Efficacy and safety of insulin degludec U100 and insulin glargine U100 in combination with meal-time bolus insulin in hospitalized patients with type 2 diabetes: an open-label, randomized controlled study

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Abstract. The short-term efficacy and safety of insulin degludec U100 (IDeg) in patients with type 2 diabetes have not been reported widely. We compared insulin IDeg and insulin glargine U100 (IGla) for glycemic control and glucose variability in hospitalized patients with type 2 diabetes. In an open-label, multicenter, randomized controlled trial, 74 patients were randomly assigned to either the IDeg (36 patients) or IGla (38 patients) group and were administered with basal-bolus therapy during hospitalization. Following the start of the treatment, on day 11, glucose variability was assessed by continuous glucose monitoring. A fasting blood glucose level of 110 mg/dL and 2-hour postprandial blood glucose level of 180 mg/dL throughout at least one day during the observation period were achieved in 31.3% (10/32) and 30.6% (11/36) of the patients in the IDeg and IGla groups, respectively. The 6-point self-monitoring of blood glucose profiles showed a significant difference between the two groups. On day 7, the intra-day variation was larger in the IDeg group than in the IGla group. The incidence of hypoglycemia or glucose variability was comparable in the two groups. This study suggests that short-term efficacy and safety of IDeg and IGla in patients with type 2 diabetes during the initial phase of basal-bolus therapy were comparable, and these results can help in deciding which treatment to opt for.

Key words: Insulin degludec U100, Insulin glargine U100, Type 2 diabetes

THE PRINCIPAL CAUSES OF TYPE 2 DIABETES are decreased insulin secretion from the pancreas and increased insulin resistance. Insulin resistance can be improved to a certain extent by diet \([1, 2]\) and exercise \([3-5]\), or use of an insulin resistance-improving agent.

However, insulin secretion decreases with age \([6]\). In particular, lower pancreatic insulin secretion due to genetic factors has been reported much more among the Japanese population than among the North American and European populations \([7]\). Furthermore, it is difficult to improve insulin secretion with existing oral antidiabetic drugs.

There is also evidence that a persistent hyperglycemic state contributes to the induction of β cell dedifferentiation \([8, 9]\). However, β cell re-differentiation is possible after the normalization of blood glucose level and elimi-
nation of glucotoxicity [9, 10]. Moreover, multiple daily insulin injections (MDIs) are often given to patients with type 2 diabetes in order to achieve rapid normalization of glycemia and preservation of β-cell function.

Previously, neutral protamine Hagedorn (NPH) insulin was widely used to supplement basic secretion of insulin. This was subsequently replaced by insulin glargine U100 (IGla) and insulin detemir, which are long-acting soluble types of insulin. However, these products not only result in unstable insulin concentrations in the blood [11] but also had a short duration of action [12, 13], often making glycemic control difficult. Moreover, when long-acting insulin is administered before sleep, hypoglycemia frequently occurs between midnight and early morning. In addition, a hyperglycemic state occurs around the time of the evening meal, on the following day [11].

Insulin degludec U100 (IDeg), was developed as an ultra-long-acting basal insulin. After subcutaneous injection, it forms soluble multi-hexamers that slowly dissociate into monomers, resulting in a flat and consistent insulin action profile [14]. IDeg has a half-life of 24 hours, while IGla has a half-life of only 12 hours, and its glucose-lowering effects are stronger during the first 12 hours after injection than during the subsequent 12 hours [15, 16]. Compared to IGla, IDeg has a flat insulin action curve and a fourfold smaller pharmacodynamic variability [17], resulting in a similar efficacy but a lower risk of hypoglycemia [18-20].

In Japan, insulin therapy is often initiated during hospitalization for approximately two weeks to help with the management of dysglycemia and to assist elderly patients in learning the proper use of insulin devices. However, owing to its long half-life, titration of IDeg is time consuming. It is generally accepted that titration should allow the monitoring of glycemia over 2–3 days, so IDeg may be unsuited for titration every 1–2 days during hospitalization because of its long duration of action. Therefore, we performed this study to evaluate the short-term efficacy and safety of IDeg administered at the start of basal-bolus therapy in patients with type 2 diabetes who required hospitalization due to poor glycemic control.

