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Title:

Treatment satisfaction and psychological well-being with insulin glargine compared with NPH in patients with Type 1 diabetes

Running title:

E. Witthaus et al.: Psychological outcomes with insulin glargine vs. NPH

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Abstract

Aims To assess satisfaction with treatment and psychological well-being associated with insulin glargine and NPH. Insulin glargine, a new long-acting insulin analogue, provides constant, peakless insulin release following once-daily administration and is associated with fewer hypoglycaemic episodes, despite metabolic control equivalent to that achieved with NPH human basal insulin. **Methods** The Diabetes Treatment Satisfaction Questionnaire (DTSQ) and Well-being Questionnaire (W-BQ) were completed at baseline and at weeks 8, 20 or 28 by 517 patients with Type 1 diabetes participating in a randomized, controlled European trial comparing insulin glargine and NPH. Analysis of covariance was performed on change from baseline scores (main effects: treatment and pooled site; covariate: baseline scores). **Results** Treatment Satisfaction improved with insulin glargine at all time points, including endpoint, but deteriorated slightly with NPH. These differences were significant throughout the study (change from baseline to endpoint: +1.27 vs. –0.56; $p = 0.0001$). Outcomes were better with insulin glargine for the DTSQ items, Perceived Frequency of Hyperglycaemia and Hypoglycaemia, with statistically significant differences at week 28 and endpoint for hyperglycaemia ($p = 0.0373$ and 0.0379) and at week 20 for hypoglycaemia ($p = 0.0024$). There was no difference in psychological well-being between the treatment groups, with mean scores increasing in both. **Conclusions** Study participants had treatment-independent improvements in General Well-being. Advantages for insulin glargine were seen in significantly improved Treatment Satisfaction throughout the study, together with lower Perceived Frequency of Hyperglycaemia than for patients on NPH, without a significant increase in Perceived Frequency of Hypoglycaemia.

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Keywords:

Type 1 diabetes, treatment satisfaction, psychological well-being, insulin glargine, NPH insulin

Abbreviations:

ANCOVA, analysis of covariance; DTSQ, Diabetes Treatment Satisfaction Questionnaire; W-BQ, Well-being Questionnaire; NPH, Neutral Protamine Hagedorn (insulin); ITT, intention-to-treat.

Introduction

New treatments for chronic diseases, including diabetes, are increasingly being evaluated for their impact on patient-oriented outcomes, such as treatment satisfaction or quality of life. The attainment and improvement of psychological outcomes is a separate but related goal of diabetes care with similar importance to clinical measures of control. Improved metabolic control may contribute to improved psychological well-being and vice versa, but a positive correlation cannot be assumed (1-3). Therefore, psychological outcomes need to be monitored in conjunction with efforts to improve diabetes control to ensure that improved metabolic control is not achieved at the expense of psychological outcomes.

Insulin glargine is a modified human insulin molecule developed to meet the need for a basal insulin with a peakless time-action profile over 24 h (4). Compared with NPH once or twice daily, insulin glargine once daily has been shown to yield at least similar glycaemic control with fewer hypoglycaemic episodes (5-8). Our study aimed to evaluate the impact of using insulin glargine on satisfaction with treatment and psychological well-being. Satisfaction with treatment was expected to be the outcome most likely to be improved with insulin glargine because it involves only one injection daily and is expected to improve glycaemic control. The well-being measure was included with a more exploratory purpose.

Patients and methods

Psychological outcomes were assessed during a randomized, controlled, open-label study of the efficacy and safety of insulin glargine versus NPH human insulin. The study population consisted of people with Type 1 diabetes with a minimum experience of one year of previous insulin use and was recruited from 10 European countries. The study was approved by the appropriate ethics committees, and signed patient consent was obtained prior to the conduct of any study-related procedures.

