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Effects of oral glibenclamide versus subcutaneous insulin on perinatal outcome of patients with gestational diabetes mellitus: A randomized clinical trial

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Abstract

Background: The first-line treatment for gestational diabetes mellitus remains insulin, but oral hypoglycemic agents are easier and cheaper to use. The aim of the current study was to compare the efficacy and safety of oral glibenclamide and subcutaneous insulin on the serum glucose control and perinatal outcome of patients with gestational diabetes mellitus.

Materials and methods: This randomized clinical trial was conducted during a 2-year period from 2017 to 2019 in two tertiary healthcare centers in Shiraz, Iran. We included 84 singleton pregnancies between 24 and 34 weeks of gestation diagnosed with gestational diabetes mellitus. Patients were randomly assigned to oral glibenclamide ($n = 44$) or subcutaneous insulin ($n = 40$) according to a standard protocol and followed until delivery. The primary endpoint was to compare the glycemic level of patients, and the secondary outcomes included pregnancy adverse events and neonatal complications such as preeclampsia, preterm and premature rupture of membranes, preterm labor, placental abruption, maternal hypoglycemia, birth weight, neonatal hypoglycemia, hyperbilirubinemia, respiratory distress syndrome, and neonatal intensive care unit admission.

Results: The two study groups had comparable baseline characteristics. After treatment, the two study groups were comparable regarding fasting blood glucose ($p = 0.398$) and 2 h postprandial glucose ($p = 0.085$). There was no significant difference between the two groups regarding the rate of preeclampsia ($p = 0.250$), preterm rupture of membranes ($p = 0.998$), preterm labor ($p = 0.495$), hypoglycemia ($p = 0.476$), and abruption ($p = 0.815$). There was no significant difference between the two study groups in birth weight ($p = 0.863$) and the Apgar score at 1 ($p = 0.190$) and 5 min ($p = 0.055$). The rates of neonatal adverse events including hypoglycemia ($p = 0.999$), hyperbilirubinemia ($p = 0.160$), neonatal intensive care unit admission ($p = 0.852$), and respiratory distress syndrome ($p = 0.665$) were comparable between the two groups.

Conclusion: The results of the current study demonstrate that oral glibenclamide is as effective and safe as subcutaneous insulin in glycemic control and maternal and neonatal outcomes in women with gestational diabetes mellitus. Thus, it could be used as first-line treatment of gestational diabetes mellitus.

Keywords

Insulin, glibenclamide, gestational diabetes mellitus, pregnancy, perinatal outcome

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Introduction

Gestational diabetes mellitus (GDM) is a common complication of pregnancy that is associated with adverse pregnancy outcomes.[1,2] The rate of the GDM is increasing worldwide and several lines of evidence have demonstrated that improving glycemic control during pregnancy is associated with improved neonatal outcomes as well as decreased maternal mortality and morbidity.[3–5] Uncontrolled blood glucose during pregnancy has been associated with increased rates of macrosomia, neonatal death, and delivery complications, and increased risk of diabetes mellitus in the neonate.[6] Thus, blood glucose control is recommended during pregnancy, especially during the third trimester.[7,8]

Insulin remains the first line of treatment in patients with GDM in many countries according to the American College of Obstetricians and Gynecologists and has been approved by the Food and Drug Administration (FDA).[9] However, insulin administration is associated with several disadvantages including high price, route of administration (several subcutaneous injections), and risk of hypoglycemic events due to inappropriate dosing. Thus, oral hypoglycemic agents come into consideration including metformin and glibenclamide.[10] Research during the past decade has been performed on the subject with inconclusive results.[11,12] Glibenclamide (glyburide) has been demonstrated to be more effective

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Table 3. Neonatal outcome of 84 singleton pregnancies with gestational diabetes mellitus in the two study groups.

	Glibenclamide ($n=44$)	Insulin ($n=40$)	p-value
Birth weight (g)	3400.45 ± 631.23	3377.50 ± 581.07	0.863
Apgar			
1-min	8.70 ± 0.82	8.32 ± 1.70	0.190
5-min	9.98 ± 0.15	9.72 ± 0.87	0.055
Umbilical cord pH	7.30 ± 0.65	7.31 ± 0.54	0.485
Ultrasonography			
Normal (%)	40 (90.9%)	38 (95.5%)	0.682
IUGR (%)	1 (2.3%)	1 (2.5%)	
AC > 97%	1 (2.3%)	0 (0.0%)	
Polyhydramnios (%)	1 (2.3%)	1 (2.5%)	
Oligohydramnios (%)	1 (2.3%)	0 (0.0%)	
Adverse events			
Hypoglycemia (%)	2 (4.5%)	2 (5.0%)	0.999
Hyperbilirubinemia (%)	7 (15.9%)	2 (5.0%)	0.160
Polycythemia (%)	0 (0.0%)	0 (0.0%)	–
Hypocalcemia (%)	0 (0.0%)	0 (0.0%)	–
NICU admission (%)	6 (13.6%)	5 (12.5%)	0.852
RDS (%)	2 (4.5%)	3 (7.5%)	0.665
Intubation (%)	0 (0.0%)	0 (0.0%)	–
Birth defects (%)	0 (0.0%)	0 (0.0%)	–
Mortality (%)	0 (0.0%)	0 (0.0%)	–

