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Comparison of thrice daily biphasic human insulin (30/70) versus basal detemir & bolus aspart in patients with poorly controlled type 2 diabetes mellitus – A pilot study

Shanmugasundar G., Anil Bhansali, Rama Walia, Pinaki Dutta & Vimal Upreti

Department of Endocrinology, Postgraduate Institute of Medical Education & Research, Chandigarh, India

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***Background & objectives*: Conventionally, biphasic human insulin (30/70, BHI) is used twice daily for the management of patients with diabetes. However, this regimen is suboptimal to control post-lunch and/or pre-dinner hyperglycaemia in some patients. This study was undertaken to compare the efficacy and safety of thrice-daily biphasic human insulin (30/70, BHI) versus basal detemir and bolus aspart (BB) in patients with poorly controlled type 2 diabetes mellitus (T2DM).**

***Methods*: In this open labelled randomized pilot study, 50 patients with uncontrolled T2DM on twice-daily BHI and insulin sensitizers were randomized either to BHI thrice-daily or BB regimen. HbA1c, six point plasma glucose profile, increment in insulin dose, weight gain, hypoglycaemic episodes and cost were compared between the two treatment groups at the end of 12 wk.**

***Results*: Mean HbA_1c (±SD) decreased from 9.0±0.9 per cent at randomization to 7.9±0.8 per cent in BHI (*P*<0.001) and from 9.4±1.3 to 8.2±1.0 per cent in BB regimen (*P*<0.001) after 12 wk of treatment. The mean (±SEM) weight gain in patients in the BHI regimen was 1.5±0.33 kg compared to 1.4±0.34 kg in the BB regimen. Insulin dose increment at 12 wk was significantly more in the BB regimen 0.46±0.32 U/kg/day compared to 0.15±0.21 U/kg/day in the BHI regimen (*P*<0.001). The incidence of major as well as minor hypoglycaemic episodes was not different in both the regimen. The BB regimen was more expensive than the BHI regimen (*P*<0.001).**

***Interpretation & conclusions*: The thrice daily biphasic human insulin regimen is non-inferior to the basal bolus insulin analogue regimen in terms efficacy and safety in patients with poorly controlled T2DM. However, these data require further substantiation in large long term prospective studies.**

Key words Biphasic human insulin 30:70 - insulin analogues - T2DM

Both Diabetes Control and Complications Trial (DCCT)[1] and United Kingdom Prospective Diabetes Study (UKPDS)[2], the two large interventional studies, which are testimony to glucose hypothesis have convincingly established the role of good glycaemic control in preventing and/or halting the progression of micro- and possibly macrovascular complications in patients with type 1 and type 2 diabetes, respectively.

Good glycaemic control, preferably HbA_1c <7 per cent can remarkably reduce the risk of such complications and this target is currently recommended in clinical practice[3].

Majority of the patients with type 2 diabetes mellitus (T2DM) are initially treated with dietary and lifestyle modifications and oral hypoglycaemic agents (OHAs). However, with advancing duration of disease, there is progressive and inexorable loss of β cell function/mass and eventually most of the patients need treatment with exogenous insulin[4,5]. This implies a once daily long-acting insulin or twice daily insulin treatment with a pre-mixed preparation. However, even with the above mentioned regimen many patients do not achieve their glycaemic targets and require intensification of insulin therapy such as basal-bolus (BB) regimen, which is near physiological and is considered as standard of care in clinical practice. Basal-bolus regimen can be practiced with either conventional insulin or insulin analogues and require four to five pricks per day. Insulin analogues have advantage over conventional insulin in terms of convenience of administration and decreased risk of nocturnal hypoglycaemia, though these are quite expensive. Biphasic human insulin (BHI) given twice a day even in reasonably high doses to avoid multiple injections is a common clinical practice. However, this is associated with post-lunch and/or pre-dinner hyperglycaemia particularly in late diners. To overcome this, biphasic insulin analogues have been given thrice a day and shown to be as efficacious as basal-bolus regimen[6], however, BHI (30:70) has not been tried thrice a day. Therefore, this study was planned to assess the efficacy and safety of biphasic human insulin thrice-daily in comparison to basal bolus analogues regimen in patients with T2DM.

