First Outpatient Clinical Trial of a Full Closed-Loop Artificial Pancreas System in South America

Fabricio Garelli, Dr. Eng.[1,2], Emilia Fushimi, Dr. Eng.[1,2], Nicolás Rosales, Dr. Eng.[1,2], Delfina Arambarri, Eng.[1], Leandro Mendoza, Mr.[1], María Cecilia Serafini, Eng.[1,3], Marcela Moscoso-Vásquez, Dr. Eng.[2,4], Marianela Stasi, BSc.[5], Patricia Duette, BSc.[5], Julia García-Arabehety, MD[5], Javier Nicolás Giunta, MD[5], Hernán De Battista, Dr. Eng.[1,2], Ricardo Sánchez-Peña, PhD[2,4], and Luis Grosembacher, MD[5]

Abstract

Background: The first two studies of an artificial pancreas (AP) system carried out in Latin America took place in 2016 (phase 1) and 2017 (phase 2). They evaluated a hybrid algorithm from the University of Virginia (UVA) and the automatic regulation of glucose (ARG) algorithm in an inpatient setting using an AP platform developed by the UVA. The ARG algorithm does not require carbohydrate (CHO) counting and does not deliver meal priming insulin boluses. Here, the first outpatient trial of the ARG algorithm using an own AP platform and doubling the duration of previous phases is presented.

Method: Phase 3 involved the evaluation of the ARG algorithm in five adult participants ($n = 5$) during 72 hours of closed-loop (CL) and 72 hours of open-loop (OL) control in an outpatient setting. This trial was performed with an own AP and remote monitoring platform developed from open-source resources, called InsuMate. The meals tested ranged its CHO content from 38 to 120 g and included challenging meals like pasta. Also, the participants performed mild exercise (3-5 km walks) daily. The clinical trial is registered in ClinicalTrials.gov with identifier: NCT04793165.

Results: The ARG algorithm showed an improvement in the time in hyperglycemia (52.2% [16.3%] OL vs 48.0% [15.4%] CL), time in range (46.9% [15.6%] OL vs 50.9% [14.4%] CL), and mean glucose (188.9 [25.5] mg/dl OL vs 186.2 [24.7] mg/dl CL) compared with the OL therapy. No severe hyperglycemia or hypoglycemia episodes occurred during the trial. The InsuMate platform achieved an average of more than 95% of the time in CL.

Conclusion: The results obtained demonstrated the feasibility of outpatient full CL regulation of glucose levels involving the ARG algorithm and the InsuMate platform.

Keywords
artificial pancreas, clinical trial, closed-loop control, artificial pancreas platform

Introduction

During the last years, numerous clinical trials and meta-analysis have been published regarding the artificial pancreas (AP).[1,2] Most of them analyzed hybrid-loop algorithms, which deliver manual meal priming boluses to counteract meals and rely on closed-loop (CL) control to adjust basal delivery. While hybrid-loop systems have shown to improve glycemic control compared with open-loop (OL) or traditional insulin therapy, they still depend on information provided by the user (time of intake and carbohydrate [CHO]

[1]Grupo de Control Aplicado, Instituto LEICI (UNLP-CONICET), Facultad de Ingeniería, Universidad Nacional de La Plata, La Plata, Argentina
[2]Consejo Nacional de Investigaciones Científicas y Técnicas, Argentina
[3]Comisión de Investigaciones Científicas de la Provincia de Buenos Aires, Buenos Aires, Argentina
[4]Instituto Tecnológico de Buenos Aires, Buenos Aires, Argentina
[5]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

Corresponding Author:
Fabricio Garelli, Dr. Eng., Grupo de Control Aplicado, Instituto LEICI (UNLP-CONICET). Depto. Electrotecnia, Facultad de Ingeniería, Universidad Nacional de La Plata, 48 esq. 116, La Plata 1900, Argentina.
Email: fabricio@ing.unlp.edu.ar

