Hybrid closed-loop insulin delivery versus sensor-augmented pump therapy in children aged 6–12 years: a randomised, controlled, cross-over, non-inferiority trial

Dulanjalee Kariyawasam, Carole Morin, Kristina Casteels, Claire Le Tallec, Annie Sfez, Cécile Godot, Erik Huneker, Nathalie Garrec, Pierre-Yves Benhamou, Michel Polak, Guillaume Charpentier, Sylvia Franc, Jacques Beltrand

Background Time in range (TIR) goals are rarely met in children with type 1 diabetes, except at the cost of increased hypoglycaemia episodes. Our objective was to evaluate the safety and efficiency of the Diabeloop DBL4K (Diabeloop, Grenoble, France) hybrid closed-loop system in prepubescent children.

Methods We did a multicentre, open-label, randomised, controlled, non-inferiority, two-session crossover study in the paediatric endocrinology departments of three university hospitals in France and Belgium. Eligible participants were aged 6–12 years with type 1 diabetes for at least 1 year, glycated haemoglobin A_{1c} 9% (75 mmol/mol) or less, and insulin pump treatment for at least 3 months. Participants were randomly assigned (1:1) to a closed-loop device or sensor-augmented pump (open loop) therapy. Randomisation was by a permuted block randomisation scheme, using an interactive web-based response system, and was stratified on centre (block size 6). The assessed closed-loop device, the Diabeloop for Kids DBL4K hybrid closed-loop system, is an automated blood glucose regulation system composed of a handset, insulin pump, and continuous glucose monitor. The open-loop system is defined as a sensor-augmented pump therapy composed of the usual insulin pump used by the patient and a continuous glucose monitor. A 72-h in-patient period was followed by a 6-week home phase. After a 1-week washout period, the participants crossed over to the other device. The primary outcome, assessed in the intention-to-treat population, was the mean proportion of time spent in hypoglycaemia (3·9 mmol/L [<70 mg/dL]) during the hospital phase, with a non-inferiority margin of –2·5% (absolute value). Safety was assessed in the intention-to-treat population on a per-protocol basis. This study was registered with ClinicalTrials.gov, NCT03671915.

Findings Between May 6 and Dec 23, 2019, we included 21 participants (closed loop then open loop, n=10; open loop then closed loop, n=11). The proportion of time spent in hypoglycaemia was significantly lower with the closed-loop system than the open-loop system in both groups (2·04% [95% CI 0·44 to 3·64] *vs* 7·06% [5·46 to 8·66]; non-inferiority one-sided p<0·0001). No severe ketoacidosis, nor severe hyoglycaemic events or fatal adverse events occurred. All 25 adverse events (18 with the closed-loop system, seven with the open-loop system) were related to the treatment.

Interpretation The closed-loop Diabeloop system decreased hypoglycaemic episodes and provided good metabolic control in prepubescent children with type 1 diabetes, under real-life conditions. This finding supports the safe use of closed-loop technology in this paediatric population.

Funding Diabeloop.

Introduction

The management of type 1 diabetes has changed rapidly over the past two decades, with the introduction of new insulin analogues, continuous glucose monitors (CGMs), and smart pumps with different bolus delivery modes and built-in dosage calculators. During the same period, type 1 diabetes has been increasingly diagnosed in younger patients.[1] Intensive diabetes treatment benefits all patients with type 1 diabetes but is even more crucial before 10 years of age,[2] when poor glycaemic control markedly increases the cardiovascular risk[2] and can adversely affect brain and cognitive-skills development.[3,4,5,6] The 2018 American Diabetes Association and International Society for Paediatric and Adolescent Diabetes (ISPAD) guidelines now recommend that glycated haemoglobin A_{1c} (HbA_{1C}) be kept at less than 7% (<53 mmol/mol),[7] which corresponds to a time in range (TIR) greater than 65–75% as measured by CGM.[8,9] For patients with hypoglycaemia unawareness or limited access to insulin analogues or advanced insulin delivery devices, the target is a TIR greater than 60%.

Children and adolescents rarely reach these TIR goals with insulin delivery by pump or multi-injections combined with CGM.[10] In children, TIR improvements are often obtained only at the expense of more frequent

Institut de Recherches Biomédicales des Armées, Université Paris Saclay, Evry, France (S Franc)

Correspondence to:
Prof Jacques Beltrand, Endocrinology, Diabetology, Gynecology Department, Necker-Enfants Malades University Hospital, Assistance Publique des Hôpitaux de Paris–Centre, Paris 75015, France
jacques.beltrand@aphp.fr

Research in context

Evidence before this study

We searched PubMed from database inception to July 20, 2021, for randomised controlled trials published in English using the terms "artificial pancreas" OR "closed-loop" AND "type 1 diabetes mellitus" OR "diabetes" AND "paediatric patients" OR "children". We limited our search to single-hormone systems. We identified 13 randomised controlled trials including paediatric participants, most of which also included adult populations. All these studies compared hybrid closed-loop systems against sensor augmented pump therapy, either including exclusively children (<18 years old) or including adults and children. Most of these studies assessed short-term use of hybrid closed-loop systems (between 48 h and 7 days). Only two studies assessed longer term use (12–16 weeks) of hybrid closed-loop systems at home exclusively in children and two studies assessed the hybrid closed-loop system among adults and children, either during 6 months or during 12 weeks. All these studies showed an increase of proportion of the time in range or an improvement in hypoglycaemic events with a closed-loop system. Over the past year, multiple other non-controlled studies assessed hybrid closed-loop systems in paediatric patients.

Added value of this study

This multicentre, open-label, randomised, controlled, non-inferiority, two-session crossover study is one of the first to assess a closed-loop system versus a sensor-augmented pump in prepubescent children without including adults, with both a short (72 h) in-hospital phase and a longer (6 weeks) phase at home under usual living conditions. This is also one of the first studies assessing both metabolic targets and the quality of life of the patients and parents while comparing sensor-augmented therapy to a hybrid closed-loop system. Our findings suggest a decrease in hypoglycaemic episodes (primary outcome), as well as an increase in the proportion of time spent within the target range with the closed-loop system during the 6-week home phase. The closed-loop device was well accepted and was associated with positive psychosocial and quality-of-life effects.

