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ORIGINAL ARTICLE

The 'flash' adhesive study: a randomized crossover trial using an additional adhesive patch to prolong freestyle libre sensor life among youth with type 1 diabetes mellitus

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Abstract

Aims Although strategies to prevent premature sensor loss for flash glucose monitoring (FGM) systems may have substantial benefit, limited data are available. This study among youth with high-risk type 1 diabetes evaluated whether an additional adhesive patch over FGM sensors would reduce premature sensor loss frequency and not cause additional cutaneous adverse events (AEs).

Methods This is a six-month, open-label, randomized crossover trial. Participants were recruited at completion of prior 'Managing Diabetes in a Flash' randomized controlled trial and allocated to three months of Freestyle Libre FGM sensors with either standard adhesive (control) or additional adhesive patches (RockaDex, New Zealand) (intervention), before crossing over to the opposite study arm. Participants self-reported patch use or non-use, premature sensor loss and cutaneous AEs fortnightly via an electronic questionnaire.

Results Thirty-four participants were enrolled: mean age (± SD) 17.0 (± 2.2) years; mean HbA1c (± SD) 89 (± 16) mmol/mol (10.3% ± 1.4%). The response rate of questionnaires was 77% (314/408). Premature sensor loss was reported in 18% (58/314) of questionnaires: 20% (32/162) from intervention and 17% (26/152) from control ($p = 0.56$). Thirty-eight percent (118/314) of questionnaires were non-compliant to protocol allocation. However, per-protocol analysis showed similar findings. No significant difference in AEs was reported between compliant adhesive patch use and non-use (6% [5/78] and 3% [3/118], respectively, $p = 0.27$).

Conclusions The adhesive patch investigated in this study does not appear to prevent premature FGM sensor loss. However, the low risk of AEs and low cost of an adhesive patch suggest an individualized approach to their use may still be warranted. Further research is needed to explore alternative strategies to prevent sensor loss.

Keywords Adhesive patch · Adolescent · Cutaneous adverse event · Flash glucose monitoring · Type 1 diabetes · Youth

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Introduction

Continuous glucose monitoring (CGM) and flash glucose monitoring (FGM) systems for the management of type 1 diabetes mellitus (T1D) are an increasingly used alternative to traditional self-monitored capillary blood glucose (SMBG) [1, 2]. CGM and FGM systems measure interstitial glucose values and have a range of potential advantages in comparison with SMBG, including improvement in glycemic control [3, 4], especially when used consistently [5–7].

Premature sensor loss is a common experience [8–10] and contributes to negative sensor experiences, particularly when the user has self-funded the technology. Hence, the use of an additional adhesive in an attempt to improve sensor longevity is a common strategy used by patients in real life. However, there are no data available to support whether this strategy is effective. Further, sensor adhesives, particularly those containing isobornyl acrylate, have led to increasingly reported cutaneous adverse events (AEs) [11, 12]. Thus, there is concern that additional adhesives may compound this risk. While common, the emerging literature specific to FGM suggests cutaneous AEs are predominantly rated as mild [4, 9, 12–14] and rarely result in the cessation of use [3, 4, 14]. Currently, measures used to prevent and mitigate cutaneous AEs include education on good hygiene regarding site preparation and sensor insertion; barrier sprays, creams and tapes; and hydrocortisone cream [15, 16]. Newer alternatives for the management of cutaneous AEs include fluticasone spray, of which research is ongoing [17].

Although data concerning the epidemiology and prevention of AEs are expanding, literature discussing sensor duration and methods to optimize comfort and duration is limited. Previous data have suggested 7–32% of CGM sensors [8] and 24% of FGM sensors [9] end prematurely. In particular, one study found the majority of users experienced at least one episode of premature sensor loss, the majority of which were due to adhesive issues and not cutaneous AEs [9]. Furthermore, sensor duration has recently been raised as one of the key barriers to adolescent use and success with FGM [10]. Particular concerns arise among children and adolescents engaged in activities such as contact sport, physical work and even the action of changing clothes, which all present opportunities for sensor adhesive to become compromised and may contribute to reduced sensor life [14–16].

Given the substantial costs to patients and health systems of funding sensors, strategies to optimize sensor adhesion and sensor life could be of considerable benefit. Therefore, this study aimed to evaluate whether adding an additional adhesive patch to FGM sensors among youth with T1D: (1) reduces the frequency of premature sensor loss and (2) does not contribute to additional cutaneous AEs.

Methods

Participants and study design

This was a six-month, open-label, randomized crossover study. All participants, at completion of the six-month 'Managing Diabetes in a Flash' randomized controlled trial (RCT) [18], were invited to be included in this adhesive sub-study. In brief, participants were aged 13–20 years at the commencement of the RCT, with T1D duration ≥ 12 months, and high-risk glycemic control (mean pre-study HbA1c ≥ 75 mmol/mol [≥ 9%] over the previous 6 months). There were no additional inclusion or exclusion criteria for this sub-study. Participants who consented to the adhesive sub-study were randomized into two groups by an offsite biostatistician. For the first three months of this study, group one were allocated to receive the intervention phase first and were provided with a three-month supply of adhesive patches to place over the sensor. Group two were allocated to the control phase first and instructed not to use any additional adhesive products to prevent sensor loss. For the second three-month portion of this study, each group crossed over (Fig. 1).

