Efficacy and Safety of Short Term Usage of Insulin Co-Formulation (IDegAsp) in Treatment Naive Type 2 Diabetes Mellitus Patients, Presenting with Severe Hyperglycemia and/ or Osmotic Symptoms-A Real World Observational Study

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Abstract

Background: Clinicians adapted early insulinisation as one of the strategies in patients with marked hyperglycemia and/or osmotic symptoms. Recently two Indian studies used basal insulin as the initial choice in such patients. Indians having a carbohydrate predominant diet have higher contribution of post prandial plasma glucose (PPPG) even in higher tertiles of glycosylated hemoglobin (HbA1c). Newer co-formulation insulin degludec/insulin as part (IDegAsp) in which the individual properties of basal and prandial insulins are preserved presents an opportunity to correct both fasting and post-prandial glucose with an advantage of single prick and simple regime.

Aim: Retrospective data of early insulinisation with co-formulation insulin was looked at for evaluating the efficacy and safety of this insulin.

Methods: Retrospective data of the treatment naïve recently diagnosed type 2 diabetes patients who were initiated on co-formulation insulin therapy along with metformin at the first visit were reviewed from the medical records of outpatients department (OPD) of diabetes and endocrinology of a tertiary care hospital at Kolkata. Total 41 subjects fulfilled the eligibility criteria for analysis. These subjects had a minimum follow-up of 12 weeks in the OPD setting.

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Results: Significant improvement in FPG, PPPG and HbA1cwas observed over the 12 week study period with 85.4% of the patients receiving once daily IDegASp. No significant changes in weight were noted. Only two patients reported symptomatic hypoglycemia and none were found to experience documented, severe or nocturnal hypoglycaemia during the entire study period.

Conclusion: Administration of insulin IDegAsp once or twice daily is an effective and safe option for insulin naive Indian patients, presenting with severe hyperglycemia and/or osmotic symptoms.

Keywords: New onset Type 2 Diabetes; Osmotic Symptoms; Severe Hyperglycemia; Insulin Co-Formulation

Abbreviations: FPG: Fasting Plasma Glucose; PPPG: Postprandial Plasma Glucose; HbA1c: Glycosylated Haemoglobin; T2D: Type 2 Diabetes; OAD: Oral Anti-Diabetic Agents; OPD: Out-Patient Department.

Core Tip

The new co-formulation insulin degludec/insulin aspart (IDegAsp), in which one basal (degludec) and one prandial insulin (as part) are combined together, has recently become available. This study is a small step towards a simple way of using insulin for a short period, not only to reduce HbA1c effectively but also to achieve a target HbA1C of less than 7% over a period of three months without any undue weight gain or increased risk of hypoglycaemia. The novelty in our study is the particular co-formulation insulin we have used, which addresses both the fasting and postprandial hyperglycemia. This regimen was used keeping in mind that PPPG in Indian subjects significantly contributes even at higher HbA1C levels ≥ 9%. In this regimen, we have avoided using Sulphonylureas and/or Thiazolidinediones and achieved spectacular Hba1c control within three months with minimal side effects.