Implications of all the available evidence

The hybrid closed-loop system was safe in prepubescent children, decreased hypoglycaemic events, and improved the time spent within the target blood glucose range. These results support previous data suggesting that the use of an artificial pancreas improves blood glucose control in prepubescent children with type 1 diabetes in everyday life conditions with glucose remote monitoring in both the short and long term.

hypoglycaemic episodes. Quality of life of young patients with type 1 diabetes and their parents also deserves careful attention, as striving for elusive glycaemia goals can cause emotional distress.[11] Recently developed hybrid closed-loop systems combine a CGM, an insulin pump, and an algorithm that uses data from the CGM and pump to automatically adjust the amount of insulin delivered. These devices might help to reach glycaemia targets more reliably but have chiefly been assessed in adults and adolescents.[12] Closed-loop systems might be superior over sensor-augmented pump (open loop) delivery in maintaining glycaemia values within the target range[13] and also have a good level of acceptance.[14–16] In adolescents with poor glycaemic control, a closed-loop system has been shown to increase the TIR without increasing hypoglycaemia or ketoacidosis events.[17,18]

An increasing number of studies have assessed hybrid closed-loop systems in children younger than 14 years;[17,19–30] however, only a few studies have assessed hybrid closed-loop systems under conditions resembling everyday life in the long-term, during day and night, in participants exclusively younger than 14 years in a parallel-group, randomised trial showing an improvement in the TIR without increasing hypoglycaemia.[22,25]

The first-generation Diabeloop device (DBLG1; Diabeloop, Grenoble, France) is, to date, the only hybrid closed-loop system that allows customisation of several parameters according to the patient's physiology. In adults, the Diabeloop device increased the TIR compared with an open-loop device in a 12-week study.[31] Diabeloop for Kids (DBL4K; Diabeloop) is an adaptation of the adult DBLG1 medical device.[31]

Our primary objective was to assess the non-inferiority of DBL4K in terms of protection from hypoglycaemia versus an open-loop device during a 72-h hospital stay in prepubescent children aged 6–12 years. Secondary objectives were to compare closed-loop and open-loop therapy over the 72-h hospital period and a 6-week home period regarding hypoglycaemic events, TIR, technical performance, and patient-related outcomes.

Methods

Study design and participants

We did a multicentre, open-label, randomised, controlled, non-inferiority, two-session crossover study in the paediatric endocrinology departments of three university hospitals in France (Necker-Enfants Malades University Hospital, Paris; and University Hospital, Toulouse) and Belgium (UZ Leuven, Leuven).

Paediatric, prepubescent patients aged 6–12 years (Tanner stage I) at screening were eligible if they had type 1 diabetes for at least 1 year with confirmed HbA_{1c} of 9% or less (≤75 mmol/mol), a daily insulin requirement of 8 units or more, and insulin delivery via an external insulin pump for at least 3 months. The participants and their parents or guardians had to live in an area with

internet and mobile phone coverage and to agree to spend 72 consecutive hours in hospital. We excluded participants with two or more episodes of severe hypoglycaemia, one or more episodes of ketoacidosis, or both, in the previous 6 months, as well as participants with impaired awareness of hypoglycaemia (Gold score >4).

Potential participants were identified and screened by their treating clinicians who invited their parents to contact the research team of the clinic facility. Written informed consent was obtained from the participants and their parents or guardian before study inclusion.

The appropriate ethics committees in France (Comité de Protection des Personnes) and Belgium (Ethische Commussie UZ Leuven) approved the trial. The trial was also approved by the French Medicine Safety Agency (Agence Nationale de Sécurité du Médicament) and by the Belgian Federal Agency for Medicines and Health Products.

The study protocol is available in appendix 2 (pp 41–159). The CONSORT, CONSORT-AI, and SPIRIT-AI checklists are also shown in appendix 2 (pp 32–40).

Randomisation and masking

Participants were randomly assigned (1:1) to either a closed-loop system first or an open-loop system first for 72 h in hospital then, at the two French sites, for 6 weeks at home. After a 1-week washout period, the participants crossed over to the other device, again for 72 h in the hospital and, at the French sites, 6 weeks at home.

A permuted block randomisation scheme was generated by a validated system using automated computerised software connected to an interactive web-based response system (ClinInfo, Lyon, France) that ensured concealment. Randomisation was stratified on centre and block size was fixed to 6. Random assignment was done at each centre. Neither the investigators nor the participants and parents were masked to treatment allocation.

Procedures

The investigators and clinical staff at each site provided the children and parents with a training session on how to insert and calibrate the subcutaneous CGM, interpret the data displayed on the real-time CGM device (DexCom G6; DexCom, San Diego, CA, USA), and adjust insulin doses on the basis of glycaemia. The participants then used the device for 72 h in hospital. The Dexcom G6 CGM system is designed for continuous measurement of glucose concentrations in the 2·2–22·2 mmol/L (40–400 mg/dL) range for 10-day wear and continuously beams data directly to a receiver (or a smartphone). The transmitter is wireless and sends glucose data to the receiver or a Diabeloop handset.

After this run-in period, the participants received insulin via either an open-loop system or the closed-loop Diabeloop device. Open-loop therapy was with each participant's usual pump, preprogrammed with the usual basal settings and the same CGM (Dexcom G6) as

in the closed-loop phase. No additional functions were activated. All participants used their usual fast-acting insulin analogue (lispro or aspart).

