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ORIGINAL ARTICLE

No Effect of Insulin Pen with Memory Function on Glycemic Control in a Patient Cohort with Poorly Controlled Type 1 Diabetes: A Randomized Open-Label Study

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Abstract

Background:

Injection compliance is a major problem in patients with type 1 diabetes. Increased compliance with mealtime insulin injections significantly improves metabolic control. Using an insulin pen with memory function might facilitate corrective dosing to avoid postprandial blood glucose peaks and therefore might improve overall glycemic control.

Methods:

This randomized, open-label, 24-week multicenter study evaluated if patients with inadequately controlled type 1 diabetes [hemoglobin A1c (HbA1c) ≥ 8%] who were randomized to use the HumaPen® Memoir™, an insulin pen device with memory function, for their mealtime insulin injections achieved superior glycemic control (HbA1c change from baseline) than patients who used the conventional device HumaPen Luxura™. Hemoglobin A1c, hypoglycemia, and pen acceptance were assessed at baseline and after 12 and 24 weeks.

Results:

Of 263 patients randomized, 257 were eligible for analysis: HumaPen Memoir 129, HumaPen Luxura 128; mean [standard deviation (SD)] baseline HbA1c 9.09% (0.99%); mean (SD) age 39.8 (16.5) years; 87.9% ≥18 years old; and mean (SD) diabetes duration 16.0 (11.2) years. Least square mean (95% confidence interval) changes of HbA1c up to week 24 were not significantly different between the HumaPen Memoir [0.43% (-0.59%,-0.28%)] and the HumaPen Luxura group [0.48% (0.64%, 0.32%); $p = .669$]. The overall incidence of hypoglycemic episodes did not differ significantly between groups ($p = .982$). Average satisfaction with insulin delivery was high in both groups.

Conclusions:

In this patient sample, usage of a memory function pen was not associated with superior glycemic control, suggesting that adherence to mealtime injection schedules was not improved in a relevant manner. The memory function might be helpful for specific patient populations only, e.g., children or forgetful patients.

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Abbreviations: (ANCOVA) analysis of covariance, (CI) confidence interval, (HbA1c) hemoglobin A1c, (IDSQ) insulin delivery system questionnaire, (LS) least square, (SD) standard deviation

Keywords: clinical study, insulin, insulin pen, memory function, type 1 diabetes

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Introduction

Injection compliance is a major problem in children and adolescents with type 1 diabetes.[1,2] Mechanisms to support pediatric patients or to help their parents or guardians supervise injection compliance might have the potential to improve mealtime injection frequency. Missed insulin bolus injections have been considered as one reason for worsening of glycemic control. In pediatric patients, an increase in hemoglobin A1c (HbA1c) of 1.0% has been estimated for every four missed meal boluses per week.[2] An HbA1c effect of -0.5% for only two boluses per week not missed has been estimated.[2] For adults with type 1 diabetes, an increase in mealtime injection compliance has also been shown to improve metabolic control.[3–5] A decrease of HbA1c in the magnitude of 0.5% is clinically relevant for this patient population, as shown by the large Diabetes Control and Complications Trial.[6,7]

The HumaPen® Memoir™ (Eli Lilly and Company, Indianapolis, IN) is a mechanical insulin pen with an electronic display. It is equipped with a memory function that records the dose, date, and time of the past 16 injections.[8] In a patient population with poorly controlled diabetes despite multiple daily insulin injections (a regimen that is considered to be the gold standard), a high frequency of noncompliance issues can be expected, caused, e.g., by forgetfulness. Use of a pen device with integrated memory function might improve glycemic control as compared with a conventional pen device because of the decreased probability that mealtime bolus injections are forgotten and the facilitation of corrective dosing.

This randomized pen comparison study was conducted to evaluate this hypothesis. The study investigated if patients with inadequately controlled type 1 diabetes randomized to use the HumaPen Memoir for their mealtime insulin injections achieved superior glycemic control when compared with patients who used the conventional insulin injection device HumaPen Luxura™ (Eli Lilly and Company).

