Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.1794-18
Intern Med 58: 2943-2948, 2019
http://internmed.jp

【 ORIGINAL ARTICLE 】

The Effect of High-concentration Insulin Glarigine on the Quality of Life of Patients with Type 2 Diabetes Mellitus: A Pre-post Study (HIGH-QOL STUDY)

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Abstract:

Objective We compared the pain accompanying the injection of high-concentration (300 units/mL) insulin glargine (U300G) with that accompanying the injection of conventional (100 units/mL) insulin glargine (U100G).

Methods U100G was switched to U300G at basically the same dosage. Visual analog scales were used to assess the quality of life (QOL). The primary outcome was the change in the pain accompanying injections in those using ≥30 units of U100G compared with those using <30 units at baseline. Standardized mean differences (Cohen's d) were used to measure the effect size.

Patients Adult patients with type 2 diabetes mellitus using U100G.

Results One hundred and eight patients were recruited. The numbers of patients who used U100G at ≥30 units, 20 to <30 units, 10 to <20 units, and <10 units were 13, 14, 34, and 47, respectively. The improvement in the pain score was not significant for ≥30 units compared with <30 units (-50.3±24.0 vs. -40.4±28.5, p=0.25, d=0.38), but a significant difference was observed for ≥20 units compared with <20 units (-50.8±22.7 vs. -38.4±29.1, p=0.03, d=0.48), as well as for ≥10 units compared with <10 units (-48.1±25.0 vs. -33.0±29.7, p<0.01, d=0.56). When all patients were analyzed together, significant improvements in the pain score (-41.5±28.0, p<0.01), ease of use score (-37.5±32.2, p<0.01), force needed to inject score (-46.5±28.6, p<0.01), and preference for U300G compared with U100G score (-45.8±33.1, p<0.01) were observed.

Conclusion There is possibility that switching from U100G to U300G might be associated with better QOL for patients who require insulin glargine injections. To prove this hypothesis, a randomized controlled trial (preferably double-blinded) will be required in the future.

Key words: type 2 diabetes mellitus, injection, pain, insulin glargine, concentration

(Intern Med 58: 2943-2948, 2019)
(DOI: 10.2169/internalmedicine.1794-18)

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Received: July 12, 2018; Accepted: April 16, 2019; Advance Publication by J-STAGE: June 27, 2019
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Introduction

Pain associated with insulin injection is a factor that may affect the quality of life (QOL) of patients with diabetes mellitus who need insulin therapy by increasing discomfort, which is considered an important clinical outcome for the QOL (1, 2).

Recently, high-concentration (300 units/mL) insulin glargine (U300G) was introduced to the Japanese market. The volume of U300G preparation is one third of that of the conventional (100 units/mL) insulin glargine (U100G) preparation containing the same amount of insulin glargine. A previous study using 0.9% sodium chloride suggested that the pain associated with subcutaneous injections is related to injection volume (3). Another study comparing the pain accompanying the injection of U-500 (500 U/mL) regular insulin with U-100 (100 U/mL) regular insulin reported an improvement in the pain score when using U-500 regular insulin (4).

Visual analog scale (VAS) is used to measure various aspect of the QOL, especially for the assessment of the pain. There are two types of VASs: one is measured twice (before and after the intervention) and the other is measured only once (after the intervention) by asking the patients to compare the two treatments. For the latter purpose, a 150-mm VAS with a neutral point in the middle can be used (5).

To compare the pain and other QOL-related factors accompanying the injection of U300G and that of U100G, we conducted a pre-post intervention study using a 150-mm VAS with a neutral point in the middle.

Materials and Methods

U100G was switched to U300G at basically the same dosage (if necessary, the maximum plus or minus 20% change in insulin dosage). Lantus® (U100G) or Lantus® XR (U300G) with SoloSTAR® pens (Sanofi, Tokyo, Japan) and Nanopass® 34 G needles (Terumo, Tokyo, Japan) were used. Lantus® (U100G) and Lantus® XR (U300G) contain the same additive chemical substances (m-cresol, glycerin, sodium zinc, and pH adjusters) aside from different concentrations of insulin glargine. Patients were supervised in order to ensure they injected the insulin using the standard procedure at each research site.