After the hospital phase, the participants in the French centres continued to use the randomly allocated device for 6 weeks at home. In the open-loop group, the subcutaneous sensor was replaced every 10 days by the participant under parental supervision. Then, during a washout period of at least 1 week, the participants returned to their usual insulin pump treatment (usual fast-acting insulin analogue; ultra-fast-acting insulin was not allowed). Participants did not use the DexCom G6 CGM device during the washout but were permitted to use either their previous CGM system or flash glucose monitoring (all used flash glucose monitoring). Real-time CGM was done either at home by the participants with parental supervision or at the clinical investigation site by the research team, 24 h to 72 h before crossing over.

The participants then crossed over to the other device, for 72 h in the hospital, then, at the French sites, for 6 weeks at home, during which the participants used the same insulin scheme as during the 72-h hospital phase.

After the second 72-h hospital phase in Belgium and the second 6-week home phase in France, the participants returned to the insulin pump therapy they had used before the study and to the usual CGM they had before random assignment or to flash glucose monitoring.

During the closed-loop home phase, participants were contacted by telephone or email for assessments of safety and adherence and for a review of the technical aspects of the treatment.

Participants assigned to the Diabeloop closed-loop system used the Kaleido insulin pump (ViCentra, Utrecht, Netherlands) managed by the DBLG1 application installed on an Android smartphone (Sony XZ1), connected to the Dexcom G6 CGM system using Bluetooth low-energy technology, as detailed in appendix 2 (p 30). The French centres could use the Yourloops web-based platform, a remote monitoring server transmitting participant data (sensor glucose concentrations, insulin doses, and intercurrent events) to the health-care team via a secured website, as described in appendix 2 (p 31). Participants were taught by a dedicated nurse how to use the various components of the system and how to respond to an alarm. Nurses were responsible for remote monitoring 24 h per day, 7 days per week, and telephone interaction with participants.

Diabeloop software embeds a regulation algorithm to automatically regulate the participant's glycaemia. It takes as input the interstitial glucose value received every 5 min from the CGM and participant inputs related to meals and physical activities and calculates the amount of insulin to be delivered. The Diabeloop sends this information to the pump that automatically delivers the calculated quantity of insulin. Customisation of the closed-loop system required it to be tuned through eight

settings, which could be done during the initial 24 h or at the end of the 72-h hospital phase. The DBLG1 system combines an algorithm based on machine learning within a physiological framework with an expert system and self-learning algorithms. The algorithm also featured additional settings that were manually accessible and designed to modulate the reactivity of regulation, to better fit with individual metabolic profiles. Details of the algorithm have been published previously[29] (appendix 2 pp 30–31). The target glucose concentration was set at 6·05 mmol/L (110 mg/dL) for the first days but could be decreased to 5·55 mmol/L (100 mg/dL) according to the glycaemic pattern reported by the CGM system.

For each participant, CGM data and other clinically relevant data were collected into an electronic case-report form in accordance with Good Clinical Practice guidelines. The participants and parents completed the Diabetes Treatment Satisfaction Questionnaire, the Paediatric Quality of Life Inventory (PedsQoL), and the Artificial Pancreas Acceptance Questionnaire at baseline (visit 2) and at the end of each phase (fourth day of the hospital phase at visit 3 or 7 and during the home phase at visit 5 or 9 in the closed-loop group). The Diabetes Technology Questionnaire was completed by the parents and participants at the two French sites, at the same timepoints.

An independent Data Safety Monitoring Board (DSMB) comprised a chairperson and two experts. The DSMB was informed of all serious adverse event data at periodic intervals. The DSMB reported to the study management committee any safety concerns and recommendations for suspension or early termination of the investigation.

Outcomes

Only a few hybrid closed-loop systems have been assessed in the paediatric population and the Diabeloop system's safety and efficiency have been reported only in an adult population. Therefore, because the Diabeloop system has not been tested in paediatric populations, the French Medicine Safety Agency required a safety outcome as a primary outcome in a supervised hospital setting. Thus, we chose as the primary outcome the mean proportion of time spent in hypoglycaemia (<3·9 mmol/L [<70 mg/dL]) recorded by the CGM during the 72-h hospital phase.

The secondary outcomes were mean glycaemia, the low blood-glucose index and high blood-glucose index, TIR (the proportion of time spent with sensor glucose within 3·9–10·0 mmol/L [70–180 mg/dL]), the coefficient of variation of glucose, and the Blood Glucose Risk Index, all assessed 24 h per day during the 72-h hospital phase, between 2300 h and 0700 h during the 72-h hospital phase, and during the home phase. The exploratory outcomes were the proportion of time the closed-loop system was active during the 72-h hospital phase, the duration of glucose monitoring with both systems during the 72-h hospital phase, and patients' and

their guardians' perceptions of lifestyle change, satisfaction, and diabetes management assessed with the Diabetes Treatment Satisfaction Questionnaire, the Diabetes Technology Questionnaire, the PedsQoL, and the Artificial Pancreas Acceptance Questionnaire.

The safety outcomes were the time spent with sensor glucose concentrations less than 3·0 mmol/L (<54 mg/dL) and less than 3·3 mmol/L (<60 mg/dL) assessed 24 h per day during the 72-h hospital phase, between 2300 h and 0700 h during the 72-h hospital phase, and during the home phase; the number of severe hypoglycaemic events (requiring assistance from another person to actively administer carbohydrate, glucagon, or other resuscitative actions); the number of participants who had severe hypoglycaemia; the proportion of time spent with sensor glucose concentrations greater than 10·0 mmol/L (>180 mg/dL), greater than 13·9 mmol/L (>250 mg/dL), and greater than 16·7 mmol/L (>300 mg/dL), all assessed 24 h per day during the 72-h hospital phase, between 2300 h and 0700 h during the 72-h hospital phase, and during the home phase; and the number of severe diabetic ketoacidosis events. Data for the predefined endpoint of fasting blood glucose were not automatically collected because this was unpractical and not useful in assessing metabolic control (details of this endpoint are in appendix 2 p 23).

The utility endpoints were measured as insulin daily dose.

Statistical analysis

With a sample size of 20, a paired t test with a 2·5% one-sided significance level would have 80% power to reject the null hypothesis that the closed-loop system was inferior to the open-loop system for the primary outcome, assuming a non-inferiority margin of –2·5% (absolute value) and a standard deviation of the differences of 3·7%.