Introduction

Experimental models showed that exposure to glucotoxicity and oxidative stress for a prolonged periods can lead to β-cell destruction resulting in worsening of hyperglycaemia and related complications [1-3]. Early and effective intervention at disease onset can break this cycle of worsening hyperglycaemia and its complications [4-7]. The natural history of type 2 diabetes mellitus (T2D) is a relentless progression of pancreatic β-cell failure with increasing metabolic derangement. Insulin remains the only glucose-lowering therapy that is efficacious throughout this continuum. However, the timing of introduction of insulin therapy remains a contentious issue. The U.K. Prospective Diabetes Study (UKPDS) study showed that tight glycaemic control in newly detected T2D patients can significantly reduce micro-vascular complications [8]. Though not evident and statistically insignificant during the study period, macro-vascular benefit became obvious in the tightly controlled group when the study population was followed-up for ten more years ("legacy effect") [9]. Similar finding was noted in the other landmark studies e.g. Diabetes Control and Complications Trial (DCCT) and its follow-up Epidemiology of Diabetes Intervention and Complications (EDIC) study [10]. Early insulinisation for patients with marked hyperglycemia is one of the leading strategies. In patients presenting with high plasma glucose and/or hyperglycaemic osmotic symptoms, a dual or triple-agent therapy may be considered [5]. The American Diabetes Association (*ADA*) and the European Association for the Study of Diabetes (*EASD*) recommends that insulin therapy should be considered as a part of any initial combination regimen in patients with severe hyperglycaemia (blood glucose being ≥300mg/dl and/or HbA1c ≥10%), particularly if the patient is symptomatic or if there is any evidence of any catabolic features e.g. weight loss or ketosis [5]. It suggests that once the glucotoxicity resolves, the regimen can potentially be simplified. The Indian guidelines for initiation of insulin recommends the criteria (FPG>250mg/dl, PPPG>300mg/dl & HbA1c>9%) at diagnosis which need to be met, for a physician to initiate insulin [6]. On the other hand, IDF global guideline for type 2 diabetes recommends initiation of insulin with either basal insulin or premixed insulin when first line and second-line therapies fail to achieve glycaemic target of HbA1c <

7.0%. It also states that similar proportion of people reach an HbA1c target of < 7.0% using either basal or premixed insulins.[7]Though the "guideline approach" does recognize the need of initial insulin therapy in selected patients with severe hyperglycaemia, guidelines are not unanimous regarding the initial choice of insulin to be used, premixed in Indian Insulin guideline [6] vs basal in ADA/AACE guideline[8].

Recent years have seen great advances in insulin pharmacyotherapeutics and have helped to achieve greater safety and tolerability in treatment of diabetes. Insulin degludec is a recently developed ultra-long-acting basal insulin analogue, having duration of action lasting up to 42 hours and also has flexibly in time of administration. Insulin as part, on the other hand, is a fast-acting insulin analogue. It allows a flexible dosing schedule, which allows patients to adjust their insulin according to any changes in their eating habits. The safety and efficacy of insulin as part in real-life clinical practice was established in the A1chieve study [9]. IDegAsp (Insulin degludec/insulin as part) is the first soluble co-formulation which combines these two insulin analogues, and provides effective basal and prandial glycaemic coverage [10]. This co-formulation (IDegAsp) with significantly lower risk of hypoglycaemia and weight gain, heralds the beginning of a new era of convenient insulin regime. With the flexibility of being used either once or twice daily and capability to lower the postprandial surge along with control of fasting hyperglycaemia, it may become the insulin of choice while initiating therapy.

Aims and Objectives

The objective of this study is to evaluate the efficacy and safety of Insulin co-formulation (IDegAsp) in new onset, drug naïve type 2 diabetes mellitus patients, presenting with severe hyperglycaemia and/ or osmotic symptoms.

Materials and Methods

It is a single centre retrospective observational study.

- Study Area-Out patients' department of diabetes and endocrinology of a tertiary care hospital at Kolkata, India.
- Study Period –April 2016 to December 2017

- Study Population – From April 2016 to December 2017, we retrospectively reviewed the medical records of outpatients using the following inclusion and exclusion criteria for analysis-

Inclusion Criteria

- Age > 18 years and <70years
- Treatment naïve recently diagnosed type 2 diabetes
- Baseline fasting plasma glucose≥ 250 mg/dL or post prandial glucose > 300 mg/dl or HbA1c ≥9.0 or patients with any value of hyperglycaemia presenting with osmotic symptoms
- All blood tests on 1st visit and Final month visit were done (including HbA1c by HPLC method) and reports were documented
- Patients who were initiated co-formulation insulin therapy along with metformin at the first visit.

Exclusion Criteria

- Patients not completing three months follow-up
- Patients not having HbA1c or other blood investigation records on presentation and at three months follow-up or had HbA1c done using non HPLC methods

Treatment protocol

All patients received standard diet and life-style advice and were educated about symptoms and management of hypoglycaemia as per standard of care. All of them were taught self-monitoring of blood glucose technique (SMBG) and insulin dose adjustment as per SOP of the Department. All patients were initiated on 10 units of IDegAsp and advised to monitor pre-meal capillary blood glucose {pre-breakfast, pre-lunch and pre-dinner: any one or two in accordance with the once or twice daily dosing of co formulation} every three days and to increase or decrease insulin dose according to a uniform titration algorithm provided to all (Table 1). All patients were also initiated on a one gram/day of metformin extender release (ER) which was gradually up-titrated to two gram/day dose and DPP4 Inhibitor was introduced once down titration of insulin was being done. They were advised to note and report any adverse incidence like hypoglycaemia (symptomatic/documented), significant gastro-intestinal disturbances (i.e. nausea, vomiting and diarrhea) or skin allergy.

