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Long-term outcomes of an advanced hybrid closed-loop system: a focus on different subpopulations.

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Title

Long-term outcomes of an advanced hybrid closed-loop system: a focus on different subpopulations.

Running title: One-year results of the 780G in specific groups.

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Abstract

Background. The long-term benefit provided by advanced hybrid closed-loop (AHCL) systems needs to be assessed in general populations and specific subpopulations.

Methods. A prospective evaluation of subjects initiating the AHCL system 780G was performed. Time in range (70-180 mg/dl) (TIR), <70 mg/dl, <54 mg/dl, >180 mg/dl and >250 mg/dl were compared, at baseline and after one year, in different subpopulations, according to previous treatment (pump *vs* MDI), age (> or ≤25 years old) and hypoglycaemia risk at baseline.

Results. 135 subjects were included (age: 35±15 years, 64% females, diabetes duration: 21±12 years). An increase in TIR was found, from 67.26±11.80% at baseline to 77.41±8.85% after one year (p<0.001). All the subgroups showed a significant improvement in TIR, time >180 mg/dl and >250 mg/dl. At the 1-year evaluation, no significant differences were found, between previous pump users and MDI subjects. Children and young adults had a lower time <70 mg/dl than adults. Subjects with a high risk of hypoglycaemia at baseline had a higher time spent at <70 mg/dl and <54 mg/dl than low-risk individuals.

Conclusion. The initial benefit provided by the AHCL system is sustained in the long term. MDI subjects obtain the same outcomes as subjects with pump experience.

Keywords: type 1 diabetes, closed-loop systems, artificial pancreas, hypoglycaemia.

Introduction

Closed-loop systems have brought a paradigm shift in the management of type 1 diabetes and their use is rapidly spreading around the world. The advanced hybrid closed-loop (AHCL) system MiniMed™ 780G uses a model based adaptative algorithm with a PDI (Proportional Integral Derivative) with insulin feedback module; the system delivers microboluses of insulin, to reach personalised glucose targets (100 mg/dl, 110 mg/dl or 120 mg/dl); also, auto-correction boluses are delivered when the infusion from microboluses is not enough to keep sensor glucose below 120 mg/dl; additional safety features, as the Safe Meal Bolus feature, are included in the algorithm [1]. A rapid improvement in glycaemic control, which is sustained after 3 to 6 months, has been reported by our group and other groups in many countries, showing a time in range (70-180 mg/dl) between 75.6% and 80.4% [2-7]. Also, a large number of downloads from anonymised subjects have been analysed, showing similar outcomes [8,9]. Patient-reported outcomes analysis has shown an increase in patient satisfaction with the system [3,10,11]. Nevertheless, the long-term outcomes of the AHCL system have not been reported. Additionally, analysis of the performance of the AHCL system in specific populations is scarce. Subpopulations may have different diabetes care requirements, glycaemic disturbances and targets [12]. Knowledge concerning the performance of the AHCL systems in different subgroups of individuals is required, to assist healthcare

professionals in tailoring their therapeutic choices for type 1 diabetes people with various needs.

The study aimed to evaluate if the benefit reported with the use of this AHCL system was sustained in the long-term in both the general population of type 1 diabetes and in specific subgroups of subjects with different baseline characteristics that could influence those outcomes.

Material and Methods

Subjects with type 1 diabetes consecutively initiated the use of the MiniMed™ 780G system with Guardian™ Sensor 3 at Badajoz University Hospital. A longitudinal prospective evaluation was performed. Pregnant women were excluded. A 2-week system download was collected at baseline and again at the end of one year using the system. Time in range (70-180 mg/dl), time below range (< 70 mg/dl) and < 54 mg/dl and time above range (> 180 mg/dl) and 250 mg/dl, according to International Consensus [13], were collected. Glucose Management Indicator (GMI) (%), coefficient of variation of glucose (CV) (%), sensor use (%) and parameters related to the use of the system were also evaluated.

The baseline data consisted of 2 weeks using continuous glucose monitoring with Guardian™ Sensor 3 in all the patients, to assure that data from the same sensor were compared at baseline and at the end of follow-up. Pump therapy or MDI was maintained during those 2 weeks, according to the therapy that the subjects were previously using.

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Three different subgroups of subjects were defined, representing specific subpopulations, based on particular characteristics at baseline. These groups were defined as follows: Group 1, according to previous treatment: pump therapy *vs* MDI, Group 2, according to age: children and young adults (≤ 25 years-old) *vs* adults (26 to 65 years old), and Group 3, according to hypoglycaemia risk: high hypoglycaemia risk (time < 70 mg/dl ≥ 4% or time < 54 mg/dl ≥ 1% at baseline) *vs* low hypoglycaemia risk (time < 70 mg/dl < 4% and time < 54 mg/dl < 1% at baseline).

Time in range (70-180 mg/dl), time < 70 mg/dl and 54 mg/dl and time > 180 mg/dl and 250 mg/dl, GMI (%), CV (%) and sensor use were compared at baseline and after one year for each of these subgroups. These same variables, as well as variables related to the use of the system, were compared between subgroups (pump therapy *vs* MDI, adults *vs* children and young adults and low *vs* high hypoglycaemia risk) at the end of the follow-up.

The study protocol followed the Declaration of Helsinki principles and was approved by the Badajoz University Hospital Ethics Committee. All of the participants were informed of the protocol and signed a consent form.

Data analysis was performed using the SPSS statistics software v22. A descriptive analysis of continuous variables was performed by calculating their mean and standard

deviation. Categorical variables were expressed as percentages. The normal distribution of the variables was checked by Kolmogorov-Smirnov's test. A paired Student's t-test or a Wilcoxon signed-rank test was used for the analysis of differences. For unpaired samples, the independent samples t-test was used. Comparisons between proportions were analysed by a chi-squared test. Correlation analysis was performed using the Pearson method. The sample size was estimated using the Granmo software. A p-value < 0.05 was considered statistically significant.

