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Effect of minimally invasive insulin therapy on primary and secondary outcomes in gestational diabetic women.

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Abstract

Purpose: To find comparative beneficial treatment from either lispro insulin or minimally invasive lispro insulin therapy on primary and secondary outcomes in gestational diabetes mellitus (GDM) patients.
Methods: The present study was carried out on GDM patients enrolled in minimally invasive lispro insulin treatment group with hollow microneedle inserted 1 mm under skin and another group of lispro insulin therapy. In present study, 65 females with GDM enrolled for treatment with minimally invasive therapy at 8th-12th week after conception. Hospital Records of the past 10 years was used to abstract data for insulin treatment to GDM patients. Data of 100 GDM subjects treated with insulin therapy was included. The primary outcomes monitored include composite outcomes, hypoglycemia, respiratory distress, need of phototherapy and birth injury. Changes in blood glucose and complications in GDM patients were secondary outcomes.
Results: The primary endpoints in minimally invasive lispro insulin treatment group as compared to lispro insulin treatment GDM subjects were slightly ameliorated but statistically insignificant to find any conclusion. Minimally invasive insulin therapy results in lower neonatal composite complications as compared to insulin therapy but is not significant. The GDM hypertension and maternal glycemic control were significantly ameliorated in Group II than Group I.
Conclusion: The minimally invasive lispro insulin therapy significantly ameliorated secondary outcomes as compared to lispro insulin treatment in GDM subjects. Ironically, a primary outcome in GDM patients with minimally invasive lispro insulin therapy and lispro insulin treatment was statistically indifferent.

Keywords: Minimally invasive, Insulin, Outcomes and Gestational diabetes.

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Introduction

The Gestational diabetes mellitus (GDM) affects millions of patients globally in both developed as well as developing countries with the prevalence of 6% - 8%. The GDM was associated with prior occurrence of diabetes, obesity, lifestyle, and genetic factors [1-3]. Diabetes mellitus is a lifestyle related disorder in which blood glucose level and its regulation through insulin is affected [4].

The GDM affect the health outcome of pregnant mother and her fetus. In case of GDM patients, there might be changes in blood glucose before and during pregnancy resulting in induction of lifestyle related diabetes and hypertension. GDM patients might suffer from pre-existing diabetes [5-9]. GDM possibly affect not just -ve medical outcomes yet also mental-health status along with ancillary adverse outcomes on psychological wellbeing as well as Quality of Life (QoL). Pregnancy is a specific time for all the women. This state becomes much more frangible if there is GDM diagnosis that leads to needed controls as well as treatments which would have inevitable effect on women lives. GDM could lead to risks for mother, fetus, as well as child development, as well as clinically relevant -ve effects on maternal mental-health, primarily with regards to reduced QoL perinatal mortality risk is not raised yet macrosomia risk is. Further perinatal risks are hypoglycemia, birth injuries like nerve palsies and bone fractures, and shoulder dystocia. Longterm adverse health outcomes noted in infants of GDM mothers were sustained glucose tolerance impairment, future obesity (though not when size adjusted), and impairment of intellectual achievements [10,11].

Maternal alcohol and dietary fat intake resulted in insulin resistance in adult rat offspring. Pregnancy related adverse outcomes in GDM patients were independently associated with obesity and genetic risk [12,13]. Combination of obesity and genetic risk has more impact on outcomes than either risk factor alone. Macrosomia, hypoglycemia, emergency requirement of phototherapy, and discomfort in respiration, fetal death, birth injury, adjusted birth weight, preterm birth, labor pain, complications and caesarean delivery are primary and secondary outcomes seen in GDM patients and fetus [14].

GDM management consist special diet schedules and planned physical activity, daily blood glucose tests and insulin therapy. Subcutaneous insulin administration is established as delivery standard, although the method is inconvenient/painful and mostly lead to poor patient compliance. Recent advance is an intra-dermal insulin delivery owing to less invasive nature and faster onset of action (rich capillary bed in dermis might enable rapid drug uptake). However, there is a paucity of studies in such area [10,15-17]. The present study aimed at finding comparative beneficial treatment from either lispro insulin or minimally invasive lispro insulin therapy on primary and secondary outcomes in GDM patients.