Materials and Methods

Patients

This study involved subjects with type 2 diabetes, aged ≥20 but <80 years, hospitalized for control of glycemia at either the Yokohama City University Medical Center or the Fujisawa City Hospital. The inclusion criteria were (1) insulin naïve, drug-free, or treated only with an oral antidiabetic drugs, (2) HbA1c levels ≥8.0% and <14.0% on admission, and (3) fasting blood glucose levels ≥200 mg/dL or a 2-hour postprandial blood glucose of ≥300 mg/dL, 2 days after admission and requiring insulin therapy due to poor glycemic control. The exclusion criteria were: (1) history of diabetic ketoacidosis or diabetic coma within 6 months prior to selection for this study, (2) severe infection or severe trauma, (3) scheduled to undergo surgery during the observation period of this study, (4) severe liver dysfunction (Child-Pugh score class C), (5) renal insufficiency (serum creatinine >2.0 mg/dL or estimated glomerular filtration rate [eGFR] <30 mL/min), (6) pregnant or breast-feeding, and (7) history of hypersensitivity to IGla or IDeg.

This study was performed in accordance with the ethics and principles of the Declaration of Helsinki, and the study protocol was approved by the Ethics Committees of the Yokohama City University School of Medicine and the Fujisawa City Hospital. All patients gave written informed consent, and patient anonymity was preserved. The protocol was registered with the UMIN Clinical Trial Registry as UMIN000010447.

Study protocol

This open-label, multicenter, randomized controlled trial was designed to assess the efficacy and safety of IGla and IDeg, though comparing the two agents was not the primary objective. All patients were hospitalized and randomly assigned to an IGla or an IDeg group (1:1 ratio) by a minimization method stratified according to fasting plasma glucose (FPG), age, and sex. The allocation was performed at the data center for clinical trials of the Yokohama City University.

During hospitalization, participants were tested 6 times daily, before every meal and 2 hours after every meal using a finger-stick glucose monitoring kit (Glutest Every; Sanwa Kagaku Kenkyusho, Aichi, Japan). Diet therapy with a pre-determined energy content (ideal body weight) × 25–27 kcal/day) was also initiated upon admission. Meal times were as follows: breakfast 8:00 am, lunch 12:00 pm, and dinner 6:30 pm. The first two days were used for observation, and the basal-bolus therapy was started on the third day. The first day of insulin treatment was considered as day 1, with day 0 being the baseline. All oral antidiabetic drugs were discontinued before the commencement of insulin treatment. Insulin titration was performed by an expert endocrinologist; basal insulin (IGla or IDeg) was administered before sleep, and insulin aspart, insulin lispro, or insulin glulisine was administered as bolus insulin. Insulin treatment was commenced with 4 units of bolus insulin before each meal, and 4 units of basal insulin. Basal insulin was adjusted based on the glycemia measured before breakfast. Bolus insulin was titrated in accordance
with the algorithm presented in Table 1, based on blood glucose levels, before lunch, before dinner, and 2 hours after dinner for the morning, afternoon, and evening administrations, respectively. Considering the half-life of IDeg, the quantity of insulin was adjusted every 2 days. On Day 11, continuous glucose monitoring (CGM) was performed using iPro2 (Medtronic Minimed, Northbridge, CA, USA).

Table 1 The insulin adjustment algorithm

| Adjustment of basal insulin (insulin glargine U100 or insulin degludec U100) | Blood glucose before breakfast |
| --- | --- |
| <80 mg/dL | Decrease by 2 units |
| 80–109 mg/dL | No adjustment |
| 110–140 mg/dL | Increase by 1 unit |
| 141–180 mg/dL | Increase by 2 units |
| 181–250 mg/dL | Increase by 3 units |
| ≥251 mg/dL | Increase by 4 units |

| Adjustment of bolus insulin |
| --- |
| Bolus insulin adjustment before breakfast |
| Blood glucose before lunch |
| <56 mg/dL | Decrease by 4 units |
| 56–79 mg/dL | Decrease by 2 units |
| 80–109 mg/dL | No adjustment |
| 110–140 mg/dL | Increase by 1 unit |
| 141–180 mg/dL | Increase by 2 units |
| 181–250 mg/dL | Increase by 3 units |
| ≥251 mg/dL | Increase by 4 units |

