Designer Insulins Regimens in Clinical Practice - Pilot Multicenter Indian Study

SR Joshi *, S Kalra**, M Badgandi***, YS Rao****, M Chawla*****

Abstract

Background: Newer insulin analogues viz., premix insulin analogue (biphasic insulin aspart) and insulin glargine are now available in India. A multicenter all-India study was done to document the patient profile and responses to these analogues in routine clinical practice.

Methods: The study was conducted prospectively at 4 diabetes care clinics in different regions of India and collected data on the use of either of the two regimens A. Premix insulin analogue given twice-daily B. Basal-bolus analogue regimen (insulin aspart with every meal and insulin glargine once-a-day at bedtime). The centers collected all data at 3 time-points - baseline, 4 weeks later and end of 12 weeks. The study measures were FPG (fasting plasma glucose), PPPG (postprandial plasma glucose), HbA1c and insulin dose. FPG and PPPG were recorded at each of the three time points. HbA1c was recorded at baseline and end of study. Safety was assessed based on reported adverse drug reactions and occurrence of hypoglycaemias.

Results: Data of 145 patients was available for analysis (n=114 on premix insulin analogue and n=31 on basal-bolus analogue regimen). Baseline demography was comparable in the two groups. Both the regimens lowered all blood glucose parameters including HbA1c significantly as compared to baseline. However, the premix insulin analogue fared better than the basal-bolus regimen in lowering HbA1c (1.58 vs. 1.16% respectively; p<0.05). Also 41% more patients in the premix group could achieve target HbA1c of < 7% at the end of study. The mean insulin dose was lower with the premix analogue group at the end of 12 weeks. There was no significant difference between the two groups in terms of change in body weight. No major hypoglycaemias were reported and the percentage of patients experiencing a minor episode was lower with the premix analogue than the basal-bolus regimen both at 4 and 12 weeks (11.4 vs. 35.48%; 16.7 vs. 58.06% respectively). No adverse drug reactions were reported throughout the study.

Conclusion: We conclude that both premix analogue administered twice a day and four times a day basal bolus regimen appear to be a convenient, safe and effective way of initiating insulin therapy in people with type-2 diabetes. The premix analogues achieves target better than the basal bolus regimen as has better compliance.

INTRODUCTION

Studies like UKPDS have shown that most patients with type 2 diabetes will require insulin therapy at some point in their lifetimes because of the progressive nature of the disease and due to the decline in beta-cell function.1,2 As postprandial glycaemic control contributes significantly to overall glycaemic control as measured by glycosylated Haemoglobin (HbA1c), controlling postprandial glucose levels (PPPG) is important.3 The growing evidence supporting the importance of controlling postprandial glucose levels led to the development of rapid-acting insulin analogues, such as insulin aspart, lispro that targets PPPG. These analogues have a rapid onset and short duration of action and hence provides better control of postprandial glucose levels.4

Initiating and maintaining insulin therapy is often difficult. While one strives to achieve the most physiological regimen, the final outcome is often dependent on factors like patient acceptance and compliance. Basal-bolus regimens, while being physiological are difficult to comply with. On the other hand, premix insulin administered twice a day can
achieve similar if not better results because of better acceptance and compliance, especially in people with type 2 diabetes.

Biphasic insulin aspart is a novel premix insulin analogue formulation of insulin aspart containing 30% insulin aspart and 70% protaminated insulin aspart. When administered at mealtime this has been shown to lower postprandial glucose levels better than conventional premixed insulin 30/70 administered 30 min before meal. The premix insulin analogue, given twice-daily has been compared in a recent multicentric study with insulin glargine given once-daily in combination with oral antidiabetic drugs. This study demonstrated that the premix insulin analogue was more effective in achieving HbA1c targets especially in those with HbA1c > 8.5%. The premix insulin analogue is available in India as a prefilled new generation insulin delivery device called FlexPen® which has been shown to have better patient acceptance because it offers greater flexibility and convenience to the end-user. The first premix analogue launched in India is biphasic Aspart and also other premix analogues biphasic lispro 25 and biphasic lispro 50 are not yet available in India. Rapid acting analogues viz. Aspart (NovoRapid®), Lispro (Humalog®) and Glargine (Lantus®) are already available for basal bolus strategy of insulin. Given the availability and increasing use of these insulin analogues in day to day management of type 2 diabetes, we undertook a study of the patient profiles and responses to these analogues over a 3-month period in routine clinical practice setting.