Results

One hundred and thirty-five people with type 1 diabetes were included. Subject characteristics are summarised in Table 1. BMI was 24.7 ± 4.7 Kg/m2, 51% of the subjects had normal weight, 11% were underweight and 38% were overweight or obese.

Regarding insulin treatment, baseline treatment was MDI for 27% (n = 36) of the patients. The subjects who were already on pump therapy before the study (73%, n = 99)) used mostly sensor-augmented pump systems with predictive low-glucose suspend function (n = 86). Eight subjects were on pump therapy without continuous or flash glucose monitoring, 4 subjects were using a non-advanced hybrid closed-loop system and 1 subject was on pump therapy with continuous glucose monitoring. In previous pump users, the duration of pump therapy before the start of using the AHCL system was 6.6 ± 3.3 years.

Regarding glucose monitoring, 71% (n = 96) of the participants were using continuous glucose monitoring (Guardian™ Sensor 3: n = 90, Dexcom 6®: n = 5, Eversense®: n = 1), 22% (n = 30) used flash glucose monitoring and 9 subjects were on SMBG.

Two additional subjects had stopped using the system after 7 months and 10 months respectively, and one subject used the auto-mode only sporadically; those individuals were excluded from the analysis.

Outcomes in time spent in different glycaemic ranges at the one-year follow-up in the whole population are shown in Figure 1. Time in range (70-180 mg/dl) at the one-year evaluation was 77.41 ± 8.85% (range: 53% to 96%). The mean improvement in time in range (70-180 mg/dl) was 10.15 ± 10.83%. The percentage of subjects reaching the target of a time in range (70-180 mg/dl) > 70% was increased from 40% (n = 54) at baseline to 79% (n = 107) and the last visit (p = 0.003). Also, 53% (n = 71) of the individuals reached the combined target of time in range (70-180 mg/dl) > 70% and time < 70 mg/dl < 4% at the one-year visit and 42% (n = 57) of the individuals reached a time in range (70-180 mg/dl) > 80% (Figure 2).

Additionally, the individuals who were already reaching the target of time in range (70-180 mg/dl) > 70% at baseline (n = 54) achieved a significant improvement in time in range (70-180 mg/dl) from 78.07 ± 5.03% to 81.33 ± 6.97% (p = 0.01), as well as a reduction in time below and above range. Nevertheless, this improvement in time in range (70-180 mg/dl) was significantly lower than the amelioration in subjects with

baseline time in range (70-180 mg/dl) below target (n = 81), which was increased from 60.06 ± 9.22% to 74.79 ± 9.04% ($p < 0.001$).

GMI was reduced from 6.98 ± 0.49 % to 6.67 ± 0.32%, mean glucose and standard deviation of sensor glucose were reduced from 154 ± 20 mg/dl to 141 ± 13 and from 53 ± 9 mg/dl to 47 ± 8 mg/dl respectively (all $p < 0.001$), while the coefficient of variation (CV) did not change (34.0 ± 4.5% *vs* 33.5 ± 4.3%, $p = 0.286$). The use of the sensor was increased from 84.7 ± 12.3% to 90.4 ± 9.3% ($p < 0.001$).

Regarding the use of the system, time in auto-mode was 95.6 ± 7.2% and the number of exits was 0.98 ± 0.99 per week. The number of SMBG and calibrations per day were 3.2 ± 0.9 and 3.0 ± 0.9 respectively. Total insulin dose was 46.8 ± 22.3 units per day, basal insulin was 42.6 ± 9.7%, bolus insulin 56.9 ± 8.2% and auto-corrections represented 31.8 ± 14.1% of bolus insulin (27.2 ± 9.4 boluses per day, 8.3 ± 5.9 units per day).

The subjects received 3.8 ± 3.5 hypoglycaemia alarms and 2.2 ± 2.0 hyperglycaemia alarms per day. The hypoglycaemia alarms were not significantly different compared to baseline, but the hyperglycaemia alarms were reduced from the 3.1 ± 3.0 alarms they received at baseline ($p = 0.001$). The number of meals per day was 4.2 ± 1.7 and the carbohydrate intake was 144.8 ± 84.7 grams per day.

The auto-correction feature was ON in all the subjects; 84% (n = 113) of the subjects used a glucose target of 100 mg/dl, 12% (n = 16) 110 mg/dl and 4% (n = 6) 120 mg/dl; active insulin time was 2 hours in 76% of the subjects (n = 102), between 2 and 3 hours in 22% (n = 29) and more than 3 hours in 4 people.

A positive correlation was found between time in range (70-180 mg/dl) and time in auto-mode (Pearson coefficient r = 0.442, p < 0.001) and a negative correlation was observed between time in range (70-180 mg/dl) and the percentage of auto-correction insulin (Pearson coefficient r = -0.369, p < 0.001) .

The differences in the glycaemic outcomes in the predefined subpopulations are shown in Table 2. In Group 2, the mean age was 43 ± 9 years old in adults and 16 ± 5 years old in children and young adults (p < 0.001). Time in range (70-180 mg/dl), time > 180 mg/dl and time > 250 mg/dl, GMI, mean sensor glucose and standard deviation of sensor glucose were reduced, after one year of use of the system, in all the groups. The sensor used was increased in all the groups except for the MDI group.

No significant differences were found in the improvement in time in range (70-180 mg/dl) between the groups: 9.82 ± 11.13% in previous pump users *vs* 11.03 ± 10.05% in MDI subjects; 9.89 ± 10.81% in adults *vs* 10.70 ± 10.98% in children and young adults; 11.48 ± 11.57% in people with low hypoglycaemia risk *vs* 8.42 ± 9.62% in people with high hypoglycaemia risk at baseline (all p > 0.005). Additionally, the percentage of subjects achieving the target of time in range (70-180 mg/dl) > 70% was not significantly different between subgroups.

The MDI group and the people with age ≤ 25 years old showed a reduction in time below range (< 70 mg/dl), compared to baseline, from 3.86 ± 3.93% to 2.5 ± 2.27% (p = 0.027) and from 3.41 ± 2.73 to 2.22 ± 1.84% (p = 0.009) respectively, but not in time < 54 mg/dl.