| Bolus insulin adjustment before dinner |
| --- |
| Blood glucose before dinner |
| <56 mg/dL | Decrease by 4 units |
| 56–79 mg/dL | Decrease by 2 units |
| 80–109 mg/dL | No adjustment |
| 110–140 mg/dL | Increase by 1 unit |
| 141–180 mg/dL | Increase by 2 units |
| 181–250 mg/dL | Increase by 3 units |
| ≥251 mg/dL | Increase by 4 units |

| Blood glucose 2 hours after dinner |
| --- |
| <56 mg/dL | Decrease by 2 units |
| 56–79 mg/dL | Decrease by 1 unit |
| 80–180 mg/dL | No adjustment |
| 181–250 mg/dL | Increase by 1 unit |
| ≥251 mg/dL | Increase by 2 units |

The primary endpoint was the achievement of target glycemic control during the first 12 days and the time (days) taken to achieve it. Target glycemic control included fasting blood glucose below 110 mg/dL and 2-hour postprandial blood glucose below 180 mg/dL, throughout a day. Glycemic control was assessed by a 6-point self-monitoring of blood glucose (SMBG). This was based on the blood glucose levels reported to be efficacious for inhibiting the development of microvascular complications, in the Kumamoto Study [21]. The secondary endpoints were average fasting and 2-hour postprandial blood glucose levels, and the parameters of glucose variability as standard deviation (SD), the coefficient of variation (CV), and mean amplitude of glucose excursions (MAGE) in the SMBG data at baseline (day 0), day 7, and day 12. The changes from baseline were also evaluated on day 7 and day 12. The frequency of hypoglycemia was considered as the endpoint for assessing the safety of IDeg and IGla.

Statistical methods

The primary analysis calculated the proportion of patients who achieved the target glycemic control in the IDeg and IGla groups. These proportions were tested against the null hypothesis value of 20% (this value was pre-determined clinically). Each drug was considered effective if the proportion of patients achieving target glycemic control exceeded 20% with a one-sided p-value <0.05. Time to achievement of target glycemic control was summarized and compared using the t-test. A secondary analysis compared the proportions of patients who achieved glycemic control in the two groups, using the Chi-squared test. It also compared the incidence of hypoglycemia, 6-point SMBG profiles (adjusted mean and its error, change from baseline, SD, CV, and MAGE on day 7 and day 12), insulin units, CGM profiles (glucose mean, SD, CV, MAGE, and hypoglycemia duration in minutes). Comparisons were performed using the t-test and Wilcoxon test. We also performed post hoc analysis: analysis of covariance adjusting for the unbalanced baseline characteristics.

The sample size was calculated based on the assumption that the true probability of achieving the target glycemic control was 40% in each group [22-24]. The required sample size was at least 30 in each group to test against the null hypothesis probability of 20% with a statistical power of 80% at the one-sided alpha of 5%. Analyses were performed using SAS version 9.4 (SAS institute, Cary, NC, USA).
Results

Patient characteristics

A total of 74 patients were randomized between April 2013 and March 2015. Of these, 2/38 patients in the IGla group and 4/36 patients in the IDeg group dropped out before completion of the study, due to withdrawal of consent (n = 2), emergency surgery (n = 2), violation of the rules on starting medication (n = 1), and missing data (n = 1) (Fig. 1). These patients were excluded from the final analysis. After obtaining consent, 24-hour CGM was performed in 50/68 subjects who completed this study (28 in the IGla group and 22 in the IDeg group), starting at 6:00 pm on Day 11.

The baseline characteristics of the 74 subjects are shown in Table 2. Significant differences between the IGla and IDeg groups in the levels of HbA1c (10.4 ± 1.9 vs. 11.3 ± 1.4, p = 0.019) and eGFR (72.8 ± 17.3 vs. 82.8 ± 17.6, p = 0.024) were noted. Furthermore, there were more patients on sulfonylurea drugs in the IGla group compared to the IDeg group (20 patients [57.1%] vs. 8 patients [25.8%]). No other significant differences were noted between the two groups.

