


BRIEF REPORT

Evaluation of a Premixed Insulin Analog Suspension in Japanese People with Type 2 Diabetes and the Clinical Importance of Improved Injection Techniques: A Cross-Sectional Pilot Study

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ABSTRACT

Introduction: Patients with type 2 diabetes, who live in Asian countries, often use premixed insulin analogs. However, if these solutions are insufficiently mixed prior to use, patients will receive inaccurate doses of intermediate- and/or short-acting insulin, which could affect diabetes control. This study aimed to determine whether insulin users were correctly resuspending premixed insulin analog solutions prior to use.

Methods: We investigated whether Japanese patients with type 2 diabetes were correctly resuspending their premixed insulin analog solutions by assessing the optical densities (ODs) of the solutions.

Results: Among 476 patients who used premixed insulin analogs, we found that the ODs of residual insulin differed significantly from the control values, particularly for high-mix insulin suspensions.

Conclusion: Our findings suggest that patients should be educated about the importance of properly resuspending these insulin analog solutions prior to use.

Trial Registration: University Hospital Medical Information Network (UMIN No. 000022329).

Keywords: Diabetes control; Optical density; Premixed insulin analogs; Type 2 diabetes

INTRODUCTION

Premixed insulin analogs, such as biphasic insulin aspart 30, 50, and 70 (NovoRapid 30, 50, and 70; Novo Nordisk A/S, Søborg, Denmark) and lispro mix 25 and 50 (Eli Lilly and Company, Indianapolis, IN, USA), are forms of insulin therapy commonly used by patients with type 2 diabetes in Asian countries [1, 2]. Each premixed insulin analog contains a fixed ratio of intermediate-acting protaminated insulin aspart or lispro and a rapid-acting insulin analog. Protaminated insulin aspart and lispro are cloudy, and the degree of cloudiness should correspond to the ratio of rapid-acting insulin in a prefilled pen. Therefore, insulin cartridges and pens prefilled with insulin–protamine complex in binding mode will require adequate mixing to ensure a complete resuspension [3, 4]. Insufficient mixing will cause patients to receive inaccurate doses of intermediate- and/or short-acting insulin, which could

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significantly affect diabetes control. In this study, we investigated whether insulin users were correctly resuspending their premixed insulin analogs by measuring the optical densities (ODs) of the insulin solutions, which has been reported as the simplest method for assessing cloudiness [5].

METHODS

Subjects

Four hundred and seventy-six patients with type 2 diabetes who had received premixed insulin analog therapy for at least 12 months were recruited for this study. Of these patients, 179 used NovoRapid 30 (mean age 59.9 ± 19.2 years, diabetes duration 20.1 ± 12.8 years, hemoglobin A1c [HbA1c] level $8.5 \pm 1.6\%$ [69 mmol/mol]), 66 used NovoRapid 50 (mean age 48.3 ± 14.9 years, diabetes duration 16.9 ± 8.9 years, HbA1c level $8.0 \pm 1.3\%$ [66 mmol/mol]), 33 used NovoRapid 70 (mean age 43.9 ± 20.0 years, diabetes duration 11.3 ± 6.9 years, HbA1c level $8.3 \pm 1.0\%$ [67 mmol/mol]), 58 used lispro mix 25 (mean age 67.5 ± 14.3 years, diabetes duration 22.1 ± 7.7 years, HbA1c level $8.9 \pm 2.6\%$ [74 mmol/mol]), and 140 used lispro mix 50 (mean age 65.4 ± 10.7 years, diabetes duration 14.7 ± 12.8 years, HbA1c level $8.1 \pm 1.9\%$

[65 mmol/mol]). Further information about the study population is provided in Table 1. The study protocol was approved by the Ethical Committee of Dokkyo Medical University (No. 28023). The trial was registered with the University Hospital Medical Information Network (UMIN No. 000022329). All patients provided informed consent and received conventional diabetes education and insulin therapy comprising premixed insulin analogs.

Optical Density Measurement

All patients enrolled in this study declared that they resuspended premixed insulin analogs by inversion at least 10 times before every injection, according to insulin injection best practice. Patients provided their current prefilled insulin pens for analysis. The ODs of the insulin solutions in these pens were measured at a wavelength of 415 nm, using a plate reader (Perkin Elmer, Inc., Waltham, MA, USA) [5]. Briefly, residual insulin volumes representing at least 5% were accurately mixed and compared with the range of OD values obtained from a series of correctly mixed, unused control insulin pens. The ODs of insulin solutions from the pens provided by patients were measured in triplicate, and the means of these measurements were used. The OD of the residual insulin was compared to standard insulin curves.