Material & Methods

This was an open-labelled randomized, study comparing BHI thrice daily with BB regimen in subjects with T2DM in whom glycaemic targets were not achieved with the use of BHI twice daily along with insulin sensitizers (metformin 2 g/day and pioglitazone 30 mg/day). The number of patients studied was arbitrarily defined, as it was a pilot study. The patients were recruited from out patient department at Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India between June 2008 and December 2009. The trial was conducted at PGIMER, Chandigarh, India. The trial protocol was approved by the institute ethics committee. Written informed consent was obtained from all the subjects.

Subjects: Patients with T2DM who were inadequately controlled while receiving BHI twice a day, metformin 2 g/day and pioglitazone 30 mg/day were recruited in the study after satisfying the following criteria: HbA_1c >7 per cent, single time insulin dose exceeding >25 units and having post-lunch and/or pre-dinner hyperglycaemia. Exclusion criteria for the study were patients with deranged liver function tests, serum creatinine >1.5 mg/dl, decompensated heart failure/unstable angina/myocardial infarction within last 6 months, untreated proliferative retinopathy/ maculopathy, pregnancy, any other acute co-morbid illness, drug or alcohol dependence and if he/she was unable to understand the regimen.

Study protocol and treatment: Patients were randomized to either BHI or BB regimen for 12 wk (Fig.). Metformin 2 g/day and pioglitazone 30 mg/day were continued. Lifestyle modifications were reinforced. Hypertension and dyslipidaemia were treated according to the guidelines[3]. BHI (Mixtard 30:70, Novo Nordisk, Denmark) was administered 30 min before each meal. The total daily dose of BHI being received by the patient was distributed in 40:20:40 ratio (breakfast: lunch: dinner) and was later on adjusted according to self monitoring of blood glucose (SMBG). In basal bolus regimen, aspart (Novorapid, Novo Nordisk, Denmark) was injected immediately before breakfast, lunch and dinner, while detemir (Levemir, Novo Nordisk, Denmark) was administered at the bedtime (2200-

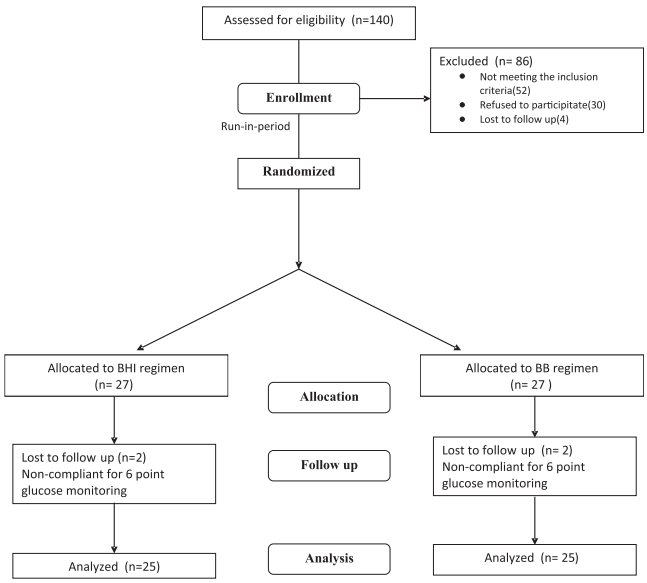

Fig. Flow chart showing study plan.

2300 h). The total daily dose was split between insulin aspart and detemir as 60 and 40 per cent, respectively. Doses were adjusted throughout the treatment period according to scheduled self monitored 6-point plasma glucose profile using glucometer –Optium Xceed; Abbott Diabetes Care Inc, Alameda CA, USA (fasting, 2 h post-breakfast, 2 h post-lunch, pre-dinner, 2 h post-dinner and at 0300 h) targeting the ranges recommended by the American Association of Clinical Endocrinologist (fasting/pre-prandial plasma glucose: 80-110 mg/dl and 2 h post-prandial plasma glucose <140mg/dl) done on day 4, 7, 14 and then every two weekly[3]. In BB regimen, if pre-dinner blood glucose target was not achieved, then detemir was administered twice a day.