**MATERIALS AND METHODS**

The study was conducted prospectively at 4 diabetes care clinics representative of tertiary clinical diabetes care practice in different regions of India after approval of ethics committees. The investigators agreed on a common data-capture format and on maintaining patient confidentiality. The study gathered data on consecutive patients prescribed either of the two regimens; 1. Premix insulin analogue given twice-a-day (biphasic insulin aspart containing 30% insulin aspart and 70% protaminised insulin aspart; NovoMix®30 manufactured by Novo Nordisk A/S, Denmark); 2. Basal-bolus analogue regimen consisting of insulin aspart (NovoRapid® manufactured by Novo Nordisk A/S, Denmark) as the basal insulin given with every meal and insulin glargine (Lantus®, manufactured by Sanofi Aventis Pharmaceuticals) as the basal insulin, given once-a-day. We compiled data of 145 consecutive patients recruited with type 2 diabetes who were prescribed either of the two regimens between March and August 2004. The dose of the insulin analogues was titrated as in routine clinical practice and based on the prescribing information and the clinician’s judgment and experience. The target was to reach a HbA1c of <7% with minimal risk of hypoglycemia using the least dose of insulin.

At the end of the study period, 114 patients had received the premix analogue and 31 patients had received the basal-bolus analogue regimen.

Patients were advised to inject the premix analogue (NovoMix® 30 manufactured by Novo Nordisk A/S, Denmark) upto 15 min before a meal either twice-daily using the FlexPen® insulin delivery device. Patients on basal-bolus regimen were advised to inject insulin aspart (NovoRapid® manufactured by Novo Nordisk A/S, Denmark) upto 15 min before every main meal using a FlexPen® and insulin glargine (Lantus®, manufactured by Sanofi Aventis Pharmaceuticals) only at bedtime using a vial and syringe.

The investigators collected all data at 3 time-points - beginning of the study period, 4 weeks later and at the end of 12 weeks.

The study measures included were FPG, PPPG, HbA1c and insulin dose. FPG and PPPG were recorded at each of the three time-points, HbA1c was recorded at baseline and at the end of 12 weeks. Laboratory testing was not centralized and blood glucose measures were obtained at the laboratory attached to the respective centers.

Safety was assessed based on reported adverse drug reactions during the study period and the occurrence of hypoglycaemic episodes. Hypoglycaemic episodes were classified into three groups – 1. symptoms of hypoglycaemia without blood glucose measurement or when measured, blood glucose levels >50 mg/dl and patient able to take care of himself; 2. minor hypoglycaemia, defined as blood glucose levels <50 mg/dl and patient able to take care of himself or herself; 3. major hypoglycaemia, defined as hypoglycaemia wherein the patient requires help from others. Compliance to prescribed therapy was assessed as in routine practice.

Statistical analysis: All values were expressed as mean ± SD. We compared baseline values between the two groups using independent samples t-test. The change in glucose control measures viz., FPG, PPPG, HbA1c and weight among the 3 visits within each group were compared using One-Way repeated measures ANOVA followed by a Bonferroni multiple comparisons test (pairwise comparisons). If the differences were significant, the changes in above measures between the groups from baseline to end of 4-weeks and from baseline to end of 12-weeks respectively were compared using independent samples t-test. All categorical variables – proportion of target HbA1c achievers, of patients with complications, of patients on prior oral antidiabetic drugs and insulin and of patients experiencing hypoglycemia between the groups were compared using Chi-square test. Wherever the Chi-Square test failed due to expected cell frequencies less than 5, the Fisher’s Exact probabilities were computed. All differences were
RESULTS

Data on a total of 145 subjects was available at the end of the study period for analysis. Baseline demography was comparable in the two groups as there was no statistically significant difference in the various parameters including age, duration of diabetes, weight and glycaemic parameters (Table 1).