Subjects with low hypoglycaemia risk at baseline (time < 70 mg/dl < 4% and time < 54 mg/dl < 1%) improved their time in range (70-180 mg/dl), time > 180 mg/dl, time > 250 mg/d, GMI, mean sensor glucose and standard deviation of glucose, but showed an increase in time < 70 mg/dl and < 54 mg/dl, compared to baseline. People with high hypoglycaemia risk at baseline improved their time in range (70-180 mg/dl), time > 180 mg/dl, time > 250 mg/d, GMI, mean sensor glucose and standard deviation of glucose and also reduced their time < 70 mg/dl and < 54 mg/dl, compared to baseline.

When comparing the results after one year between the different groups, no differences were found between the previous pump users and the MDI group in any of the variables (Table 2). Regarding age groups, younger subjects had a lower time spent at < 70 mg/dl and higher mean sensor glucose than older subjects. Individuals with high hypoglycaemia frequency at baseline had a higher time spent at < 70 mg/dl and < 54 mg/dl, lower GMI and mean sensor glucose than subjects with lower hypoglycaemia frequency at baseline.

Discussion

The MiniMed™ 780G system was launched in Europe and other countries around the world in October 2020. Pre-commercialization studies showed an improvement in time in range (70-180 mg/dl) from 5.7% to 12.5% after 1 to 3 months of use in different groups of subjects [14-16]. After commercialization, several reports have confirmed the benefit shown in the preliminary data [2-7]. Our data showed an improvement in time in range

(70-180) mg/dl of 12.8% after 3 months in 52 previous pump users[3]. Cost analyses have been performed, showing the cost-effectiveness of the use of this AHCL system [17.18]. Retrospective long-term outcomes with other AHCL systems have been reported, in 9000 users [19], but no data are available for the 780G system.

Our data show the sustainability of the short-term results after one year of use of the system in real-life in a relatively high number of subjects with various baseline situations, regarding previous therapy, age and hypoglycaemia frequency. The whole population and all the subgroups achieved an improvement in terms of time in range (70-180 mg/dl), time in hyperglycaemia > 180 mg/dl and > 250 mg/dl, GMI, mean sensor glucose and standard deviation of sensor glucose. The use of the most aggressive settings (i.e. a glucose target of 100 mg/dl and 2 hours of active insulin time) in most of the subjects was key in obtaining the maximum benefit from the AHCL system.

Concerning the time below range (< 70 mg/dl), no significant improvement was seen in the whole population, the previous pump users or the adult subjects. MDI subjects and children and young adults significantly reduced their time in mild hypoglycaemia.

People with high hypoglycaemia risk reduced their time in hypoglycaemia < 70 mg/dl and < 54 mg/dl, but both remained above the International Consensus recommendations [13]. On the other hand, subjects with low hypoglycaemia risk increased both their time in mild hypoglycaemia and time in clinically relevant hypoglycaemia but remained below the recommended targets in International Consensus.

When comparing the one-year outcomes in the different subpopulations, no differences were seen if the subjects had previous pump experience or had initiated closed-loop therapy directly from MDI. This finding should guide the selection of candidates for the AHCL system by giving the same opportunities to all the people with type 1 diabetes, independently of their previous treatment. Interestingly, the MDI group was relatively well controlled at baseline, with a mean GMI of 7.01%, a time in range (70-180 mg/dl) of 65.72% and hypoglycaemia levels below the recommended targets. Still, this group significantly improved its GMI, time in range (70-180 mg/dl), time in hyperglycaemia > 180 mg/dl and > 250 mg/dl and time below range (< 70 mg/dl), showing that intensification of glycaemic control is feasible, even in subjects with nearly optimal glycaemic control without previous pump experience.

Children and young adults showed a higher time spent below range (< 70 mg/dl) and lower mean sensor glucose than adult individuals, demonstrating a tendency for hypoglycaemia avoidance in the most vulnerable population.

In the group divided by their baseline hypoglycaemia risk, the subjects with a higher risk showed a higher time in hypoglycaemia < 70 mg/dl and < 54 mg/dl, a lower GMI and mean sensor glucose than the subjects with a lower risk. In other words, the high-risk group improved its hypoglycaemia frequency in comparison to the baseline situation but still showed higher hypoglycaemia risk than the people with low risk at baseline, meaning that there is still room for improvement in the algorithm's management of hypoglycaemia in the subjects with more problematic hypoglycaemia.

The main limitation of the study lies in the subgroup analysis, due to the limited number of subjects in each subgroup. Also, some individuals are represented in more than one subgroup, according to their shared baseline characteristics. Prospective, randomised large-scale trials are needed, specifically evaluating the performance of the different AHCL systems on the market in populations with particular situations (i.e. young children, elderly people, people with impaired awareness of hypoglycaemia, pregnant women, very physically active subjects, etc. [12]).

The main strengths of the present study are the long-term follow-up and the prospective design, allowing for evaluation of the benefit provided by the AHCL system in a real-world scenario and in a relatively large and heterogeneous population of users. Additionally, to the best of our knowledge, the present study represents the first insight into the analysis of the use of the 780G system comparatively in different specific subpopulations.

In conclusion, the benefit of the advanced hybrid closed-loop system is sustained in the long term and it is extended to subpopulations of people with type 1 diabetes with various baseline situations according to their previous pump experience or inexperience, younger or older age and higher or lower hypoglycaemia risk.

Declarations

The authors received no funding from an external source.

PB reports speaker fees from Medtronic and Lilly. FA reports speaker fees from Medtronic and Novo Nordisk. EG reports speaker fees from Medtronic and Novo Nordisk. The rest of the authors declare no conflict of interest.

Ethics approval: Approval was obtained from the ethics committee of Badajoz University Hospital. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

All of the authors contributed to the design and implementation of the research, the analysis of the results and the writing of the manuscript.