At the end of a 4-week screening phase, patients were allocated to insulin glargine or NPH by central randomization carried out by an independent agency. During the screening phase, patients were familiarized with the use of the OptiPen® and the blood glucose meter (One Touch II®/Lifescan) provided for the determination of blood glucose at home. During the 28-week treatment phase, insulin glargine was administered by subcutaneous injection once daily at bedtime while NPH human insulin was administered by subcutaneous injection either once or more than once daily, depending on the regimen followed prior to the study. Dose adjustments for both insulins were targeted at a self-monitored pre-meal blood glucose concentration of 4.4 - 6.7 mmol/l (80 – 120 mg/dl). In addition to insulin glargine and NPH, regular human insulin was administered before each meal. With the intention of standardising other aspects of treatment patients previously using insulin lispro were switched to regular human insulin. Study participants not already using the OptiPen® changed over to this injection device for the administration of insulin glargine or NPH. These requirements were driven by the clinical study protocol with the intention of standardizing treatment circumstances as far as possible.

Questionnaires

The Diabetes Treatment Satisfaction Questionnaire status version (DTSQs) measures satisfaction with treatment regimen (hereafter referred to as Treatment Satisfaction) (6 items), Perceived Frequency of Hyperglycaemia (1 item) and Perceived Frequency of Hypoglycaemia (1 item) over the past few weeks (3). The Well-being Questionnaire (W-BQ) provides an overall measure of General Well-being (22 items), incorporating 4 subscales to measure Depression, Anxiety, Energy and Positive Well-being (9). The reliability and factor structure of the eight language versions used in this study are reported elsewhere (10, 11). To ensure a high response rate, patients were asked to complete the questionnaires during the clinic visit and to return them in a sealed envelope to study site personnel.

Statistical analysis

The primary outcome variables were the changes from baseline to final assessment in the DTSQ and W-BQ scores. Only these two variables were subject to hypothesis testing; probability statements for other variables are included for descriptive purposes only. An intention-to-treat (ITT) analysis was performed, including all patients who were randomized and treated and who had completed both a pre-treatment and at least one on-treatment questionnaire.

The sample size calculation was based on the primary clinical variable, glycohaemoglobin. Nevertheless, prior studies (3, 12, 13) suggested that the sample size was more than sufficient to detect meaningful differences in change between insulin glargine and NPH in psychological outcomes. It was estimated that the available sample size had at least 80% power to detect an effect size of 0.20. Effect size was defined as the difference between the mean changes from baseline for the

two treatment groups divided by the baseline standard deviation. As for health status and other outcomes, an effect size of 0.20 or more is considered clinically meaningful for psychological outcomes (14).

An analysis of covariance (ANCOVA) was performed with treatment and pooled site as main effects and baseline score as the covariate. The difference in mean change from baseline was estimated using the adjusted mean together with the associated standard error and a 95% confidence interval from the ANCOVA model. All statistical tests were two-sided and performed at a significance level of $\alpha = 5\%$. Since the assumptions of normality of the residuals and equal variances were not met, the probability statements were based on the ANCOVA with ranked observations. In order to assess the robustness of the primary model, an expanded model including the treatment-by-pooled site and treatment-by-baseline score interactions was examined to check whether the interactions were more than just numeric variation. No statistically significant interactions were found. The same ANCOVA was performed on the W-BQ12 total scale and subscale scores with an intention to explore the responsiveness of this abbreviated version.

Subgroup analyses were performed to assess the effect of: the number of basal insulin injections prior to the study; previous insulin lispro use; and compulsory OptiPen® use. The consistency of treatment effects across countries was also examined.

Results

The psychological ITT population comprised 517 patients, representing 94% of the clinical study population. Patients not included in the analysis provided only baseline or on-treatment data. At baseline there were no significant differences between the two treatment groups in terms of demographic, clinical and psychological variables, apart from the Energy subscale score of the W-BQ ($p = 0.006$) (Table 1). Patients allocated to insulin glargine reported more energy at baseline. Treatment Satisfaction and General Well-being scores at baseline were high in this population. Thirty-one patients (6%) had a maximum baseline score of 36 for Treatment Satisfaction on the DTSQ, and 189 patients (36.6%) scored between 31 and 36. Five patients (1%) had a maximum baseline score of 66 for General Well-being on the W-BQ, and 85 patients (16.4%) scored between 58 and 66.

Table 1.