The values for the efficacy measures are shown in Table 2. Both the regimens could lower all the blood glucose parameters including HbA1c significantly as compared to baseline.

However analysis of the change in various efficacy measures showed that premix insulin analogue fared better than the basal-bolus analogue therapy in lowering HbA1c (1.58% vs. 1.16% respectively, p<0.05). Also 41% more patients in the premix group could achieve target HbA1c of < 7% at the end of 12 weeks (45.61% vs. 32.26%).

The body weight did not change significantly in either group at the end of the study.

Throughout the study period of 12 weeks, there were no major hypoglycaemic episodes reported in both the treatment groups. The percentage of patients experiencing a minor hypoglycaemia was significantly lower in the premix group than in the basal-bolus group at 4 weeks (11.4% vs. 35.48%, p < 0.05) and also at 12 weeks (16.7% vs. 58.06%, p < 0.05) (Fig 1). Otherwise no adverse drug reactions were reported in both groups throughout the study period.

The two groups were comparable on usage of oral antidiabetic drugs which continued throughout the study for the majority of patients along with both the insulin regimens.

DISCUSSION

This study compared two different insulin analogue regimens in the management of type 2 diabetes in a routine clinical practice setting. Insulin therapy with the premix analogue given twice-daily lowered HbA1c to a greater extent as compared to basal-bolus analogue.

(p-values computed by * Independent samples t-test; ** Chi-square test; *** Fisher’s Exact test.)

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Premix analogue</th>
<th>Basal-bolus analogue</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>114 (76M, 38F)</td>
<td>31 (24M, 7F)</td>
<td>—</td>
</tr>
<tr>
<td>Age, years</td>
<td>52.41± 10.04</td>
<td>51.10 ± 14.04</td>
<td>0.63*</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td>9.53 ± 5.08</td>
<td>11.98 ± 9.01</td>
<td>0.15*</td>
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<tr>
<td>Weight, Kg</td>
<td>70.40 ± 12.18</td>
<td>69.63 ± 10.31</td>
<td>0.75*</td>
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<tr>
<td>FPG, mg/dl</td>
<td>186.59 ± 47.35</td>
<td>190.23 ± 55.63</td>
<td>0.72**</td>
</tr>
<tr>
<td>PPPG, mg/dl</td>
<td>287.29 ± 58.40</td>
<td>281.42 ± 68.76</td>
<td>0.63*</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>8.79 ± 1.13</td>
<td>8.53 ± 1.22</td>
<td>0.27*</td>
</tr>
<tr>
<td>Complications, n (%)</td>
<td>67 (58.77%)</td>
<td>18 (58.07%)</td>
<td>0.89*</td>
</tr>
<tr>
<td>Prior insulin, n (%)</td>
<td>62 (54.39%)</td>
<td>21 (67.74%)</td>
<td>0.26*</td>
</tr>
<tr>
<td>Prior OAD, n (%)</td>
<td>102 (89.47%)</td>
<td>25 (80.65%)</td>
<td>0.22***</td>
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Table 2: Glucose control measures