Methods

Study Design

This randomized, open-label, 24-week study was conducted at 32 sites in Germany (NCT00985712). Patients with inadequately controlled type 1 diabetes were randomized to use either the HumaPen Memoir or the HumaPen Luxura for all mealtime insulin injections. The HumaPen Luxura was chosen as conventional comparator device to minimize the bias by different pen types; the mechanical pen platforms of both HumaPens are identical. During the study, patients were asked to continue their previous insulin dosage schedule; however, insulin doses could be adjusted as needed. Because both insulin pens are designed for use with Lilly insulins only, a prerequisite for this study was that patients who were not already using Lilly insulins had to change their mealtime injections of short-acting insulin analogs or human regular insulin to the same dose of the corresponding Lilly brand at baseline. Injection of previous basal insulin was continued unchanged.

Clinical visits occurred at screening, baseline, week 12, and week 24. During an initial 2 week screening period, patients continued on their previous insulin therapy and their previous insulin injection devices. At baseline, patients were randomly assigned at a ratio of 1:1 to receive their previous insulin regimen for 24 weeks with either HumaPen Memoir or HumaPen Luxura as sole insulin injection device for mealtime insulin. At each visit, capillary blood samples were collected for central laboratory HbA1c measurement (IKFE GmbH, Mainz, Germany; high-pressure liquid chromatography method). Data on insulin treatment, hypoglycemia, and concomitant medication were collected at each visit. Hypoglycemic episodes were defined based on the recommendations of the American Diabetes Association.[9] Adverse events and pen complaints were recorded. Furthermore, patients were asked to complete the validated "insulin delivery system questionnaire" (IDSQ) to provide feedback on their satisfaction with the respective pens.[8,10]

The study was approved by the responsible ethics committee in Germany and was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. All patients signed informed consent before conducting any study procedures.

Patients

Patients with type 1 diabetes mellitus (World Health Organization criteria)[11] were eligible if they were ≥8 years of age, had received intensified insulin regimes for at least 2 months, and had a HbA1c ≥ 8% at screening. Patients (and parents/guardians/legal representatives, if applicable) had to be well motivated to improve their glycemic control in the investigator's opinion.

Statistical Analysis

Assuming that the HbA1c after 24 weeks would be 0.5% lower in the HumaPen Memoir than in the HumaPen Luxura group, and assuming a common standard deviation (SD) of 1.2%, at least 123 completers per group (total 246 patients) were needed to conclude a significant difference with a power of 90%. This sample size calculation was based on a two-sided *t*-test at a 5% significance level. Assuming a dropout rate of 5%, approximately 130 patients per group (total 260 patients) had to be enrolled.

All randomized patients who completed the baseline visit and had at least one post-baseline measurement for the dependent variable (full analysis set) were included in the analyses. The primary analysis evaluated the difference in the change in mean HbA1c (HumaPen Memoir minus HumaPen Luxura) using a mixed model for repeated measures (adjusting for baseline and screening HbA1c) and change/no change of mealtime insulin type at baseline and included patient as random effect. The proportion of patients achieving HbA1c targets, reporting hypoglycemic episodes, and experiencing at least one adverse event were compared using chi-square tests, or Fisher's exact tests if the chi-square test was not appropriate. IDSQ scores were evaluated using a corresponding analysis of covariance (ANCOVA). Complaints were evaluated descriptively.

Results

Of 263 patients randomized (HumaPen Memoir/Luxura, 130/133), 261 (130/131) patients started to use the study pen, 257 (129/128) patients with at least one post-baseline HbA1c measurement were included in the primary analysis, and 250 (123/127) patients completed the study. Baseline characteristics were similar in both pen groups (**Table 1**). The majority of patients (87.9%) were adults, with a mean (SD) age of 39.8 (16.5) years and a mean (SD) diabetes duration of 16.0 (11.21) years. The mean (SD) HbA1c at baseline was 9.09% (0.99%), and 40.9% of patients had a baseline HbA1c > 9%. Most patients (83.5%) used the short-acting insulin lispro for mealtime insulin injections. Sixty-three percent needed three mealtime insulin injections per day while 35.0% needed ≥4. The mean (SD) basal insulin dose was 0.39 (0.18) IU/kg per day. The mean (SD) prandial insulin dose was 0.43 (0.24) IU/kg per day. Mean basal and prandial insulin doses remained unchanged during the study.

