Treatment Satisfaction With Inhaled Insulin in Patients With Type 1 Diabetes

A randomized controlled trial

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OBJECTIVE — In patients with type 1 diabetes, glycemic control can be achieved as effectively with an inhaled insulin regimen, comprising preprandial inhaled intrapulmonary insulin plus a bedtime ultralente injection, as with a conventional subcutaneous insulin regimen involving two to three injections per day. Our objective was to compare patient satisfaction between inhaled insulin and subcutaneous insulin.

RESEARCH DESIGN AND METHODS — Subjects with type 1 diabetes participated in a 12-week open-label trial and were randomized to either an inhaled insulin regimen or a subcutaneous insulin regimen. Subjects ($n = 69$) were asked to complete a 15-item self-administered satisfaction questionnaire, the Patient Satisfaction with Insulin Therapy (PSIT) Questionnaire, at baseline and week 12. Outcomes included mean percentage changes in global (overall) satisfaction and two subscales: convenience/ease of use and social comfort.

RESULTS — The mean percentage improvement in overall satisfaction with inhaled insulin (35.1%, 95% CI 18.0–52.2) was greater than with subcutaneous insulin (10.6%, 4.7–16.5) ($P < 0.01$), as was the improvement in convenience/ease of use: inhaled insulin 41.3% (22.9–59.6) versus subcutaneous insulin 11.2% (4.1–18.3; $P < 0.01$). Improvement in social comfort was greater with inhaled insulin but was not statistically significant. The 12-week change in HbA_{1c} was associated with improved overall satisfaction ($r = -0.27$, $P = 0.04$).

CONCLUSIONS — Inhaled insulin may offer the first practical, noninvasive alternative to insulin injections. For patients with type 1 diabetes, inhaled insulin maintains glycemic control and provides greater overall satisfaction and convenience/ease of use than subcutaneous insulin.

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Despite studies such as the Diabetes Control and Complications Trial (DCCT) (1) and the Stockholm Diabetes Intervention Study (SDIS) (2), which have highlighted the benefits and impact of good glycemic control, intensive insulin therapy for the treatment of type 1 diabetes has been slow to gain acceptance in clinical practice (3,4). This may stem from the inconvenience and poor patient acceptability of multiple daily insulin injections.

Clinical development studies of a novel, noninvasive inhaled delivery system for insulin show that inhaled insulin in a dry powder formulation offers an effective and well-tolerated alternative to preprandial insulin injections for the treatment of type 1 diabetes (5). However, little research exists on whether inhalation delivery of insulin can influence patient satisfaction. This is partly because measures of treatment satisfaction were developed and used when only injected insulin delivery forms (e.g., syringe, pen, pump) were available (6–8). Recently, a patient satisfaction questionnaire to assess novel forms of insulin delivery, such as inhaled insulin, has been developed (9,10).

This report, based on a randomized, controlled multicenter clinical trial, is the first comparative study of multiple patient satisfaction aspects (scales) with inhaled insulin versus subcutaneous insulin injection.

RESEARCH DESIGN AND METHODS

Study design

The design and clinical results of this trial in type 1 diabetes have been reported previously (5). In brief, the trial was a 12-week randomized, open-label, multicenter, parallel study conducted at 10 centers in the U.S. It consisted of a 4-week baseline lead-in phase, in which subjects continued their usual injected insulin regimen (two to three injections daily) and received instruction on a weight-maintaining diet and blood glucose monitoring, followed by randomization to either an inhaled insulin regimen or a conventional subcutaneous insulin regimen for 12 weeks. The inhaled insulin regimen consisted of rapid-onset inhaled insulin administered immediately before meals using a dry powder aerosol delivery system (Inhale Therapeutic Systems, San Carlos, CA) plus bedtime subcutaneous ultralente insulin. The subcutaneous insulin regimen involved the subject's usual split/mixed insulin regimen given two or three times per day. The target glucose range was 5.6–8.9 mmol/l. Administration of insulin, inhaled or injected, was preceded by a blood glucose measurement. Patients were followed weekly for review of blood glucose monitoring and adjustment of insulin dosage, if required.

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Abbreviations: PSIT, Patient Satisfaction with Insulin Therapy.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Each center's institutional review board approved the protocol, and all subjects gave written informed consent.