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4-weeks</th>
<th>12-weeks</th>
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<tbody>
<tr>
<td>FPG, mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premix analogue</td>
<td>186.59 ± 47.35</td>
<td>133.82 ± 23.97</td>
<td>114.83 ± 18.68</td>
</tr>
<tr>
<td>Basal-bolus analogue</td>
<td>190.23 ± 55.63</td>
<td>126.10 ± 20.10</td>
<td>110.61 ± 16.79</td>
</tr>
<tr>
<td>PPPG, mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premix analogue</td>
<td>287.29 ± 58.40</td>
<td>203.00 ± 36.24</td>
<td>171.54 ± 28.75</td>
</tr>
<tr>
<td>Basal-bolus analogue</td>
<td>281.42 ± 68.76</td>
<td>197.71 ± 34.20</td>
<td>177.52 ± 24.72</td>
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<tr>
<td>HbA1c, %</td>
<td></td>
<td></td>
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<tr>
<td>Premix analogue</td>
<td>8.79 ± 1.13</td>
<td>7.20 ± 0.83</td>
<td>7.20 ± 0.83</td>
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<td>Basal-bolus analogue</td>
<td>8.53 ± 1.22</td>
<td>7.37 ± 0.83</td>
<td>7.37 ± 0.83</td>
</tr>
<tr>
<td>Weight, Kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premix analogue</td>
<td>70.40 ± 12.18</td>
<td>70.54 ± 11.61</td>
<td>70.61 ± 11.23</td>
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<tr>
<td>Basal-bolus analogue</td>
<td>69.63 ± 10.31</td>
<td>69.65 ± 9.92</td>
<td>69.68 ± 9.58</td>
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<tr>
<td>Insulin dose, units/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premix analogue</td>
<td>38.23 ± 11.80</td>
<td>40.56 ± 14.10</td>
<td>40.19 ± 16.90</td>
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<tr>
<td>Basal-bolus total daily dose</td>
<td>57.39 ± 24.49</td>
<td>56.03 ± 27.33</td>
<td>52.77 ± 29.90</td>
</tr>
<tr>
<td>Basal analogue</td>
<td>23.32 ± 10.67</td>
<td>23.90 ± 10.94</td>
<td>24.52 ± 12.11</td>
</tr>
<tr>
<td>Bolus analogue</td>
<td>34.07 ± 17.52</td>
<td>32.13 ± 21.39</td>
<td>28.26 ± 23.23</td>
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(•: p<0.0001, **: p=0.001, p-values as compared to baseline within the same groups.)
regimen. The reductions in HbA1c (0.42%) provided a significant and clinically relevant treatment improvement for subjects in the premix analogue group, allowing significantly more premix analogue–treated subjects to achieve HbA1c target of <7% as recommended by American Diabetes Association (ADA). The results of our study (HbA1c difference of 0.42%) are comparable with those of a recent study of 28 week multicentric INITIATE study comparing the regimens with premix analogue with insulin glargine in type 2 diabetes and demonstrated that the twice-daily premix analogue was significantly more effective (HbA1c difference of 0.43%) than insulin glargine given once-daily at bedtime, as recommended. Similar to our study, INITIATE study also showed that more number of patients achieved target HbA1c levels of either <7% as recommended by ADA or <6.5% as recommended by the American college of endocrinology (ACE) with the premix analogue as compared to insulin glargine. Conventional premix insulin given twice-daily alone was compared in a recent study with insulin glargine given along with oral antidiabetic drugs (sulphonylureas and metformin). This study found that insulin glargine produced greater HbA1c reduction at the end of the study period of 24 weeks. However, the premix group was disadvantaged by not allowing use of oral antidiabetic drugs especially metformin which has been shown to be effective when combined with insulin. Furthermore the study compared the conventional premix and not the premix insulin analogue with insulin glargine. Studies have shown that the premix insulin analogue produces better postprandial control at a lower risk of hypoglycaemia than insulin glargine given once-daily at bedtime, as recommended. Similar to our study, INITIATE study also showed that more number of patients achieved target HbA1c levels of either <7% as recommended by ADA or <6.5% as recommended by the American college of endocrinology (ACE) with the premix analogue as compared to insulin glargine. Conventional premix insulin given twice-daily alone was compared in a recent study with insulin glargine given along with oral antidiabetic drugs (sulphonylureas and metformin). This study found that insulin glargine produced greater HbA1c reduction at the end of the study period of 24 weeks. However, the premix group was disadvantaged by not allowing use of oral antidiabetic drugs especially metformin which has been shown to be effective when combined with insulin. Furthermore the study compared the conventional premix and not the premix insulin analogue with insulin glargine. Studies have shown that the premix insulin analogue produces better postprandial control at a lower risk of hypoglycaemia than insulin glargine given once-daily at bedtime, as recommended. Similar to our study, INITIATE study also showed that more number of patients achieved target HbA1c levels of either <7% as recommended by ADA or <6.5% as recommended by the American college of endocrinology (ACE) with the premix analogue as compared to insulin glargine. Conventional premix insulin given twice-daily alone was compared in a recent study with insulin glargine given along with oral antidiabetic drugs (sulphonylureas and metformin). This study found that insulin glargine produced greater HbA1c reduction at the end of the study period of 24 weeks. However, the premix group was disadvantaged by not allowing use of oral antidiabetic drugs especially metformin which has been shown to be effective when combined with insulin. Furthermore the study compared the conventional premix and not the premix insulin analogue with insulin glargine. Studies have shown that the premix insulin analogue produces better postprandial control at a lower risk of hypoglycaemia than insulin glargine given once-daily at bedtime, as recommended. Similar to our study, INITIATE study also showed that more number of patients achieved target HbA1c levels of either <7% as recommended by ADA or <6.5% as recommended by the American college of endocrinology (ACE) with the premix analogue as compared to insulin glargine. Conventional premix insulin given twice-daily alone was compared in a recent study with insulin glargine given along with oral antidiabetic drugs (sulphonylureas and metformin). This study found that insulin glargine produced greater HbA1c reduction at the end of the study period of 24 weeks. However, the premix group was disadvantaged by not allowing use of oral antidiabetic drugs especially metformin which has been shown to be effective when combined with insulin.