All randomly assigned participants were included in the primary analysis on an intention-to-treat basis. In non-inferiority trials, the intention-to-treat analysis can bias towards the null, which might lead to false claims of non-inferiority;[32] therefore, the primary outcome was also assessed in the per-protocol population, defined as all patients who were randomly assigned and treated according to the protocol with no important protocol deviation. Non-inferiority was documented only if both the intention-to-treat and per-protocol analyses led to the same conclusion.

If non-inferiority was documented (with a one-sided significant p value), superiority was also assessed (with a two-sided p value). Superiority was documented only if both the intention-to-treat and per-protocol analyses led to the same conclusion.

Comparisons between treatment groups for the primary endpoint were based on a mixed effect model for repeated measures (MMRM). This model included treatment (closed loop and open loop) and crossover

period as fixed effects, participant as a random effect, and period baseline (ie, proportion of time spent with sensor glucose concentration <3·9 mmol/L at visit 2 and at visit 6) as covariates. Adjusted mean values, as well as treatment contrasts, were presented together with the two-sided 95% CIs and one-sided p value and two-sided p value if non-inferiority was documented. As stated in the statistical analysis plan (appendix 2 pp 160–439), sensitivity analyses were done with an MMRM without multiple imputation, an MMRM using a different covariance structure, and the generalised estimating equation approach with a γ distribution and a log link function.

Missing data were imputed using the multiple imputation method. Missing baseline data were replaced with the mean value of non-missing baselines in the corresponding period, as planned in the statistical analysis plan.

Continuous secondary endpoints were analysed in the population of participants who used the assigned device at least once during the first period and at least once during the second period, using the same model as described for the primary endpoint. Adjusted mean values and treatment contrasts were computed with their 95% CIs and two-sided p values (superiority analysis). The safety outcomes were analysed in the intention-to-treat population.

SAS software (version 9.4) was used for the sample size estimation and all statistical analyses. This study was registered with ClinicalTrials.gov, NCT03671915.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Between May 6 and Dec 23, 2019, 21 participants were screened, included, randomly assigned, and treated (sequence of randomisation in appendix 2 p 1). Among them, ten were assigned to the closed-loop system first and 11 assigned to the open-loop system first (figure 1). One participant who started with the closed-loop system did not complete the study for medical reasons (allergic reaction to the Dexcom G6 patch while in the open-loop phase at home) and was included in the intention-to-treat analysis only (available data were used to calculate means). The first 6-week home phase was completed by 17 participants, eight assigned to the closed-loop system first and nine assigned to the open-loop system first. For the French centres, the median duration of device use was 46·7 days (IQR 43·2–47·7) with the closed-loop system and 46·8 days (44·0–46·9) with the open-loop system. At the Belgian centre, the median duration of device use was 4·9 days (4·8–5·0) with the closed-loop system and 4·9 days (4·9–5·0) with the open-loop system. The per-protocol population analysis was identical to the analysis in the full analysis set.

Baseline characteristics of the 21 participants are shown in table 1. Comparing the effect of the different subgroups in the intention-to-treat population shows the absence of significant differences (appendix 2 p 1). Results for the primary and secondary outcomes are shown in table 2. Sensor data availability during the 72-h
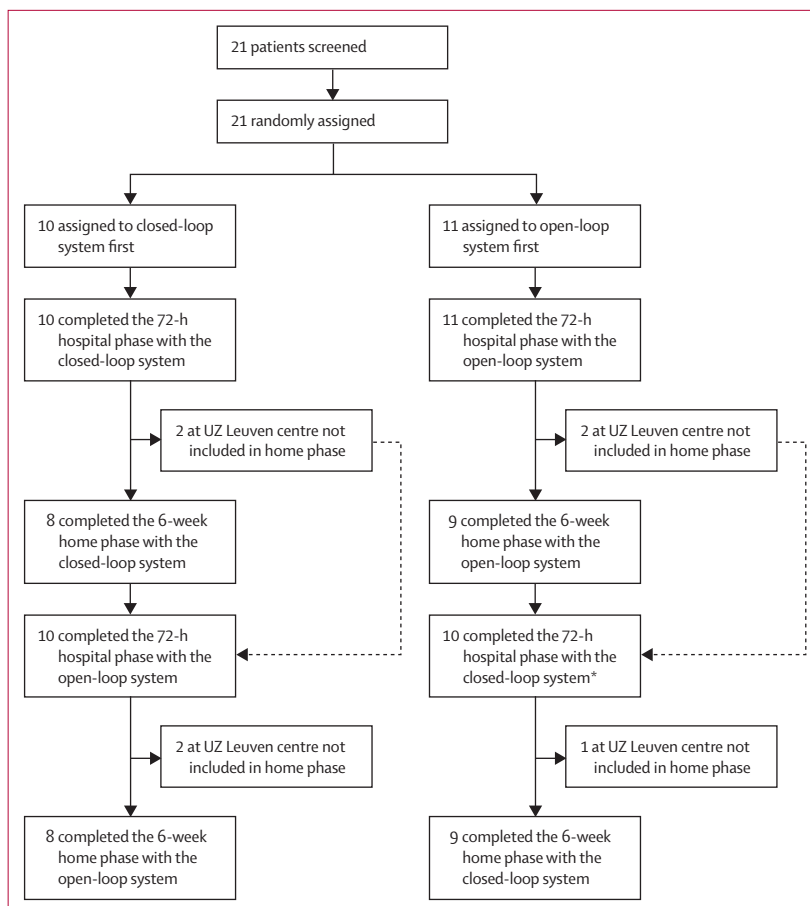

Figure 1: Trial profile
*One patient from the UZ Leuven centre was excluded for medical reasons (allergic reaction to the Dexcom G6).