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Plasma glucose measurements		
Mean/lowest pre-breakfast/pre-evening meal		**Adjustment, U**
mmol/l	mg/dl	
<3.1‡	<56	–4 (or, if dose >45 U, reduce by 10%)
3.1–3.9‡	56–70	–2 (or, if dose >45 U, reduce by 5%)
4.0–5.0	71–90	0
5.1–7.0	91–126	+2
7.1–8.0	127–144	+4
8.1–9.0	145–162	+6
>9.0	>162	+8

Table 1: Titration algorithm used for IDegAsp in our study sample with Type 2 Diabetes.

Data Collection

Baseline demographic characteristics were reviewed for the following data: age, gender, height, body weight, body mass index (BMI), Duration of Insulin Therapy (Days), Duration of total follow-up (Weeks), fasting plasma glucose (FPG), postprandial plasma glucose (PPPG), HbA1c and serum creatinine. Data were retrieved of their first visit (i.e. the day when treatment was initiated) and of 2nd and final visits (viz. at about 4 weeks and 12 weeks respectively) and were tabulated in the prescribed tabulation format.

Statistical Methods

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD and results on categorical measurements are presented in Number (%). Significance is assessed at a level of 5%.

Normality of data was tested by simultaneous Anderson Darling test, Shapiro-Wilk test and graphically by QQ plot. Paired t-test was used to find the significance of study parameters measured on two occasions for same/related group of patients. Repeated measures ANOVA with post-hoc Bonferroni adjustment method has been used to find the significance of study parameters measured on three occasions between same/related groups of patients. We took into account both Greenhouse Geiser correction and Huynh-Feldt correction, where assumption of sphericity was violated by Mauchly's test of sphericity. Unpaired t-test has been used to find the significance of study parameters between two groups of patients.

Statistical Software

The Statistical software namely SAS (Statistical Analysis System) version 9.2 for windows, SAS Institute Inc. Cary, NC, USA, Statistical Package for Social Sciences (SPSS Complex Samples) Version 21.0 for windows, SPSS, Inc., Chicago, IL, USA were used for the analysis of the data and Microsoft word and Excel 2010(Microsoft Corp, Redmond, WA,USA) have been used to generate graphs, tables etc.

Results

Adapted from Rodbard HW, Cariou B, Pieber TR, Endahl LA, Zacho J, et al. Treatment intensification with an insulin degludec (IDeg)/insulin aspart (IAsp) co-formulation twice daily compared with basal IDeg and prandial IAsp in type 2 diabetes: a randomized, controlled phase III trial.

Total 41 patients were followed for 3 months (mean follow up 12.88+/-1.63 weeks) (Table 2).

Demographic profile: N=41	
Male, n (%)	27 (65.90%)
Female, n (%)	14 (34.10%)
Age(years), Mean ± SD	46.88 ± 12.45
Height (centimetres), Mean ± SD	162.83 ± 6.41
Body weight(Kg), Mean ± SD	70 ± 7.92

BMI(kg/m2), Mean ± SD	25.9 ± 2.58
Duration of Insulin Therapy, Days	48.19 ± 10.16
Duration of total follow-up, Weeks	12.88 ± 1.63
Laboratory data	
FPG(mg/dl), Mean ± SD	325.22 ± 30.45
PBG(mg/dl), Mean ± SD	402.71 ± 51.56
HbA1c (%), Mean ± SD	12.95 ± 0.94%
Serum Creatinine, mg/dL	0.95 ± 0.21

Table 2: The baseline characteristic features.