Clinical studies in people with type 2 diabetes have shown that intensifying treatment is associated with a higher rate of hypoglycemia. Our results show that hypoglycemia will be lesser if patients are advised a twice-a-day premix analogue regimen as compared with a basal-bolus regimen.

The total daily dose of insulin used was greater in the basal-bolus analogue group as compared to the premix analogue group. While this might have been expected, the clinical implication is that the total burden of exogenous insulin to be handled by the body is much lesser with a premix analogue regimen as compared with a basal-bolus regimen. The lesser total dose along with the lesser number of injections makes the premix regimen a better option to the patient in terms of cost-savings, convenience and acceptance. Also by improving compliance with only 2 injections, the therapeutic outcome can be maximised with the premix analogues leading to optimal glycaemic control.

The laboratory testing of glucose control measures was not centralized in our study. However, this was not considered a limitation of the study as each patient was tested in the same center with the same method at all visits. We also recognize the other limitations of our study such as its uncontrolled design, short duration and possible investigator bias. However, it is well known that applying the findings from controlled studies to real time practice poses a difficult challenge to practicing physicians. Since our results are comparable with similar studies conducted under strictly controlled conditions, we believe our results offer additional evidence in favour of the premix analogue.

We conclude that among the newer insulin analogues available in India, the premix insulin analogue offers a better option to treat insulin-requiring type 2 diabetes in routine practice. The premix insulin analogue appears to be an appropriate insulin to initiate insulin therapy in people with type 2 diabetes.

Acknowledgement
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REFERENCES


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**Announcement**

*5th International Symposium on Diabetes*

**Venue:** Mumbai  
**Date:** 21st & 22nd January 2006  
**Theme:** Master Class for Clinicians and Educators for Emerging Treatments in Diabetes and Complications

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Prof. K. Sreekumaran Nair  
David Murdock Dole Professor of Medicine, Mayo Clinic College of Medicine  
Division of Endocrinology, Mayo Clinic, 200 First Street S.W.  
Rochester, MN 55905 USA

**Core faculty:**  
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