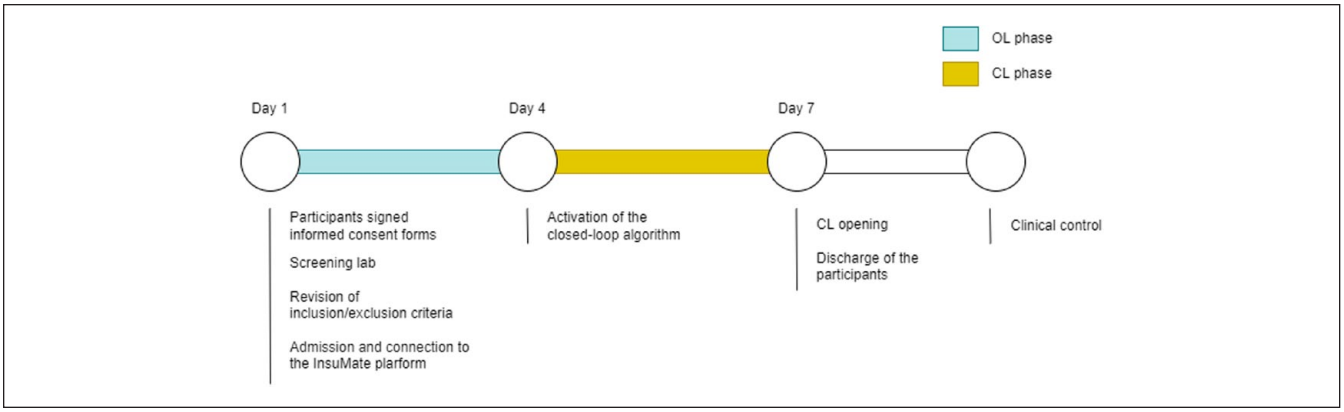

Figure 1. Timeline of the protocol.
Abbreviations: CL, closed-loop; OL, open-loop.

content of each meal), which makes the system prone to errors and is burdensome. Single-hormone, full CL algorithms are still being researched, and very few outpatient trials have been carried out. These AP systems have the advantage of diminishing patient intervention since they do not depend on meal announcement or CHO counting for prandial glucose regulation.

Parallel to the progress of our research, other researchers developed and published works with full CL algorithms (single[3,4] and dual-hormone[5,6]) in outpatient and supervised settings involving people with type 1 diabetes (T1D) at hotels, or hospitalized people with type 2 diabetes.[7]

The first clinical trials of an AP system carried out in Latin America took place in 2016, in an inpatient setting, at the Hospital Italiano de Buenos Aires (HIBA). A hybrid-loop algorithm developed by the University of Virginia, implemented in the Diabetes Assistant (DiAs) AP platform, was tested in five adult participants during 36 hours of hybrid-loop control.[8] These first trials provided our research group with valuable know-how regarding clinical trials and protocols, and familiarization with the DiAs platform. Then, in 2017, a second clinical trial involving five adult participants in the same hospital setting took place, but this time, the control algorithm evaluated was the so-called automatic regulation of glucose (ARG) algorithm,[9] implemented in the DiAs platform. The ARG algorithm is a full CL controller, since it does not require CHO counting and does not deliver meal insulin boluses.[10] This trial served as a feasibility trial prior to the outpatient study of the ARG algorithm reported in this article. To sum up, the purpose of phase 1 was to acquire training in the management of patients in CL. Next, phase 2 aimed to test the ARG under highly controlled conditions for 36 hours.

In these last years, due to the unavailability of the DiAs platform, the research team from the National University of La Plata developed an AP platform called the InsuMate.[11] This platform is based on open-source resources and allows the remote monitoring of up to 40 users in real time. During the COVID-19 pandemic, the InsuMate was readapted and successfully used to monitor the glucose evolution of adult and pediatric patients in COVID-19 intensive care units.[12]

In this article, the third pilot clinical trial of an AP system in Argentina is described and analyzed. This study was the first registered AP outpatient clinical trial in Latin America. Five adult participants spent six days (72 hours of OL and 72 hours of CL control), doubling the time analyzed in the two previous trials, in a hotel. The evaluated algorithm was the ARG, implemented for the first time in an open-source–based platform such as InsuMate. The participants performed mild exercise daily and the meals tested were challenging. The aim of the trial was to evaluate the feasibility of conducting a home-use trial involving the ARG algorithm and the InsuMate platform in a larger sample size for a prolonged period of time.