The least square (LS) mean change of HbA1c from baseline up to week 24 did not significantly differ between the pen groups [group difference, HumaPen Memoir minus HumaPen Luxura, 0.05; 95% confidence interval (CI) -0.17 to +0.26; $p = .669$; **Figure 1**]. Mean HbA1c decreased with both pens. The LS mean (95% CI) changes from baseline were -0.43% (-0.59% to -0.28%) points with HumaPen Memoir and -0.48% (-0.64% to -0.32%) points with HumaPen Luxura ($p = .669$). Superiority of the memory function pen could not be concluded (**Figure 1**). Four patients (3.1%) in the HumaPen Memoir group and seven patients (5.5%) in the HumaPen Luxura group achieved the HbA1c target of ≤7.0% ($p = .355$).

Table 1.
Baseline Characteristics[a]

	HumaPen Memoir (*N* = 129)	HumaPen Luxura (*N* = 128)	Total (*N* = 257)
Age, years			
Mean (SD)	38.3 (17.37)	41.2 (15.52)	39.8 (16.50)
Categories (%)			
Adults (≥18 years)	109 (84.5)	117 (91.4)	226 (87.9)
Adolescents (12–17 years)	17 (13.2)	8 (6.3)	25 (9.7)
Children (8–11 years)	3 (2.3)	3 (2.3)	6 (2.3)
HbA1c at baseline, %			
Mean (SD)	9.12 (1.04)	9.06 (0.94)	9.09 (0.99)
Sex, *n* (%)			
Female	56 (43.4)	52 (40.6)	108 (42.0)
Male	73 (56.6)	76 (59.4)	149 (58.0)
Race, *n* (%)			
White	128 (99.2)	127 (99.2)	255 (99.2)
Black or African American	1 (0.8)	1 (0.8)	2 (0.8)
Body mass index, kg/m^2			
Mean (SD)	26.75 (5.35)	26.78 (5.04)	26.77 (5.19)
Duration of diabetes, years			
Mean (SD)	15.2 (11.46)	16.7 (10.95)	16.0 (11.21)
Daily basal insulin dose, IU/kg			
Mean (SD)	0.38 (0.17)	0.41 (0.18)	0.39 (0.18)
Daily prandial insulin dose, IU/kg			
Mean (SD)	0.41 (0.21)	0.45 (0.27)	0.43 (0.24)
Prandial injections per day, *n* (%)			
1–2 injections	1 (0.8)	4 (3.1)	5 (2.0)
3 injections	114 (65.9)	77 (60.2)	162 (63.0)
4 injections	29 (22.5)	21 (24.2)	60 (23.3)
≥5 injections	14 (10.9)	16 (13.3)	30 (11.7)

[a] *N* = total number of patients per group; *n* = number of evaluable patients.

The proportion of patients reporting hypoglycemic episodes (confirmed or unconfirmed) between baseline and week 24 did not differ significantly between both pen groups. At least one hypoglycemic episode was reported by 81 patients (62.3%; severe 1 patient, 0.8%) in the HumaPen Memoir and by 79 patients (60.8%; severe 2 patients, 1.5%) in the HumaPen Luxura group (p = .799). At least one nocturnal episode was reported by 45 patients (34.6%) with HumaPen Memoir and by 54 patients (41.5%) with HumaPen Luxura (p = .250).