We used 150-mm VAS with a neutral point in the middle to assess the change in the QOL after the intervention (5); values more favorable to U300G were on the right side, and those more favorable to U100G were on the left side. The survey was done once, between 2 and 16 weeks after switching from U100G to U300G. The pain score, ease of use score, force needed to inject score, and preference for U300G compared with U100G score were obtained by assessing the VAS for each score. Patients were asked to respond to the self-administrated questionnaire, including the VAS, after providing their written consent to the study investigators or their assistants.

The primary outcome was the change in the pain accompanying injections measured as a pain score using the VAS in patients using ≥30 units of U100G compared with those using <30 units at baseline. Secondary outcomes were the change in the pain score in those using ≥20 units of U100G compared with those using <20 units at baseline, change in pain score in those using ≥10 units of U100G compared with those using <10 units at baseline, change in pain score for all patients, ease of use score for all patients, force needed to inject score for all patients, and preference for U300G compared with U100G score for all patients.

Participants were men and women with type 2 diabetes mellitus ≥18 years of age and using either ≥30 units or <30 units of U100G at baseline. Exclusion criteria included patients who had already used U300G, those who were pregnant or under preconception care, or those for whom the usage of insulin glargine was inappropriate for any reason. We aimed to recruit a maximum of 150 patients in total (75 patients using ≥30 units and 75 patients using <30 units of U100G at baseline). As there was no pilot study using U300G to assess the pain accompanying injection, we were unable to calculate the ideal sample size for this study. However, as previous studies recruited 18 patients (3) or 325 patients (4), we decided to use an intermediate sample size from the viewpoint of feasibility.

The study was approved by the Ethics Committee of NHO Kyoto Medical Center (15-018) and registered to the UMIN Clinical Trials Registry (UMIN-CTR: UMIN 000023842).

Statistical analyses

The full analysis set was used in this study. Obtained data were compared using an independent *t*-test or one-sample *t*-test. Pearson's correlation coefficients were calculated among baseline characteristics and among pain score, ease of use score, force needed to inject score, and preference for U300G compared with U100G score. An absolute r value of 0.00-0.19 indicates "very weak", 0.20-0.39 "weak", 0.40-0.59 "moderate", 0.60-0.79 "strong", and 0.80-1.00 "very strong".

Standardized mean differences (Cohen's d) were used to measure the effect size. The size and direction of the difference was graded based on Cohen's d as follows: <0.10, trivial difference; 0.10 to <0.20, small difference; 0.20 to <0.60, medium difference; 0.60 to <1.20 large difference; and ≥1.20, a very large difference. A multiple linear regression analysis was used to compare changes in the pain score between the two groups after adjusting for confounding factors. Data were analyzed using the IBM SPSS Statistics for Windows software version 20.0 (IBM, Armonk, USA). P values of <0.05 were considered significant.

Table 1. Characteristics of the Participants.