Table 1 Clinical characteristics of the subjects

	NovoRapid 30	NovoRapid 50	NovoRapid 70	Lispro mix 25	Lispro mix 50
Full analysis set (<i>n</i>)	179	66	33	58	140
Age (years)	59.9 ± 19.2	48.3 ± 14.9	43.9 ± 20.0	67.5 ± 14.3	65.4 ± 10.7
Sex (M/F)	77/102	28/38	20/13	26/32	61/79
HbA1c % (NGSP)	8.5 ± 1.6	8.0 ± 1.3	8.3 ± 1.0	8.9 ± 2.6	8.1 ± 1.9
Body mass index (kg/m^2)	25.5 ± 4.6	23.0 ± 3.2	24.1 ± 2.9	22.8 ± 4.0	24.6 ± 3.5
Duration of diabetes (years)	20.1 ± 12.8	16.9 ± 8.9	11.3 ± 6.9	22.1 ± 7.7	14.7 ± 12.8
Insulin dose (U/day)	18.3 ± 10.0	18.7 ± 11.7	25.1 ± 9.9	21.1 ± 11.1	20.3 ± 10.0
Oral hypoglycemic agents, <i>n</i> (%)	127 (70.9%)	49 (74.2%)	15 (45.4%)	46 (79.3%)	121 (86.4%)

Data are mean \pm SD

Statistical Analysis

Data are expressed as percentages of mixtures (%) and medians and interquartile ranges. All results are expressed as box and whiskers plots. Differences between groups were assessed using the Kruskal–Wallis test. *P* values less than 0.05 were considered statistically significant. All analyses were performed using Prism 6 (Graph-Pad Software, Inc., San Diego, CA, USA) or StatMate V (Nihon 3B Scientific Inc., Niigata, Japan).

RESULTS

The following ODs were measured for the insulin solutions sampled from patients' premixed insulin analog pens: NovoRapid 30 mix, $108.1 \pm 12.0\%$; NovoRapid 50 mix, $121.6 \pm 56.9\%$; NovoRapid 70 mix, $142.4 \pm 51.6\%$; lispro mix 25, $112.1 \pm 21.5\%$; and lispro mix 50, $110.5 \pm 23.2\%$. The ODs of residual insulin from the high-mix biphasic insulin aspart suspensions (NovoRapid 50 and 70 mix) differed significantly from the expected values (Fig. 1).

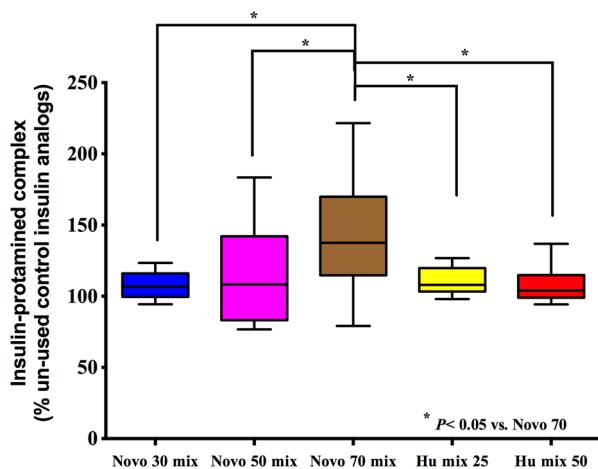


Fig. 1 Box and whisker plots of premixed insulin analogs. Data are expressed as percentages of the mixtures (%) and medians and interquartile ranges. Differences between groups were analyzed using the Kruskal–Wallis test. **P* < 0.05 vs. NovoRapid 70

DISCUSSION

The present study results demonstrate that inadequate resuspension of premixed insulin analogs before injection is common among patients with diabetes who received conventional diabetes education at our hospital. An intensified insulin regimen, basal-bolus therapy, is known to be superior to conventional premixed insulin regimens with respect to changes in HbA1c levels and the onset and early-stage progression of microangiopathy in subjects with type 2 diabetes [6, 7]. However, premixed insulin has become more commonly used by patients with type 2 diabetes and stable lifestyles, such as elderly individuals [8, 9]. According to the consensus algorithm for patients with type 2 diabetes from ADA/EASD2015, premixed insulin is considered moderately complex but not very flexible [9], whereas basal-bolus therapy is recommended because it is more flexible than other regimens. Although guidelines do not strongly recommend this practice, premixed insulin can be adopted after considering a patient's condition, lifestyle, and situation, especially in Japan [10]. Although we did not investigate a correlation between improved HbA1c levels and insulin injection techniques, physicians and patients must be educated about the proper method for resuspending premixed insulin in order to improve diabetes control and ensure safety. Additional information from future clinical studies with regard to mixing premixed insulin analogs is needed to address these results in patients with type 2 diabetes. Although we did not evaluate the correlation between OD and insulin concentration, Brown et al. indicated that there is a reasonable correlation between the insulin concentration, as measured by immunoassay, and ODs, which is considered to be a suitable marker for the state of insulin mixing [5].