Subjects were contacted by telephone or visit to the clinic on above days to discuss dose modifications. Subjects were also asked to test glucose whenever they experienced symptoms that might be related to hypoglycaemia and to record the results. Hypoglycaemia are classified as major, documented symptomatic, probable symptomatic, asymptomatic, relative and nocturnal hypoglycaemia (2200 to 0600 h)[7].

Baseline height, weight, body mass index, waist circumference and blood pressure were measured and fundus examination was done at the entry of the study. Haemogram, renal and liver function test, lipid profile, urinary albumin excretion and HbA_1c were estimated at baseline. HbA_1c was assayed by high performance liquid chromatography method (Bio-Rad Laboratories Inc, USA) and urinary albumin was done by immunoturbidometry (Hemocue, Sweden). All measurements and investigations were repeated at the end of the study.

Outcome measures: The primary outcome measure was improvement in 6-point plasma glucose profile and HbA_1c level. Secondary outcome measures were change in weight, BMI, hypoglycaemic episodes and cost-effectiveness.

Statistical analysis: The statistical analysis was carried out using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 15.0 for Windows). All quantitative variables were estimated using measures of central location (mean, median) and measures of dispersion (standard deviation and standard error). Normality of data was checked by measures of skewness and Kolmogorov Smirnov tests of normality. For normally distributed data means were compared using student's t-test for two groups. For skewed data Mann - Whitney test was applied. For time related comparison paired t-test or Wilcoxon signed rank test was applied. Qualitative or categorical variables were described as frequencies and proportions. Proportions were compared using Chi square or Fisher's exact test whichever was applicable.

Results

One hundred and forty consecutive patients were screened and finally 50 patients were randomized to either the BHI (n = 25) or the BB (n = 25) regimen for 12 wk of treatment (Fig.). The two treatment groups were well matched for the baseline characteristics (Table I). There were no significant difference between the two groups in the mean fasting lipid profile, serum creatinine, liver function tests, haemoglobin and urinary protein excretion (data not shown).

Patients in both groups had improvement in the overall glycaemic control during the study as evidenced by the decrease in HbA_1c levels from 9.0±0.9 per cent at randomization to 7.9±0.8 per cent (P<0.001) in the BHI group and from 9.4±1.3 per cent to 8.2±1.0 per cent (P<0.001) in the BB regimen after 12 wk of treatment. The difference in HbA_1c at the end of the study from the baseline in the BHI group was -1.1±0.5 per cent and was comparable with HbA_1c reduction of -1.2±0.6 per cent in the BB regimen. Of the total 50 patients, only eight achieved HbA_1c <7 per cent, four in each group.

Table I. Baseline characteristics of the study population

Characteristics	BHI (n=25)	BB (n=25)
Age (yr)	53.9±8.1	53.8±9.5
Male : Female	10:15	15:10
Duration of diabetes (yr)	14.1±5.1	13.2±6.4
BMI (kg/m^2)	29.2±4.8	31.25±4.7
Waist (cm)	101.1±9.13	107.2±10.5*
Body fat (%)	35.8±5.87	36.16±7.01
Duration of insulin treatment (yr)	4.2±3.7	3.7±3.1
Doses of insulin received (units)	58.9±7.01	60.2±6.75
Insulin per kg bw (units/kg)	0.8±0.15	0.72±0.1
Mean FPG (mg/dl)	166.7±63.7	186.6±80.8
HbA_1c (%)	9.0±0.9	9.4±1.3
Fasting C-peptide (ng/ml)	1.87±0.72	1.99±1.02

BHI, biphasic human insulin; BB, basal bolus; FPG, fasting blood glucose; *P<0.05 compared to BHI

Table II. Sub-hoc analysis of hypoglycaemic episodes during study period

Hypoglycaemia	BHI	BB	*P* value
Major	2	3	0.64
Minor	53	37	0.06
Documented symptomatic	30	16	0.03
Probably symptomatic	2	6	0.09
Asymptomatic	17	11	0.44
Relative	4	4	1.0
Nocturnal	15	13	0.44

BHI, biphasic human insulin thrice daily; BB, basal bolus regimen

The mean fasting plasma glucose decreased from 166.7±63.7 to 102.7±18.7 mg/dl (P<0.001) in the BHI regimen and from 186.6±80.8 to 111.7±13.7 mg/dl (P<0.001) in BB regimen.