Methods

Clinical Protocol

The trial is registered at ClinicalTrials.gov with identifier: NCT04793165. The clinical protocol was approved by the HIBA's ethics committee (IRB00010193) as Protocol No.5302.

This trial aimed to compare two different treatments: "Conventional treatment" or OL, using continuous subcutaneous insulin infusion (CSII) with an insulin pump and a continuous glucose monitor (CGM), for three consecutive days and "AP" or CL, using an insulin pump integrated to a CGM through the InsuMate platform and the ARG algorithm, for three consecutive days.

Figure 1 shows a timeline of the protocol. During the first day of the trial, all subjects signed a written consent form prior to undergoing a screening evaluation. This evaluation included a physical examination, routine blood count, platelets, ionogram, HbA1c, glycemia, ketonemia, hepatogram, uremia, creatinine, and an electrocardiogram. The participants were

handed out an Accu-Check Spirit Combo insulin pump and a Dexcom CGM. Then, the engineering team connected the CGM and pump to the Android smartphone and initialized the InsuMate app in OL mode.

During the OL period, each participant oversaw their glucose control, using their usual mechanism to calculate the meal boluses according to the CHO content of the meals, and their usual basal infusion. After the 72 hours with OL control, the loop was closed, and the insulin pump was commanded by the ARG algorithm for another 72 hours. Although this clinical trial was not randomized, the information from the OL phase was not used to inform the CL algorithm.

For both the OL and the CL phases, the participants performed mild exercise (3-5 km walks). Subjects were allowed to eat more than the stipulated menu if they desired. Meals eaten at lunch and dinner had between 50 and 60 g of CHO while breakfasts and afternoon snacks had a CHO content of 35 to 40 g.

The participants stayed in a hotel close to the HIBA. For the entire duration of the trial, the participants were monitored through InsuMate's remote monitoring from another room by at least one member of the health care team and one member from the engineering team.

Subjects

Five subjects who had been diagnosed with T1D at least two years ago, were between 18 and 65 years old, had been using CSII therapy for at least six months, were trained in CHO counting, had a HbA1c $<10\%$, and were treated with fast acting insulin therapy were randomly selected for this study. The sample size was determined by the availability of five insulin pumps and is in line with other pilot studies of full CL algorithms.[13-15] Subjects were excluded if they had been hospitalized in the last 12 months due to ketoacidosis, had severe hypoglycemia with loss of consciousness in the last 12 months, had uncontrolled hypertension, were undergoing oncological treatment, were pregnant or breastfeeding, among other criteria.

CL System's Components

Glucose levels were monitored with a Dexcom G6 CGM and sent via Bluetooth to an Android smartphone every five minutes. The smartphone held the InsuMate app, where the main glucose controller (the ARG algorithm) calculated the insulin dosage. Then, the calculated insulin was delivered by an Accu-Chek Spirit Combo (Roche, Basilea) insulin pump, also connected to the Android phone via Bluetooth. Last, the InsuMate platform counted with a multiple remote monitoring system, held in a web server (www.insumate.com.ar/remoto), accessible through username and password. See the Supplemental Appendix for more details regarding the InsuMate platform.

Glucose Controller

The controller used to regulate glycemia was the ARG algorithm.[10] Its control structure aims to reduce patient intervention by commanding the insulin infusion without the need of feedforward insulin boluses.