Category name	All	Category 10 units		Category 20 units		Category 30 units	
Variables/Cut-off value		≥10 units (n=61)	<10 units (n=47)	≥20 units (n=27)	<20 units (n=81)	≥30 units (n=13)	<30 units (n=95)
Age, years	65.0 (12.6)	62.7 (12.6)*	67.9 (12.2)	63.7 (13.2)	65.4 (12.5)	61.9 (16.5)	65.4 (12.1)
Male sex, %	52.8	54.1	51.1	55.6	51.9	61.5	51.6
BMI, kg/m^2	25.9 (4.6)	27.6 (23.7)*	23.7 (3.5)	30.3 (4.7)*	24.5 (3.5)	31.9 (5.1)*	25.1 (0.4)
Diabetes duration, years	19.0 (10.5)	20.0 (9.6)	17.7 (11.5)	20.1 (9.5)	18.6 (10.8)	19.1 (10.0)	19.0 (10.6)
HbA1c, %	7.8 (1.1)	8.2 (1.1)*	7.4 (0.8)	8.4 (1.3)*	7.6 (0.9)	8.7 (1.2)*	7.7 (1.0)
Diabetic retinopathy, %	52.8	62.3*	40.4	59.3	50.6	76.9	49.5
Diabetic nephropathy, %	41.7	32.8*	54.3	37.0	43.8	23.1	44.7
Diabetic Neuropathy, %	62.3	72.9*	48.9	81.5*	55.7	92.3*	58.1
Medication, %	7.4	4.9	10.6	0	9.9	0	8.4
Insulin							
Glargine	14.1 (10.3)	20.0 (10.3)*	6.4 (1.8)	28.4 (10.2)*	9.3 (4.1)	36.5 (9.2)*	11.0 (5.6)
Total daily insulin dose, units	27.5 (21.6)	36.2 (23.6)*	16.1 (10.9)	51.7 (26.5)*	19.5 (11.6)	65.4 (24.1)*	36.5 (9.2)
Oral diabetes medications, %							
Biguanides	28.7	34.4	21.3	25.9	29.6	23.1	29.5
Thiazolidinediones	3.7	1.6	6.4	0	4.9	0	4.2
Sulfonylureas	13.0	14.8	10.6	7.4	14.8	0	14.7
Glinides	16.7	14.8	19.1	18.5	16.0	15.4	16.8
DPP4 inhibitors	41.7	45.9	36.2	40.7	42.0	23.1	44.2
Alpha-glucose inhibitors	23.1	21.3	25.5	14.8	25.9	7.7	25.3
SGLT2 inhibitors	7.4	8.2	6.4	7.4	7.4	15.4	6.3

*p<0.05 (≥10 units vs. <10 units, ≥20 units vs. <20 units, ≥30 units vs. <30 units).

Table 2. Correlation Coefficients among Baseline Characteristics of Participants.

	1. Age	2. Male sex	3. BMI	4. Diabetes duration	5. HbA1c	6. Dose of U100G
1. Age	-	0.111	-0.316*	0.292*	-0.077	-0.119
2. Male sex		-	-0.096	0.069	-0.041	-0.022
3. BMI			-	-0.010	0.248*	0.572*
4. Diabetes duration				-	0.197*	0.013
5. HbA1c					-	0.392
6. Dose of U100G						-

*p<0.05.

Results

Characteristics of the participants

One hundred and eight patients were recruited. Patients were 65.0±12.6 years of age (diabetes duration 19.0±10.5 years), 52.8% men, with a mean body mass index (BMI) of 25.9±4.6 kg/m^2 and HbA1c 7.8±1.1% (Table 1). Concerning diabetic complications, 52.8% had diabetic retinopathy (post-photocoagulation: 23.1%), 57.9% had diabetic nephropathy (micro-albuminuria: 27.1%, macro-albuminuria: 21.5%, renal insufficiency: 8.4%, end-stage renal insufficiency: 0.9%), and 62.3% had diabetic neuropathy. Significant differences were observed in the BMI and HbA1c for ≥30 units compared with <30 units, as well as for ≥20 units compared with <20 units and ≥10 units compared with <10 units (Table 1). There was a moderate correlation between the BMI and dosage of U100G at baseline (r=0.572) (Table 2).

The numbers of patients who used U100G at ≥30 units, 20 to <30 units, 10 to <20 units, and <10 units were 13, 14, 34, and 47, respectively. In 85.2% of the patients, the dosage of U300G was identical to that of U100G. In 10.2% of the patients, the dosage of U300G was greater than that of U100G, and in 4.6% of the patients, the dosage of U300G was smaller than that of U100G. In 1.9% of the patients, the dosage of U300G was more than 20% greater than that of U100G, and in 0.9% of the patients, the dosage of U300G was more than 20% smaller than that of U100G.

The assessment of the QOL

For the full-set analysis (n=108), the improvement in the pain score was not significant for ≥30 units compared with <30 units, but significant differences were observed for ≥20 units compared with <20 units, as well as for ≥10 units compared with <10 units by independent *t*-test (Table 3). However, the effect sizes for category 30 units, 20 units, and

Table 3. Comparison of the Improvement in the Pain Score.