DTSQ

There was a statistically significant mean increase of 1.27 points in the Treatment Satisfaction score in the insulin glargine group between study entry and last assessment ($p = 0.001$). Treatment Satisfaction decreased by 0.56 points in the NPH group ($p = 0.1499$). The difference between treatments was 1.83 points ($p < 0.001$, Table 2) and represents an effect size of 0.34. This result remains statistically significant even after applying a Bonferroni correction for the large number of statistical tests (i.e., 10) reported in this article. All but one of the six satisfaction items contributed to the differences between treatments, with the largest differences coming from Item 8 (wish to continue) and Item 4 (convenience). In contrast, NPH produced very little change on most of the items and a decrease on some (Table 3).

The changes in Treatment Satisfaction score from baseline to weeks 8, 20 and 28 revealed a pattern of steady increase over time with insulin glargine; in contrast, there was a small but consistent decrease in the NPH group. The difference between treatments was statistically significant at each assessment point (Fig. 1).

Table 2.

Table 3.

Fig. 1.

Perceptions of blood glucose control

Both groups of patients reported a consistent mean decrease in Perceived Frequency of Hyperglycaemia, both at endpoint and at all interim time points. This decrease was more pronounced with insulin glargine than with NPH and the difference was statistically significant at week 28 ($p = 0.037$) and at endpoint ($p = 0.038$). The results for Perceived Frequency of Hypoglycaemia revealed a small increase in mean change from baseline for both treatment groups at most time points except for week 20 when there was a significant difference in favour of insulin glargine ($p = 0.0024$).

W-BQ

The mean score for General Well-being showed an increase (i.e., a greater sense of well-being) at endpoint of 1.22 points (-0.12; 0.94; 1.44 at weeks 8, 20 and 28, respectively) in the insulin glargine group and of 1.57 points (0.31; 0.98; 1.79 at weeks 8, 20 and 28, respectively) in the NPH group, with all four subscales contributing to these small improvements (Table 2). While both these within-group increases from baseline were statistically significant, there was no difference between treatments, either at endpoint or at any interim time point during the study.

Centre / country effects

Treatment Satisfaction scores at baseline differed significantly between country pools, with the highest scores in Austrian (baseline mean 31.7) and the lowest scores in French (23.7) pools (Fig. 2). Irrespective of these differences, however, the direction of response was largely identical across country pools, i. e. there was no country by treatment interaction (p=0.331). With the exception of Norway and France, responses were more favourable, or less unfavourable, in the insulin glargine group than in the NPH group.

Fig. 2

Effect of previous treatment regimen

Increases in Treatment Satisfaction with insulin glargine were observed irrespective of whether the patients had previously been on a once-daily or more than once-daily NPH insulin regimen. In contrast, patients who switched back from insulin lispro to standard insulin at the start of the study showed significant reductions in Treatment Satisfaction compared with those who remained on standard insulin ($p = 0.025$). Nevertheless, the advantage of insulin glargine over NPH was still present, indicating that the difference between treatments was independent of the previous short-acting insulin. Treatment Satisfaction with both treatments increased in the small number of patients who changed from conventional syringes to the OptiPen®. Irrespective of the previous injection device, greater satisfaction was noted with insulin glargine than with NPH.

Discussion

In this study, patients with Type 1 diabetes who started to use insulin glargine had greater satisfaction with treatment than those remaining on NPH insulin. The difference in favour of insulin glargine was statistically significant at each study visit and increased over time. The observed effect size fulfils the criteria for a clinically meaningful change (14). There were only small changes in patients' perception of metabolic control and insulin glargine showed a somewhat more favourable impact than NPH. General Well-being increased during the study with both insulin glargine and NPH and there was no significant difference between the treatments.