Two linear quadratic Gaussian (LQG) controllers are switched to have different responses to fasting and prandial periods. One LQG controller is conservative and performs slight changes on the patient's insulin basal rate. The other one is aggressive and is selected when higher insulin doses are needed, for example at mealtimes. A safety auxiliary feedback element (SAFE) block adapts (reduces) the insulin infusion when a constraint on the active insulin (insulin on board [IOB]) is reached.[16]

To switch between the conservative and aggressive modes, any meal detection algorithm can be used.[17] However, just like in the inpatient study of the ARG, a cautious approach was followed during this trial. Here, the participants had to announce the mealtime. Thus, the ARG algorithm was alerted that a meal could be ingested. That announcement did not generate any meal-related insulin bolus. It only triggered the control algorithm to a listening mode. During that mode, the CGM trend was analyzed for 90 minutes at most, and the aggressive mode was selected only if rising glucose values were detected. On the other hand, the switching from aggressive to conservative was made automatically after one hour of aggressive control.

Outcomes

For this trial, the general outcome was to evaluate the safety and effectiveness of the AP without CHO counting in people with T1D in an outpatient setting. Then, the primary outcomes were the percentage of the time in range (TIR; ie, blood glucose (BG) 70-180 mg/dl) and the percentage of time below range (TBR; ie, BG <70 mg/dl). Last, the secondary outcomes were the percentage of time of the BG in the range 70 to 250 mg/dl, the percentage of time above range (TAR; ie, BG >180 mg/dl), the number of symptomatic and asymptomatic hypoglycemia episodes, episodes of technical failure of the system's components, comparison between OL and CL metrics, evaluation of the meal compositions and their influence on the effectiveness of the glucose regulation, and the percentage of time of the AP system working correctly.

The results of this clinical trial are descriptive, and no statistical analysis of the results was carried out due to the small sample size ($n = 5$).

Results

Table 1 summarizes the parameters of the five participants. All participants completed the 72 hours of OL and the 72 hours of CL control. No adverse events took place during the trial.

Table 1. Participant's Demographics.

	Subject	Weight (kg)	Total daily insulin (U)	A1c (%)	Gender	Age (years)	Duration (years)
	1	65.2	26.2	8.0	Female	48	32
	2	63.5	40.4	8.9	Female	41	15
	3	68.0	32.4	6.5	Female	43	25
	4	85.0	59.0	6.8	Male	29	24
	5	78.4	62.2	7.3	Male	22	15
Mean		72.0	44.0	7.5		36.6	22.2
SD		9.3	16.0	1.0		10.7	7.3

Abbreviation: SD, standard deviation.

Table 2. Metrics (Mean [SD]) of OL vs CL Control Obtained for the 72 Hours of the Trial, the Daytime Metrics of the Last Day of the Trial, and the American Diabetes Association (ADA) recommendations for CGM Data.

	72 hours		Daytime (last day)		ADA recommendations[14]
n = 5	OL	CL	OL	CL	
Mean BG	188.9 (25.5)	186.2 (24.7)	184.5 (47.0)	164.8 (15.6)	
% (70, 250) mg/dL	84.1 (6.6)	80.9 (8.3)	86.54 (16.1)	89.1 (6.3)	
% (70, 180) mg/dL	46.9 (15.6)	50.9 (14.4)	57.7 (18.5)	68.3 (13.4)	>70%
% >180 mg/dL	52.2 (16.3)	48.0 (15.4)	40.8 (19.7)	31.1 (13.9)	<25%
% <70 mg/dL	0.9 (0.8)	0.9 (1.4)	1.6 (2.6)	0.6 (1.3)	<4%
% <54 mg/dL	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	<1%

Abbreviations: OL, open-loop; CL, closed-loop; CGM, continuous glucose monitor; BG, blood glucose; SD, standard deviation.

Table 2 shows the results (mean [standard deviation, SD]) of OL vs CL control obtained in the 72 hours of the trial, the daytime metrics of the last day of the trial, and the American Diabetes Association (ADA) recommendations for CGM data interpretation.[18]

When analyzing the full duration of the trial, TIR increases while the TAR decreases, as does the mean BG. On the other hand, the TBR and the time in severe hypoglycemia (BG <54 mg/dl) remain similar across methods, both achieving the recommended value.

