Safety and effectiveness of Do-It-Yourself Artificial Pancreas System (DIYAPS) compared with continuous subcutaneous insulin infusions (CSII) in combination with Free Style Libre (FSL) in people with Type 1 diabetes

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SHORT TITLE: Do-It-Yourself Artificial Pancreas System (DIYAPS) vs continuous subcutaneous insulin infusions (CSII) with Free Style Libre (FSL)

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Novelty statement

Previously known

Þ FreeStyle Libre and continuous subcutaneous insulin infusion (CSII) are established therapies, with robust efficacy data from control trials and the real-world. This is in contrast to unapproved do-it-yourself artificial pancreas systems (DIYAPS)

Þ Previous research demonstrated numerous benefits of DIYAPS including improved glycaemia, reduced diabetes distress, and improved quality of life

New findings

Þ This study explored the clinical benefits of DIYAPS in comparison to two conventional therapies

Potential implications

Þ This analysis utilised clinical audit data and provides some reassurance on the safety and efficacy of DIYAPS , as such it may help inform future practice

Abstract

The use of do-it-yourself artificial pancreas systems (DIYAPS) amongst people with type 1 diabetes is increasing. At present, it is unclear DIYAPS comepares to other technologies such as FreeStyle Libre (FSL) and continuous subcutaneous insulin infusion (CSII).

The aim of this analysis is to compare safety, effectiveness and quality of life outcomes of DIYAPS use with the addition of FSL to CSII.

Method: Data from two large UK hospitals were extracted from the Association of British Clinical Diabetologists (ABCD) DIYAPS and FSL audits. Outcomes included HbA1c, glucose TBR (time-below-range), TIR (time-in-range), Diabetes Distress Scores (DDS) and Gold hypoglycaemia Score. Any adverse events were noted. Changes at follow-up were assessed using paired t-tests and ANOVA in Stata; TIR/TBR at follow-up assessed using unpaired T-Tests; Chi-square tests assessed the change in frequency of health utilisation (e.g. hospital admissions).

RESULTS: DIYAPS (n=35) and FSL+CSII (n=149) users, with median follow-up duration of 1.4 (IQR 0.8-2.1) and 1.3 (IQR 0.7-1.8) years respectively, were included. HbA1c with DIYAPS use changed by -10mmol/mol [0.9%] ($p<0.001$, 95% CI 5, 14 [0.5, 1.3%]) significantly lower ($p<0.001$) than in the FSL+CSII group -3 mmol/mol [0.25%] ($p<0.001$, 95% CI 1, 4 [0.1, 0.4%]). TIR was higher and TBR was lower in the DIYAPS group. Adverse events were rare in both groups and no significant differences were observed in the frequency of healthcare utilisation.

Conclusion: DIYAPS use was associated with a lower HbA1c levels, higher TIR and lower TBR compared to FSL+CSII. There was no significant increase in adverse events, although this should be interpreted cautiously given the low numbers of users. Full results from the ABCD DIYAPS audit are awaited.

Introduction

Established in 2014, the #WeAreNotWaiting movement has been at the forefront of efforts to accelerate development of and access to novel diabetes-related technologies to improve clinical outcomes. One such development that is gaining momentum having been developed by the community is referred to as "open-sourced" or "do-it-yourself" automated delivery systems or do-it-yourself artificial pancreas systems (DIYAPS). DIYAPS is a community developed closed loop system, self-built by the user, and made up of 3 components: a continuous glucose monitor (CGM), an insulin pump and either a smartphone or microcomputer which contains the algorithm that makes decisions on optimal insulin delivery[1]. Currently, there are three available DIYAPS platforms developed: OpenAPS, AndroidAPS and Loop, each using algorithms to constantly collect and analyse an individual's glucose levels. Orders on adjustments to insulin delivery are issued to the insulin pump, taking into consideration the individualised settings and target glucose levels[2].