$p < 0.05$ considered as statistically significant, p computed by repeated measure ANOVA to find over-all significant difference between the three visits with multiple comparison post-hoc test by Bonferroni method to find pairwise difference between two groups. a – probability of chance difference between baseline & 2nd visit, b- probability of chance difference between baseline &Final visit, c - probability of chance difference between 2nd visit &Final visit

We noted a significant reduction for both FPG and PPPPG, measured on the three subsequent visits, $p < 0.0001$ Further post-hoc pairwise comparison test by Bonferroni adjustment method also revealed significant decline in FPG and PPPPG between 1st&2nd visit, 1st&Final visit and also between 2nd&Final visits. There was a significant difference between HbA1c measured on the first visit and last visit, which reduced from 12.95±0.94% to 7.11±0.57%, $p < 0.0001$ (Table 3). This improvement was maintained till the end of observation period at 12 weeks.

Parameter	Baseline Mean±SD,	2nd visit Mean±SD	Final visit Mean±SD	P(Repeated Measure ANOVA/Paired-t-test**)	Post-hoc Test
Weight, kg	69.97 ± 7.92	70.41 ± 7.84	69.39 ± 7.82	P=0.053, f=3.83	a=0.397,b=0.306,c=0.054
BMI, kg/m2	26.41 ± 2.58	26.61 ± 2.76	26.29 ± 2.40	P=0.055, f=3.13	a=0.397,b=1.00,c=0.065
Scr, mg/dL	0.71 ± 0.11	NA	0.66 ± 0.14	P=0.897**, t=0.001	NA
FPG(mg/dl)	325.22 ± 30.45	149.02± 23.40	108.41± 16.85	P<0.001, f=963.81	a<0.001, b<0.001.,c<0.001
PPPG(mg/dl)	402.71 ±51.55	183.17± 28.28	137.51± 19.37	P<0.001, f=632.32	a<0.001, b<0.001.,c<0.001
HbA1c (%)	12.95 ± 0.94	NA	7.11 ± 0.57	P<0.001**, t=44.28	

Table 3: Changes in laboratory values between 1st 2nd and Final visit (after 4 weeks and 12 weeks respectively).

Two patients reported symptomatic hypoglycemia, one between first and second visit and another between second and final visit, none of the patients reported documented or severe hypoglycaemia during the entire study period (Table 4). The couple of patients reporting symptomatic hypoglycaemia were both on once daily dosing of IDegAsp and had either delayed or skipped a meal.

Parameter	Baseline (number)	2nd visit (number)	Final visit (number)
Asymptomatic hypoglycemia	0	0	0
Symptomatic hypoglycemia	0	1	1
Severe hypoglycemia	0	0	0
Nocturnal hypoglycemia	0	0	0

Table 4: Hypoglycemia Table.

Insulin was initiated in 41 patients, of whom 35 (85.4%) received once daily dosing and remaining six (14.6%) received twice daily dosing. By the second visit, insulin was discontinued in four patients (9.7%) and the rest of 37 (90.2%) patients were receiving insulin only once daily.

The percentage of patients' achieving HbA1c targets till the end of study is illustrated in Table 5.

HbA1c	Number	Percentage (%)
<6.5%	7	17.07
6.5-7%	14	34.14
7-7.5%	13	31.7
>7.5%	7	17.07

Table 5: Percentage of patients achieved HbA1c targets.

Discussion

Insulin therapy is the most effective and quick way to achieve normoglycemia and reduce glucotoxicity in patients with severe hyperglycaemia. Basal Insulin therapy is the initial choice for patients presenting with severe hyperglycemia (blood glucose >300mg/dl or HbA1c >10%) or catabolic symptoms (weight loss) as per ADA 2018 guideline. When insulin becomes necessary, a single daily dose of basal insulin is the initial choice of insulin in AACE guidelines also [11]. Basal insulin is recommended at diagnosis in patients with much lower HbA1c (> 9%) with symptoms, in a proposed Indian guidelines also [12]. Recently two studies used basal insulin as the initial choice in such patients with the advantage of single prick and simple regime [13,14]. But even when basal insulin is adequately titrated, some patients also need prandial insulin to achieve or maintain individual glycemic targets over time [15]. Indians having a carbohydrate predominant diet might have a higher contribution of PPPG even in higher tertiles of HbA1c.Wang and colleagues using CGM in Asian type 2 diabetes patients have demonstrated PPPG 24 and 4 h after meals as the predominant contributor to excess hyperglycaemia in well controlled patients and as equally important as fasting glucose or preprandial glucose in moderately to poorly controlled patients with mean HbA1c up to 10% [16]. The addition of prandial insulin to basal insulin has been shown to further reduce HbA1c levels. However, this approach is generally limited by multiple injections (3 or more), hypoglycemia and weight gain [17,18].