Regarding the daytime metrics, they are particularly relevant as no meal boluses were infused to compensate for meals. It can be noted that by the end of the trial, the glycemic outcomes improved, with CL control achieving lower TAR, TBR, and mean BG, and higher TIR, close to the recommended values. In addition, the SD of the metrics is also reduced by the CL algorithm. Also, during the last day of the trial, participant 1 suffered from some consecutive CGM disconnections which caused his/her BG values to increase. If these metrics are calculated without considering participant 1, the CL achieved 159.4 mg/dL mean BG, 73.8% TIR, 25.4% TAR, and 0.8% TBR.

Regarding insulin dosage, the total daily insulin with OL therapy was 53.68 ± 16.71 U, while with CL control was 48.5 ± 9.67 U.

Figure 2 shows the daytime and nighttime metrics for the 72 hours of OL and 72 hours of CL control. It can be seen how the mean TIR increases for both days and nights when the glucose is regulated by the ARG algorithm. During the day, there is a reduction in the TBR, and the mean TAR is slightly lowered compared with OL therapy, but with an increase in the SD. During the night, the TAR is reduced, but the TBR is increased.

Regarding the percentage of time in CL, the results were 99.64% for subject 1, 91.01% for subject 2, 96.26% for subject 3, 96.41% for subject 4, and 93.68% for subject 5. In every case, the devices were connected, and the platform operated properly for more than 90% of the time, with an average of 95.4% of time in CL, demonstrating the feasibility of using the InsuMate platform for CL control. There were a total of 25 disconnections, 11 of which were due to manual pump disconnections when the participants showered, and 14 due to a disconnection in the communication with the CGM.

Figure 3 shows the individual CGM data for the five participants during the OL and the CL phase. It can be seen that even though the performance is similar across OL and CL, the severe hyperglycemia episodes during the OL phase are more persistent than in CL.

Last, as an illustrative example of the ARG operation, Figure 4 shows the 72 hours of CL control for participant 3. The first subfigure shows the glucose evolution over time. The purple triangles indicate meal announcements. It can be seen how the glycemic control was adequate, keeping the participant in the desired range (green circles) for most of the time. On the other hand, the scarce hypoglycemic episodes