	Group 1: closed loop then open loop (n=10)	Group 2: open loop then closed loop (n=11)
Age at inclusion, years	8·5 (7·0–10·0)	8·0 (6·0–9·0)
Sex		
Female	6 (60%)	5 (45%)
Male	4 (40%)	6 (55%)
Weight, kg	30·0 (26·0–41·0)	30·0 (25·0–33·0)
Time from diabetes discovery to inclusion, years	6·0 (5·0–7·0)	5·0 (3·0–8·0)
Time from first use of pump to inclusion, years	5·5 (3·0–6·0)	3·0 (2·0–5·0)
Last HbA$_{1c}$, %	7·6% (7·2–7·7)	7·0% (6·4–7·3)
Last HbA$_{1c}$, mmol/mol	60 (55–61)	53 (46–56)
Last c-peptide concentration, ng/mL	0·0 (0·0–0·0)	0·0 (0·0–0·0)

Data are median (IQR) or n (%). HbA$_{1c}$=glycated haemoglobin A$_{1c}$.

Table 1: Baseline characteristics

hospital phase and the 6-week home phase are shown in table 3.

During the 72-h hospital phase, significantly less time was spent in hypoglycaemia (<3·9 mmol/L) with the closed-loop system than with the open-loop system (adjusted mean 2·04% [SE 0·79, 95% CI 0·44–3·64] vs 7·06% [0·79, 5·46–8·66]; p<0·0001; table 2). The difference was also significant for the time spent with

	72-h hospital phase			6-week home phase		
	Closed loop (n=21)	Open loop (n=21)	p value (two-sided)	Closed loop (n=17)	Open loop (n=17)	p value (two-sided)
Proportion of CGM time in glucose range						
3·9–10·0 mmol/L						
Adjusted mean (SE, 95% CI)	68·73% (2·47, 63·70 to 73·75)	70·53% (2·45, 65·55 to 75·52)	0·54	66·19% (1·50, 63·11 to 69·27)	58·68% (1·49, 55·61 to 61·75)	<0·001
Median (IQR)	71·6% (58·1 to 74·9)	72·0% (66·5 to 75·4)	..	65·6% (64·2 to 67·0)	58·1% (53·1 to 63·0)	..
>10·0 mmol/L						
Adjusted mean (SE, 95% CI)	28·88% (2·49, 23·80 to 33·95)	22·28% (2·48, 17·22 to 27·35)	0·024	31·10% (1·78, 27·42 to 34·77)	36·11% (1·78, 32·44 to 39·78)	0·015
Median (IQR)	28·1% (21·8 to 41·3)	21·7% (18·0 to 25·8)	..	32·3% (29·8 to 32·7)	35·8% (29·5 to 42·0)	..
>13·9 mmol/L						
Adjusted mean (SE, 95% CI)	7·55% (1·07, 5·37 to 9·73)	5·12% (1·07, 2·94 to 7·30)	0·080	8·05% (1·10, 5·80 to 10·31)	12·95% (1·10, 10·69 to 15·20)	0·002
Median (IQR)	6·1% (4·8 to 11·1)	5·2% (4·1 to 6·3)	..	8·5% (6·2 to 10·4)	14·9% (8·0 to 15·9)	..
>16·7 mmol/L						
Adjusted mean (SE, 95% CI)	2·01% (0·45, 1·09 to 2·93)	1·13% (0·46, 0·21 to 2·06)	0·13	2·18% (0·52, 1·11 to 3·26)	4·40% (0·52, –3·33 to 5·47)	0·003
Median (IQR)	1·6% (0·3 to 3·5)	0·9% (0·0 to 1·9)	..	1·7% (1·0 to 3·3)	4·2% (2·8 to 6·1)	..
<3·9 mmol/L*						
Adjusted mean (SE, 95% CI)	2·04% (0·79, 0·44 to 3·64)	7·06% (0·79, 5·46 to 8·66)	<0·0001†	2·62% (0·54, 1·49 to 3·76)	5·24% (0·54, 4·11 to 6·38)	<0·0001
Median (IQR)	2·0% (0·8 to 2·6)	5·0% (3·1 to 9·6)	<0·001‡	2·2% (1·7 to 3·2)	4·4% (3·1 to 7·1)	..
<3·0 mmol/L						
Adjusted mean (SE, 95% CI)	0·35% (0·25, –0·15 to 0·85)	1·14% (0·25, 0·64 to 1·64)	0·030	0·57% (0·17, 0·21 to 0·94)	1·01% (0·17, 0·64 to 1·37)	0·003
Median (IQR)	0·1% (0·0 to 0·7)	0·6% (0·2 to 1·8)	..	0·4% (0·3 to 0·7)	0·7% (0·5 to 1·1)	..
Number of hypoglycaemic episodes <3·9 mmol/L (SE, 95% CI)	0·93 (0·61, –0·30 to 2·16)	5·15 (0·61, 3·92 to 6·39)	<0·0001	25·51 (5·42, 14·21 to 36·81)	48·16 (5·39, 36·91 to 59·42)	<0·0001
Mean glycaemia, mmol/L (SE, 95% CI)	8·71 (0·19, 8·33 to 9·09)	7·69 (0·19, 7·31 to 8·07)	<0·001	8·83 (0·17, 8·47 to 9·19)	9·05 (0·17, 8·69 to 9·41)	0·21
Coefficient of variation of glucose						
Adjusted mean (SE, 95% CI)	34·02 (1·14, 31·71–36·33)	39·69 (1·11, 37·42 to 41·95)	<0·001	36·35 (1·02, 34·23 to 38·46)	42·16 (1·01, 40·08 to 44·25)	<0·0001
Mean (SD)	33·8 (3·6)	39·8 (5·9)	..	36·4 (3·3)	42·2 (4·5)	..
LBGI (SE, 95% CI)	0·59 (0·16, 0·28–0·91)	1·65 (0·16, 1·33 to 1·97)	<0·0001	0·67 (0·11, 0·44 to 0·91)	1·22 (0·11, 0·98 to 1·46)	<0·0001
HBGI (SE, 95% CI)	6·48 (0·50,5·46–7·50)	4·79 (0·50, 3·77 to 5·81)	0·011	6·86 (0·47, 5·89 to 7·84)	8·43 (0·47, 7·46 to 9·41)	0·009
BGRI (SE, 95% CI)	7·12 (0·49,6·13–8·11)	6·48 (0·49, 5·49 to 7·47)	0·28	7·54 (0·42, 6·68 to 8·40)	9·65 (0·42, 8·80 to 10·51)	<0·001