The datasets generated during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Methods. A prospective evaluation of subjects initiating the AHCL system 780G was performed. Time in range (70-180 mg/dl) (TIR), <70 mg/dl, <54 mg/dl, >180 mg/dl and >250 mg/dl were compared, at baseline and after one year, in different subpopulations, according to previous treatment (pump *vs* MDI), age (> or ≤25 years old) and hypoglycaemia risk at baseline.

Results. 135 subjects were included (age: 35±15 years, 64% females, diabetes duration: 21±12 years). An increase in TIR was found, from 67.26±11.80% at baseline to 77.41±8.85% after one year (p<0.001). All the subgroups showed a significant improvement in TIR, time >180 mg/dl and >250 mg/dl. At the 1-year evaluation, no significant differences were found, between previous pump users and MDI subjects. Children and young adults had a lower time <70 mg/dl than adults. Subjects with a high risk of hypoglycaemia at baseline had a higher time spent at <70 mg/dl and <54 mg/dl than low-risk individuals.

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Closed-loop systems have brought a paradigm shift in the management of type 1 diabetes and their use is rapidly spreading around the world. The advanced hybrid closed-loop (AHCL) system MiniMed™ 780G uses a model based adaptative algorithm with a PDI (Proportional Integral Derivative) with insulin feedback module; the system delivers microboluses of insulin, to reach personalised glucose targets (100 mg/dl, 110 mg/dl or 120 mg/dl); also, auto-correction boluses are delivered when the infusion from microboluses is not enough to keep sensor glucose below 120 mg/dl; additional safety features, as the Safe Meal Bolus feature, are included in the algorithm [1]. A rapid improvement in glycaemic control, which is sustained after 3 to 6 months, has been reported by our group and other groups in many countries, showing a time in range (70-180 mg/dl) between 75.6% and 80.4% [2-7]. Also, a large number of downloads from anonymised subjects have been analysed, showing similar outcomes [8,9]. Patient-reported outcomes analysis has shown an increase in patient satisfaction with the system [3,10,11]. Nevertheless, the long-term outcomes of the AHCL system have not been reported. Additionally, analysis of the performance of the AHCL system in specific populations is scarce. Subpopulations may have different diabetes care requirements, glycaemic disturbances and targets [12]. Knowledge concerning the performance of the AHCL systems in different subgroups of individuals is required, to assist healthcare

professionals in tailoring their therapeutic choices for type 1 diabetes people with various needs.

The study aimed to evaluate if the benefit reported with the use of this AHCL system was sustained in the long-term in both the general population of type 1 diabetes and in specific subgroups of subjects with different baseline characteristics that could influence those outcomes.

Material and Methods

Subjects with type 1 diabetes consecutively initiated the use of the MiniMed™ 780G system with Guardian™ Sensor 3 at Badajoz University Hospital. A longitudinal prospective evaluation was performed. Pregnant women were excluded. A 2-week system download was collected at baseline and again at the end of one year using the system. Time in range (70-180 mg/dl), time below range (< 70 mg/dl) and < 54 mg/dl and time above range (> 180 mg/dl) and 250 mg/dl, according to International Consensus [13], were collected. Glucose Management Indicator (GMI) (%), coefficient of variation of glucose (CV) (%), sensor use (%) and parameters related to the use of the system were also evaluated.

The baseline data consisted of 2 weeks using continuous glucose monitoring with Guardian™ Sensor 3 in all the patients, to assure that data from the same sensor were compared at baseline and at the end of follow-up. Pump therapy or MDI was maintained during those 2 weeks, according to the therapy that the subjects were previously using.

Pump therapy or MDI was maintained during those 2 weeks, according to the therapy that the subjects were previously using. Auto-mode was started after 2 to 10 days of manual mode. The predictive low-glucose suspend function was activated in all the patients during the manual mode period.

Three different subgroups of subjects were defined, representing specific subpopulations, based on particular characteristics at baseline. These groups were defined as follows: Group 1, according to previous treatment: pump therapy *vs* MDI, Group 2, according to age: children and young adults (≤ 25 years-old) *vs* adults (26 to 65 years old), and Group 3, according to hypoglycaemia risk: high hypoglycaemia risk (time < 70 mg/dl ≥ 4% or time < 54 mg/dl ≥ 1% at baseline) *vs* low hypoglycaemia risk (time < 70 mg/dl < 4% and time < 54 mg/dl < 1% at baseline).

Time in range (70-180 mg/dl), time < 70 mg/dl and 54 mg/dl and time > 180 mg/dl and 250 mg/dl, GMI (%), CV (%) and sensor use were compared at baseline and after one year for each of these subgroups. These same variables, as well as variables related to the use of the system, were compared between subgroups (pump therapy *vs* MDI, adults *vs* children and young adults and low *vs* high hypoglycaemia risk) at the end of the follow-up.

The study protocol followed the Declaration of Helsinki principles and was approved by the Badajoz University Hospital Ethics Committee. All of the participants were informed of the protocol and signed a consent form.

Data analysis was performed using the SPSS statistics software v22. A descriptive analysis of continuous variables was performed by calculating their mean and standard

deviation. Categorical variables were expressed as percentages. The normal distribution of the variables was checked by Kolmogorov-Smirnov's test. A paired Student's t-test or a Wilcoxon signed-rank test was used for the analysis of differences. For unpaired samples, the independent samples t-test was used. Comparisons between proportions were analysed by a chi-squared test. Correlation analysis was performed using the Pearson method. The sample size was estimated using the Granmo software. A p-value < 0.05 was considered statistically significant.

Results

One hundred and thirty-five people with type 1 diabetes were included. Subject characteristics are summarised in Table 1. BMI was 24.7 ± 4.7 Kg/m2, 51% of the subjects had normal weight, 11% were underweight and 38% were overweight or obese.

Regarding insulin treatment, baseline treatment was MDI for 27% (n = 36) of the patients. The subjects who were already on pump therapy before the study (73%, n = 99)) used mostly sensor-augmented pump systems with predictive low-glucose suspend function (n = 86). Eight subjects were on pump therapy without continuous or flash glucose monitoring, 4 subjects were using a non-advanced hybrid closed-loop system and 1 subject was on pump therapy with continuous glucose monitoring. In previous pump users, the duration of pump therapy before the start of using the AHCL system was 6.6 ± 3.3 years.