Proponents of such technologies have highlighted the higher level of precision that can be achieved compared to conventional therapies - with some studies reporting significant improvements in glycaemic control and the positive impact on the Quality of Life[3-5]. While commercial hybrid closed-loop systems are now available, access has been limited. Commercial closed loop systems have demonstrated improvements in both time-in-range and quality of life outcomes[6]. Evidence comparing DIYAPS to earlier versions of these commercially available alternatives are limited, but positive[7]. Additionally, because DIY systems must be self-built, they are not regulated or managed by any commercial organization, nor approved by the Food and Drug Administration (FDA) or Medicines and Healthcare Regulatory Agency (MHRA). This may present ethical or potential medico-legal dilemmas for clinicians[8].

Although DIYAPS as a whole are not regulated, the constituent parts are. For example, the efficacy of continuous subcutaneous insulin infusion (CSII) - the "insulin pump" component of the DIY system - in

reducing HbA1c and rates of severe hypoglycaemia in comparison to multiple daily insulin (MDI) injections is well recognised[9-13]. In addition to CSII, many DIYAPS use flash (intermittently scanned) CGM (isCGM) such as FreeStyle Libre (FSL). This is an alternative to conventional finger-prick testing and measures interstitial glucose concentrations[14, 15]. Previously conducted studies on the use of FSL have demonstrated reduction of time spent in hypoglycaemia, lower frequency of hypoglycaemic events and greater satisfaction[16, 17].

Given the described benefits, combining isCGM or CGM with insulin pump therapy might be expected to yield significant benefits to the user without the addition of an APS algorithm. However, to date, there has been no analysis of the effectiveness and quality of life outcomes of DIYAPS compared with FSL when used in combination with CSII (FSL+CSII). Thus the aim of this analysis is to compare the glycaemic, safety and quality of life outcomes in users of DIYAPS in comparison to users of FSL+CSII using clinician verified data from the ABCD audit tools which aim to provide real-world data on the use of DIYAPS and FSL in the UK[18, 19].

Methods

Data for this analysis were extracted from two separate audits conducted by UK ABCD on the use of DIYAPS[18] and on the use of FSL[19] in routine clinical practice. Data from two large UK hospitals – University Hospitals of Derby & Burton NHS Trust and Nottingham University Hospitals NHS Trust – were utilised. For this analysis, people with Type 1 diabetes managed with CSII , ≥18 years, who were commencing DIYAPS or FSL between 2016 and 2021 were included. In addition, included individuals were non-pregnant; with baseline and at least partial follow-up data. The use of DIYAPS was defined as the use of either AndroidAPS, Loop, or OpenAPS. Subanalysis of each algorithm was not performed due to relatively small numbers and the similarities between the DIY systems. No distinction was made between those using alternative CGM devices to FreeStyle Libre in the DIY system as numbers were few and, with the addition of a MiaoMiao reader, the FreeStyle Libre is converted into CGM with the option of alarms.

As a clinical audit, the baseline and follow-up data were captured during routine clinical practice. Baseline data prior to commencing the respective therapies included age, gender, ethnicity, duration of diabetes and the date of DIYAPS or FSL commencement. Outcomes of interest including glycaemic metrics, quality of life, healthcare utilisation and hypoglycaemia were collected at baseline and follow-up as detailed below.

The data collected through routine clinical practice for the "ABCD Nationwide DIYAPS audit" and "ABCD Nationwide FreeStyle Libre audit" programmes have Caldicott Guardian approval[20]. The NHS encourages audit of clinical practice using guidelines, which were followed for this audit. In particular, contributing centres only collect data from routine practice, and all data collected were anonymized at the point of submission to the central database.