In the IGla group, the rapid-acting insulin types used were insulin aspart in 10 (26.3%) patients, insulin lispro in 28 (73.7%), and insulin glulisine in 0 (0%) patients. In the IDeg group, those used were insulin aspart in 11 (30.6%) patients, insulin lispro in 25 (69.4%) patients, and insulin glulisine in 0 (0%) patients.

Glycemic control and frequency of hypoglycemia

While 11/36 (30.6%) patients achieved target glycemic control in the IGla group [90% confidence interval (CI) 18.2%–45.5%, one-sided p-value = 0.057], 10/32 (31.3%) patients achieved the same in the IDeg group [90% CI, 18.0%–47.2%, one sided p-value = 0.056] (Table 3a). The difference between the two groups was not statistically significant (Chi-squared p-value = 0.951). The average number of days ± SD to achieve target glycemic control in the IGla and IDeg groups was 8.0 ± 3.4 and 8.7 ± 1.6, respectively (p = 0.559) (Table 3a).

The frequency of hypoglycemia (blood glucose ≤70 mg/dL) during the insulin titration period (day 1 to day 12) was calculated. While 15 (41.7%) and 13 (40.6%) patients in the IGla and IDeg groups, respectively had hypoglycemia from 54 to 70 mg/dL, 4 (11.1%) and 3 (9.4%) patients in the IGla and IDeg groups, respectively had hypoglycemia lower than 54 mg/dL (p = 0.782,
Mantel-Haenszel Chi-squared test) (Table 3a). The number of hypoglycemic events per patient was 0.5 (0–7) in the IGla group and 0.5 (0–5) in the IDeg group ($p = 0.932$), with no significant difference.

Table 2  Baseline characteristics of the patients

|                        | Total                      | Insulin glargine U100 group (n = 38) | Insulin degludec U100 group (n = 36) | $p$ value |
|------------------------|----------------------------|-------------------------------------|-------------------------------------|-----------|
| Male                   | 19 (52.8%)                 | 19 (59.4%)                          | 0.631                               |
| Age (years)            | 61.8 ± 9.4                 | 58.9 ± 10.5                         | 0.248                               |
| BMI (kg/m$^2$)         | 24.8 ± 3.5                 | 25.7 ± 5.0                          | 0.382                               |
| Disease duration (years)| 6.6 ± 8.2                  | 3.9 ± 4.6                           | 0.110                               |
| FPG (mg/dL)            | 207.0 ± 89.4               | 185.8 ± 43.2                        | 0.226                               |
| HbA1c (%)              | 10.4 ± 1.9                 | 11.3 ± 1.4                          | 0.019                               |
| eGFR (mL/min/1.73 m$^2$)| 72.8 ± 17.3                | 82.8 ± 17.6                         | 0.024                               |
| Fasting CPR (ng/mL)    | 2.5 ± 0.8                  | 2.5 ± 1.1                           | 0.815                               |
| CPR index              | 1.35 ± 0.50                | 1.36 ± 0.59                         | 0.751                               |
| Urine albumin (mg/gCr) | 53.8 ± 176.1               | 19.8 ± 43.1                         | 0.333                               |
| Urine albumin, median [range] | 8.7 [0–983.4] | 7.2 [0–215.9] | 0.694 |

Oral antidiabetic drugs before the start of the study; n (%)

|                        | Total                      | Insulin glargine U100 group (n = 38) | Insulin degludec U100 group (n = 36) | $p$ value |
|------------------------|----------------------------|-------------------------------------|-------------------------------------|-----------|
| Metformin              | 8 (22.9%)                  | 6 (18.8%)                           | 0.769                               |
| Sulfonylurea           | 20 (57.1%)                 | 8 (25.8%)                           | 0.013                               |
| DPP-4 inhibitor        | 15 (42.9%)                 | 13 (40.6%)                          | 1.000                               |
| α-Glucosidase inhibitor| 7 (20.6%)                  | 4 (12.9%)                           | 0.516                               |
| Pioglitazone           | 2 (5.9)                    | 4 (12.5)                            | 0.420                               |
| Glinide                | 1 (2.9%)                   | 0 (0%)                              | 1.000                               |