On the IDSQ scale, which ranges from 1–7, with higher scores reflecting a more positive evaluation, the mean (SD) IDSQ scores for insulin delivery were 5.6 (1.20) for the HumaPen Memoir and 5.5 (1.41) for the HumaPen Luxura group, and the respective IDSQ scores on the ease of dosing were 6.1 (0.84) and 6.0 (0.88), respectively. Of those patients using HumaPen Memoir, 76.7% were mostly or definitely willing to continue using the study pen, as were 78.1% of those using HumaPen Luxura. The ANCOVA did not identify any significant difference for the different subscale ratings at week 24 (delivery satisfaction, p = .315; perceived blood sugar control, p = .895; ease of dosing, p = .116; lifestyle impact, p = .889; willingness to continue, p = .907). Pen-related functional complaints were reported by 12 patients (9.2%) in the HumaPen Memoir and by 2 patients (1.5%) in the HumPen Luxura pen group. Eleven of the 12 pen-related functional complaints in the HumaPen Memoir group related to a dysfunction of the electronic display. None of the complaints were associated with an adverse event.

Fifty-two patients (40.0%) in the HumaPen Memoir and 56 patients (42.7%) in the HumaPen Luxura group experienced at least one adverse event. The proportions of patients reporting any adverse event or any serious adverse event did not differ between the two pen groups (p = .652 and p = .779, respectively). Nasopharyngitis was the most frequent adverse event in both groups (HumaPen Memoir 9.2%, HumaPen Luxura 11.5%), followed by urinary tract infection (HumaPen Memoir 1.5%, HumaPen Luxura 2.3%) and diabetic foot (HumaPen Memoir 2.3%, HumaPen Luxura 0.8%).

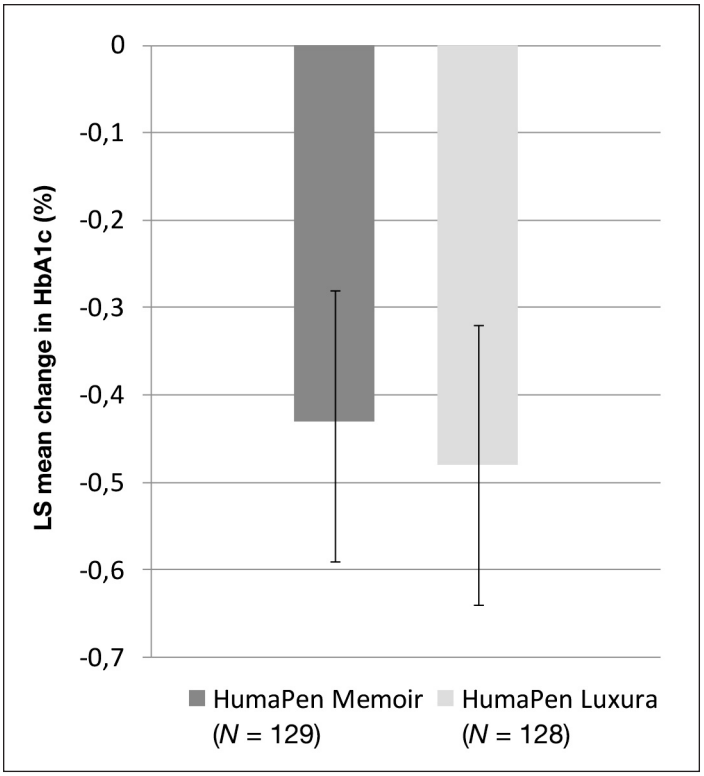

Figure 1. Change in HbA1c from baseline to week 24. Data presented are LS means derived from the mixed model repeated measures and the respective 95% CIs. MMRM, mixed model repeated measures.