The study was not blinded and participants knew which treatment they were receiving. It could be argued, therefore, that the increase in Treatment Satisfaction might have initially reflected patients being pleased with their allocation to the new insulin formulation. However, the early improvements in Treatment Satisfaction were maintained and even increased throughout the course of the study. If all of the perceived benefits were introduced by unmet expectations of patients or clinicians these benefits should have been more transient. Also physicians' and patients' attitudes do not necessarily go in the same direction. It should be noted that blinded designs have their weaknesses particularly in studying psychological effects of treatment. In the case of our study it is questionable whether blinding would have been successful. If blinding was successful, the experience of factors other than the pharmacological effect, such as the method and frequency of administration which affect the convenience of the treatment and its impact on lifestyle could have been missed. The improvements in treatment satisfaction observed with insulin lispro are mainly attributable to the convenience of lispro in requiring no injection-meal

interval. Our individual item analysis showed improvements across most of the Treatment Satisfaction items, with particular emphasis on convenience and desire to continue treatment involving insulin glargine. Such convenience-related treatment characteristics would be confused in a blinded design which, in the case of insulin glargine, would require additional placebo injections.

The improvements in Treatment Satisfaction with insulin glargine were largely confirmed in the various subgroup analyses. As expected from previous research (12, 15), patients who switched back from insulin lispro to standard soluble insulin had marked reductions in satisfaction with treatment. However, this did not affect the differences in responses between insulin glargine and NPH. A similar pattern of responses was seen in most of the country pools except Norway where satisfaction improved slightly with NPH and deteriorated slightly with insulin glargine, and France and Denmark where satisfaction deteriorated in both treatment groups. Since the pooled site by treatment interaction was not significant, however, the general applicability of the main results still holds.

Psychological well-being increased in both treatment groups and this change involved all subscales of the W-BQ22 and W-BQ12 although not all subscales reached significance in their own right. The W-BQ12 showed a very similar pattern to that of the W-BQ22 with very little loss of sensitivity. There was no difference between treatments in well-being scores. This is consistent with a non-specific study effect whereby participation in the clinical trial improved psychological well-being regardless of treatment allocation. Insulin glargine was less likely to produce advantages over NPH insulin in psychological well-being than it was for Treatment

Satisfaction. It is reassuring that there was no deterioration in well-being and that patients maintained their high levels of psychological well-being during the study.

Although the DTSQ and W-BQ have been shown to be sensitive to change (15-17) the true treatment effect may have been underestimated in our study. Like many other psychological outcome measures, the instruments often produce skewed distributions of scores and a proportion of respondents already have optimal scores at baseline (2, 18). This phenomenon of ceiling and floor effects, which limits opportunities for improvements (19, 20), was also observed in the present study population. Despite this, a significant improvement in Treatment Satisfaction occurred in the insulin glargine group.

Increases in Treatment Satisfaction were reported from a number of unblinded trials with insulin lispro in comparison with regular human insulin (12, 15, 17). It would have been of interest to compare the magnitude of effect observed in these trials with our findings. However, due to publication of cross-over results in aggregate form (21, 22) the results of these trials are not suitable for meaningful comparison with our results.

In conclusion, other studies of glargine versus NPH have reported improvements in metabolic outcomes of diabetes care (5, 6, 8). The present study also demonstrates improvements in Treatment Satisfaction with glargine including subjective perceptions of hyperglycaemia and hypoglycaemia which are consistent with objective findings. A combination regimen of insulin glargine together with insulin lispro or another rapid-acting insulin is likely to improve these outcomes yet further. It will be worthwhile to explore this possibility in future research.

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APPENDIX

Diabetes Treatment Satisfaction Questionnaire (DTSQ)

The DTSQ is an 8-item questionnaire that measures satisfaction with diabetes treatment. Each of the eight items is scored on a scale from 0 to 6. The DTSQ generates a sum score for Treatment Satisfaction from Items 1, 4, 5, 6, 7, and 8 (with a possible minimum (maximum) score of 0 (36), and two individual item scores for Perceived Frequency of Hyperglycaemia (Item 2) and Perceived Frequency of Hypoglycaemia (Item 3). Cronbach's alpha coefficients ranged from 0.747 to 0.865 for the translations used in this study (10).