Study participants

Subjects were aged 18–55 years and were following a stable insulin administration schedule (for at least 2 months) involving two to three injections daily. Screening and prerandomization HbA_{1c} values were between 7.0 and 11.9%, with fasting plasma C-peptide ≤0.2 pmol/ml. Body weight of each subject was 80–130% of ideal (Metropolitan Life Insurance Tables). Subjects were nonsmokers (for at least 6 months), gave normal results on a chest x-ray and pulmonary function tests, and had an electrocardiogram showing normal sinus rhythm (rate 50–100 bpm). All subjects performed blood glucose monitoring four times daily: before breakfast, before lunch, before supper, and at bedtime.

Patient satisfaction

A 15-item self-administered patient satisfaction questionnaire, the Patient Satisfaction with Insulin Therapy (PSIT) Questionnaire, was completed by each subject at baseline and week 12. The PSIT Questionnaire is shown in Table 1 and is available from the corresponding author of this study upon request. The PSIT underwent rigorous empirical development, had reliable properties, and had an interpretable and rich factor structure (9,10). The PSIT measures global (overall) satisfaction and two domains (subscales): convenience/ease of use and social comfort (9,10). The questionnaire asks subjects to rate statements such as "I find it easy to take insulin the way I take it now," "I have no discomfort taking insulin," "I find it convenient to take insulin," and "I am self-conscious about taking insulin away from home." Responses to each item consisted of a five-point Likert scale ranging from "strongly agree" to "strongly disagree."

Patient satisfaction scores for overall satisfaction, convenience/ease of use, and social comfort were calculated. Responses to each item were analyzed so that a higher item score indicated more satisfaction. All 15-item scores were summed equally to arrive at the overall satisfaction score (range 15–75). Pearson correlations (r) and analysis of covariance were used to assess the association between overall satisfaction and 12-week change in HbA_{1c}, after controlling for treatment regimen.

Table 1—*PSIT Questionnaire*

1. I find it easy to take insulin the way I take it now.
2. I have no discomfort taking insulin the way I take it now.
3. I find it convenient to take insulin the way I take it now.
4. I am self-conscious about taking insulin away from home.
5. I find it easy to take all the doses of insulin my doctor recommends.
6. I find the time it takes for each dosing acceptable.
7. I find that my eating schedule can be flexible with few problems.
8. I prefer to stay home rather than take insulin away from home.
9. I do not mind measuring my blood glucose before each meal.
10. I feel good on my current insulin treatment schedule.
11. I find it difficult to take every dose of insulin my doctor recommends.
12. I find it difficult to take insulin away from home.
13. I would find it difficult to take insulin four times a day.
14. I find it easy to travel for a few days and take all my doses of insulin.
15. Overall, I am satisfied with my current way of taking insulin.

Items in the convenience/ease of use domain (items 1, 2, 3, 5, 6, 7, 9, 10, 14, and 15) were analyzed so that 1 = strongly disagree, 2 = slightly disagree, 3 = neither agree nor disagree, 4 = slightly agree, and 5 = strongly agree. Items in the social comfort domain (items 4, 8, 11, 12, and 13) were analyzed so that 1 = strongly agree, 2 = slightly agree, 3 = neither agree nor disagree, 4 = slightly disagree, and 5 = strongly disagree. A higher item score (range 1 to 5) indicated a more favorable attitude.

Item scores were summed equally to create scores for the domains on convenience/ease of use and social comfort. Scores on convenience/ease of use (10 items, range 10–50) and social comfort (5 items, range 5–25) were each used to calculate a percentage change in satisfaction from baseline for each subject. Within-group percent change was evaluated with a paired Student's t test (11). The difference in the (arithmetic) mean percent change between treatment groups was evaluated with a Student's t test for two independent samples (11). Statistical significance was based on a 5% two-tailed test.

One statement was rated only at the end of the study: "I would like to continue to take insulin the way I took it during the study." It was analyzed like other items on the PSIT so that a score of 1 correlated with "strongly disagree" and 5 correlated with "strongly agree." A treatment group difference on its 5-point ordinal response was evaluated by the Wilcoxon's rank-sum test (11).

RESULTS — A total of 73 subjects with type 1 diabetes were enrolled in the trial. One subject discontinued treatment before randomization during the inpatient evaluation period. Two subjects randomized to subcutaneous insulin dropped out of the study for administrative reasons and are not included in the analysis. Identical results, therefore, would be obtained from an evaluable analysis and an intent-to-treat analysis on treatment satisfaction. One subject in the subcutaneous group did not fill out a questionnaire at baseline; therefore, only 69 subjects were considered for analysis. At baseline, there were no statistical differences between groups randomized to the two treatment regimens (Table 2).