BGRI=blood-glucose risk index predicting glucose variability. CGM=continuous glucose measurement. HBGI=high blood-glucose index indicating the probability of hyperglycaemia from self-monitoring blood glucose. LBGI=low blood-glucose index indicating the probability of hypoglycaemia from self-monitoring blood glucose. *Primary endpoint: one-sided statistical analysis (p one-sided) is in the intention-to-treat population for non-inferiority analysis of the primary endpoint; two-sided statistical analysis (p two-sided) is in the intention-to-treat population for superiority analysis of the secondary endpoints and the primary endpoint, on the adjusted means. †One sided. ‡Two sided.

Table 2: **Primary and secondary outcomes in the 72-h phase and 6-week home phase**

glycaemia less than 3·0 mmol/L. The number of hypoglycaemic events (<3·9 mmol/L) was significantly lower with the closed-loop system than the open-loop system (table 2).

Also during the 72-h hospital phase, mean time spent with sensor glucose within the 3·9–10·0 mmol/L range was not significantly different between the two devices (table 2). The mean time spent with sensor glucose greater than 10·0 mmol/L was significantly greater with the closed-loop system than with the open-loop system (table 2; figure 2A). No significant between-group differences were found for the mean times spent with glycaemia greater than 13·9 mmol/L (>250 mg/dL) or greater than 16·7 mmol/L (>300 mg/dL) in the 72-h hospital phase. The coefficient of variation of glucose was significantly lower with the closed-loop system than the open-loop system in the 72-h hospital phase (table 2).

Primary endpoint and secondary safety and efficacy endpoints between 2300 h and 0700 h during the hospital phase are summarised in appendix 2 (p 2). The utility endpoints (insulin daily dose) are summarised in appendix 2 (p 3).

The majority of the telephone calls from participants to nurses during the 6-week home phase in the closed-loop group occurred during the first 2 weeks: 63 (61%) of 103 calls (appendix 2 p 4). Some calls were related to the daily use of the system but could also lead to glycaemic target change or algorithm customisation during the closed-loop period under investigators' supervision.

Mean time spent with glycaemia less than 3·9 mmol/L was significantly lower with the closed-loop system than with the open-loop system during the 6-week home phase (table 2; figure 2B), as was mean time with glycaemia less than 3·0 mmol/L. The number of hypoglycaemic events (<3·9 mmol/L) was significantly smaller with the closed-loop system than with the open-loop system in the 6-week home phase (table 2).

Conversely to the 72-h phase, in the 6-week home phase, the closed-loop system was associated with a significantly longer mean time spent with glycaemia 3·9–10·0 mmol/L and with a significantly shorter mean time spent with hyperglycaemia (>10·0 mmol/L), compared with the open-loop system. Mean times spent with glycaemia greater than 13·9 mmol/L and greater than 16·7 mmol/L were also significantly shorter with the closed-loop system than the open-loop system in the 6-week home phase (table 2). The coefficient of variation of glucose was significantly lower with the closed-loop system than the open-loop system in the 6-week home phase (table 2).

The adjusted mean proportion of time with glycaemia less than 3·3 mmol/L (<60 mg/dL) during the 72-h hospital phase was significantly lower with the closed-loop system (0·74% [SE 0·45, 95% CI –0·18 to 1·65]) than with the open-loop system (2·55% [0·45, 1·64 to 3·46]; p=0·008). The adjusted mean proportion

of time with glycaemia less than 3·3 mmol/L during the hospital phase was also significantly lower with the closed-loop sytem (1·07% [SE 0·29, 95% CI 0·46 to 1·68]) than the open-loop system (2·09% [0·29, 1·48 to 2·70]; p<0·0001). No severe hypoglycaemic event in any patient was documented with either system.

Glycaemic target was reduced by the investigators from 6·1 mmol/L (110 mg/dL) to 5·6 mmol/L (100 mg/dL) in eight participants (appendix 2 p 31).

	Closed loop (n=21)	Open loop (n=21)
Proportion of time sensor data were available during the 72-h hospital phase	97·4% (5·7)	98·1% (5·4)
Proportion of time sensor data were available during the 6-week home phase (French centres only)	94·6% (4·3)	92·3% (10·2)

Data are mean (SD).

