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Evaluation of Effective Insulin Preparations for Glycemic control among Type II Diabetes patients in a Tertiary Care Hospital

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Abstract
Introduction: *The intensification of diabetes treatment that is, the transition from oral antidiabetic drugs to injectable treatments such as insulin is often delayed in many patients, which substantially increases the risk of diabetes-related complications. Therefore, in the present study, we evaluated the clinical effectiveness of different types of insulin preparations in patients with type II diabetes for glycemic control.*
Methodology: *Prospective Observational Study and it was conducted in the outpatient department of General Medicine, Karuna Medical College Hospital Palakkad in the duration of six months (November 2017 to April 2018). Patients with T2DM and treated with either Insulin Glargine or Premixed insulin preparations (70% NPH/ 30% RI, 50% NPH/50% RI or NPH or lispro and apart in a ratio of 70/30 or 75/25) using pen injector or insulin syringe were included and Baseline and after three months (Review) FBS, PPBS, RBS, HbA1c values were recorded.*
Results and Discussion: *After 3 months (Review I), PHI group reached statistically significant reduction on FBS (P=0.0001***), PPBS (P=0.0001***) and HbA1c (P=0.0004***). PIA group reached statistically significant small reduction on FBS (P=0.0565*), RBS (P=0.0366*), PPBS (P=0.0177*) as compared than PHI group. GLA group reached statistically significant reduction on FBS (P=0.0048**) and PPBS (P=0.0009***) only and there was no significant reduction of HbA1c.*
Conclusion: *Insulin Glargine and Premixed Insulin Analogues with or without OHAs are less effective insulin preparations when compared with Premixed Human Insulin (significant reduction in FBS (mg/dL), PPBS (mg/dL), and HbA1c (%)) for patients with T2DM who were inadequately controlled with OHAs.*
Keywords: *Insulin, Type II diabetes, Glycemic Control.*

Introduction

Type 2 diabetes mellitus (T2DM) is a progressive disease in which poor glycemic control is exacerbated over time and pancreatic β-cell function declines.[1] It is estimated that by the year 2030, over 70% of people with diabetes will reside in developing countries.[2] India is one of the epicenters of the global diabetes mellitus epidemic and has the second highest number of people with the disease in the world.[3] The incidence of T2DM in Asian Indian people is among the highest in the

world and the peak prevalence of the disease was reached ~10 years earlier in Asian Indian individuals compared with Chinese people and Japanese people.[4,5] The intensification of diabetes treatment that is, the transition from oral antidiabetic drugs to injectable treatments such as insulin is often delayed in many patients, which substantially increases the risk of diabetes-related complications. In a population-based analysis, 25% of patients with T2DM initiated insulin therapy within 1.8 years and 50% of patients initiated insulin therapy within 5 years of failure to achieve or maintain glycemic control despite multiple oral antidiabetic drugs, even in the presence of diabetes-related complications. Treatment regimens comprising premixed insulin are an established treatment option when starting insulin in type 2 diabetes patients. Indeed, insulin therapy is recommended by authorities such as the International Diabetes Federation and American Association of Clinical Endocrinologists in treatment initiation regimens, especially where HbA1c levels are high (> 10%). Human premixed insulin, often known as biphasic human insulin 30 (BHI 30), contains a fixed soluble human insulin component and neutral protamine Hagedorn (NPH) insulin (the remaining 70%).The soluble component, when injected 30 min before a meal, aims to lower postprandial glucose excursions, while NPH provides basal insulin coverage. Together, they can lower glycaemia and provide good glycemic control in patients with type 2 diabetes. Human premixed insulin is, however, associated with relatively high risks of hypoglycemia, probably owing to the mismatch between its pharmacokinetic profile and the physiological need. However, premixed insulin alone can be insufficient to achieve and sustain optimal glycemic control, and there are often additional concerns regarding hypoglycemia, weight gain, and lifestyle restrictions. Premixed insulin analogues, such as biphasic insulin aspart 30／70 (BIAsp 30) and lispro mix 25 (Mix 25) are, on the other hand, associated with a pharmacokinetic profile that more closely mimics insulin needs. As a result, better postprandial glucose control has been seen compared with human insulin premixes.[6,7] A regimen that may make initiation of insulin simpler and more effective has been tested in several small studies. Glargine, a long-acting insulin analog with a more favorable 24-hour time action profile than long- or intermediate-acting human insulin preparations, may be especially suited to this regimen. A single bedtime injection of long-acting insulin is added while prior oral agents are continued, and insulin is systematically titrated, seeking a defined fasting glucose target. The transferring patients with T2DM from premixed insulin to once daily insulin glargine plus OADs provides a convenient, safe and effective treatment option that significantly improves metabolic control.[8,9]Therefore, in the present study, we evaluated the clinical effectiveness of different types of insulin preparations in patients with type II diabetes.