Discussion

In this sample of mainly adult patients with inadequately controlled type 1 diabetes, use of an insulin pen with integrated memory function was associated neither with an additional improvement in glycemic control nor with a lower rate of hypoglycemia when compared with a conventional pen device. Based on IDSQ assessment, both pens were accepted with no apparent difference in patient satisfaction between groups (although there was a higher rate of functional complaints about the HumaPen Memoir, relating to a dysfunction of the electronic display). There are several possible explanations for the failure to discriminate between the two injection devices. The assumed main benefit of the memory function, to facilitate corrective insulin injections, may have started too late after a meal with a forgotten preprandial injection to prevent the majority of postprandial blood glucose peaks. There may have been too few corrective actions to observe a relevant HbA1c reduction. According to literature, two missed mealtime injections per week would be associated with an HbA1c increase of 0.5%.[2] Also, in poorly controlled diabetes patients, correction of mealtime insulin dosing alone might not be sufficient to achieve a relevant HbA1c reduction independently of fasting blood glucose control. Patients continued their basal insulin unchanged during the study. It has been shown that patients with HbA1c levels > 9% commonly have poorly controlled fasting glucose values; in this study, the proportion of patients with baseline HbA1c > 9% was 40.1%. The fact that the basal insulin dose was not adjusted per protocol may have minimized any effects in changes of prandial insulin delivery.[12]

Further, a patient population with poor diabetes control for any reason, as included in this study, might not be appropriate to demonstrate the effect of the memory function.[13] The reasons for poor diabetes control were not recorded but can be expected to include medical problems such as the dawn phenomenon[14] as well as a general noncompliance with insulin injections[15] or just forgetfulness. Only the subgroup of just forgetful patients can be expected to benefit from a memory function pen. A second subgroup of patients who might benefit from the memory pen would be children and adolescents who require supervision of insulin dosing by their parents, guardians, or other caregivers; the memory function would facilitate this supervision and corrective insulin injections. However, the patient population in this study mainly included adult patients (89.7%).

Regardless of the study outcome, the opportunity for health care professionals to supervise patient compliance by checking the memory function might possibly add value for all patients, especially during the insulin dose finding and titration process.

The study has several limitations potentially affecting the validity of the results. Children and adolescents were underrepresented due to the feasibility issues associated with enrolling pediatric study patients in Germany. Therefore, no specific insight could be gained regarding the impact of the memory function pen on this age group. The overall number of missed insulin bolus injections and the number of corrective actions taken based on the memory function were not recorded. The study was not designed to recruit patients who were representative of the entire population of patients with type 1 diabetes. Only patients "well-motivated to improve their glycemic control in the investigator's opinion" should have been recruited, but this inclusion criterion was somewhat weak and difficult to quantify. Noncompliant patients were probably overrepresented, as indicated by the high proportion of patients with baseline HbA1c > 9% (40.1%). Such poor diabetes control is uncommon for type 1 diabetes patients in Germany for whom standardized diabetes education is well established and blood glucose meters plus test strips are easily available and reimbursed. An additional psychological effect may have been introduced by study participation *per se*. Due to the study interventions, patients may have been less forgetful and/or more engaged in their diabetes management than they would be in routine practice and therefore might be in less need for the memory function pen. Finally, the memory function pen was used only for mealtime insulin injections. The impact of basal insulin treatment on the HbA1c results could not be evaluated, because blood glucose profiles were not assessed. Therefore, it was not possible to evaluate to which extent high HbA1c values were caused by high fasting or by high postprandial blood glucose values.

Conclusions

In conclusion, use of a pen device with memory function was not associated with superior glycemic control when compared with a conventional device in the sample of mainly adult patients with poorly controlled type 1 diabetes assessed in this study. The memory function might be helpful for specific patient populations only, e.g., children and adolescents or forgetful patients; further studies should evaluate this question.

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Disclosures:

Axel Haupt and Elisabeth Moennig are employees of Lilly Deutschland GmbH, Bad Homburg, Germany. Thomas Forst serves as consultant for Lilly Deutschland. Jürgen Deinhard is an employee of Accovion GmbH, Eschborn, Germany; this company conducted the statistical analysis on behalf of Lilly Deutschland. Thomas Danne has received honoraria or grant support from several pharmaceutical companies (Abbott, Sanofi, Bayer, Roche, Johnson & Johnson, Lilly, Medtronic, DexCom, NovoNordisk) for the conduct of studies or scientific meetings.

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