Glycaemic metrics

Glycaemic control was assessed using glycated haemoglobin (HbA1c)[21, 22]. During follow-up clinical visits, real-time interstitial glucose data were captured. Time In Range (TIR) was defined as the percentage of glucose values between 3.9 to 10.0mmol/L; time below range (TBR) was the percentage below 3.9mmol/L[23]. Change in TIR and TBR was captured for those commencing DIYAPS and assessed using paired t-tests, but not for those using FSL (as no sensor was in place at baseline to capture this data). A comparison of TIR and TBR was performed to assess the differences between the results achieved at follow-up only given the absence of baseline data for FSL+CSII users.

Healthcare utilisation and adverse events

Frequencies of healthcare utilisations because of adverse events since the commencement of DIYAPS or FSL+CSII, were collected from patient reporting and corroborated with local hospital records. Reasons for hospital admissions or paramedic callouts recorded included: hyperglycaemia/DKA, hypoglycaemia, severe hypoglycaemia, other diabetes-related reasons (e.g. insulin over-delivery or under-delivery, worsening of retinopathy etc.) and other non-diabetes-related reasons. User's awareness of hypoglycaemia was assessed using the validated seven-point Gold Score (where 1= Always aware, 7 = Never aware) in which a score ≥4 indicate impaired awareness of hypoglycaemia (IAH)[24].

DIYAPS User Opinion on Quality of Life and Treatment Satisfaction

Diabetes distress was assessed using the Diabetes Distress Score (DDS2), a two-item questionnaire, using a six-point Likert scale (where 1 = Not a problem, 6 = A very serious problem). The questions included are DDS-1: Feeling overwhelmed by the demands of living with diabetes and DDS-2: Feeling that I am failing with my diabetes routine. For part of the analysis the DDS was converted into a categorical variable using a mean of DDS-1 and DDS-2 and defining high distress as a mean DDS ≥3.

In the DIYAPS audit, at follow-up, users were also asked to rate their opinion of treatment through two questions using a seven-point Likert scale. The two questions included were: 1) What impact would you rate DIYAPS has had on your quality of life? (1 = Extremely negative impact, 4 = No impact, 7 = Extremely positive impact); 2) Would you recommend the system to other people with diabetes? (1 = Not recommend at all, 4 = Neutral, 7 = Recommend extremely highly).

Statistical Analysis

Data analysis was performed using Stata SE16. Descriptive statistics were utilised for baseline characteristics including mean (±standard deviation), median (interquartile range) and percentages (including n/N). Comparisons between baseline characteristics were conducted using unpaired t-tests or Chi-square. Changes from baseline in HbA1c, Gold Score and DDS were assessed using paired t-tests (within groups) and ANOVA (between groups). The Chi-square test was applied for categorical variables at follow-up (hospital admissions, paramedic callouts, severe hypoglycaemia) and to assess the changes in numbers achieving recognised glycaemic targets and suffering diabetes distress (as defined using DDS) before and after treatment. Where baseline data was not available for TIR and TBR, analysis of follow-up data was conducted using unpaired t-tests. A two-tailed P value <0.05 was deemed statistically significant. DIYAPS user opinion and treatment satisfaction are reported using simple descriptive statistics.

Results

User distribution and demographics

2,943 users' data were extracted from both the audit tools as presented in **Figure 1.** 184 people with diabetes met the pre-specified inclusion criteria with baseline visit data with at least one follow-up. Of these 184, 35 individuals (18%) were on DIYAPS, versus 149 (82%) on FSL+CSII. Reasons for exclusion included age less than 18 years (n=527), not using CSII alongside FSL (n=2,150), or insufficient follow-up data (n=84). The baseline characteristics of those included are outlined in **table 1**. These are broadly the same between the groups other than weight and BMI, with the DIYAPS group weighing more at baseline than the FSL+CSII group. There was also a trend towards more DIYAPS users being male which failed to reach significance (p=0.06) but may account for some of the discrepancy in weight. Median follow-up was 1.4 (IQR 0.8-2.1) years for the DIYAPS group and 1.3 (IQR 0.7-1.8) years for FSL+CSII. Sensitivity analysis of the baseline characteristics of those excluded due to insufficient follow-up data revealed no statistically significant differences.