Methodology

The study was a Prospective Observational Study and it was conducted in the outpatient department of General Medicine, Karuna Medical College Hospital, Palakkad for a period of six months (November 2017 to April 2018).Patients with T2DM and treated with either Insulin Glargine or Premixed insulin preparations (70%NPH/ 30%RI, 50%NPH/50%RI or NPH or lispro and aspart in a ratio of 70/30 or 75/25) using pen injector or insulin syringe were included in this study and patients with cognitive impairment, hearing loss, T1DM, women with current or anticipated pregnancy, lack of lab investigations and not coming for review were excluded. Baseline and after three months (Review) FBS, PPBS, RBS, HbA1c values were recorded. In all the visits patients profile, treatment chart, lab investigations were monitored. Finally we evaluated the effectiveness (reduction in FBS, PPBS, RBS, and HbA1c) of all insulin preparations from the baseline to review. Results were assessed by t–student distribution test via Chi-square test.

Results and Discussion

Totally 295 cases were included in this study. Among them, 39.6% were male patients and 60.3% were female patients. From this 46.77% patients are in the age group of 50-65 years. Followed by 37.96% patients aged>65 years. 13.55% and 1.62% aged 35-50 years and<35 years respectively. Out of 295 patients, 57(19.3%) patients had macrovascular complications and 238(80.67%) patients with microvascular complications. IHD 35(11.8%), CVA 18(6.10%) and CAD (CABG done) 4(1.3%) are the macrovascular complications recorded.

Retinopathy, Neuropathy, Nephropathy are the microvascular complications of type 2 diabetic patients found in the studyOut of 295 patients, 46(15.6%) had mono therapy with Premixed Human Insulin, 12(4%)had mono therapy with Insulin Glargine and 3(1%) had mono therapy with PIA.234 patients (79.3%) had combination of insulin with oral hypoglycemic agents. In this combination therapy group, 170(72.6%) patients had premixed human insulin+OHAs, 48(20.5%) patients had insulin Glargine+OHAs, 16(6.83%) had long acting Insulin analogues+OHAs and 3(1.29%) had long acting Insulin Analogues. At the start of the study and against three months (Review) FBS, PPBS, RBS, HbA1c values were recorded. Patients who were not coming for regular follow up and patients lacking lab investigations were excluded from the study. 295 patients treated with Insulin were screened at the start of the study. Among the 295 patients, PHI was prescribed to 216 patients, PIA to 19 patients and Insulin Glargine to 60 patients. During review, 145 patients were excluded from PHI group because of lack of lab values or not PHI, 19 patients with PIA and 60 patients with Insulin GLA were studied and FBS (mg/dL), RBS (mg/dL), PPBS (mg/dL) and HbA1c (%) were monitored

Table: 1 Baseline clinical characteristics of study populations

S.No	Parameters	Premixed Human Insulin (n=216)	Insulin Glargine (n=60)	Premixed Insulin Analogue (n=19)
1	Sex n (%)			
	Male	89(41.2)	23(38.33)	8(42.1)
	Female	127(58.7)	37(61.6)	11(57.8)
2	Age in years (Mean± SD)	55.32±10.2	65.7±11.3	60±13
3	BMI (kg/m^2) (Mean± SD)	23.67±3.94	22±3.7	28.2±6.92
4	Duration of diabetes (yrs) (Mean± SD)	14.96±7.34	11.28±8.25	15.93±11.8
6	Macrovascular Complications			
	CAD	4(1.85)	0	1(0.46)
	CVA	12(5.5)	2(0.92)	5(2.3)
	IHD	25(11.5)	3(1.38)	8(3.70)
	Microvascular Complications			
	Retinopathy	3(1.3)	1(1.66)	1(5.26)
	Neuropathy	1(0.46)	5(1.83)	1(5.26
	Nephropathy	6(2.7)	1(1.66)	1(5.26)
	Retinopathy +Neuropathy	36(16.6)	6(10.0)	0
	Retinopathy+ Nephropathy	31(14.3)	2(3.33)	2(10.552)
	Neuropathy+ Nephropathy	34(15.7)	7(11.6)	4(21.05)
	Retinopathy+ Neuropathy+ Nephropathy	86(39.8)	18(30.0)	2(10.52)

Table :1 shows the baseline characteristics of PHI (n=216) and Insulin Glargine (n=60) groups were (higher in PHI) and duration of diabetes (higher in PHI).The baseline characteristics of PIA (n=216) and INS. GLA. (n=60) groups were similar, not similar in Age (higher in INS. GLA.), BMI except for BMI.