Complications; n (%)

|                        | Total                      | Insulin glargine U100 group (n = 38) | Insulin degludec U100 group (n = 36) | $p$ value |
|------------------------|----------------------------|-------------------------------------|-------------------------------------|-----------|
| Diabetic retinopathy   | 7 (21.2%)                  | 3 (10.7%)                           | 0.319                               |
| Urinary albumin below 30 mg/gCr | 22 (61.1%) | 22 (68.8%) | 0.199 |
| 30–299 mg/gCr          | 8 (22.2%)                  | 9 (28.1%)                           | 1.000                               |
| above 300 mg/gCr       | 6 (16.7%)                  | 1 (3.1%)                            | 1.000                               |

CGM evaluated patients

|                        | Total                      | Insulin glargine U100 group (n = 28) | Insulin degludec U100 group (n = 22) | $p$ value |
|------------------------|----------------------------|-------------------------------------|-------------------------------------|-----------|
| Male                   | 14 (50%)                   | 14 (63.6%)                          | 0.398                               |
| Age (years)            | 61.1 ± 10.1                | 57.6 ± 12.1                         | 0.273                               |
| BMI (kg/m$^2$)         | 25.0 ± 3.2                 | 25.9 ± 5.5                          | 0.434                               |
| Disease duration (years)| 6.0 ± 8.3                  | 4.7 ± 5.0                           | 0.526                               |
| HbA1c (%)              | 10.3 ± 1.9                 | 11.4 ± 1.3                          | 0.031                               |
| FPG (mg/dL)            | 202.0 ± 87.9               | 185.4 ± 44.7                        | 0.423                               |

Data are presented as mean ± SD

BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; CPR, C-peptide immunoreactivity; CGM, continuous glucose monitoring.

CPR index: C-peptide immunoreactivity index; serum C-peptide immunoreactivity/fasting plasma glucose × 100

All oral antidiabetic drugs were stopped before starting insulin treatment.
Six-point SMBG profile data

The 6-point SMBG profiles at baseline (day before starting of insulin treatment, day 0), day 7, and day 12, with mean, SD, CV, and MAGE as indices of glucose variability on each day, are shown in Table 3b. Comparisons between the groups were adjusted with the baseline levels of HbA1c. No significant differences were noted between the Igla and IDeg groups on both days 7 and 12; but a significant difference was noted in the SD on day 7 (Igla group: 36.9 ± 2.7%, IDeg group: 45.3 ± 2.9%, \( p = 0.041 \)) and in CV on day 7 (Igla group: 25.7 ± 1.6%, IDeg group: 30.8 ± 1.7%, \( p = 0.037 \)) (Table 3b). Groups with and without adjustment for baseline HbA1c had comparable results.

Insulin units

The number of insulin units administered on day 1, 7, and 12 is shown in Table 3c. No significant differences were noted between the two groups in the total daily insulin dose. There was also no significant difference in the basal and bolus insulin doses.

CGM glucose data

Data on glucose variability parameters (mean, SD, CV, and MAGE) for the 50 patients (28 and 22 in the Igla and IDeg groups, respectively) in whom CGM was performed for 24 hours starting at 6 pm on day 11 are shown in Table 4. The CGM profiles are shown in Fig. 2. No differences were seen in glucose variability between the two groups, throughout the period of either hypoglycemia or hyperglycemia, even during the night (0 am–6 am).

Discussion

In this open-label randomized controlled trial, the primary endpoint was the proportion of patients who achieved target glycemic control, which exceeded the pre-specified threshold for both groups, although it was not statistically significant. Furthermore, there was no significant difference in the frequency of glycemic control between the two groups. The 6-point SMBG profiles showed no significant differences in the mean blood glucose levels at baseline (day 0) and on days 7 or 12. However, the glucose variability parameters such as SD and CV on day 7 were significantly greater in the IDeg group than in the Igla group. No significant differences were noted in (a) the number of insulin units used on day 7 or day 12, (b) incidence of hypoglycemia, (c) any of the glucose variability parameters (mean, SD, CV, and MAGE), (d) duration of hypoglycemia, and (e) the results of CGM performed between day 11 and day 12.