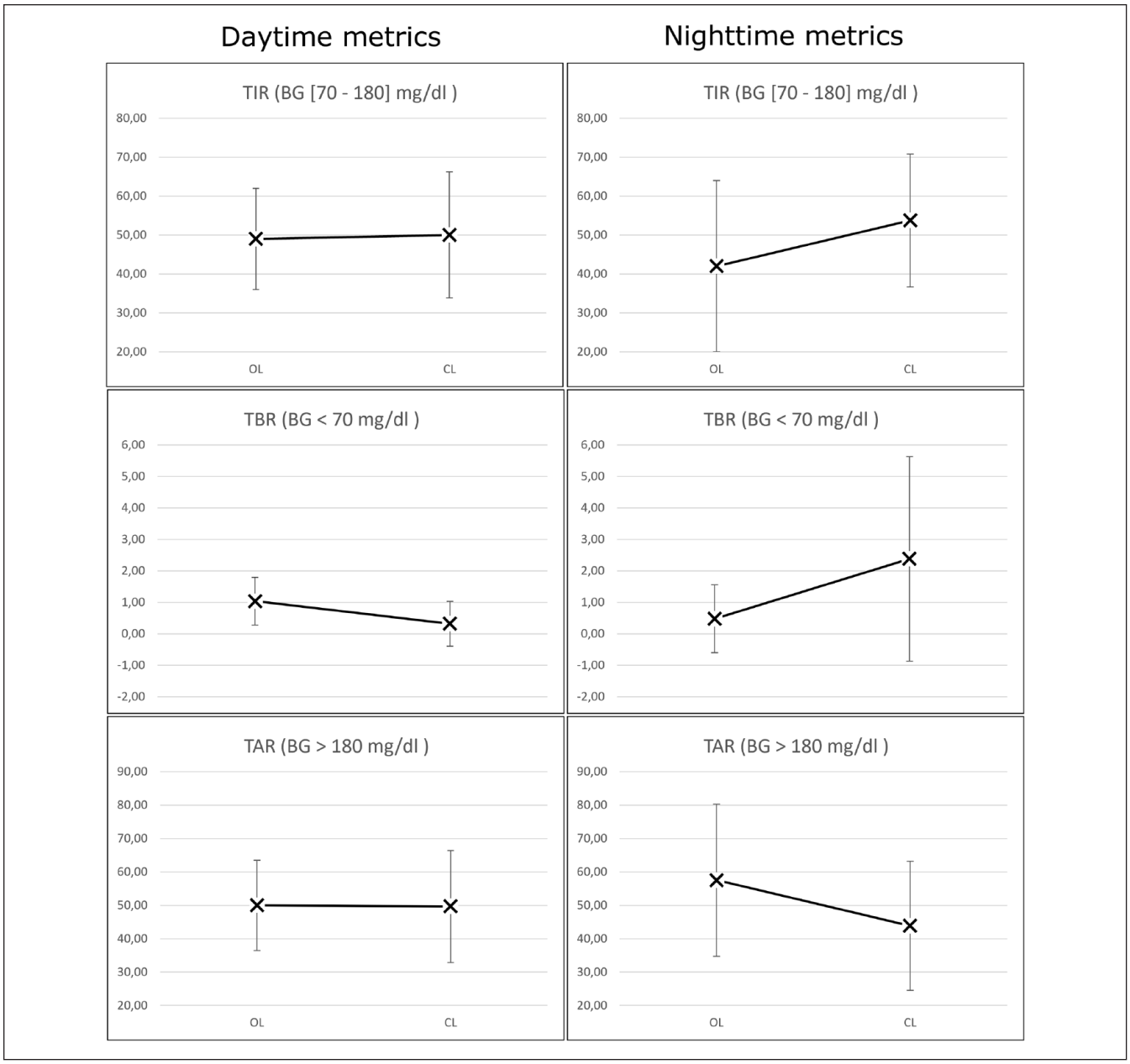

Figure 2. Daytime and nighttime metrics.
Abbreviations: TIR, time in range; BG, blood glucose; TBR, time below range; TAR, time above range.

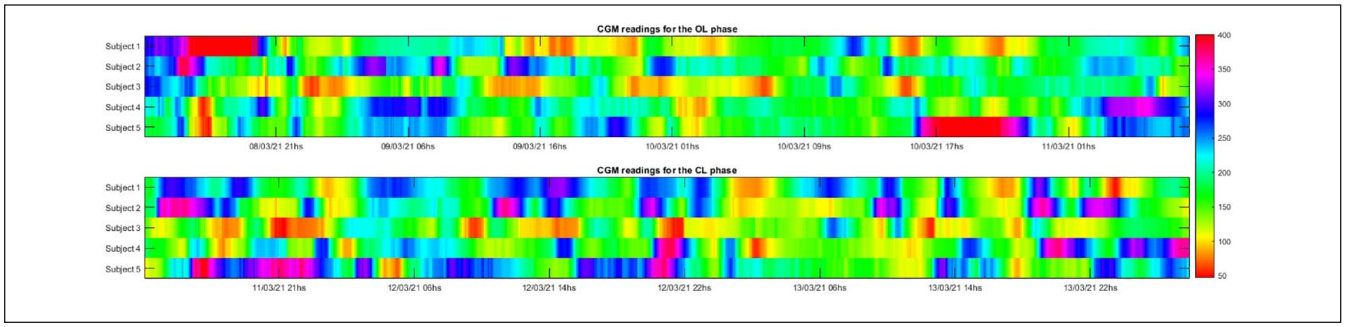

Figure 3. CGM data for the five participants during the OL and the CL phase.
Abbreviations: CGM, continuous glucose monitor; OL, open-loop; CL, closed-loop.