The 6-point plasma glucose profiles were comparable between both treatment groups at baseline, during the study period and at the end of the study. In either group, the mean plasma glucose values were lower at all points after 12 wk of treatment than at the baseline.

Mean total doses of insulin were similar between the two treatment groups at the start of the study; 0.8±0.15 U/kg in the BHI group and 0.72±0.1 U/kg in the BB regimen. At the end of the study, the subjects required 0.94±0.21 U/kg in the BHI group and 1.18±0.36 U/kg in the BB group. However, the insulin dose increment from the baseline was more in the BB regimen 0.46±0.32 U/kg compared to 0.15±0.21 U/kg in the BHI regimen groups (P<0.001).

The mean body weight significantly increased in both the groups from 74.6±11.9 to 76.0±11.6 kg (P<0.001) in the BHI regimen and from 85.5±14.0 to 86.9±14.4 kg (P<0.001) in the BB regimen. The difference in weight gain between BHI regimen (1.45±0.33 kg) and BB regimen (1.38±0.34 kg) was not statistically significant. The body mass index increased by 0.58±0.61 kg/m^2 in the BHI group and 0.62±0.6 kg/m^2 in the BB regimen.

Major hypoglycaemic episodes were reported by two patients (one episode in each) in the BHI group and by three patients (one episode in each) in the BB group. None of the patients required hospital admission for these episodes. There was no statistically significant difference in hypoglycaemic episodes including major, minor or nocturnal episodes between both the groups.

Table III. Hypoglycaemic episodes by number of patients affected and number of episodes

	BHI			BB		
Characteristics	N (%)	E	Rate	N (%)	E	Rate
Major	2 (8)	2	0.35	3 (12)	3	0.52
Minor	20 (80)	53	9.2	15 (44)	37	6.4
Nocturnal	12 (48)	15	2.6	8 (32)	13	2.3

N, number of subjects with hypoglycaemic episodes; %, Proportion of subjects exposed in the given period having hypoglycaemic episodes; E, Number of hypoglycaemic episodes; Rate, Episodes per subject year of exposed subjects; Nocturnal hypoglycaemic episodes are defined as episodes occurring between 1000 and 0600 h, both times included

However, sub-hoc analysis of minor hypoglycaemic events showed significantly more number of documented symptomatic hypoglycaemic episodes in BHI regimen (P= 0.03) (Table II). No other adverse events were observed during the study. The numbers of hypoglycaemic episodes in both treatment groups are shown in Table III.

The cost for the insulin therapy per day at the baseline [₹ 23 (0.5 US$)] in BHI and [₹ 28 (0.61 US$) in BB regimen] was not significantly different between the two groups. But at the end of the study, cost of insulin therapy was [₹ 216.1 (4.71 US$)] in the BB regimen compared to [₹ 23.8 (0.52 US$)] for the BHI regimen which is nine times higher (P<0.001). None of the patients required hospital admission for major hypoglycaemia.

Discussion

This pilot study showed the efficacy and the safety of the biphasic human insulin thrice-daily in comparison with the basal detemir and bolus aspart for glycaemic control in patients with T2DM. There was no difference between the groups in glycaemic control, weight gain, major, minor or nocturnal hypoglycaemic episodes except for documented symptomatic hypoglycaemic episodes. The BHI regimen was less expensive as compared to the BB regimen.