Well-being Questionnaire (W-BQ)

The W-BQ22 is a 22-item questionnaire providing an overall measure of General Well-being (combining all 22 items) and is composed of four subscales: Depression (Items 1 - 6), Anxiety (Items 7 - 12), Energy (Items 13 - 16) and Positive Well-being (Items 17 - 22). Each of the 22 items is scored on a scale from 0 to 3, where 0 = not at all, and 3 = all the time. The W-BQ22 generates a sum score (0 – 66) and four subscale scores: Depression (0 – 18), Anxiety (0 – 18), Energy (0 – 12) and Positive Well-being (0 – 18). The W-BQ12 is an abbreviated version of the W-BQ22 with 12 items, three subscales and an improved factor structure. Cronbach's alpha coefficients for the translations used in this study ranged from 0.884 to 0.916 for the W-BQ22 and from 0.806 to 0.871 for the W-BQ12 (11).

Translations of the DTSQ and W-BQ were improved as necessary prior to the study, particularly the Swedish Energy subscale.

Scoring

The DTSQ and W-BQ scales and subscales are scored in the direction of the scale or subscale label, i.e., an increase in the score signifies an increase in the label. For example, a higher score on General Well-being indicates greater well-being, and a higher score on the Depression subscale indicates more depressed mood.

Access to questionnaires

The DTSQ and W-BQ are presented and reviewed in (3, 9), together with scoring instructions and details of the psychometric development. Access to the questionnaires and permission for use can be obtained from the copyright holder, Professor Clare Bradley, Health Psychology Research, Department of Psychology, Royal Holloway, University of London, Egham, Surrey TW20 0EX, UK.

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Table 1. Demographic, clinical and psychological variables at baseline

Variable	Insulin glargine	NPH
n	261	256
Age (years)	40.1 (12.31)	39.4 (11.90)
Age range (years)	17 –77	18 – 77
Sex (% male)	54.4	56.6
GHb (%)	7.82 (1.15)	7.95 (1.15)
Previous treatment (%)		
NPH once daily	49.8	50.4
Insulin lispro	16.5	13.3
OptiPen®	12.7	10.2
Other pen	85.4	85.0
Conventional syringes	2.0	4.9
DTSQ scores:		
Treatment Satisfaction	27.84 (5.92)	28.09 (5.38)
Perceived Frequency of Hyperglycaemia	2.8 (1.48)	3.0 (1.56)
Perceived Frequency of Hypoglycaemia	2.1 (1.40)	2.1 (1.42)
W-BQ scores:		
General Well-being	50.34 (9.01)	49.40 (9.25)
Depression	3.50 (2.63)	3.58 (2.60)
Anxiety	3.98 (3.03)	4.20 (3.22)
Energy	8.49 (2.15)	7.91 (2.39)**
Positive Well-being	13.33 (3.23)	13.18 (2.96)

All data (except n, age range, sex % male and previous treatment %) are means (± SD)

** significant difference between treatment groups, $p<0.01$

Table 2. Psychological outcomes: an overview

	Changes from baseline to endpoint within treatment groups				Differences in changes from baseline to endpoint between treatment groups		
	Insulin glargine	*p* value	NPH	*p* value	Δ	95% CI	*p* value
DTSQ:							
Treatment Satisfaction	1.27	0.001**	-0.56	NS	1.83	0.82; 2.84	< 0.001***
Perceived Frequency of Hyperglycaemia	-0.55	< 0.001***	-0.30	< 0.001***	-0.3	-0.49, -0.02	0.038*
Perceived Frequency of Hypoglycaemia	0.10	NS	0.15	NS	-0.0	-0.27, 0.18	NS
W-BQ22:							
General Well-being	1.22	0.005**	1.57	< 0.001***	-0.35	-1.50; 0.81	NS
Depression	-0.19	NS	-0.24	NS	0.06	-0.31: 0.42	NS
Anxiety	-0.31	0.039*	-0.53	< 0.001***	0.22	-0.17; 0.62	NS
Energy	0.33	0.008**	0.40	0.001**	-0.07	-0.40; 0.25	NS
Positive Well-being	0.39	0.017*	0.35	0.030*	0.04	-0.39; 0.46	NS
W-BQ12:							
General Well-being	0.78	0.004**	1.12	< 0.001***	-0.34	-1.05; 0.37	NS
Negative Well-being	-0.22	NS	-0.52	< 0.001***	0.29	-0.01; 0.60	NS
Positive Well-being	0.24	0.0344	0.21	NS	0.03	-0.27; 0.32	NS

All data are adjusted means. 95% CI = 95% confidence interval of adjusted means. * < 0.05, ** < 0.01, *** < 0.001, NS = not significant.

