose greater than or equal to 95 mg/dL or two hours postprandial greater or equal to 120 mg/dL) after at least two weeks on a standard dietary intervention (25-30 Kcal/kg, 50/20/30, low in simple carbohydrates).

After informed consent was obtained, the subjects were randomized by sealed envelopes to receive either standard insulin therapy (0.5 to 0.7 U/kg/day starting dose, titrated to target) or acarbose 25 mg TID starting dose, which could be increased up to 100 mg in 25 mg TID dose increments every two weeks, according to tolerance and goal reaching. If the oral drug was not tolerated or if despite reaching the maximum dose allowed in this protocol, glycemic goals were not met, the patient was initiated on insulin therapy and considered as treatment failure. A greater number of patients was decided in the insulin therapy group considering it as the gold standard treatment for GD. Data concerning the product and perinatal outcomes were obtained from the clinical chart, and patients discontinued the study intervention at the time of delivery.

Nominal variables are reported as proportions; continuous variables were tested for normal distribution using a Kolmogorov-Smirnov test. For normally distributed variables, mean and standard deviations are reported, for non-normally distributed variables, median, and interquartile ranges are reported. To compare groups, the appropriate independent group test is reported.

Results

A total of 104 patients were randomly assigned into two groups, the acarbose group (n = 40 patients) with a mean age of 30.68 years (SD 3.93 years) and a mean pre-pregnancy BMI of 32.6 (SD 5.56), and the second group managed with insulin (n = 64 patients), with a mean age of 30.85 years (SD 4.42 years) and a mean pre-pregnancy BMI of 31.45 (SD 5.54). Two patients in the acarbose group and six in the insulin group were randomized but withdrew their consent before any study intervention due to personal preferences.

Demographic characteristics are presented in Table 1. No significant differences were found regarding age, gestational age at randomization, BMI, family history of diabetes, previous GD, previous macrosomia, and blood glucose at baseline and at 60 minutes during the oral glucose tolerance test. A greater proportion of nulliparous patients

Table 1. — *Fasting blood glucose and OGTC results.*

Test	Acarbose	Insulin	*p*
Fasting blood glucose	167 ± 26.27 (131-241)	164 ± 29.57 (80-285)	> 0.05
Basal OGTC	112 ± 37.62 (77-258)	106 ± 35.14 (63-268)	> 0.05
1 hour OGTC	200 ± 34.43 (138-299)	195 ± 23.45 (163-289)	> 0.05
2 hour OGTC	186 ± 31.93 (130-274)	171 ± 25.37 (144-278)	0.019
3 hour OGTC	160 ± 24.96 (110-214)	142 ± 29.62 (88-277)	0.004

OGTC, oral glucose tolerance curve. N = 96 patients (38 patients in the acarbose group and 58 insulin treated patients).

Table 2. — *Perinatal outcomes.*

Variable	Acarbose	Insulin	*p*
Cesarean delivery %	55.26	48.27	> 0.05
Macrosomia %	14.15	15.51	> 0.05
Weight (g)	3301 ± 575.58	3489 ± 456.61	> 0.05
Height (cm)	49.65 ± 2.30	50.02 ± 2.45	> 0.05
Capurro (weeks)	38.93 ± 1.32	38.68 ± 0.95	> 0.05
APGAR (5')	8.26 ± 1.00	8.51 ± 1.20	> 0.05
APGAR (10')	8.92 ± 0.42	8.96 ± 0.32	> 0.05

All values are means ± standard deviation, unless otherwise noted. N = 96 patients (38 patients at acarbose group and 58 insulin treated patients).

was observed in the insulin group (13 *vs.* 29%) and the 120 and 180 minutes post-load blood glucose were higher in the acarbose group. In the acarbose group, 27/38 subjects (71%) achieved and maintained glycemic targets until delivery although 21 patients required an increase in dose, while 11/38 (29%) received rescue insulin therapy and discontinued the study drug. One patient reported poor drug tolerance presenting with gastrointestinal side effects and later discontinued the study drug due to a lack of efficacy. All the insulin treated subjects reached the glycemic targets.

No differences were found between the acarbose and insulin groups in birth weight (3301 grams [SD 575] *vs*. 3489 grams [SD 456], respectively), gestational age at birth by Capurro's method, length, and Apgar scores at one and five minutes (Table 2).

In the acarbose group, 3/38 cases had peripartum complications, one showed fetal distress, one patient had with severe preeclampsia, and acute kidney injury, and one delivery was complicated by shoulder dystocia. In the insulin treated group, 5/58 cases had peripartum complications, one showed fetal distress, two had severe preeclampsia, and two deliveries had shoulder dystocia associated with uterine atony.

Discussion

Zarate *et al.* [10] reported on six patients with GD treated with acarbose who achieved good glycemic control with no evidence of maternal or fetal complications. Based on this limited experience, the authors designed this randomized study to analyze the proportion of subjects who may be insulin free after failing standard medical nutritional therapy. In the present study group, more than two-thirds of the patients who failed an initial intervention with medical-nutritional therapy did not require insulin during follow-up while on acarbose therapy. Most of the acarbose-treated patients tolerated it and only one patient reported gastrointestinal side effects that were severe enough to stop the study drug.

Insulin therapy in GD can represent a significant burden for both the patient and the healthcare provider, mainly due to an increased use of medical resources, increased cost of therapy [13], an increase in hypoglycemia rates [14], the need of intensive blood glucose monitoring, and patient distress related to lack of knowledge and support [15]. Thus, simpler and safer alternatives, including acarbose, may help relieve the difficulties represented by GD. This study would need to be replicated in a blinded manner and it may serve as a basis to properly calculate the sample size to be included in a more definitive trial. Currently, in the clinicaltrials.gov website, a large, multicenter clinical trial on comparing prandial insulin and acarbose is registered; the clinical community is looking forward to its results. In the meantime, the present results provide reassurance on the safety and scientific background needed to promote the study of acarbose as a treatment option during GD.

Conclusion

In this study, acarbose was found to be a safe and effective alternative to insulin therapy. Insulin therapy and its burden were avoided in over 70% of the GD patients failing nutritional therapy. Studies with a larger sample size and long-term follow-up are needed.

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Conflict of Interest

The authors declare no conflict of interest.

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