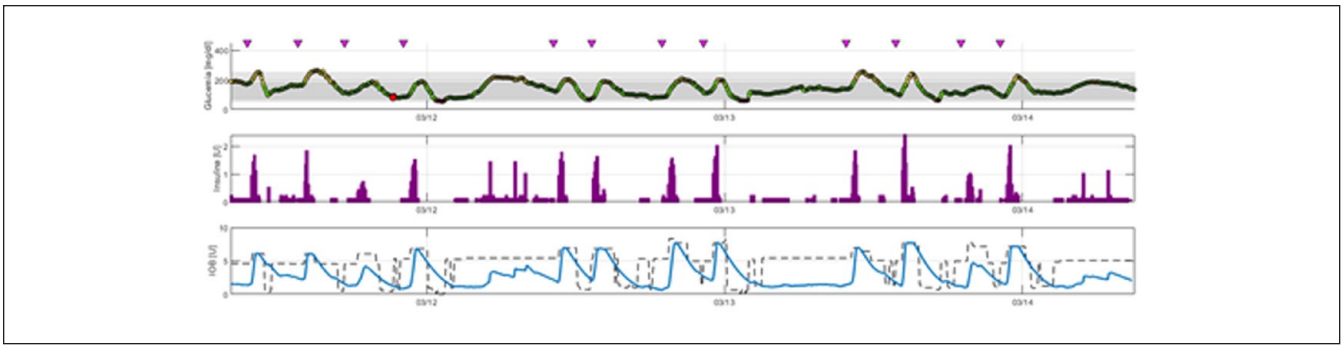

Figure 4. Seventy-two hours of closed-loop control for participant 3. The first subfigure shows the glucose evolution over time and the purple triangles indicate meal announcements. The second subfigure shows the insulin dosage. The third subfigure shows the IOB and the IOB constraint.
Abbreviation: IOB, insulin on board.

were brief and did not require medical intervention or rescue CHO intake from the patient. The second subfigure shows the insulin dosage by the CL algorithm. On one hand, the large insulin spikes close to meal intake are automatically generated by the aggressive LQG controller together with the SAFE layer; while on the other hand, the conservative LQG controller adjusts basal delivery during fasting periods. The IOB alongside with the IOB constraint is shown in the last subfigure. It can be observed how the SAFE attenuates or shuts off the controller action to avoid the violation of the IOB constraint, particularly during the postprandial period.

Discussion

As previously mentioned, very few outpatient trials involving single-hormone, full CL algorithms have been carried out. Cameron and colleagues[4] reported the evaluation of a full CL algorithm based on multiple model probabilistic predictive control in an inpatient setting for 30 hours in ten patients, and in a supervised hotel for 54 hours in 15 patients. Then, Forlenza and colleagues[3] reported a study involving the same full CL algorithm in another supervised hotel setting. The AP system was tested for 72 hours in six adults and four adolescents with daily exercise, and three announced (with manual insulin bolus by patient) and six unannounced meals. Other relevant full CL studies are presented, for instance, by Boughton and colleagues[7] but for type 2 diabetes critical hospitalized patients, and by Blauw et al[5] and Tsoukas et al[6] using bi-hormonal AP schemes.

In the study carried out by Forlenza and colleagues,[3] the daytime mean TIR was 68%, the mean TBR was 2.1%, and the mean TAR was 29.5%. Then, in the trial by Cameron and colleagues,[4] the mean daytime CGM was 163.4 mg/dl, with 58.8% TIR, 2.8% TBR, and 38.4% TAR. Even though the TIR and TAR for the full 72 hours of CL control with the ARG algorithm, mean BG 186.2 (24.7) mg/dL, with 50.9% (14.4%) TIR, 48.0% (15.5%) TAR, and 0.9% (1.4%) TBR, are poor compared with these studies, the daytime metrics of the last 24 hours are well within the range of what has been reported, mean BG 164.8 (15.6) mg/dL, with 68.3% (13.4%) TIR, 31.1% (13.9%) TAR, and 0.6% (1.3%) TBR. Also, the TBR is lower for all the time intervals analyzed. However, it should be kept in mind that these results are illustrative as no formal conclusion can be drawn due to the limited sample size.