Premix insulin is a reasonable option effective in almost all the stages of the T2D with the unique advantage of being simple, safe, easy to initiate and continue [6]. It is well-known that PPPG control (especially in India) may play a crucial role in achieving near normal glycemia in the lower range of HbA1c values and also do contributes to the HbA1C values even at higher ranges of Hba1c values (>9%) [16]. Elevated PPPG levels are a substantial contributor to daytime hyperglycemia and premix insulin once or twice daily dosage lower the postprandial surge along with control of fasting hyperglycaemia, leading to a greater reduction of HbA1C.However, premixed insulins provide less dosing flexibility and are associated with a higher frequency of hypoglycemic events compared to basal or basal-bolus regimens [11]. The 'shoulder' effect which is likely to occur in the hours following mealtime owing to interaction between the protaminated and non-protaminated soluble insulins extends the action of the short-acting prandial component, further potentiating the risk of hypoglycaemia [19]. Premixed insulin analogue may be preferred over premixed human insulin due to lower rates of hypoglycemia [6]. Several studies have shown that premixed insulin analogues are superior over human premix insulin in decreasing PPPG with an added advantage of less hypoglycemia [6].

The new co-formulation insulin degludec/insulin aspart (IDegAsp), in which one basal (degludec) and one prandial insulin (aspart) are combined together, has recently become available. This study is a small step towards a simple way of using insulin for a short period as a safe and effective regimen, not only to reduce HbA1c effectively but also to achieve a target HbA1C of less than 7% over a period of three months without any undue weight gain or increased risk of hypoglycaemia. The novelty in our study is the particular co-formulation insulin we have used, which addresses both the fasting and postprandial hyperglycemia. This regimen was used keeping in mind that PPPG in Indian subjects significantly contributes even at higher HbA1C levels≥ 9% [16]. In this regimen, we have avoided using Sulphonylureas and/or Thiazolidinediones and achieved spectacular Hba1c control within three months with minimal side effects.

Initial use of basal insulin (glargine) at diagnosis with severe hyperglycaemia and its effectiveness has been studied in India [13]. The present study is the first to demonstrate the efficacy and safety of co-formulation insulin in new onset treatment naïve type 2 diabetes

patients. At efficacy parameters, a drop in HbA1c of 5.84±0.37% was greater than that achieved (5.35±1.1%) by Ray, et al. [13] and Mukherjee, et al. (3.35± 0.77%) [14] Who used four weeks of initial basal therapy plus triple OAD therapy which continued beyond 4th weeks? Fasting plasma glucose in our patients reduced by 216.81 ±13.6 mg/dl in comparison to a drop of 186.3 ±3.96 mg/dl achieved by Ray, et al. and 153.45±32.06 mg/dl achieved by Mukherjee, et al. [14].

Similarly, our patients showed a drop of 265.2±32.18 mg/dl in PPPG which was greater than that of 239.23± 37.47mg/dl achieved by Mukherjee, et al. [14]. Interestingly, the post prandial drop was less than the drop of 295.74± 8.28mg/dl achieved by Ray, et al. [13]. Due to the presence of Aspartin co-formulation, we expected a greater drop of HbA1c and PPPG, which however was not seen uniformly. This discrepancy may be accounted for, by the fact that a large number of patients were working population [age between 34-59 years and only five females were homemakers] who had their major meal of the day at night or at breakfast and thus their co-formulation was administered prior to breakfast / dinner, hence the drop in PPPG was perhaps not fully reflected in the post lunch values, which is conventionally measured in most patients.