Table 3. Treatment Satisfaction: individual item analysis

DTSQ Item	Changes from baseline to endpoint within treatment groups		Differences in changes from baseline to endpoint between treatment groups	
	Insulin glargine	NPH	Δ	*p* value
Item 1: Satisfaction	0.37	0.08	0.29	0.002**
Item 4: Convenience	0.32	0.09	0.41	< 0.001***
Item 5: Flexibility	0.25	0.00	0.25	< 0.001***
Item 6: Understanding	-0.03	0.06	-0.09	NS
Item 7: Recommend to others	0.00	-0.31	0.32	0.003**
Item 8: Wish to continue	0.39	-0.24	0.63	<0.001***

All data are adjusted means. * < 0.05, ** < 0.01, *** < 0.001, NS = not significant.

Legends for Figures

Figure 1. Time profile of changes from baseline in Treatment Satisfaction

Figure 2. Change in Treatment Satisfaction by country

Figure 1. Time profile of changes from baseline in Treatment Satisfaction

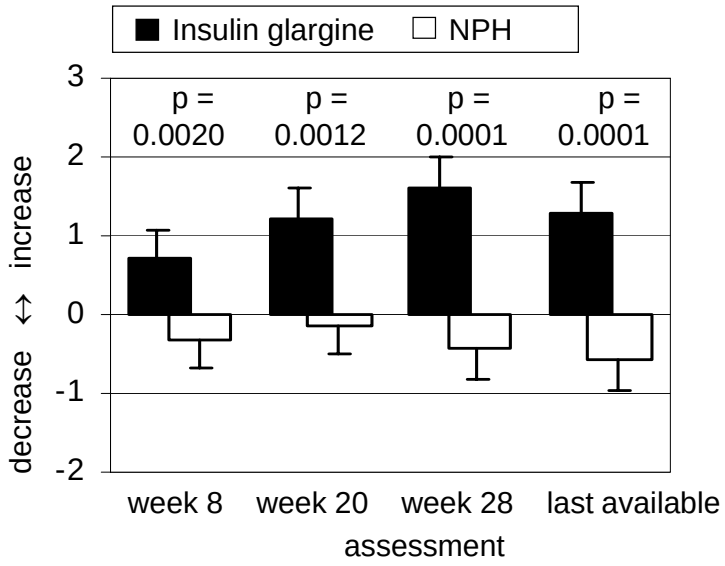
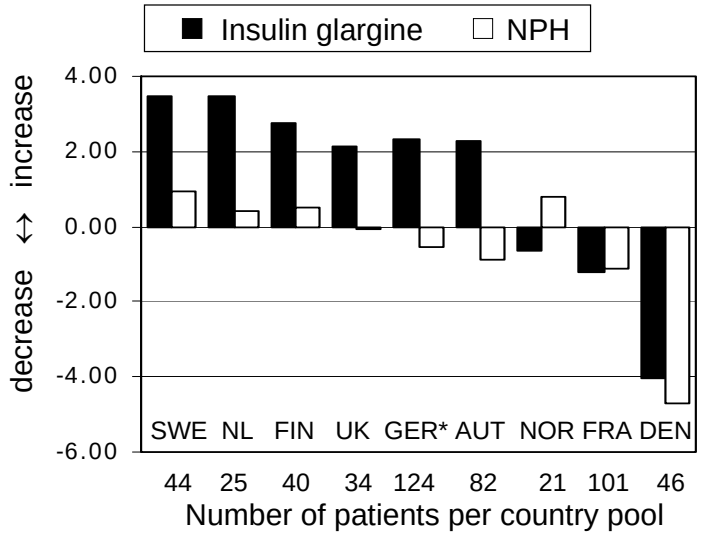


Figure 2. Change in Treatment Satisfaction by country



* includes 13 patients from Switzerland