Regarding glucose monitoring, 71% (n = 96) of the participants were using continuous glucose monitoring (Guardian™ Sensor 3: n = 90, Dexcom 6®: n = 5, Eversense®: n = 1), 22% (n = 30) used flash glucose monitoring and 9 subjects were on SMBG.

Two additional subjects had stopped using the system after 7 months and 10 months respectively, and one subject used the auto-mode only sporadically; those individuals were excluded from the analysis.

Outcomes in time spent in different glycaemic ranges at the one-year follow-up in the whole population are shown in Figure 1. Time in range (70-180 mg/dl) at the one-year evaluation was 77.41 ± 8.85% (range: 53% to 96%). The mean improvement in time in range (70-180 mg/dl) was 10.15 ± 10.83%. The percentage of subjects reaching the target of a time in range (70-180 mg/dl) > 70% was increased from 40% (n = 54) at baseline to 79% (n = 107) and the last visit (p = 0.003). Also, 53% (n = 71) of the individuals reached the combined target of time in range (70-180 mg/dl) > 70% and time < 70 mg/dl < 4% at the one-year visit and 42% (n = 57) of the individuals reached a time in range (70-180 mg/dl) > 80% (Figure 2).

Additionally, the individuals who were already reaching the target of time in range (70-180 mg/dl) > 70% at baseline (n = 54) achieved a significant improvement in time in range (70-180 mg/dl) from 78.07 ± 5.03% to 81.33 ± 6.97% (p = 0.01), as well as a reduction in time below and above range. Nevertheless, this improvement in time in range (70-180 mg/dl) was significantly lower than the amelioration in subjects with

baseline time in range (70-180 mg/dl) below target (n = 81), which was increased from 60.06 ± 9.22% to 74.79 ± 9.04% ($p < 0.001$).

GMI was reduced from 6.98 ± 0.49 % to 6.67 ± 0.32%, mean glucose and standard deviation of sensor glucose were reduced from 154 ± 20 mg/dl to 141 ± 13 and from 53 ± 9 mg/dl to 47 ± 8 mg/dl respectively (all $p < 0.001$), while the coefficient of variation (CV) did not change (34.0 ± 4.5% *vs* 33.5 ± 4.3%, $p = 0.286$). The use of the sensor was increased from 84.7 ± 12.3% to 90.4 ± 9.3% ($p < 0.001$).

Regarding the use of the system, time in auto-mode was 95.6 ± 7.2% and the number of exits was 0.98 ± 0.99 per week. The number of SMBG and calibrations per day were 3.2 ± 0.9 and 3.0 ± 0.9 respectively. Total insulin dose was 46.8 ± 22.3 units per day, basal insulin was 42.6 ± 9.7%, bolus insulin 56.9 ± 8.2% and auto-corrections represented 31.8 ± 14.1% of bolus insulin (27.2 ± 9.4 boluses per day, 8.3 ± 5.9 units per day).

The subjects received 3.8 ± 3.5 hypoglycaemia alarms and 2.2 ± 2.0 hyperglycaemia alarms per day. The hypoglycaemia alarms were not significantly different compared to baseline, but the hyperglycaemia alarms were reduced from the 3.1 ± 3.0 alarms they received at baseline ($p = 0.001$). The number of meals per day was 4.2 ± 1.7 and the carbohydrate intake was 144.8 ± 84.7 grams per day.

The auto-correction feature was ON in all the subjects; 84% (n = 113) of the subjects used a glucose target of 100 mg/dl, 12% (n = 16) 110 mg/dl and 4% (n = 6) 120 mg/dl; active insulin time was 2 hours in 76% of the subjects (n = 102), between 2 and 3 hours in 22% (n = 29) and more than 3 hours in 4 people.

A positive correlation was found between time in range (70-180 mg/dl) and time in auto-mode (Pearson coefficient $r = 0.442$, $p < 0.001$) and a negative correlation was observed between time in range (70-180 mg/dl) and the percentage of auto-correction insulin (Pearson coefficient $r = -0.369$, $p < 0.001$) .

The differences in the glycaemic outcomes in the predefined subpopulations are shown in Table 2. In Group 2, the mean age was 43 ± 9 years old in adults and 16 ± 5 years old in children and young adults ($p < 0.001$). Time in range (70-180 mg/dl), time > 180 mg/dl and time > 250 mg/dl, GMI, mean sensor glucose and standard deviation of sensor glucose were reduced, after one year of use of the system, in all the groups. The sensor used was increased in all the groups except for the MDI group.

No significant differences were found in the improvement in time in range (70-180 mg/dl) between the groups: 9.82 ± 11.13% in previous pump users *vs* 11.03 ± 10.05% in MDI subjects; 9.89 ± 10.81% in adults *vs* 10.70 ± 10.98% in children and young adults; 11.48 ± 11.57% in people with low hypoglycaemia risk *vs* 8.42 ± 9.62% in people with high hypoglycaemia risk at baseline (all $p > 0.005$). Additionally, the percentage of subjects achieving the target of time in range (70-180 mg/dl) > 70% was not significantly different between subgroups.

The MDI group and the people with age ≤ 25 years old showed a reduction in time below range (< 70 mg/dl), compared to baseline, from 3.86 ± 3.93% to 2.5 ± 2.27% ($p = 0.027$) and from 3.41 ± 2.73 to 2.22 ± 1.84% ($p = 0.009$) respectively, but not in time < 54 mg/dl.

Subjects with low hypoglycaemia risk at baseline (time < 70 mg/dl < 4% and time < 54 mg/dl < 1%) improved their time in range (70-180 mg/dl), time > 180 mg/dl, time > 250 mg/d, GMI, mean sensor glucose and standard deviation of glucose, but showed an increase in time < 70 mg/dl and < 54 mg/dl, compared to baseline. People with high hypoglycaemia risk at baseline improved their time in range (70-180 mg/dl), time > 180 mg/dl, time > 250 mg/d, GMI, mean sensor glucose and standard deviation of glucose and also reduced their time < 70 mg/dl and < 54 mg/dl, compared to baseline.