Overall satisfaction

As reported previously (5), for subjects who responded to all 15 items on the survey, the mean percentage improvement from baseline in global (overall) satisfaction with inhaled insulin (35.1%, 95% CI 18.0–52.2) was considerably greater ($P < 0.01$) than with subcutaneous insulin (10.6%, 4.7–16.5) (Fig. 1). Therefore, inhaled insulin resulted in 24.5% (6.6–42.5) more improvement in overall satisfaction than subcutaneous insulin. The mean percentage improvement within each treatment group was statistically significant from zero ($P < 0.01$).

In the current research, a significant relationship between better glycemic control and greater satisfaction was found. The 12-week change in HbA_{1c} was associated with improved overall satisfaction ($r = -0.27$, $P = 0.04$). In addition, a 1% absolute improvement (reduction) in HbA_{1c} from baseline to week 12 was associated with an average 9.7% improvement in overall satisfaction, after controlling for treatment regimen.

Convenience/ease of use

The mean percentage improvement in convenience/ease of use was substantially

Table 2—*Baseline demographic, clinical, and satisfaction characteristics*

	Inhaled insulin	Subcutaneous insulin
n	35	34
Sex (M/F)	19/16	18/16
Age (years)	35.4 ± 9.0 (18.0–51.0)	39.6 ± 8.7 (20.0–55.0)
Duration of diabetes (years)	14.6 ± 9.3 (2.0–35.0)	14.5 ± 9.5 (1.2–34.0)
Race/ethnic group		
White	29 (83)	26 (76)
Black	1 (3)	1 (3)
Hispanic, other	5 (14)	7 (21)
Weight (kg)		
Men	81.1 ± 11.3 (58.6–103.6)	81.4 ± 10.5 (56.3–103.0)
Women	64.6 ± 7.0 (53.6–76.5)	63.6 ± 8.1 (50.2–76.7)
BMI (kg/m^2)		
Men	25.1 ± 2.7 (21.0–31.0)	25.9 ± 2.7 (22.0–31.0)
Women	24.5 ± 2.3 (20.0–28.0)	24.3 ± 3.3 (19.0–31.0)
HbA_{1c} (%)	8.5 ± 1.1 (6.5–10.6)	8.5 ± 1.1 (6.4–11.2)
Treatment satisfaction scores		
Global (overall)	52.9 ± 12.9 (21–73)	52.7 ± 11.2 (28–75)
Convenience/ease of use	35.4 ± 8.7 (15–48)	35.4 ± 9.1 (17–50)
Social comfort	17.5 ± 5.5 (6–25)	17.3 ± 4.9 (5–25)

Data are *n*, mean ± SD (range), or *n* (%). Variables are not statistically different between groups ($P > 0.05$)

greater with inhaled insulin (41.3%, 22.9–59.6) than with subcutaneous insulin (11.2%, 4.1–18.3; $P < 0.01$) (Fig. 1). Therefore, inhaled insulin resulted in 30.1% (10.7–49.5) more improvement in convenience/ease of use than subcutaneous insulin. The mean percentage improvement within each treatment group was statistically significant from zero ($P < 0.01$).

Social comfort

The mean percentage improvement in social comfort with inhaled insulin (28.0%, 8.0–47.9) was higher than subcutaneous insulin (18.0%, 2.9–33.0) but not statistically significant from it (95% CI −14.6 to 34.6%; $P = 0.42$) (Fig. 1). The mean percentage improvement within each treatment group was statistically significant from zero (inhaled insulin, $P < 0.01$; subcutaneous insulin, $P = 0.02$).

Preference

Subjects in the inhaled insulin group gave significantly more agreement than those in the subcutaneous group (Wilcoxon's rank-sum test; $P < 0.01$) on the 5-point Likert scale item "I would like to continue to take insulin the way I took it during the study" asked at the end of the study.

Clinical measures

As reported previously (5), the adjusted mean difference between the 12-week change in HbA_{1c} for inhaled insulin ($n = 35$; −0.64 ± 0.98%) and for subcutaneous insulin ($n = 35$; −0.83 ± 0.92%) was deemed equivalent (95% CI −0.2 to 0.5%). Changes in fasting and postprandial glucose concentrations as well as occurrence and severity of hypoglycemia were also similar between groups. Inhaled insulin was well tolerated and had no effect on pulmonary function.