In Japan, insulin therapy is often started during hospitalization. For all patients, this helps with the management of dysglycemia. For elderly people, it also helps in learning how to use the insulin devices properly. To date, Igla has been used in many cases when introducing basal-bolus treatment in hospitals. Igla is one of the standard long-acting soluble insulins, and its safety has been established [25]. It is frequently used owing to its

| Table 3 | Data on study endpoints |
|---------|------------------------|
| (a) Proportion of patients achieving target glycemic control and frequency of hypoglycemia |
| | Insulin glargine U100 group \((n = 36)\) | \( p \) value | Insulin degludec U100 group \((n = 32)\) | \( p \) value |
| Proportion of patients achieving target glycemic control | | | | |
| Achieved \((n, \%)\) | 11 (30.6%) | 0.057* | 10 (31.3%) | 0.056* |
| Not achieved \((n, \%)\) | 25 (69.4%) | | 22 (68.7%) | |
| Days to achievement \((mean ± SD)\) | 8.0 ± 3.4 | | 8.7 ± 1.6 | 0.559 |
| Frequency of hypoglycemia | | | | |
| Patients \((n, \%)\) | | | | |
| No hypoglycemia | 17 (47.2%) | | 16 (50.0%) | 0.782 |
| Hypoglycemia (from 54 to 70 mg/dL) | 15 (41.7%) | | 13 (40.6%) | |
| Hypoglycemia (lower than 54 mg/dL) | 4 (11.1%) | | 3 (9.4%) | |
| Events per patient \((median [min–max])\) | | | | |
| 70 mg/dL or below† | 0.5 [0–7] | | 0.5 [0–5] | 0.931 |
| lower than 54 mg/dL | 0 [0–1] | | 0 [0–1] | 0.825 |

*\( p \) value for the null hypothesis: proportion of patients achieving target glycemic control 20%
†includes less than 54 mg/dL
comparatively short half-life, which makes insulin adjustment every 1–2 days easy. In recent years, however, IDeg has appeared on the market as the new, long-acting, soluble insulin, with a better stable concentration in the blood compared to IGla [14-17]. However, most of the evidence is based on comparatively long-term studies.

IDeg has a long duration of action of at least 42 hours, [26] and a steady state is achieved after 2–3 days of once a day administration [27]. However, this increases the risk of erratic glycemic variations, thereby enhancing the risk of hypoglycemia and requiring titration every 1–2 days. There are concerns that this could be a disadvantage for the short-term use of IDeg.

In this study, the proportion of patients who achieved target glycemic control during insulin titration in the hospital was not statistically significant because our expected value of 40% was higher than the results observed. Glycemic control was similar in the two groups, and there was no significant difference in the number of days taken to achieve this target as shown in Table 3a.

Regarding safety, previous studies have shown that the risk of hypoglycemia particularly nocturnal, is lower with IDeg than with IGla [18-20]. This finding has also been reported in Phase III studies on IDeg [22, 28, 29]. Moreover, IDeg is safer than IGla with respect to frequency of severe hypoglycemia in a long-term study in patients with type 2 diabetes [30]. In this study, the incidence of hypoglycemia was low and showed no difference between the two groups. This could be due to the short trial period and controlled titration, preventing