When comparing the results after one year between the different groups, no differences were found between the previous pump users and the MDI group in any of the variables (Table 2). Regarding age groups, younger subjects had a lower time spent at < 70 mg/dl and higher mean sensor glucose than older subjects. Individuals with high hypoglycaemia frequency at baseline had a higher time spent at < 70 mg/dl and < 54 mg/dl, lower GMI and mean sensor glucose than subjects with lower hypoglycaemia frequency at baseline.

Discussion

The MiniMed™ 780G system was launched in Europe and other countries around the world in October 2020. Pre-commercialization studies showed an improvement in time in range (70-180 mg/dl) from 5.7% to 12.5% after 1 to 3 months of use in different groups of subjects [14-16]. After commercialization, several reports have confirmed the benefit shown in the preliminary data [2-7]. Our data showed an improvement in time in range

(70-180) mg/dl of 12.8% after 3 months in 52 previous pump users[3]. Cost analyses have been performed, showing the cost-effectiveness of the use of this AHCL system [17.18]. Retrospective long-term outcomes with other AHCL systems have been reported, in 9000 users [19], but no data are available for the 780G system.

Our data show the sustainability of the short-term results after one year of use of the system in real-life in a relatively high number of subjects with various baseline situations, regarding previous therapy, age and hypoglycaemia frequency. The whole population and all the subgroups achieved an improvement in terms of time in range (70-180 mg/dl), time in hyperglycaemia > 180 mg/dl and > 250 mg/dl, GMI, mean sensor glucose and standard deviation of sensor glucose. The use of the most aggressive settings (i.e. a glucose target of 100 mg/dl and 2 hours of active insulin time) in most of the subjects was key in obtaining the maximum benefit from the AHCL system.

Concerning the time below range (< 70 mg/dl), no significant improvement was seen in the whole population, the previous pump users or the adult subjects. MDI subjects and children and young adults significantly reduced their time in mild hypoglycaemia.

People with high hypoglycaemia risk reduced their time in hypoglycaemia < 70 mg/dl and < 54 mg/dl, but both remained above the International Consensus recommendations [13]. On the other hand, subjects with low hypoglycaemia risk increased both their time in mild hypoglycaemia and time in clinically relevant hypoglycaemia but remained below the recommended targets in International Consensus.

When comparing the one-year outcomes in the different subpopulations, no differences were seen if the subjects had previous pump experience or had initiated closed-loop therapy directly from MDI. This finding should guide the selection of candidates for the AHCL system by giving the same opportunities to all the people with type 1 diabetes, independently of their previous treatment. Interestingly, the MDI group was relatively well controlled at baseline, with a mean GMI of 7.01%, a time in range (70-180 mg/dl) of 65.72% and hypoglycaemia levels below the recommended targets. Still, this group significantly improved its GMI, time in range (70-180 mg/dl), time in hyperglycaemia > 180 mg/dl and > 250 mg/dl and time below range (< 70 mg/dl), showing that intensification of glycaemic control is feasible, even in subjects with nearly optimal glycaemic control without previous pump experience.

Children and young adults showed a higher time spent below range (< 70 mg/dl) and lower mean sensor glucose than adult individuals, demonstrating a tendency for hypoglycaemia avoidance in the most vulnerable population.

In the group divided by their baseline hypoglycaemia risk, the subjects with a higher risk showed a higher time in hypoglycaemia < 70 mg/dl and < 54 mg/dl, a lower GMI and mean sensor glucose than the subjects with a lower risk. In other words, the high-risk group improved its hypoglycaemia frequency in comparison to the baseline situation but still showed higher hypoglycaemia risk than the people with low risk at baseline, meaning that there is still room for improvement in the algorithm's management of hypoglycaemia in the subjects with more problematic hypoglycaemia.

The main limitation of the study lies in the subgroup analysis, due to the limited number of subjects in each subgroup. Also, some individuals are represented in more than one subgroup, according to their shared baseline characteristics. Prospective, randomised large-scale trials are needed, specifically evaluating the performance of the different AHCL systems on the market in populations with particular situations (i.e. young children, elderly people, people with impaired awareness of hypoglycaemia, pregnant women, very physically active subjects, etc. [12]).

The main strengths of the present study are the long-term follow-up and the prospective design, allowing for evaluation of the benefit provided by the AHCL system in a real-world scenario and in a relatively large and heterogeneous population of users. Additionally, to the best of our knowledge, the present study represents the first insight into the analysis of the use of the 780G system comparatively in different specific subpopulations.

In conclusion, the benefit of the advanced hybrid closed-loop system is sustained in the long term and it is extended to subpopulations of people with type 1 diabetes with various baseline situations according to their previous pump experience or inexperience, younger or older age and higher or lower hypoglycaemia risk.

Declarations

The authors received no funding from an external source.

PB reports speaker fees from Medtronic and Lilly. FA reports speaker fees from Medtronic and Novo Nordisk. EG reports speaker fees from Medtronic and Novo Nordisk. The rest of the authors declare no conflict of interest.

Ethics approval: Approval was obtained from the ethics committee of Badajoz University Hospital. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

All of the authors contributed to the design and implementation of the research, the analysis of the results and the writing of the manuscript.