CONCLUSIONS — Administration of rapid-onset insulin by dry aerosol inhalation in patients with type 1 diabetes maintained glycemic control and achieved greater patient satisfaction. Complementary to the reported satisfaction results, and possibly more telling of overall satisfaction, are the preferences indicated by subjects. In total, 82% of subjects already on inhaled insulin elected to continue on a 1-year extension with inhaled insulin. For those who elected not

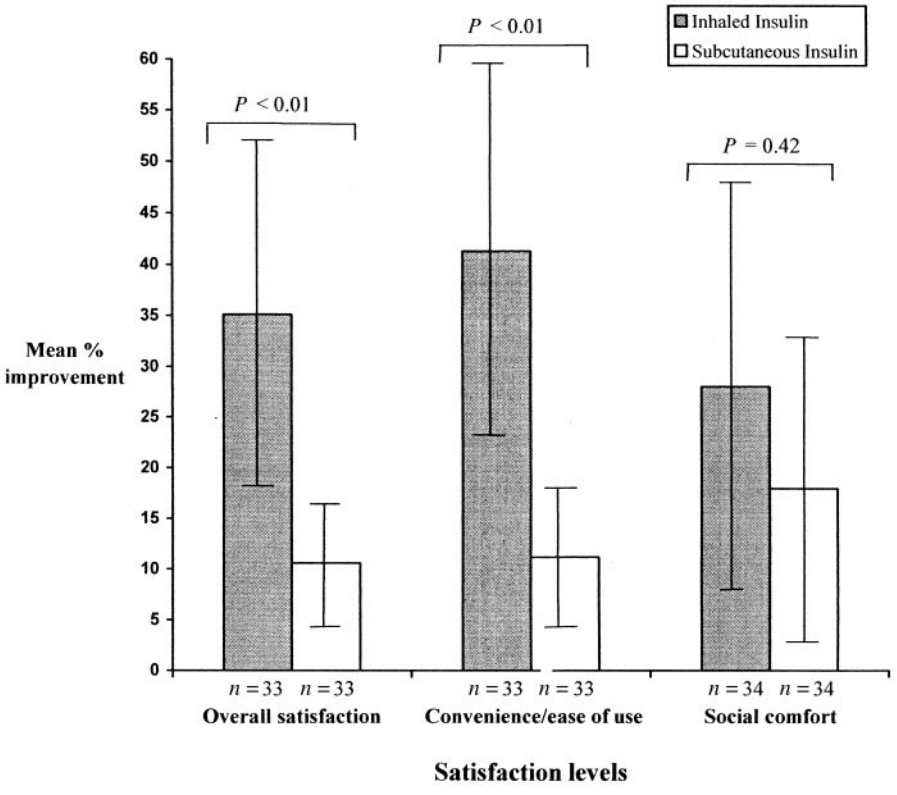

Figure 1—*Improvement in patient satisfaction with treatment at week 12: overall satisfaction, convenience/ease of use, and social comfort. Data shown are mean percent improvement (and 95% CI) in satisfaction for each treatment regimen and* P *values for between-group differences (see* RESULTS*). The reported sample size for each satisfaction measure refers to the number of subjects who completed all items in the overall scale or in each subscale at baseline and week 12. The 66 subjects who responded to all 15 items at follow-up consisted of almost all (96%) of the complete study population of 69 subjects. No discernible differences in clinical characteristics were found between the 3 subjects excluded and the 66 subjects included.*

to continue, the most common reason cited was the rigor of the clinical study protocol, particularly blood glucose monitoring and frequency of clinic visits (5). Furthermore, subjects using inhaled insulin indicated a greater desire to continue taking insulin the way it was taken during the trial than those using injected insulin.

These results have shown that, in a 12-week randomized, controlled trial, inhaled insulin provided greater improvement in treatment satisfaction than subcutaneous insulin among patients with type 1 diabetes. Previous research (5) from an item analysis showed that this improvement stemmed mainly from aspects relating to convenience and ease of use of taking insulin. In particular, six individual items showed significant evidence ($P < 0.05$) that inhaled insulin resulted in more improvement from baseline than subcutaneous insulin. Specifically, compared with subcutaneous insulin, inhaled insulin was rated higher with regard to ease of administration, comfort, convenience, time with dosing, flexibility of eating schedule, and ease of taking insulin many times a day. Patients on subcutaneous insulin therapy, however, were less self-conscious about taking insulin away from home.

The effect on social comfort is not as large as the effect on convenience and, therefore, is not statistically significant (see Fig. 1). However, this does not necessarily imply that there is no effect on social comfort. A type II error is a possibility. More likely, a larger sample size would have increased the sensitivity to detect an effect on social comfort.