Dose of U100G	Improvement in the pain score	p value (crude)	Cohen's d†	p value‡
≥30 units vs. <30 units	-50.3 (24.0) vs. -40.4 (28.5)	0.25	0.38	0.86
≥20 units vs. <20 units	-50.8 (22.7) vs. -38.4 (29.1)	0.03*	0.48	0.35
≥10 units vs. <10 units	-48.1 (25.0) vs. -33.0 (29.7)	<0.01*	0.56	0.04*

Data are means (standard deviation). *p<0.05. †Effect size. ‡Adjusted for age, sex, BMI, diabetes duration, diabetic neuropathy, and medication for diabetic neuropathy.

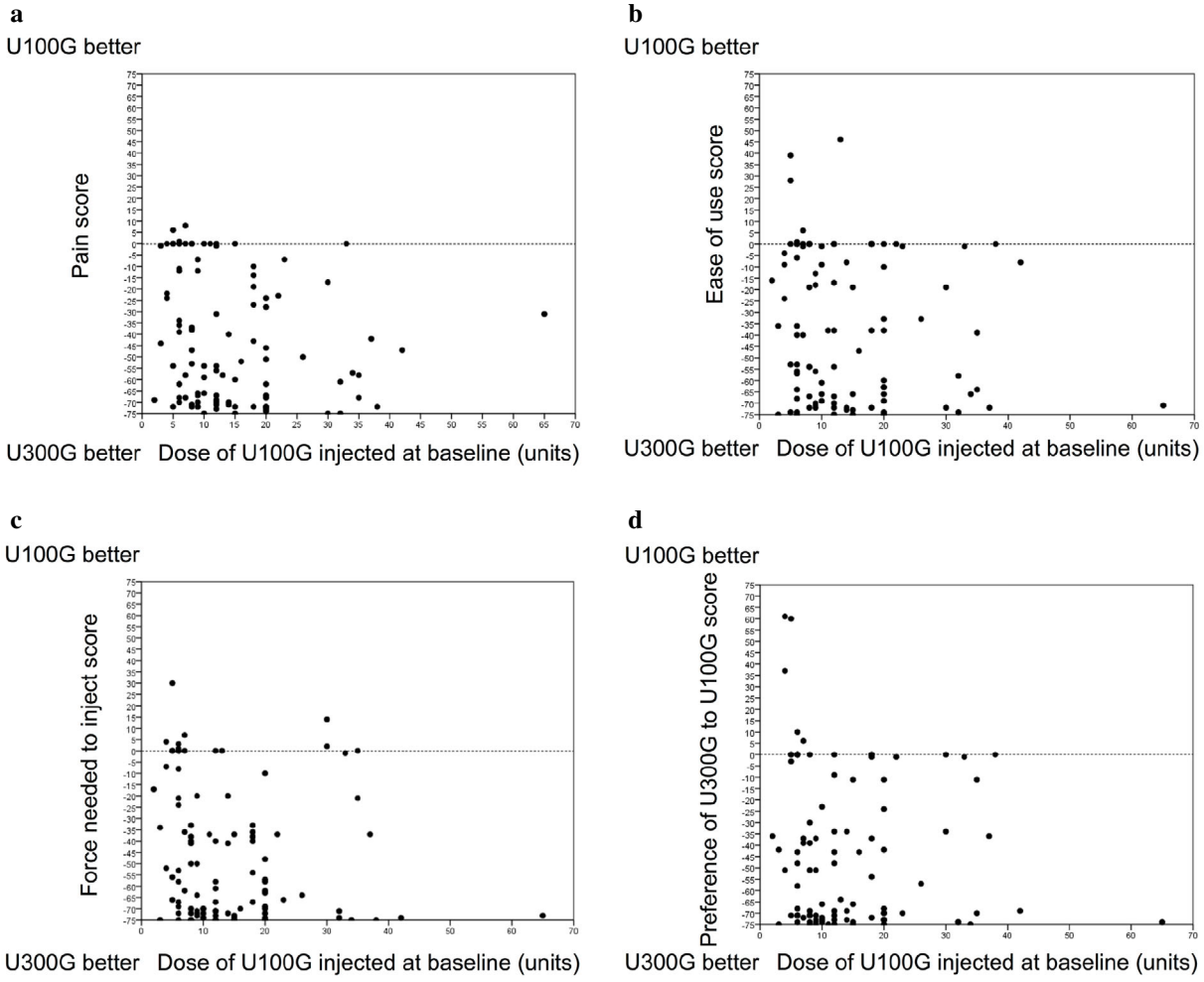

Figure. Changes in the QOL after switching to U300G from U100G. Significant improvements in the pain score (-41.5±28.0, p<0.01*) (a), ease of use score (-37.5±32.2, p<0.01*) (b), force needed to inject score (-46.5±28.6, p<0.01*) (c), and preference for U300G compared with U100G score (-45.8±33.1, p<0.01*) (d) were observed after switching to U300G from U100G (*p<0.05).