With progressive deterioration in β cell mass/function, majority of the patients with T2DM require intensified insulin therapy usually in the form of basal bolus regimen either with analogues or conventional insulin. Alternative to this is use of biphasic insulin analogues twice/thrice daily[8] or biphasic human insulin twice a day with rapid acting human insulin before lunch[9]. Biphasic human insulin twice a day is

commonly used in the clinical practice. However, with changing lifestyle, most of the people now dine late at night consequently pre-dinner hyperglycaemia is not uncommon with this twice daily regimen as the effect of the morning NPH wanes off by that time. No studies using biphasic human insulin thrice daily are available as there is a theoretical risk of hypoglycaemia/s due to 'stacking' effect[10]. However, the insulin peaks and troughs seen following a single injection of insulin suspension isophane are attenuated with the use of multiple daily isophane injections and pharmacokinetics and pharmacodynamics become similar to long acting insulin analogues[11]. With the same analogy, we tried using biphasic human insulin (30:70) thrice a day thereby presuming that short acting insulin will take care of prandial hyperglycaemia and NPH will give a basal cover throughout the day.

The glycaemic control in terms of decline in HbA_1c and mean fasting plasma glucose was comparable between the two groups in the present study. There was a significant decline in fasting plasma glucose in both the groups, however, only eight (16%) patients could achieve $HbA_1c < 7$ per cent, four in each group at the end of the study possibly due to short duration of follow up.

The insulin doses were adjusted in the two treatment groups according to the 6-point plasma glucose profile. The insulin dose requirement and the dose increment during the study was more in the BB regimen compared to the BHI. As insulin analogues have similar potency as per dose by dose in comparison with conventional insulin, the dose at the end of the study should have been comparable. However, this was not observed in our study probably because of higher content of NPH (70%) in the BHI regimen as compared to detemir (40%) in the BB regimen. The other reason might be the short duration of action of aspart as compared to regular insulin, thereby requiring higher doses of basal insulin to control interprandial hyperglycaemia[12].

Intensive insulin therapy in patient with diabetes is usually associated with greater frequency of hypoglycaemic episodes as shown in DCCT[1] in T1DM and UKPDS[2] in T2 DM. It has also been shown previously that hypoglycaemic episodes were similar between biphasic insulin analogues thrice daily and basal bolus regimen[6]. But minor hypoglycaemic episodes were more in biphasic analogues thrice daily compared to biphasic human insulin twice daily, but this was not statistically significant[10]. Our study has shown that BHI thrice daily is equally safe when compared to the BB regimen in terms of hypoglycaemic episodes. The number of hypoglycaemic episodes were 12.1 and 9.2 episodes per patient year for the BHI and BB regimen, respectively, which were comparable to the other studies[6,10]. However subgroup analysis of minor hypoglycaemic events in our study showed more episodes of documented symptomatic hypoglycaemia in the patients treated with the BHI regimen, but all these episodes occurred during daytime and were managed by patients themselves.

The weight gain was similar in both the treatment groups. Therapy with detemir usually does not result in weight gain because of decreased risk of hypoglycaemia thereby reducing interprandial snacking and probably due to its selective appetite-modulating effect at hypothalamus[13,14]. Similar increase in weight was observed in both the groups despite significantly higher dose requirement in the BB regimen probably due to the beneficial effect of detemir on appetite. Also BHI thrice daily was much less expensive than the basal bolus analogues with comparable efficacy and safety.

The limitations of our study include less number of patients, higher HbA_1c at baseline and inability to achieve target HbA_1c as duration of the study was short. As patients with near target HbA_1c are more prone for hypoglycaemic episodes, the safety of this BHI thrice a day regimen in such subjects needs to be further explored.

In conclusion, the biphasic insulin thrice daily regimen was found to be similar to the basal bolus analogues regimen in term of safety and efficacy. However, more number of patients and longer duration of follow up are required to further substantiate the safety of this regimen.

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Reprint requests: Prof. Anil Bhansali, Department of Endocrinology, Postgraduate Institute of Medical Education & Research Chandigarh 160 012, India
e-mail: anilbhansali_endocrine@rediffmail.com