The datasets generated during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Figure

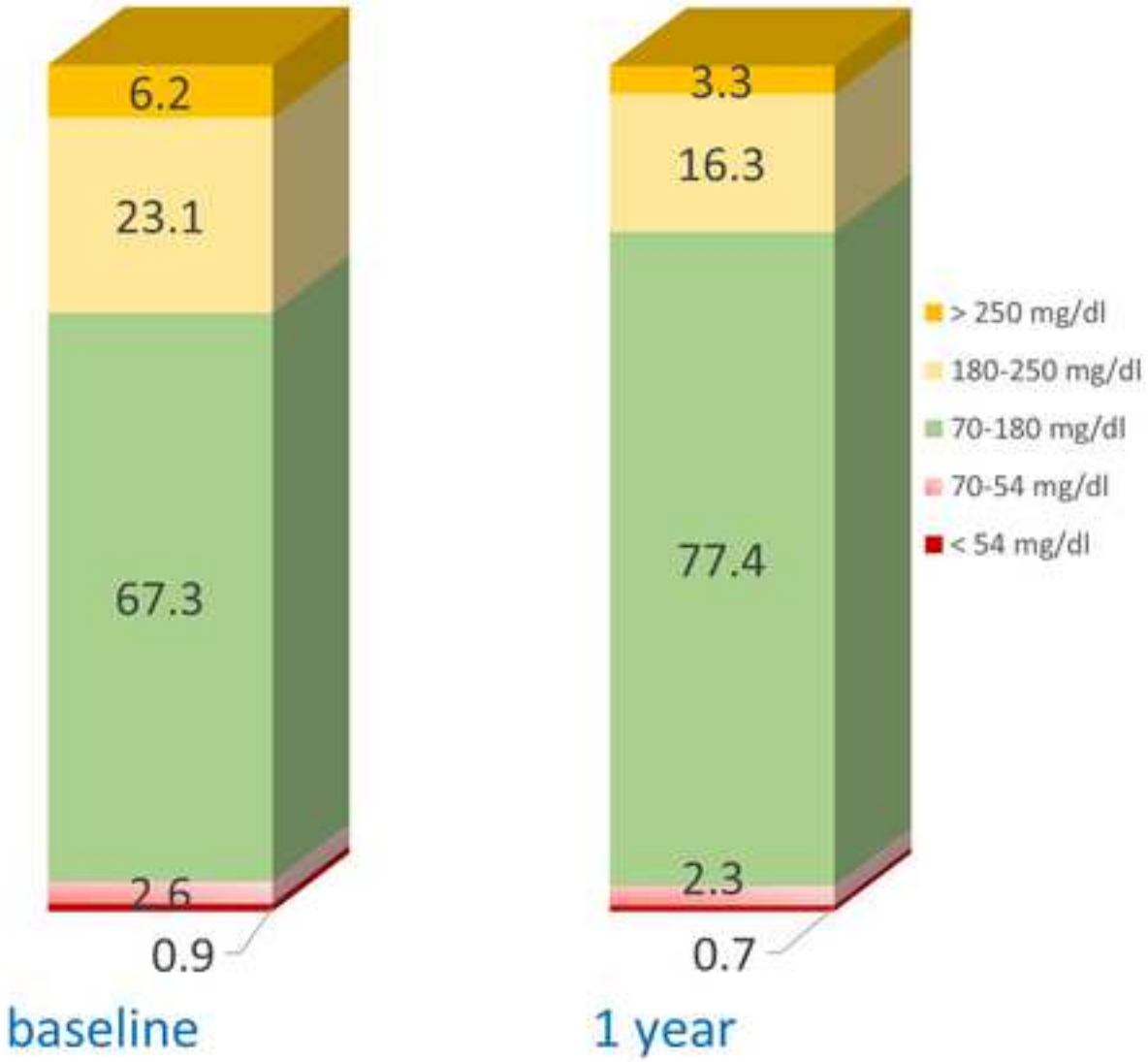

Figure 2

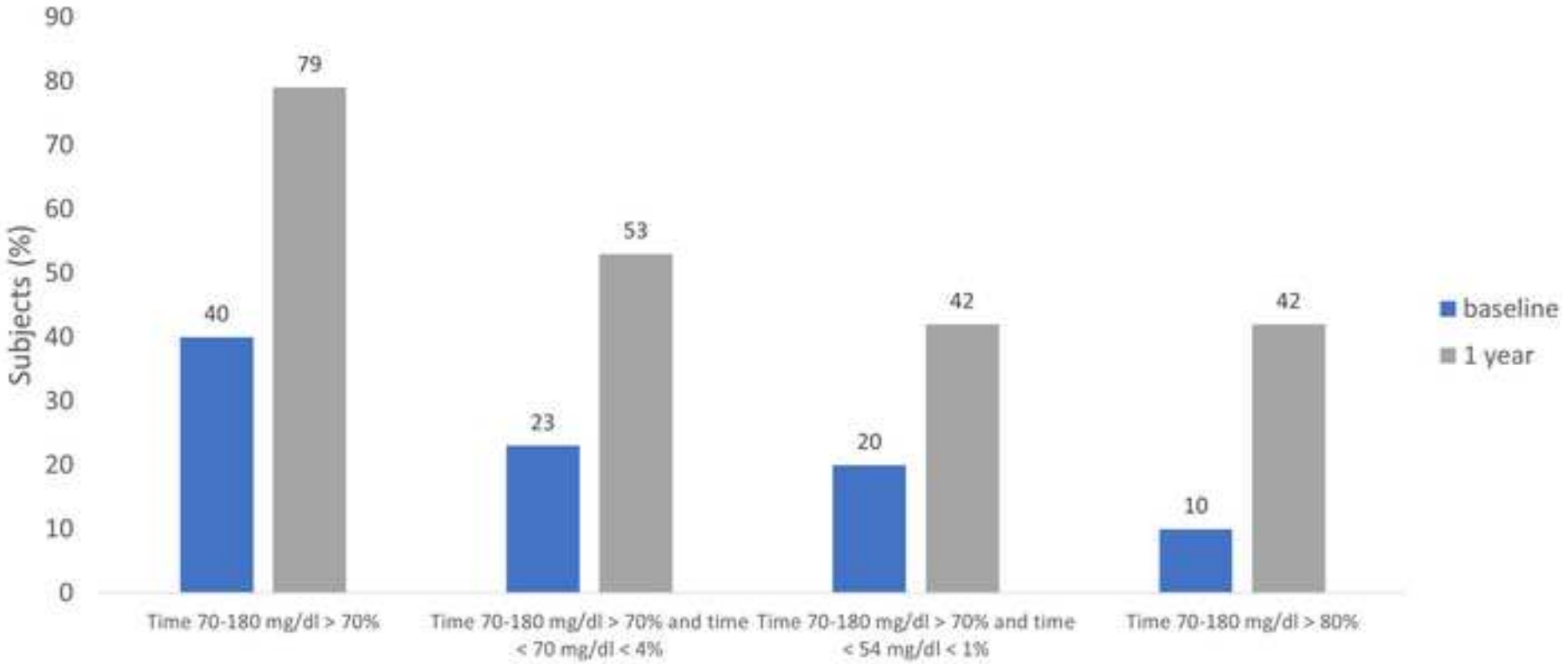

Figure 1. Time in different glycaemic ranges at baseline and after one year of follow-up (n = 135). $p < 0.001$ for time in range 70-180 mg/dl, time > 180 mg/dl and time > 250 mg/dl; $p = 0.56$ for time < 70 mg/dl, $p = 0.156$ for time < 54 mg/dl.