Table 3: Availability of sensor data during the hospital and home phases
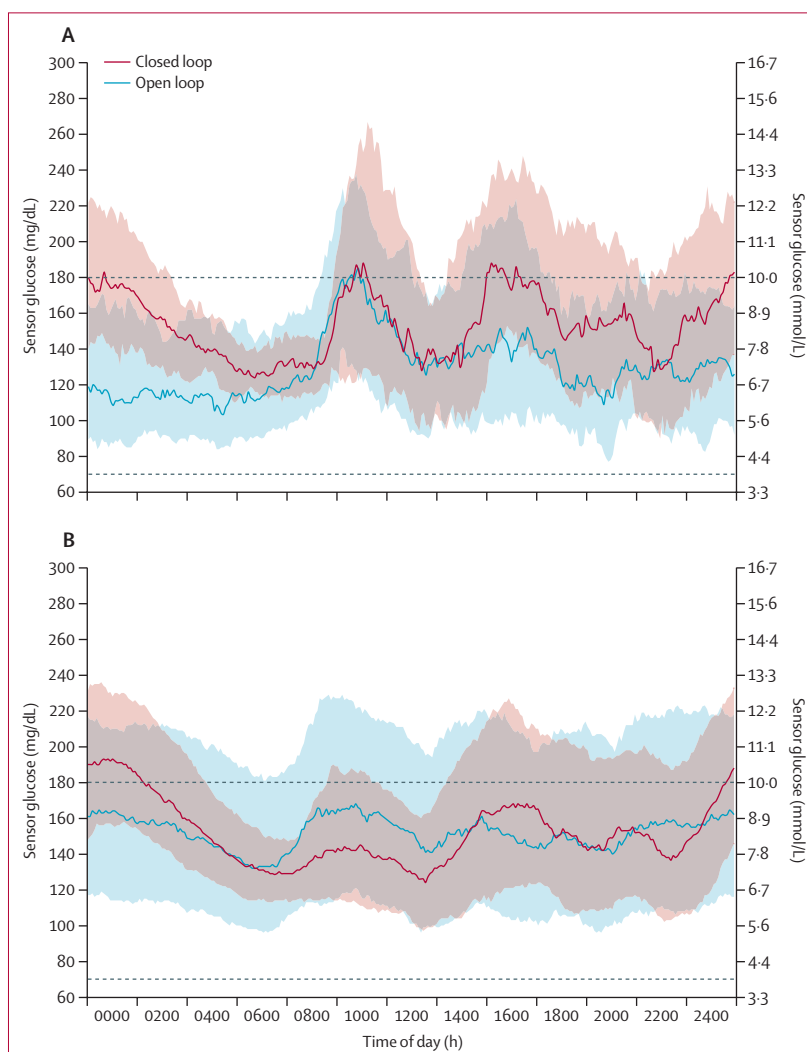
Figure 2: Mean sensor glucose per 24 h during (A) the 72-h hospital phase and (B) the 6-week home phase
Shaded areas are the 95% CI.

No severe diabetic ketoacidosis or fatal adverse events were reported with either system. Overall, there were 25 adverse events, all of which were treatment-emergent adverse events: 18 occurred with the closed-loop system (mild: eight [44%]; moderate: seven [39%]; severe: three [17%]) and seven with the open-loop system (mild: five [71%]; moderate: two [29%]). A single serious adverse event occurred, with the closed-loop system: a severe symptomatic hyperglycaemia with ketonaemia (2·9 mmol/L) related to a canula obstruction without requiring hospitalisation.

Of the 39 pump failures, 38 occurred with the closed-loop system and one with the open-loop system. We also recorded 34 DexCom-G6 CGM device failures, 27 during the closed-loop periods, three during the open-loop periods, and four between inclusion and establishment of the closed-loop or open-loop system (appendix 2 p 31).

According to the results from the Diabetes Technology Questionnaire, children had a positive opinion at baseline regarding the closed-loop device: between six (65%) and eight (89%) of nine participants agreed or strongly agreed with expecting fewer hypoglycaemic episodes; better maintenance within the target glucose range; fewer worries about their diabetes; and easier management of social life, school work, exercising, and other activities (appendix 2 pp 5–10). After using the closed-loop device, this positive opinion was maintained overall (between nine [60%] and 11 [73%] of 15 patients agreed or strongly agreed with the statements), the exceptions being the statements about fewer hypoglycaemic events, for which seven (47%) of 15 patients agreed or strongly agreed, and easier management of social life, for which eight (53%) patients agreed or strongly agreed. Parents had also very positive opinions before assessment for the same items (between eight [80%] and ten [100%] of ten parents or guardians agreed or strongly agreed overall and six [60%] to eight [80%] parents or guardians agreed or strongly agreed with the statements from the Diabetes Technology Questionnaire; appendix 2 pp 5–10). After the closed-loop assessment, parents reported feeling the treatment was flexible and easy to handle and that they had a good understanding of their child's treatment (Diabetes Treatment Satisfaction Questionnaire; appendix 2 pp 11–13).

After the study, six (50%) of 12 participants wanted to switch from their usual insulin delivery system to a hybrid closed-loop system, two (17%) did not want to switch, and eight (33%) neither agreed nor disagreed with switching. Eight (67%) of 12 parents agreed strongly or agreed to move to the closed-loop system (Acceptance Questionnaire at home phase visit 5 or 9; appendix 2 pp 16–18). The median quality of life scores from the PedsQoL were greater than 75 for children aged 8–12 years and aged 5–7 years and for parents for both devices (appendix 2 pp 24–29).

During the 72-h hospital phase across both groups, mean duration of CGM was 69·9 h (SD 2·3) using the closed-loop system and 72·4 h (4·3) using the open-loop system. During the 6-week home phase across both groups, mean duration of CGM was 40·4 days (SD 2·3) using the closed-loop system and 37·8 days (7·6) using the open-loop system. Of the available sensor data time, participants spent mean 99·3% (SD 1·0) of the time that they were assigned the closed-loop system during the 72-h hospital period on active closed loop, and mean 99·9% (0·1) of the time that they were assigned the closed-loop system during the 6-week home phase (in French centres only) on active closed loop.

Discussion

This trial is one of the first assessing a hybrid closed-loop system in an exclusively paediatric population in a short-term and long-term manner in everyday life conditions with a CGM. The DBL4K hybrid closed-loop system for prepubescent children was not inferior to an open-loop system for the primary endpoint of time spent in hypoglycaemia. The time spent in hypoglycaemia was significantly shorter with the closed-loop system than the open-loop system. Although the TIR was not significantly increased versus the open-loop system during the first days of the closed-loop system use, it became so during the 6-week home phase. The mean TIR was greater than 65% only with the closed-loop system during the home phase. The coefficient of glucose variation was significantly lower with the closed-loop system than the open-loop system. The mean time spent with blood glucose greater than 10·0 mmol/L was significantly greater with the closed-loop device than the open-loop device during the hospital phase, but not in the home phase. This study is one of few to include data on prepubescent children at home and to collect information on quality of life.[21,33]