The changes from baseline for HbA1c, proportion achieving HbA1c≤48mmol/mol, Gold score, DDS (average) and proportion with DDS≥3 are displayed in **table 2.**

Glycaemic Outcomes

Significant reductions in HbA1c were observed at follow-up in both groups. HbA1c changed by -10mmol/mol (p<0.001, 95% CI 5, 14) [0.9%, 95% CI 0.5, 1.3] following commencement of DIYAPS compared to -3mmol/mol (p<0.001, 95% CI 1, 4) [0.25%, 95%CI 0.1, 0.4] when FSL was added to pre-existing CSII **(Figure 2).** The reduction in HbA1c was significantly greater in the DIYAPS group compared to the FSL+CSII group (ANOVA p<0.002). At follow-up, the mean percentage TIR was significantly higher in the DIYAPS group compared to FSL+CSII (73%±21 vs 53±17, p<0.001). Additionally, those using DIYAPS had significantly lower mean percentage TBR compared with CSII+FSL (2.4%±2.1 vs

5.7%±5.9, p=0.020) **(Figure 3).** The proportion of the FSL+CSII group achieving HbA1c ≤48mmol/mol (≤6.5%) increased by 4.4% and in DIYAPS by 28.5%. The proportion achieving a HbA1c≤48mmol/mol in the DIYAPS at follow-up was significantly higher than in the FSL+CSII at follow-up (p<0.010).

Healthcare Utilisations and Adverse Events

Across the population, admission events were rare, with no significant difference between groups. No admissions, paramedic call-outs of episodes of severe hypoglycaemia occurred in the DIYAPS arm. In the FSL+CSII group there were 7 admissions, 4 paramedic call-outs and 3 episodes of severe hypoglycaemia.

Significant reductions in Gold score were observed in both groups with reductions of 1.3 in the DIYAPS group (95% CI 0.0, 2.6, p=0.020) and 0.8 for the FSL+CSII group (95% CI 0.5, 1.1, p<0.001). The change in Gold Score from baseline was similar in both groups, with no statistically significant difference found.

Diabetes related distress & quality of life

The decrease in DDS (the mean of the DDS-1 and DDS-2 question) over time was significant in both the FSL+CSII group (2.4, 95% CI 2.0, 2.8 p<0.001) and the DIYAPS group (2.4, 95% CI 0.7, 4.0, p=0.01) with no difference in reduction in DDS between the groups (ANOVA p=0.97).

There was a trend towards a decrease in the number of users experiencing diabetes distress, as assessed by a mean score ≥3, following commencement of therapy in both arms but failing to reach statistical significance. The number in the DIYAPS arm fell from 78% (7/9) at baseline to 8.7% (2/23) at follow-up (p=0.540) and in the FSL+CSII group from 85% (113/133) at baseline to 28% (24/86) at follow-up (p=0.020). Changes in DDS are also displayed in **table 2.**

Responses were received from all DIYAPS users included when asked to rate the impact of system on quality of life and universally scored the impact as extremely positive (7/7) and would recommend to other people with type 1 diabetes (all responses were scored 6/7 or 7/7), although free-text data emphasised the need for support and technical capabilities to initiate the system.

Discussion

This analysis is the first to evaluate the safety, efficacy and patient reported outcomes of FSL+CSII, a conventionally approved management strategy for type 1 diabetes in comparison to DIYAPS, an unregulated, off-label novel technology developed by people with type 1 diabetes, in real-world clinical practice. HbA1c improved in both groups, although the improvement was greatest in those using DIYAPS. Those using DIYAPS were more likely to be achieve the target HbA1c. Furthermore, those using DIYAPS had greater TIR with lower TBR. This increase in TIR was equivalent to an approximate 6 hours per day and demonstrates findings similar to those reported by other observational studies, anecdotal evidence, and real-world patient stories[3-5, 26]. Gold and diabetes distress scores improved in both groups, with no significant between group differences.