It is known that PPPG contributes significantly towards higher HbA1c in Indian population than patients of western origin [15]. This increased load of post prandial glucose cannot be handled only by the use of basal insulin [20]; however the available options of premixed insulin (human and analogue) had significant more risks of hypoglycaemia in comparison to basal insulin [21].

In the present study, none of the patients reported severe hypoglycemia. Only two patients (4.88%) reported symptomatic hypoglycemia, one between first and second visit and another between second and final visit, at a rate of 0.20 events per patient year. The hypoglycemia reported is comparable to a recently published study of insulin glargine conducted in treatment naive type 2 diabetes patients, where symptomatic hypoglycemia were reported in 5 (11.36%) of patients at a rate of 0.23 events per patient year [14]. In the ADVANCE trial, patients in the intensive control arm experienced minor hypoglycemic events at a rate of 1.20 events per patient per year in patients undergoing intensive control and at a rate of 0.90events per patient per year with standard control [22]. In the study by Ray, et al. [13], four (6.25%) patients experienced mild hypoglycemia [13].

A non-significant increase in weight (approximately 400 g) was noted in the first four weeks after initiating therapy due to control of osmotic symptoms and anabolic effects of insulin therapy. Nevertheless on imparting diet and lifestyle modification, there was a mild weight loss (approximately 600 g) at the end of 12 weeks from baseline. A significant part of this weight loss may be attributed to the fact that all 41 patients could be up-titrated to 2 gram /day of Metformin ER, without any major issues of GIintolerance.

Parameter	Biosimilar Insulinglargine[14] (Indian study), N=44	Innovator Insulinlargine/ Insulin Degludec[13] (Indian study), N=64	Co-formulation (IDegAsp) Insulin (Present study), N=41
FPG, mg/dL Mean ± SD	-153.45 ± 32.06	-186.44 ± 39.06	-216.81 ± 14.04
PPPPG, mg/dL Mean ± SD	-239.33± 37.47	-295.73 ±57.81	-219.54 ±32.18
HbA1c, mg/dL Mean ± SD	-3.35± 0.68	-5.32 ±0.33	-5.84 ± 0.74
Wt, kg Mean ± SD	-0.41 ±0.92*	0.39 ±0.34*	-0.58 ± 0.14
Hypoglycemia, n (%)	Severe - 0 Mild –5 (11.37)	Severe -0 Mild–4 (6.25)	Severe - 0 Symptomatic -2 (4.87)

*data for six months
Table 5: Glycemic and weight changes with different insulins after 3 months.

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Even before the UKPDS and DCCT data was published [23-25], benefit of early and aggressive insulin therapy was observed in different studies. In a 1997 study, 13 newly detected type 2 diabetes patients were treated with two weeks of continuous subcutaneous insulin infusion (CSII). Four patients failed to maintain normoglycaemia after six months but nine patients could maintain normoglycemia for 9-50 months [26]. This observation was further supported by multiple studies in the following years [27-29]. The researchers concluded that early intensive short term insulin therapy in newly diagnosed type 2 diabetes patients has beneficial effect on recovery and preservation of β-cells and may help to maintain good glycaemic control in future. However, we cannot comment on reversibility among our patients as we have retrieved only the three months follow-up data. Shifts from twice daily to once daily dose in some of our patients or discontinuation of insulin in all our patients, is an indication in this direction.

Limitations

We acknowledge that three months is a short period to observe and assess the durability of any treatment regimen with a limited sample size.

Conclusion

Our study suggests that administration of co-formulation insulin once or twice daily is associated with significant drop of FPG, PPPG and HbA1C in insulin naive Indian T2D subjects, with low incidence of hypoglycaemia and weight gain. This co-formulation insulin regimen is safe and effective and may be considered in patients presenting with marked hyperglycaemia at diagnosis. However, head-to-head study with basal and premixed insulin in randomized controlled trials, with larger sample size and longer duration are required to establish the superiority of this formulation over the basal and premixed insulin regimen.

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Contribution Statement

Both the first and the second author had contributed substantially in conceptualizing, designing the study and data collection. The third and fourth author contributed in analysis and interpretation of data. All authors reviewed and edited the final manuscript.

Ethical Approval

Our research was a retrospective and observational. Therefore, ethical approval was not necessary for this study.

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