10 units were medium differences (0.38, 0.48, and 0.56, respectively). After adjusting for the age, sex, diabetes duration, BMI, presence of diabetic neuropathy, and use of neuropathy medication, the improvement in the pain score was significantly different between ≥10 units and <10 units (Table 3). For the analysis excluding patients with changes in their insulin dosage (n=99), the improvement in the pain score was not significant for ≥30 units compared with <30 units (-49.3±24.9 vs. -39.5±28.5, p=0.28), but significant differences were observed between ≥20 units and <20 units (-50.3±23.6 vs. -37.5±29.0, p=0.03) as well as between ≥10 units and <10 units (-47.4±25.4 vs. -32.2±29.4, p<0.01).

When all patients were analyzed together by one-sample *t*-test, significant improvements in pain score (-41.5±28.0, p <0.01*) (Figure a), ease of use score (-37.5±32.2, p<0.01*) (Figure b), force needed to inject score (-46.5±28.6, p<0.01*) (Figure c), and preference for U300G compared with U100G score (-45.8±33.1, p<0.01*) (Figure d) were observed after the switch from U100G to U300G.

There was no significant difference in the pain score be-

Table 4. Comparison of Pain Score according to the Baseline Characteristics.

	Pain score	p value
Age (<65 years old vs. ≥65 years old)	-41.09 vs. -41.82	0.90
Sex (male vs. female)	-40.48 vs. -42.65	0.70
BMI (<25 kg/m^2 vs. ≥25 kg/m^2)	-37.40 vs. -47.59	0.06
Diabetes duration (<10 years vs. ≥10 years)	-27.25 vs. -44.96	<0.01*
Diabetic neuropathy (absent vs. present)	-36.95 vs. -44.56	0.18

*p<0.05.

Table 5. Correlation Coefficients among Pain Score, Ease of Use Score, Force Needed to Inject Score, and Preference for U300G Compared with U100G Score.

Variables	Pain	Ease of use	Force needed to inject	Preference for U300G compared with U100G score
Pain	1			
Ease of use	0.450*	1		
Force needed to inject	0.390*	0.509*	1	
Preference for U300G compared with U100G score	0.391*	0.568*	0.699*	1

*p<0.05.

tween patients with and without diabetic neuropathy; however, the pain score in patients with diabetes duration of ≥10 years was greater than in those with diabetes duration of <10 years (Table 4).

There was a strong correlation between the preference for U300G compared with U100G score and the force needed to inject score (r=0.699), while there was moderate correlation between the preference for U300G compared with U100G score and the ease of use score (r=0.568), between the force needed to inject score and the ease of use score (r =0.509), and between the ease of use score and the pain score (r=0.450) (Table 5).

Discussion

In this study, we observed no significant difference in pain score for ≥30 units compared with <30 units after switching to U300G from U100G. The pain score was significantly improved for ≥20 units compared with <20 units, as well as for ≥10 units compared with <10 units. The pain score for all patients improved significantly by one-sample *t*-test. These findings suggest that the subcutaneous injection of U300G might be less painful than that of conventional U100G, and the effect might be independent from the volume of the injection.