We report low rates of hospital admissions, paramedic call-outs and severe hypoglycaemia for both groups, reflecting the relative safety of modern day diabetes technologies. However, this finding should be interpreted cautiously due to relatively low numbers and vigilance for adverse events related to DIYAPS will need to be maintained.

DDS scores fell across the board and there was a trend towards reductions in the number with identified diabetes distress (defined as a mean DDS≥3) in both groups, but failing to reach significance. The magnitude of the observed reductions in DDS from baseline were not significantly different between the groups suggesting similar efficacy in this regard. Individual level factors such as self-reliance and resilience amongst DIYAPS users may have account for the reductions in DDS, but perhaps more significant reductions compared to FSL+CSII alone could have been expected if these were important factors[27]. Similar improvements in diabetes distress have been reported with some commercial closed-loop systems[28].

In the DIYAPS cohort, the majority of users reported DIYAPS had an extremely positive impact on their quality of life and would highly recommend DIYAPS to other people with type 1 diabetes. These findings fit with the authors' anecdotal experience from clinical practice, with many users of DIYAPS describing the systems as 'life changing'. However, these data may be subject to healthy user bias due to the nature of the methodology, as it is self-reported and relies on the user's motivation. Again, based on clinical experience those who opt to use DIYAPS tend to be a highly motivated, technology savvy group. Users highlighted the need for technical ability and support from the wider community of users, echoing similar recently reported findings[26, 27].

Limitations

This study is limited by the nature of observational data, especially that from audit data which is collected from routine clinical data. This means that some relevant confounding factors could not be adjusted for as they are not included in the audit datasets. In addition to this, the small numbers included limits generalisability. A further limitation of this real-world dataset is missing data at follow up. Further ongoing assessment of this cohort of DIYAPS users will be warranted.

Conclusion

Within the recognised limitations of real-world data (e.g. small number, allocation bias, and non-methodically controlled data collection between and within groups), the results of this small observational analysis demonstrated that DIYAPS use among adults with type 1 diabetes was associated with a reduction in HbA1c, increased proportions achieving the HbA1c target, higher time-in-range and reduced TBR in comparison to individuals using FSL+CSII.

Both groups, DIYAPS and FSL+CSII, demonstrated improvements in diabetes distress and hypoglycaemia awareness as assessed by Gold Score. There was no evidence that DIYAPS is less safe than FSL+CSII but small numbers may have limited the detection of such events in this study and

ongoing careful monitoring is needed. Future work is needed using larger data sets and more definitive study designs to confirm these findings. Additionally, comparisons with newer technologies, in particular advanced hybrid closed-loop systems from the commercial options available, will be of interest. The quantitative analysis demonstrated the perceived positive impact DIYAPS had on people with type 1 diabetes' quality of life, with many recommending the therapy. These data provide insight into the benefits of DIYAPS relative to non-automated insulin pump therapy.