Primary Outcomes (Related to neonates):

1. Composite outcome
2. Macrosomia
3. Need for phototherapy
4. Adjusted birth weight
5. Discomfort in respiration
6. Stillbirth or fetal death
7. Injury at birth
8. Preterm birth
9. Caesarean delivery
10. Complications of delivery
11. Secondary outcomes (Related to study subjects)
12. Weight gain
13. Hypoglycemia
14. Maternal glycaemic control (mmol/L)
15. Hypertension
16. Induction of labor

Materials and Methods

The investigation has been carried out at the people first hospital, Department of gynecology and obstetrics from January 2014 to August 2016. The written study plan and procedure was authenticated by human ethics committee of the hospital. (Protocol no. PFHZ-2014/12E-011). The study participants were informed about advantages and risks associated with present study in English and Chinese. The consent of participation was obtained from patient in front of family member and social worker as impartial witness. The patients have been informed about their right to withdraw from study whenever she feels uncomfortable. The personal details and medical history of patients kept in database with unique code. The study participants were randomized (random lottery approach) and stratified and divided into Group I and II. The inclusion and exclusion criteria for GDM were described in Table 1. The pregnant women at 8^{th}-12^{th} week of gestation were diagnosed for GDM with oral glucose tolerance level set at 130 mg per deciliter after administration of 100 g glucose with 8 h fasting. The blood glucose level measured after 45 min of glucose administration. National Diabetes Data Group (NDDG) diabetes guidelines for GDM have been followed for the study. Women found to have blood plasma glucose levels greater than 7.3 mmol/L were diagnosed as suffering from gestational diabetes. GDM patients were enrolled in minimally invasive lispro insulin treatment group with hollow microneedle (connected to a programmable syringe pump at 1mL/min rate of lispro) inserted at 90° angle at 1mm under skin in patients and another group of lispro insulin therapy (recorded data of insulin treatment as described by Gupta et al. was used for analysis) [15,16]. The control group utilized 100 U insulin formulation, while the microneedle group utilized 50U insulin that is made by diluting 100 U insulin with sterile diluent for lispro.

Table 1. *Criteria of subjects for study.*

Inclusion criteria	
1.	Women of 8-12 weeks pregnancy
2.	Singleton pregnancies
3.	Serum glucose ≥ 5.5 mmol per liter and ≤ 7.2 mmol per liter and/or 2-hour post prandial value ≥ 6.7 mmol per liter and ≤ 13.9 mmol per liter
Exclusion criteria	
1.	Pre-existing Type 1 and 2 diabetic females
2.	Female patients exposed to antidiabetic or other drug treatments
3.	Regular Smoking and alcohol consumption
4.	Teratogenic complications
5.	Organ functional damage or organ complication
6.	Highly obese (>40 BMI) population prone to insulin resistance
7.	Utero-genito complications or pre-eclampsia or sepsis

Subjects

The inclusion and exclusion criteria for GDM subjects described in Table 1. The study participants belonged to age group of 25-50 years. Additionally, they don't have maternal history of GDM and does not belong to highly obese group which might prone to insulin resistance. In present study, 65 females with GDM enrolled for treatment with minimally invasive therapy at 8^{th} to 12^{th} week after conceiving. Hospital Records of past 10 years used to abstract data for insulin treatment to GDM patients. Data of 100 GDM subjects treated with insulin therapy was included in the study. GDM subjects were excluded from study after willful withdrawal, protocol violations or adverse reaction, when needed. Serum Glucose and HbA1c spectrophotometrically analyzed with ELISA plate reader in triplicate. The neonatal outcomes of the study concluded at end of study. The maternal outcomes of the study documented after participation to 2 weeks post pregnancy.