Interestingly, some improvements in patient satisfaction were also observed in subjects taking insulin subcutaneously, even though they continued their usual insulin regimen. One possible reason may be that subjects were involved in a controlled clinical trial and many may have reaped the subsequent benefits of monitoring and care (for example, study clinicians and coordinators attended to subjects at least on a weekly basis).

In addition to quantifying the improvements in satisfaction, we sought to better understand the relationship between patient satisfaction and glycemic control, which would provide useful and clinically meaningful information to patients and clinicians. Baseline data from this trial indicated that higher overall satisfaction scores were associated with lower HbA_{1c} ($r = -0.24$, $P < 0.05$) (10). Results on other relationships of satisfaction with demographic and clinical variables are given elsewhere (10). Moreover, a previous study showed that improved satisfaction was observed with improved HbA_{1c} (8), whereas another study demonstrated that it was not (12).

In clinical practice, we expect that the interplay between increased satisfaction and improved glycemic control would be bidirectional: increased satisfaction leads to better glycemic control through better adherence to medication and that better glycemic control in turn leads to increased satisfaction. The clinical trial reported in this study, however, was not designed to measure this complex causal relationship, because glycemic control was tightly monitored for dose adjustments to optimize glycemic control based on results of glucose monitoring. As such, data from this clinical trial were not intended to show meaningful reduction in HbA_{1c} with a given increase in satisfaction. Nonetheless, the clinical trial data indicated that a 1% absolute improvement (reduction) in HbA_{1c} from baseline to week 12 was associated with an average 9.7% improvement in overall satisfaction ($r = -0.27$, $P = 0.04$), after controlling for treatment regimen. Further research in clinical practice settings is encouraged to investigate the relationship between satisfaction and glycemic control.

In summary, these results suggest that an inhaled insulin regimen is preferred and provides substantially more improvement in patient satisfaction than a conventional subcutaneous insulin regimen. In patients with type 1 diabetes, administration of rapid-onset inhaled insulin may offer the first practical, noninvasive alternative to regular insulin injections. Improved satisfaction and convenience may, in clinical practice, increase willingness of patients to initiate and comply with insulin therapy and, therefore, achieve better glycemic control.

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References

1. Diabetes Control and Complications Trial (DCCT) Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
2. Reichard P, Nilsson BY, Rosenqvist U: The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *N Engl J Med* 329:304–309, 1993
3. Lorenz R: The problem with intensive therapy. *Diabetes Care* 21:2021–2022, 1998
4. Blakeslee S: Program to cut risks of diabetes surprisingly fails to lure patients. *New York Times,* 28 Feb 1994; Sect. A, p. 1
5. Skyler JS, Cefalu WT, Kourides IA, Landschulz WH, Balagtas CC, Cheng S-L, Gelfand RA: Efficacy of inhaled human insulin in type 1 diabetes mellitus: a randomised proof-of-concept study. *Lancet* 357:331–335, 2001
6. Lewis KS, Bradley C, Knight G, Boulton AJM, Ward JD: A measure of treatment satisfaction designed specifically for people with insulin-dependent diabetes. *Diabet Med* 5:235–242, 1988
7. Bradley C, Lewis KS: Measures of psychological well-being and treatment satisfaction developed from the response of people with tablet-treated diabetes. *Diabet Med* 7:445–451, 1990
8. Bradley C: Diabetes Treatment Satisfaction Questionnaire (DTSQ). In *Handbook of Psychology and Diabetes*. Bradley C, Ed. Amsterdam, Harwood Academic Publishers, 1994, p. 111–122
9. Gerber RA, Cappelleri JC, Kourides IA, Gelfand RA, Chandler LP, Gorkin L: Improved patient satisfaction with inhaled insulin in subjects with type 1 diabetes mellitus: results from a multicenter randomized controlled trial (Abstract). *Diabetes* 48 (Suppl. 1):A13, 1999
10. Cappelleri JC, Gerber RA, Kourides IA, Gelfand RA: Development and factor analysis of a questionnaire to measure patient satisfaction with injected and inhaled insulin for type 1 diabetes. *Diabetes Care* 23:1799–1803, 2000
11. Rosner B: *Fundamentals of Biostatistics*. 4th ed. New York, Duxbury Press, 1995
12. Menzel R, Chlup R, Jutzi E, Hildmann W: 'Catheter-Pens:' an alternative to insulin pump treatment? *Exp Clin Endocrinol* 95: 157–169, 1990