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Figure Legends

Figure 1

Flow chart showing sources of patient and reasons for exclusions

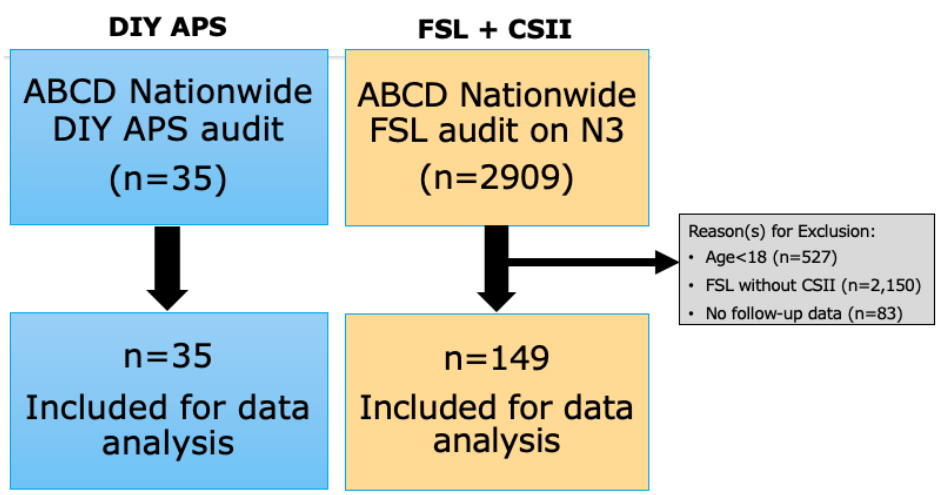

Figure 1 shows: Flowchart showing sources of patient data and reasons for exclusion

Table 1. Baseline characteristics of the cohort and of both DIYAPS and FSL+CSII subgroups. Data presented are mean±SD, median (IQR) or % (n)*

**n/N if denominator different*

Characteristic	Total n=184	DIY APS group n=35	FSL + CSII group n=149	P-Value
Age, years	46 ± 14	42 ± 10	46 ± 14	0.370
Male, %	40.2 (74)	54.3 (19)	36.9 (55)	0.060
Follow-up duration, years	1.4 (0.7-1.9)	1.4 (0.8-2.1)	1.3 (0.7-1.8)	0.860
Diabetes duration, years	25 (15-33)	25 (18-29)	25 (14-34)	0.990
Caucasian, %	94 (173)	94.3 (33)	94 (140)	0.170
HbA1c, mmol/mol	62 ± 13	60 ± 13	63 ± 13	0.250
HbA1c, %	7.8 ± 1.2	7.6 ± 1.2	7.9 ± 1.2	0.870
HbA1c≤48mmol/mol, %	11 (20/181)	9 (3/32)	11 (17)	0.740
BMI, kg/m2	27.0 ± 5.9	30.2 ± 8.5	26.7 ± 4.8	0.010
Weight, kg	79 ± 20	88 ± 24	77 ± 17	<0.010
Gold Score	2.9 ± 1.8	3.1 ± 2.0	2.9 ± 1.7	0.670
Average DDS	4.6 ± 2.0	4.7 ± 2.0	4.3 ± 1.6	0.570
DDS≥3, %	85 (120/142)	85 (7/9)	78 (113/133)	0.570
	Total n=184			

Table 2. Changes from baseline in outcomes of interest across the population as a whole and DIYAPS and FSL+CSII subgroups. Data presented are change in % (for proportions) or mean change (95% CI)

Outcomes	Total			DIY APS group			FSL+CSII group			Between groups P-value
	Change	n=	P-value	Change	n=	P-value	Change	n=	P-value	
Change in HbA1c, mmol/mol	-4 (-5, -2)	172	<0.001	-10 (-14, -5)	27	<0.001	-3 (-4, -1)	145	<0.001	<0.001
Change in HbA1c, %	-0.4 (-0.5, -0.2)	172	<0.001	-0.9 (-1.3, -0.5)	27	<0.001	-0.25 (-0.4, -0.1)	145	<0.001	<0.001
Change in proportion achieving HbA1c≤48mmol/mol, %	+8.5%		<0.001	+28.5%		0.190	+4.4%		<0.001	<0.001
Change in average DDS	-2.4 (-2.8, -2.0)	83	<0.010	-2.4 (-4.0, -0.7)	8	<0.01	-2.4 (-2.8, -2.0)	75	<0.001	0.980
Change in proportion with DDS≥3, %	-60.7%		0.140	-47.3%		0.540	-63%		0.200	0.060
Change in Gold score	-0.9 (-1.2, -0.5)	96	<0.010	-1.3 (-2.6, 0.0)	11	0.020	-0.8 (-1.1, -0.5)	85	<0.001	0.360