Maternal outcomes in insulin and minimal invasive insulin treatment group

The study participants have predefined meal plan with carbohydrates, proteins, nutritional supplements as per protocol. This has been standardized in 1^{st}-4^{th} week of enrollment in study. Study subjects were using blood glucose level with glucometer. The glucose concentration after fasting

for 8 h, before food intake, after food intake at night before sleep was noted. The acetylated hemoglobin level was measured every week of study and repeated till pregnancy. The maternal outcomes include Fasting glucose, Postprandial glucose, HbA1c labor, delivery related complications and Hypertension. The aim of the study of insulin and minimally invasive insulin therapy is to evaluate fasting, prandial and post-prandial glucose.

Neonatal outcomes in insulin and minimal invasive insulin treatment group

The birth weights of newborn were measured in both treatment groups. The neonatal outcomes were neonates transfer to ICU, spontaneous delivery, assisted delivery, preterm birth, caesarean delivery, requirement of phototherapy, and discomfort in respiration, fetal death, and birth injury. Macrosomia was weight of newborn 3500 g or more. Newborn with condition requiring artificial support for more than 150 min confirmed as respiratory distress.

Statistical analysis

The data was analyzed with SPSS version 18.0. All result data mentioned as mean ± SD. Paired t test was utilized within the groups for comparison. P values at less than 0.05 was considered as statistically significant.

Table 2. *Basic features in GDM patients.*

Characteristics	Insulin (n=100)		Minimally invasive Insulin (n=60)	
	Mean	SD	Mean	SD
Age (years)	35.1	2.2	34.8	2.4
Fasting Glucose#	5.32	0.1	5.16	0.12
Postprandial glucose#	7.9	0.21	7.3	0.16
BMI (kg/m^2)	29.1	0.9	27.6	0.94
HbA1c%	5.4	0.2	5.1	0.4

BMI: Body Mass Index; GDM: Gestational Diabetes Mellitus; HbA1c: Glycated hemoglobin; SD: Standard Deviation

#indicates mmol/l

Results

In the present study, five female subjects were withdrawn from the study due to protocol violation, adverse reaction, or willful withdrawal from the study. The present study is a parallel, randomized open labelled study of insulin treatment and minimally invasive treatment in GDM subjects. The basic features such as age, fasting glucose, postprandial glucose, HbA1C, and BMI of GDM subjects were described in Table 2. In insulin treated group, fasting glucose was (5.32 ± 0.1) mmol/L while in the minimal invasive insulin treatment, slightly to (5.16 ± 0.12) mmol/L. In insulin treatment group, postprandial glucose diagnosed as (7.9 ± 0.21) mmol/L while in minimal invasive insulin treatment group, postprandial glucose measured as (7.3 ± 0.16) mmol/L.

Table 3. *Effect of insulin and minimal invasive insulin therapy on primary outcomes.*

Characteristics	Insulin (n=100)		Minimally invasive Insulin (n=60)		P value
	No.	%	No.	%	
Composite outcome	23	23	12	20	0.071
Macrosomia	5	5	2	3.33	0.290
Hypoglycemia	9	9	6	10	-
Need for phototherapy	22	22	10	15.16	0.301
Respiratory distress	8	8	4	6.67	0.288
Stillbirth or neonatal death	0	0	0	0	-
Birth injury	0	0	0	0	-

In Table 3, primary outcome of insulin and minimal invasive insulin therapy were described. In insulin treatment group, composite outcomes recorded in 23% (23/100) of the GDM patients whereas 20% (12/20) in minimal invasive insulin therapy group. Incidence of hypoglycemia occurred in 9 subjects of insulin treatment group while 6 subjects of minimal invasive insulin therapy. In insulin treatment group, 22% of newborn required phototherapy while minimal invasive insulin therapy 15.67%. Incidence of insulin therapy resulted in respiratory distress in 8% of subjects and minimal invasive therapy 6.67% to GDM subjects.