| Table 3 | (b) 6-point Self-monitoring of blood glucose (SMBG) profile data |
|---------|---------------------------------------------------------------|
|         | Insulin glargine U100 group (n = 36)                          | Insulin degludec U100 group (n = 32) | p value for group comparison adjusted with baseline HbA1c |
| Day 0   | Day 7 | Day 12 | Day 0   | Day 7 | Day 12 | Day 0   | Day 7 | Day 12 |
| Before breakfast (mg/dL) | 196.9 ± 8.2 | 127.3 ± 6.0 | 113.5 ± 4.3 | 180.6 ± 9.1 | 119.6 ± 6.4 | 108.1 ± 4.7 | 0.200 | 0.386 | 0.402 |
| Change from Day 0 (%) | -30.9 ± 3.4 | -36.7 ± 2.9 | -30.7 ± 3.7 | -39.4 ± 3.3 | 0.979 | 0.566 |
| After breakfast (mg/dL) | 282.9 ± 14.5 | 162.0 ± 9.3 | 150.7 ± 8.9 | 278.5 ± 16.1 | 168.3 ± 9.9 | 169.2 ± 9.2 | 0.844 | 0.648 | 0.154 |
| Change from Day 0 (%) | -38.3 ± 4.6 | -41.5 ± 5.3 | -35.9 ± 5.1 | -35.0 ± 5.7 | 0.740 | 0.425 |
| Before lunch (mg/dL) | 243.7 ± 18.3 | 142.5 ± 7.6 | 114.8 ± 9.8 | 222.5 ± 20.3 | 131.3 ± 7.9 | 131.6 ± 9.8 | 0.453 | 0.319 | 0.235 |
| Change from Day 0 (%) | -31.3 ± 4.3 | -42.8 ± 5.7 | -42.4 ± 4.6 | -41.5 ± 6.0 | 0.089 | 0.882 |
| After lunch (mg/dL) | 269 ± 13.5 | 141.3 ± 10.0 | 135.5 ± 9.4 | 279.1 ± 14.9 | 168.1 ± 10.5 | 132 ± 9.8 | 0.629 | 0.069 | 0.805 |
| Change from Day 0 (%) | -39.6 ± 4.6 | -47.1 ± 4.7 | -40.9 ± 5.0 | -50.3 ± 5.3 | 0.852 | 0.665 |
| Before dinner (mg/dL) | 194.0 ± 12.3 | 118.4 ± 6.3 | 132.8 ± 10.9 | 180.5 ± 13.2 | 134.6 ± 6.6 | 127.4 ± 11.5 | 0.467 | 0.084 | 0.739 |
| Change from Day 0 (%) | -29.0 ± 4.4 | -27.9 ± 6.4 | -24.2 ± 4.5 | -29.9 ± 6.7 | 0.462 | 0.833 |
| After dinner (mg/dL) | 269.3 ± 11.2 | 158.9 ± 10.0 | 167.6 ± 10.8 | 281.0 ± 12.0 | 184.3 ± 10.5 | 145.6 ± 11.3 | 0.491 | 0.086 | 0.169 |
| Change from Day 0 (%) | -38.5 ± 4.7 | -36.5 ± 4.7 | -32.7 ± 4.8 | -48.6 ± 5.0 | 0.398 | 0.092 |
| 6-point SMBG mean (mg/dL) | 242.8 ± 11.6 | 141.9 ± 5.2 | 136.7 ± 5.6 | 237 ± 12.9 | 148.0 ± 5.5 | 136.6 ± 6.0 | 0.746 | 0.433 | 0.996 |
| SD (mg/dL) | 56.4 ± 3.7 | 36.9 ± 2.7 | 38.3 ± 4.0 | 57.7 ± 4.1 | 45.3 ± 2.9 | 41.3 ± 4.3 | 0.814 | 0.041 | 0.605 |
| CV (%) | 23.2 ± 1.1 | 25.7 ± 1.6 | 27.5 ± 2.2 | 25.0 ± 1.2 | 30.8 ± 1.7 | 29.4 ± 2.3 | 0.273 | 0.037 | 0.557 |
| MAGE (mg/dL) | 78.7 ± 5.9 | 53.9 ± 4.8 | 58.0 ± 6.6 | 74.1 ± 6.6 | 67.5 ± 5.2 | 57.1 ± 7.1 | 0.618 | 0.059 | 0.929 |

Data are presented as LS-Mean ± SE. LS, least square; CV, coefficient of variation; MAGE, mean amplitude of glucose excursions.
hypoglycemic episodes from developing.

Increased glucose fluctuation is known to be associated with elevated risks of mortality [31] and cardiovascular disorders [32]. Although several reports have compared daily glucose variability with the use of IDeg or IGla, almost all of them involved patients with type 1 diabetes. Furthermore, the reported variability was significantly smaller with IDeg than with IGla [33-35]. Following a treat-to-target trial in insulin-naïve Japanese patients with type 2 diabetes, Aso et al. have reported that the CV values 24 weeks after starting insulin treatment were significantly smaller in the IDeg group than in the IGla group [36].