Regarding the slight increase in the mean BG and SD with CL control during the day compared with the OL phase, it is most likely due to the added delay in compensating the meals effect on glucose levels compared with administering a manual insulin bolus. Then, for the nighttime metrics, an increase in the TBR was observed during the CL phase. Although it was not a specific goal, this should be solved as night control has already been successfully addressed in many clinical trials.

It is interesting to point out that the participants had a high training and control of their diabetes in their daily life. However, the change in the routine, the treatment, and the familiarization with new devices and platform during the trial, in addition to external elements like the sanitary protocols due to the COVID-19 pandemic, are factors that bias the results, both for OL and CL periods. Nonetheless, new strategies for automatic correction boluses and the online adaptation of the ARG algorithm are being evaluated.

One of the main strengths of this trial was that, even though meals had to be announced, there was no need to count the CHO content of the meals, which was very well received by the participants. Since meal announcement did not trigger an insulin bolus, the participants had the freedom of announcing a meal and then not eating it without the risk of insulin-induced hypoglycemia. Also, they performed mild exercise every day and had the freedom of eating more CHO content of what was stipulated in the menu if they desired. These last two remarks are of great importance since the team goal is to prioritize the AP user's autonomy. Some limitations of the study include the small sample size imposed by the availability of the system's components, the fact that the

trial was not randomized, and the lack of power to perform statistical analysis.

It is worth highlighting that, during the OL phase and due to the context of the clinical trial, the participants were more careful with their glucose control than in a day-to-day basis. It is reasonable to suppose than in a home-use scenario the CL benefits would be greater. Also, the increase in patient's freedom could lead to less diabetic burnout, resulting in better HbA1c values in the long term.

The CL system worked properly for more than 95% of the time on average. Also, no adverse events took place (ketoacidosis, severe hypoglycemia, or COVID-19 propagation) and no medical intervention was required. Then, the TIR in CL, with minimal intervention from the users, was similar or superior to the one achieved in OL, with the major improvement being by the end of the trial. Despite the study limitations and the fact that there is still a long way ahead for CL control in T1D, the results suggest that this kind of algorithm might be beneficial for people who avoid or forget meal boluses, or do not perform an accurate CHO counting, or simply prefer more autonomy rather than performance.

The InsuMate platform proved to be suitable and versatile for its use in AP clinical trials. Its interface was intuitive and easy to use for the participants of the clinical trial, as was the remote monitoring interface for the health care professionals. Even though some disconnections occurred, possibly associated to the use of third-party, non-official app (xDrip) to collect the readings, the average time in CL was equal or higher than the one reported for other AP platforms.

Conclusions

It can be concluded from this experience that the outpatient ARG levels using the ARG algorithm and InsuMate platform are feasible. In the future, it is expected to carry out phase 4 of the clinical trials, which will involve the home-use of the ARG algorithm and the InsuMate platform, for a longer period and for a larger sample size, eventually eliminating the meal announcement completely.

Abbreviations

AP, artificial pancreas; ARG, automatic regulation of glucose; CGM, continuous glucose monitor; CHO, carbohydrates; HIBA, Hospital Italiano de Buenos Aires; UNLP, Universidad Nacional de La Plata; IOB, insulin on board; LQG, linear quadratic Gaussian; MMPPC, multiple model probabilistic predictive control; SAFE, safety auxiliary feedback element; T1D, type 1 diabetes; TDI, total daily insulin; UVA, University of Virginia; DiAs, Diabetes Assistant; CL, closed-loop; OL, open-loop; CSII, continuous subcutaneous insulin infusion; TIR, time in range; TAR, time above range; TBR, time below range; BG, blood glucose.

Declaration of Conflicting Interests

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ORCID iDs

Emilia Fushimi https://orcid.org/0000-0001-5820-3108
Ricardo Sánchez-Peña https://orcid.org/0000-0001-9190-2576

Supplemental Material

Supplemental material for this article is available online.

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