One potential reason for the pain score not being significantly different between ≥30 units and <30 units is the small number of patients using ≥30 units. As the dosage of U300G was identical to that of U100G in 85.2% of the patients, it is less likely that the difference in the dosage of U300G and U100G could have affected the observation markedly. The prevalence of diabetic neuropathy was significantly higher for ≥30 units compared with <30 units, for ≥20 units compared with <20 units, and for ≥10 units compared with <10 units (Table 1), and there is possibility that these differences might have affected the pain score in this study. Theoretically, more severe diabetic neuropathy is associated with a lower perception of pain accompanying injections, which might result in a smaller change in the 150-mm VAS with a neutral point in the middle, as was used in this study. However, for ≥20 units compared with <20 units, and for ≥10 units compared with <10 units, the change in the pain score was greater in the arm with high prevalence of diabetic neuropathy, suggesting that the difference in the prevalence of diabetic neuropathy might not have markedly affected the observation.

Retrospectively, we could have designed this study in different ways, as we experienced difficulty in recruiting patients using ≥30 units. For example, we could have set the change in the pain score for all patients (Figure a) as the primary outcome. A future study randomizing patients to U100G and U300G would address the conclusion to the hypothesis that U300G is useful to reduce pain accompanying insulin glargine injections, and our findings would be useful for calculating the sample size for such study.

The improvement in the force needed to inject score was compatible with a previous observation measuring the force needed to inject directly (6). Why the pain score was significantly improved in patients with diabetes duration ≥10 years than in those with diabetes duration <10 years is unclear.

A strong correlation was noted between the preference for U300G compared with U100G score and the force needed to inject score, and a moderate correlation was noted between the preference for U300G compared with U100G score and the ease of use score, suggesting that patients' preference for U300G is mainly associated with the im-

provement in the injection device used for U300G.

The novelty of this study was that we used insulin glargine preparation, which has low pH profile (pH=3.5 to 4.50 for both U100G and U300G), in contrast to 0.9% sodium chloride and regular insulin used in previous studies, which have nearly neutral pH profiles (3, 4). The acidity of insulin glargine preparation might have influenced the patients' perception of pain accompanying injection. Of note, the chemical substances used as pH adjusters in U100G and in U300G are not disclosed by the manufacturer. Although the difference in the patients' perception between insulin glargine preparation and regular insulin was not directly compared in this study, a previous study reported that the pain accompanying the subcutaneous injection of citrate buffer was significantly more intense than that of histidine buffer just after injection in healthy volunteers (7). As the acidity of citrate buffer and that of histidine buffer were similar (pH=6.00 vs. pH=6.15), the chemical substance used as pH adjusters in U100G and U300G might also have influenced the patients' perception of pain accompanying injection. There is a possibility that the pH adjusters in U100G and U300G might have intensified the pain accompanying the injection of U100G and U300G, even in small doses, and this might be related to our finding that the pain score improved in dose-independent manner, unlike the hypothesis we had prior to the current study.

Limitations

This study was a non-randomized, open-labeled, pre-post study, and there is a possibility that the current observations may have been influenced by potential confounders. The self-administered questionnaire used in this study included only VAS, and did not include other validated self-administered questionnaires regarding the QOL. Multiple testing might generate false-positive results in the study, so we must carefully interpret these findings. The 150-mm VAS (5) that we adopted in this study is not commonly used, although 150-mm VAS and 100-mm length scales are interchangeable (8). The assessment of 100-mm VAS at before and after switching from U100G to U300G will be needed to confirm these results in the future research. The number of the subjects using ≥30 units (n=13) was small, but the effect size for changes in pain score was medium (0.38). Therefore, further investigations using a larger sample will be required in order to confirm our hypothesis.

Conclusion

There is possibility that switching from U100G to U300G might be associated with better QOL among patients who require insulin glargine injections. To prove this hypothesis, a randomized controlled trial (preferably double-blinded) will be required in the future.

Author's disclosure of potential Conflicts of Interest (COI).
Atsuhito Tone: Honoraria, Eli Lilly and Sanofi. Masao Toyoda: Honoraria, Eli Lilly and Sanofi.

Financial Support
This study was supported by Sanofi K.K. (Tokyo, Japan).

Acknowledgement
The study was conducted at the following institutions: National Hospital Organization Kyoto Medical Center, Okayama University Hospital, Tsuchiura Kyodo General Hospital, Aiseikai Yamashina Hospital, Tottori Prefectural Central Hospital, Terasawa Hospital, National Hospital Organization Osaka National Hospital, Kanda Naika Clinic, and Seichi Clinic.

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