Insulin degludec/insulin aspart (IDegAsp) is the most recently marketed insulin analog. IDegAsp is a fixed and soluble combination of the long-acting basal insulin, insulin degludec (IDeg; 70%), and rapid-acting insulin aspart

(IAsp; 30%) [11]. Notably, IDegAsp does not need to be resuspended to homogeneity before injection [12]. This co-formulation of IDeg and IAsp may benefit patients with type 2 diabetes who currently use conventional premixed insulin analog therapy.

CONCLUSION

This is the first study to evaluate the percentage of protaminated insulin within the premixed insulin analog pens used by patients with type 2 diabetes. Similar to previously reported findings [3–5], the current results suggest that it is important to resuspend premixed insulin analogs, especially high-mix biphasic insulin analogs, more carefully before injection.

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KS, CA, KK, and YA designed the research; KS, CA, MS, HK, and YA performed the research; KS, CA, SS, and KY analyzed data; and KS, CA, and YA wrote the paper. All authors read and approved the final manuscript.

Disclosures. K. Suzuki, C. Aoki, K. Kato, M. Shimizu, S. Sakurai, K. Yanagi, H. Kuroda, and Y. Aso have nothing to disclose.

Compliance with Ethics Guidelines. The study protocol was approved by the Ethical Committee of Dokkyo Medical University (no. 28023). All patients provided informed consent and received conventional diabetes education

and insulin therapy comprising premixed insulin analogs.

Data Availability. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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REFERENCES

1. Kaneko S, Chow F, Choi DS, et al. Insulin degludec/insulin aspart versus biphasic insulin aspart 30 in Asian patients with type 2 diabetes inadequately controlled on basal or pre-/self-mixed insulin: a 26-week, randomised, treat-to-target trial. *Diabetes Res Clin Pract.* 2015;107:139–47.
2. Yoshioka N, Kurihara Y, Manda N, et al. Step-up therapy with biphasic insulin aspart-70/30–Sapporo 1-2-3 study. *Diabetes Res Clin Pract.* 2008;85:47–52.
3. Lucidi P, Porcellati F, Marinelli Andreoli A, et al. Pharmacokinetics and pharmacodynamics of NPH insulin in type 1 diabetes: the importance of appropriate resuspension before subcutaneous injection. *Diabetes Care.* 2015;38:2204–10.
4. Jehle PM, Micheler C, Jehle DR, Breitig D, Boehm BO. Inadequate suspension of neutral protamine Hagedorn (NPH) insulin in pens. *Lancet.* 1999;354:1604–7.
5. Brown A, Steel JM, Duncan C, Duncan A, McBain AM. An assessment of the adequacy of suspension of insulin in pen injectors. *Diabet Med.* 2004;21:604–8.
6. Fritsche A, Larbig M, Owens D, Häring HU, GINGER study group. Comparison between a basal-bolus and a premixed insulin regimen in individuals with type 2 diabetes—results of the GINGER study. *Diabetes Obes Metab.* 2010;12:115–23.

7. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract.* 1995;28:103–17.
8. Coscelli C, Calabrese G, Fedele D, et al. Use of pre-mixed insulin among the elderly. Reduction of errors in patient preparation of mixtures. *Diabetes Care.* 1992;15:1628–30.
9. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2015;38:140–9.
10. Ito H, Abe M, Antoku S, et al. Effects of switching from prandial premixed insulin therapy to basal plus two times bolus insulin therapy on glycemic control and quality of life in patients with type 2 diabetes mellitus. *Drug Des Devel Ther.* 2014;23:391–6.
11. Ma Z, Parkner T, Christiansen JS, Laursen T. IDegAsp: a novel soluble insulin analogs combination. *Expert Opin Biol Ther.* 2012;12:1533–40.
12. Havelund S, Ribel U, Hubálek F, Hoeg-Jensen T, Wahlund PO, Jonassen I. Investigation of the physico-chemical properties that enable co-formulation of basal insulin Degludec with fast-acting insulin Aspart. *Pharm Res.* 2015;32:2250–8.