Table: 2 FBS, PPBS, HbA1C at Base line and Review among study population administering Premixed Human Insulin (No. of Patients=71)

S.no	Parameters	Base line (mean± SD)	Review 1 (mean± SD)	*p* value
1	FBS (mg/dl)	236.4±46.3	173.16±64.4	0.0001
2	PPBS (mg/dl)	353.6±44.07	213.2±62.4	0.0001
3	HbA1c (%)	10.20±2.37	8.55±3.02	0.0004

Table: 2 shows changes in the FBS (mg/dL), PPBS (mg/dL), HbA1C (%) at Baseline and Review among study population who were administering Premixed Human Insulin (N=71). After 3 months (Review I), PHI group reached statistically significant reduction in FBS (P=0.0001***), PPBS (P=0.0001***) and HbA1c (P=0.0004***). It indicates, PHI significantly reduced the sugar level among the study population after 3 months.

Table: 3. FBS, RBS, PPBS, HbA1C at Base line and Review among study population administering Premixed Insulin Analogues (No. of Patients=19)

Sl. No.	Parameters	Base line (mean± SD)	Review 1 (mean± SD)	*P* value
1	FBS (mg/dl)	191.15±89.9	146.6±40.4	0.0565
2	PPBS (mg/dl)	268.87±116.24	193.5±96.9	0.0366
3	RBS (mg/dl)	254.43±142.5	166.30±59.8	0.0177
4	HbA1c (%)	9.06±2.11	9.07±2.03	0.9882

Table: 3 shows changes in the FBS (mg/dL), PPBS (mg/dL), HbA1C (%) at Base line and Review among study population administering Premixed Insulin Analogues (No. of Patients=19). After 3 months, PIA group reached statistically significant small reduction in FBS (*P*=0.0565*), RBS (*P*=0.0366*), PPBS (*P*=0.0177*) compared to PHI group.

Table: 4. FBS, PPBS, HbA1C at Base line and Review among study population administering Insulin Glargine (No. of Patients=60)

Sl. No.	Parameters	Base line (mean± SD)	Review 1 (mean± SD)	*P* value
1	FBS (mg/dl)	163.41±71.0	129.38±57.2	0.0048
2	PPBS(mg/dl)	248.9±63.8	207.4±69.08	0.0009
3	HbA1c (%)	8.77±2.04	8.16±1.69	0.0771

Table: 4 shows changes in the FBS (mg/dL), PPBS (mg/dL), HbA1C (%) at Base line and Review among study population administering Insulin Glargine (N=60). After 3 months, GLA group reached statistically significant reduction in FBS (*P*=0.0048**) and PPBS (*P*=0.0009***) only and there was no significant reduction of HbA1c among study population. After 3 months (Review), PHI group reached statistically significant reduction on FBS (mg/dL), PPBS (mg/dL), and HbA1c and there was no statistically significant reduction in HbA1c among PIA and Glargine groups. In this PHI showed the better efficacy when compared to PIA and Glargine after three months. Mixed human insulin preparations are mainly used. Recently, premixed insulin preparations with rapid-acting insulin analogues have been developed to control both pre-and postprandial hyperglycemia while still preventing hypoglycemia. Theoretically, rapid-acting insulin analogues should be more effective for preventing postprandial hyperglycemia associated with higher glycemic-index foods than short-acting human (regular) insulin. Since East-Asians prefer foods with a higher glycemic index, such as rice, than Caucasians, premixed insulin preparations with rapid-acting insulin analogues should have beneficial effects on glycemic control in East-Asian patients with diabetes. However, our study did not show a beneficial effect on the glycol hemoglobin level with premixed rapid-acting insulin analogues compared with premixed human insulin in insulin-naive patients with diabetes. Thus, we speculate that a small proportion of insulin analogues, i.e. 30%, is not sufficient to prevent postprandial hyperglycemia necessary to attain greater improvements in glycol hemoglobin. A regimen that may make initiation of insulin simpler and more effective has been tested in several small studies. A single bedtime injection of long-acting (basal) insulin is added while prior oral agents are continued, and insulin is

systematically titrated, seeking a defined fasting glucose target.[10]

Conclusion

Regarding the prescribing pattern of Insulin preparations, Insulin Glargine and Premixed Insulin Analogues were prescribed in less number of patients and Premixed Human Insulin was widely prescribed. Our observational study reveals that Insulin Glargine and Premixed Insulin Analogues with or without OHAs are less effective insulin preparations compared to Premixed Human Insulin (significant reduction in FBS(mg/dL), PPBS(mg/dL), and HbA1c(%))for patients with T2DM who were inadequately controlled with OHAs. Our study included a small number of patients for a short period only. Longer term use of insulin preparations with maximum study population are warranted to confirm the effectiveness of Insulin preparations.

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