A short-term comparison of IGla and IDeg, in a randomized study of insulin naïve patients with type 2 diabetes has shown that IDeg provided glycemic control comparable to that by IGla, without increasing the frequency of hypoglycemia [37], although the study period was only 16 weeks. In a prospective observational study by Yamamoto et al., on in-patients with type 1 diabetes, CGM revealed that MAGE significantly decreased when switching from IGla to IDeg [35]. There have not been many similar reports for type 2 diabetes [38], and this is the first randomized clinical trial report, comparing the efficacy and safety of IGla and IDeg over a short term in patients with type 2 diabetes.

The SD and CV on day 7 were higher in the IDeg group, indicative of greater glucose fluctuation, some of which might be explained by higher baseline HbA1c, to begin with. However, the differences continued to be significant even after adjustment for baseline HbA1c. Additionally, no significant differences were observed in the SD and CV on day 12. Therefore, when administering IDeg, it might be necessary to check for hypoglycemia in the ultra-short period, which is within 7 days.

In the present study, IGla and IDeg were administered before sleep. However, since IDeg is long acting, administration before sleep is not imperative, and instead can be timed according to the convenience of the patients or their family members (in cases where self-administration is not possible). It has been reported that somewhat irregular administration does not adversely affect safety and efficacy [39-41]. Furthermore, the subjects in the present study were patients with type 2 diabetes, who retained some degree of insulin secretion capability. However, a report involving patients with type 1 diabetes showed that HbA1c levels, glucose profiles, the risk of hypoglycemia, and the degree of satisfaction with treatment, improved by switching from IGla or insulin detemir twice daily to IDeg once daily [42]. These findings indicate that the efficacy and safety of IDeg are comparable to those of IGla in the short term when insulin is introduced and that the use of IDeg is likely to improve the patients’ quality of life.

This study has some limitations. First, differences in the baseline HbA1c or use of oral antidiabetic drugs

| Table 3 | Insulin units administered |
|---------|---------------------------|
|         | Insulin glargine U100 group (n = 36) | Insulin degludec U100 group (n = 32) | p value |
| Total   | Day 7 (units) | 27.2 ± 9.5 | 26.1 ± 9.1 | 0.631 |
|         | Day 12 (units) | 28.5 ± 13.3 | 28.3 ± 13.9 | 0.940 |
| Basal insulin (IGla or IDeg) | Day 7 (units) | 7.3 ± 3.1 | 6.3 ± 3.0 | 0.167 |
|         | Day 12 (units) | 7.9 ± 4.6 | 6.4 ± 4.7 | 0.181 |
| Bolus insulin-Breakfast | Day 7 (units) | 7.0 ± 3.0 | 7.2 ± 2.9 | 0.798 |
|         | Day 12 (units) | 7.3 ± 4.3 | 8.0 ± 3.8 | 0.510 |
| Bolus insulin-Lunch | Day 7 (units) | 5.6 ± 2.1 | 5.7 ± 2.5 | 0.936 |
|         | Day 12 (units) | 5.6 ± 2.5 | 5.9 ± 3.6 | 0.639 |
| Bolus insulin-Dinner | Day 7 (units) | 7.3 ± 2.6 | 7.0 ± 2.5 | 0.624 |
|         | Day 12 (units) | 7.7 ± 3.6 | 8.0 ± 3.6 | 0.754 |

Data are presented as mean ± SD. IGla, insulin glargine U100; IDeg, insulin degludec U100
might have influenced the results. Further research using a larger sample size is required to validate these differences. Second, some of the improvement in glycemic control could be attributed to dietary changes, although diet therapy was started to match these conditions. Third, although CGM was carried out in this study, it could not be done for all cases, raising the possibility that insufficient data were obtained for comparing the two groups. Moreover, IGla U300 is presently commercially available in Japan, thereby increasing the options for long-acting insulin.

In conclusion, the present study showed that the efficacy and safety of IDeg and IGla are comparable in a 14-day time frame following the initial introduction of insulin. These short-term findings are meaningful because they show that an appropriate long-acting agent can be selected based on the existing reports regarding its long-term efficacy and safety [22, 43].

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Fig. 2 Comparison of 24-hour continuous glucose monitoring (CGM) profiles. Shown are the glucose levels for patients in the insulin degludec U100 (IDeg) and insulin glargine U100 (IGla) groups on day 11, 6 pm to day 12, 6 pm.

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Degludec U100 & glargine U100 efficacies

891

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