Over the past 2 years, multiple studies have assessed various hybrid closed-loop systems. The DBL4K system produced similar improvements in metabolic targets as reported for other systems such as the Minimed 670G Hybrid closed-loop system (Medtronic, Minneapolis, MN, USA)[18,29,30] or the Tandem t:slim X2 insulin pump with Control-IQ technology (Tandem Diabetes Care, San Diego, CA, USA).[22] Findings from Breton and colleagues' study[22] in 101 randomly assigned patients showed an increased TIR during 16 weeks with a t:slim X2 insulin pump with Control-IQ technology compared with a sensor-augmented insulin pump. Forlenza and colleagues'[21] randomised trial in 6–12-year-old children using the t:slim X2 insulin pump with Control-IQ technology showed an increased TIR during 3-day home-use, with no significant difference in hypoglycaemic events or time below range (TBR) compared with sensor-augmented insulin pump therapy. Findings from a randomised trial by De Bock and colleagues[34] in participants aged 12–25 years showed an increase in TIR during 6 months with a Minimed 670G Hybrid closed-loop system versus standard therapy, with or without

CGM. Ekhlaspour and colleagues[20] did a randomised trial in children and adolescents (aged 6–18 years) during a 48 h ski camp and showed an increase in TIR without any significant increase of hypoglycaemia while on closed loop with the t:slim X2 with Control-IQ technology artificial pancreas system compared with sensor-augmented insulin pump therapy. Other studies that have included children but were not in an exclusively paediatric population have shown long-term increased TIR and decreased TBR with closed-loop systems such as the t:slim X2 with Control-IQ technology compared with sensor-augmented insulin pump therapy.

Our study in an exclusively prepubescent paediatric population also compared an open-loop system with a closed-loop system during a short period in hospital and a longer period at home. Over the home period, glucose target achievement was better with the closed-loop system than the open-loop system. With the closed-loop system, the ability to customise the settings, notably the machine reactivity to hyperglycaemia and to near-normal glycaemia, probably contributed to the better results compared with the open-loop system over the longer term. The efficacy of the closed-loop system increases over time via machine learning, thereby decreasing glycaemic variability. This increase in efficacy over time would be expected to decrease hypoglycaemic events and to increase the TIR in the long term. Another factor is the accumulation of experience with the hybrid closed-loop system by health-care workers, participants, and families. Experience of the health-care workers not only increased over time but also with the number of included participants. In this study, the effects of machine learning and the manual adjustments made to the tuneable settings of the closed-loop system are confounding. Therefore, it is not possible to confirm the positive effect of machine learning. In real life conditions in which remote monitoring is reduced, it will be possible to assess the direct effect of the machine learning algorithm on metabolic control.

HbA$_{1C}$ values were not measured because the study duration in each group was only 6 weeks and 3 days. With the closed-loop system, given the mean glycaemia and TIR, the HbA$_{1C}$ values would be expected to meet ISPAD targets.

TBR in the open-loop group during the hospital period was higher than the recommended clinical targets but was closer to the recommended value during the home phase (5·24% [95% CI 4·11–6·38]). These TBR values are similar to the ones reported with closed-loop systems in other studies and the values observed in the French paediatric population using mostly scanned continuous monitoring (78% of the paediatric population with type 1 diabetes is using scanned continuous monitoring [Boissy C, Association des Jeunes Diabétiques, France, personal communication]).

The Diabeloop device allows continuous remote monitoring via YourLoops. The handset can transmit participant data (blood glucose concentrations, insulin doses, and intercurrent events) to a dedicated health-care team via a secured website. The interface is the same for the participant and health-care team or parents, and data are provided continuously in real time. The DBLG1 system has already been implemented in 3000 adult patients. A recent study[35] using DBLG1, in which remote monitoring was only used at the caregivers' discretion, showed even better glycaemic control (TIR) during 6 months of follow-up compared with the pivotal study of DBLG1,[30] in which remote monitoring was not optional. Remote monitoring is therefore not absolutely required and metabolic control can be achieved independently from this remote monitoring. However, this remote monitoring would be expected to improve follow-up, thereby potentially increasing safety compared with other closed-loop systems and reassuring parents.

Adverse events were more common with the closed-loop system than the open-loop system, most of which involved the Kaleido pump. CGM deficiencies were also more common with the closed-loop device. During the closed-loop phase, participants had a new insulin pump (Kaleido pump), whereas during the open-loop phase they used their usual pump therapy. Requests related to new pumps and devices, and pump failures related to a lack of experience in handling new devices and pumps are usually more frequent during the first weeks when a new system is implemented, regardless of the hybrid closed-loop system.[36] Moreover, as a result of data from our study showing device deficiencies, the ViCentra Company improved its processes, which decreased the number of technical issues. Some adverse events, such as pump occlusion and others related to the device will probably decrease in the future, as the Diabeloop system can be adapted to other CGMs and pumps, notably those previously used by the participants. Moreover, the Diabeloop system was first designed for adults, and the algorithm will adapt over time to the specific characteristics of children. In adolescents, algorithm adjustments would be able to counteract the effects of missed boluses. Also, continuous machine learning should gradually diminish the blood glucose variations related to puberty and to growth hormone release during the first part of the night.

In our study, adherence to the Diabeloop closed-loop system was high, even over the 6-week home phase. However, this adherence might be due in part to selection bias, because we included participants with good metabolic control and experience in using CGM systems. Our questionnaire data indicated that the closed-loop system decreased the burden of diabetes management for the participants and parents. Participants and parents had higher expectations before the study than at the study completion, which could be partly explained by the children's reluctance to try a new therapy associated with the unavoidable increase in medical and parental supervision, despite metabolic improvement.

One limitation of this study is its sample size. This study's main objective was to establish the system's safety. It is important in the future to complete long-term follow-up on a larger scale to assess that the glycaemic control improvement remains after a 6-week period.

In conclusion, the Diabeloop hybrid closed-loop system with continuous remote monitoring and an algorithm optimised by machine learning can provide good metabolic control in prepubescent children with type 1 diabetes, under real-life conditions, while decreasing the burden of diabetes management for the participants and parents.

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