AC: abdominal circumference; IUGR: intrauterine growth retardation; NICU: neonatal intensive care unit; RDS: respiratory distress syndrome.

sensitivity. Metformin (metformin and combination therapy) demonstrated a larger decrease in MMTT peak glucose concentrations than subjects taking only glyburide. Taking all these together, they showed that glibenclamide was as effective as metformin in improving insulin sensitivity and better in glycemic control in pregnant women with GDM.[18] Contrary to these results, Balsells et al.[13] conducted a meta-analysis that included randomized clinical trials comparing glyburide and insulin in GDM. They demonstrated that in short term, in women with GDM requiring drug treatment, glibenclamide was clearly inferior to both insulin and metformin, while metformin (plus insulin when required) performed slightly better than insulin.[13]

In the current study, equal results were observed in the use of glibenclamide and insulin; this indicates that glibenclamide may be an effective and safe method for the treatment of GDM. However, Sénat et al.[17] compared glyburide with subcutaneous insulin in the prevention of perinatal complications in newborns of women with gestational diabetes. They demonstrated that the use of glibenclamide was associated with an increased rate of adverse neonatal outcomes; thus, they could not recommend glibenclamide for the treatment of GDM.[17] Another meta-analysis by Guo et al.[21] found that metformin could be a safe and effective treatment for GDM. Compared with insulin, glyburide had a higher increase in neonatal hypoglycemia. The use of glyburide in pregnancy for GDM women appeared to be unclear.[21]

In our study, the rate of neonatal complications was comparable between the two study groups, and there was no significant difference between them regarding neonatal adverse events. However, Sénat et al.[17] demonstrated that glibenclamide administration was associated with increased adverse pregnancy outcomes (27.6% vs. 23.4%). The rate of neonatal hypoglycemia in the glyburide group was 12.2%; this is the same magnitude as the 9% reported by Langer et al.[22] in their insulin group, but much lower than the 33% reported by Bertini et al.[23] and the 25% reported by Silva et al.[24] in their glyburide groups. A prospective cohort study revealed that the neonates were considered to be at risk of hypoglycemia, including 40% of neonates born to a mother with diabetes. It was shown that with an on-treatment blood glucose level threshold of 47 mg/dL (2.6 mmol/L), neonatal hypoglycemia was not associated with adverse neurodevelopmental outcomes at 2 years compared with neonates with normal glucose levels.[25]

We had some limitations in the current study. First, we included a limited number of patients in two study groups. Thus, the study might have been underpowered for subgroup analysis and cox regression analysis. However, in the power calculation, it was shown that the study had 80% power in primary and secondary endpoints. Complementary larger RCTs are required to add to the value of the current research. Second, we only recorded the main outcome measures and the neonatal and glycemic control. There are many variables that could be measured to help understand the pathophysiology including insulin resistance, serum levels of different hormones such as insulin, and growth hormones as well as other biometric variables. Further studies including all these variables could shed light on the mechanism of action in GDM and different treatment options. The last limitation was the lack of information on drug adverse events. We asked the patients to record all the adverse events related to glibenclamide and insulin therapy, but the patients did not do so appropriately. In addition, we did not record the price and expenses of each study arm. Thus, we could not comment on the expenses of each treatment option.

In conclusion, the results of the current randomized clinical trial demonstrated that in short term, in women with gestational diabetes mellitus requiring drug treatment, despite having a 5% failure rate of glibenclamide (indicating that it may not be as effective as insulin) and despite the probability of maternal hypoglycemia induced by glibenclamide, glibenclamide was associated with appropriate serum glucose control and comparable pregnancy and neonatal outcome. However, we have no long-term follow-up of offspring exposed to glibenclamide, so more RCTs are suggested to complement the results of the current study.

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Authors' contribution

Azam Faraji: Project development, Data Collection, Data analysis. Lida Tahamtani: Data Collection, Data analysis. Najmeh Maharlouei: Data analysis. Nasrin Asadi: Project development, Data collection, Data analysis, Manuscript writing/editing. All authors read the manuscript and approved it.

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