In Table 4 secondary outcomes such as adjusted birth weights and maternal glycemic control have been mentioned. In insulin therapy, adjusted birth weights were (3279 g ± 76.2 g) and minimal invasive therapy group (3216 g ± 98.14 g). In Table 4, glucose level fasting, post breakfast, post-lunch and post dinner in insulin and minimal invasive insulin therapy has been described.

Table 4. *Effect of insulin and minimal invasive insulin therapy on secondary outcomes expressed as mean and SD.*

Characteristics	Insulin (n=100)		Minimally invasive Insulin (n=60)		P value
	Mean	SD	Mean	SD	
Adjusted birth weight (g)	3279	76.2	3216	98.14	0.059
Maternal glycaemic control (mmol/l)					
Fasting*	5.34	0.22	4.86	0.18	<0.001*
Post breakfast*	7.2	0.16	6.56	0.28	<0.001*
Post lunch*	6.85	0.13	6.46	0.16	<0.001*
Post dinner*	7.8	0.1	7.1	0.18	<0.001*

In Table 5, neonatal outcomes of the study have been summarized. In insulin treatment group, 8% of newborn

transferred to ICU while incidences of ICU transfer were 3.33% in minimal invasive therapy. In insulin treatment group, 14% of newborn had assisted delivery while incidences of assisted delivery were 6.67% in minimal invasive therapy. Incidence of Caesarean delivery occurred in 15 subjects of insulin treatment group while 6 subjects of minimal invasive insulin therapy. In insulin treatment group, 12% of complicated delivery occurred while 10% in minimal invasive insulin therapy.

Table 5. *Effect of insulin and minimal invasive insulin therapy on neonatal outcomes expressed as number and percentage.*

Characteristics	Insulin (n=100)		Minimally invasive Insulin (n=60)		P value
	No	%	No	%	
Neonates transfer to ICU	8	8%	2	3.33%	-
Spontaneous delivery	2	2%	-	-	-
Assisted delivery	14	14%	4	6.67%	-
Preterm birth	3	3%	1	1.67%	0.390
Induction of labour	61	61	31	51.67	0.314
Caesarean delivery	15	15%	6	10	0.424
Complications of delivery	12	12%	6	10	0.392

Discussion

In GDM, glucose tolerance was affected in most of patients. In pregnancy, intake of protein rich diet increase blood glucose level with insulin secretion. In GDM patients, decrease in insulin sensitization at periphery because of obesity results in hyperglycemia. Pregnancy related outcomes are affected with obesity and GDM. Defected post receptor Insulin signaling in GDM patients, resulted in impaired glucose regulation. Obesity and GDM same time potentiated adverse effects in fetus and GDM subjects [18-20]. Short acting insulin was better therapeutic option as beneficial in neonatal outcomes [17]. In nutshell, minimally invasive insulin therapy resulted in lower neonatal composite complications as compared to insulin therapy but are not significant. Secondary outcomes were affected by insulin therapy such as ameliorating glucose level. The minimal invasive insulin therapy was significantly ameliorated hypoglycemia in newborn than insulin therapy. The birth weights were not significantly different of newborns in both treatment groups but minimal invasive insulin treatment group has lesser incidence of macrosomia. The neonatal outcomes such as ICU admission of newborn are significantly lower in minimal invasive insulin treatment group.

The perinatal functions in both groups were clinically indifferent. The pregnancy related outcomes of type of delivery such as assisted delivery or complicated and emergency delivery were statistically not different in both treatment groups. Amelioration of hyperglycemia better observed with minimal inavasive insulin therapy. Post-prandial glucose was decreased in hyperglycemia in the better way with minimal invasive is therapy. In sum, present study concluded significantly ameliorated secondary outcomes in minimal invasive lispro insulin therapy in GDM patients' than lispro insulin therapy. Primary outcome in GDM patients with minimally invasive lispro insulin therapy and lispro insulin treatment was statistically indifferent.

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