Figure 2. Percentage of subjects reaching different glycaemic targets at the end of follow-up compared to baseline (all $p \leq 0.003$).

Table 1. Patient characteristics.

Age (years)	35 ± 15
Sex (female) n (%)	86 (64)
Diabetes duration (years)	21 ± 12
Baseline HbA1c (mmol/, %)	56 ± 10 7.30 ± 0.89
BMI (Kg/m2)	24.7 ± 4.7
Hypoglycaemia unawareness (GS or CS > 3) n (%)*	35 (30)
Severe hypoglycaemia episodes in the past year (≥ 1) n (%)*	11 (9.9)

N = 135. GS (Gold Score), CS (Clarke Score). *only in subjects older than 14 years old (n = 118).

Table 2

Table 2. Glycaemic outcomes at baseline and after 1 year of follow-up in the three different groups, according to previous therapy, age and hypoglycaemia risk.

	Group 1 Previous therapy				Group 2 Age				Group Hypoglycaemia risk			
	Pump n = 99		MDI n = 36		> 25 years-old n = 92		≤ 25 years-old n = 43		Low n = 76		High n = 59	
	baseline	1 year	baseline	1 year	baseline	1 year	baseline	1 year	baseline	1 year	baseline	1 year
Time 70-180 mg/dl (%)	67.82 ± 11.86	77.65 ± 9.03*	65.72 ± 11.65	76.75 ± 8.45*	67.99 ± 11.72	77.88 ± 8.76*	65.70 ± 11.95	76.40 ± 9.06*	65.50 ± 12.64	76.99± 9.56*	69.53 ± 10.29	77.95 ± 7.91*
Time > 180 mg/dl (%)	28.82 ± 13.30	19.10 ± 9.26*	30.42 ± 12.74	20.72 ± 8.18*	28.45 ± 13.38	18.60 ± 8.75*	30.95 ± 12.55	21.53 ± 9.25*	33.17 ± 12.99	20.59 ± 9.47*	24.19 ± 11.56	18.17 ± 8.19*
Time > 250 mg/dl (%)	6.02 ± 6.29	3.19 ± 2.74*	6.61 ± 6.05	3.50 ± 3.65*	6.15 ± 6.17	3.09 ± 2.85*	6.98 ± 6.76	3.67 ± 3.29*	7.25 ± 6.75	3.53 ± 3.26*	4.80 ± 5.18	2.95 ± 2.62*
Time < 70 mg/dl (%)	3.35 ± 3.30	3.13 ± 2.82	3.86 ± 3.93	2.50 ± 2.27*	3.54 ± 3.82	3.28 ± 2.96	3.36 ± 2.59	2.28 ± 1.88*‡	1.35 ± 0.88	2.16 ± 2.00*	6.23 ± 3.63	4.00 ± 3.11*‡
Time < 54 mg/dl (%)	0.85 ± 1.31	0.75 ± 1.07	0.92 ± 1.50	0.61 ± 0.96	0.91 ± 1.46	0.79 ± 1.14	0.77 ± 1.12	0.53 ± 0.77	0.06 ± 0.11	0.43 ± 0.81*	1.91 ± 1.51	1.07 ± 1.20*‡
GMI (%)	6.97 ± 0.49	6.65 ± 0.33*	7.01 ± 0.49	6.75 ± 0.28*	6.97 ± 0.50	6.64 ± 0.34*	7.00 ± 0.46	6.75 ± 0.23*	7.17 ± 0.45	6.74 ± 0.33*	6.77 ± 0.44	6.59 ± 0.29*‡
Mean sensor glucose (mg/dl)	154 ± 21	140 ± 14*	155 ± 20	144 ± 12*	153 ± 21	140 ± 14*	157 ± 19	145 ± 12*‡	161 ± 18	144 ± 14*	145 ± 19	138 ± 12*‡
SD sensor glucose (mg/dl)	52 ± 9	47 ± 8*	54 ± 11	48 ± 8*	52 ± 8	47 ± 8*	54 ± 11	48 ± 9*	52 ± 9	48 ± 8*	53 ± 10	47 ± 8*
CV sensor glucose (%)	33.7 ± 4.4	33.7 ± 4.4	34.8 ± 4.8	33.0 ± 3.9	33.8 ± 4.5	33.6 ± 4.4	34.4 ± 4.5	33.5 ± 4.1	31.7 ± 3.4	32.92 ± 4.24*	36.7 ± 4.2	34.3 ± 4.2*‡
Sensor use (%)	84.1 ± 12.7	90.1 ± 9.6*	86.4 ± 11.1	91.1 ± 8.4	86.7 ± 9.7	91.5 ± 7.7*	80.4 ± 15.8	88.0 ± 11.8*	84.0 ± 13.7	90.5 ± 10.6*	85.5 ± 10.4	90.2 ± 7.4*

GMI (Glucose Management Indicator), SD (standard deviation), CV (Coefficient of Variation). Hypoglycaemia risk: high risk defined as time < 70 mg/dl ≥ 4% or time < 54 mg/dl ≥ 1% at baseline. *p < 0.05 at one-year compared to baseline, ‡p < 0.05 at one-year between groups.