When participants were scheduled to receive the intervention, a variety of colored RockaDex adhesive patches (https://www.rockadex.co.nz, RockaDex, New Zealand [NZ]) were provided. RockaDex adhesive patches are kinesiology tape pre-cut for the FGM sensor and do not obscure the sensor nor the hole for ventilation. The adhesive patch is made from cotton, nylon and acrylic and contains no latex, zinc oxide or isobornyl acrylate. Funding for these patches was independent of the manufacturer. Prior to the commencement of FGM, all participants were advised on good hygiene regarding site preparation and sensor insertion (as recommended by the manufacturer) to help prevent cutaneous AEs. Adhesive removal wipes and education on patch removal were provided to all participants to allow patches to be replaced if required during an ongoing FGM sensor session. Alternatively, participants were able to apply an additional RockaDex patch over top of the existing patch.

Ethics approval was granted by the Southern Health and Disability Ethics Committee (17/STH/240) and conforms to the provisions of the Declaration of Helsinki. The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618000320257p; https://www.anzctr.org.au/ACTRN12618000320257p.aspx and was issued a Universal Trial Number (U1111–1205–5784) by the World Health Organization International Clinical Trials Registry.

Data collection

Data were collected from April 2018 to November 2019. Baseline demographic and clinical data from participants

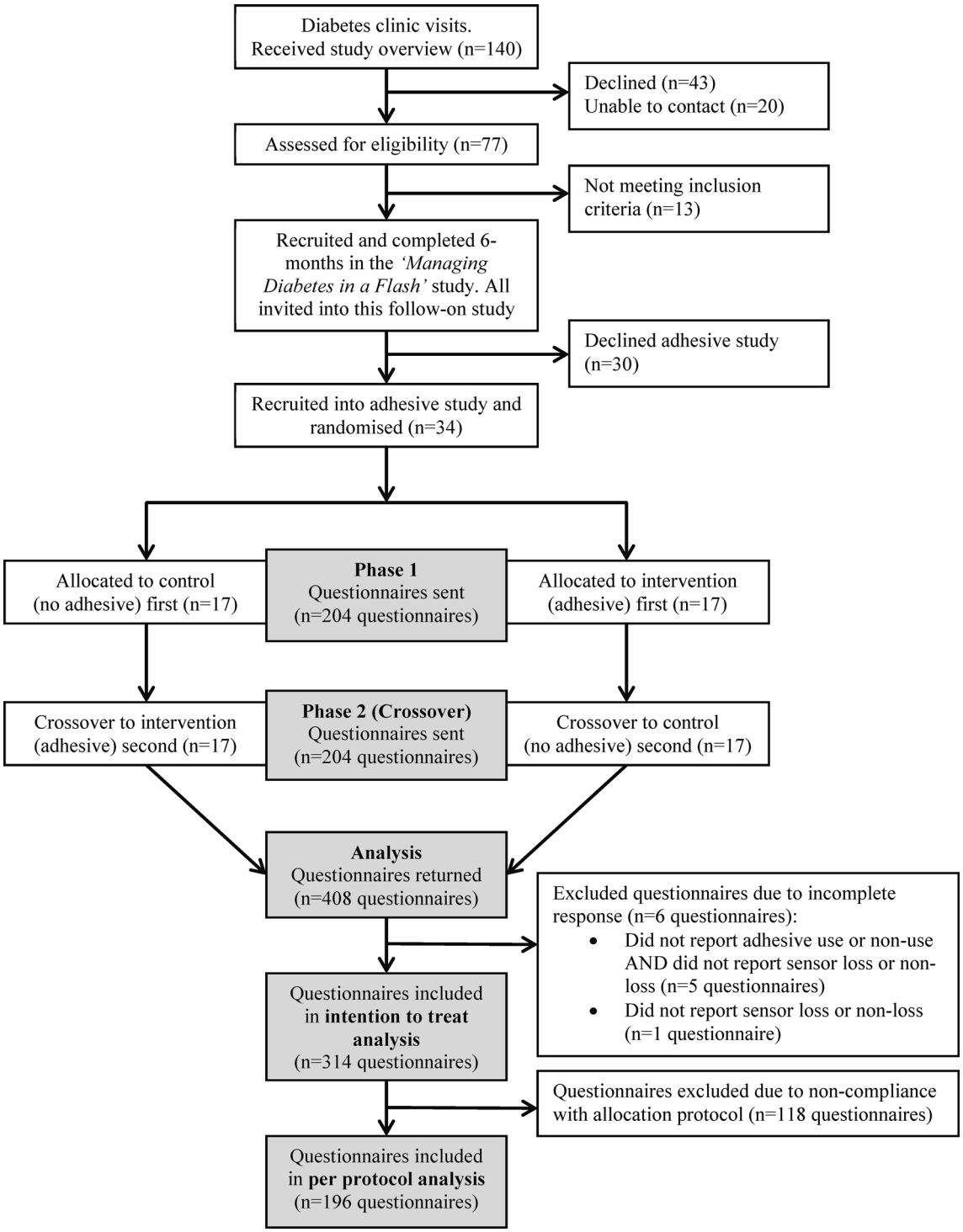

Fig. 1 Adhesive study CONSORT flow diagram; *n* represents of individuals unless otherwise stated

were collected at the start of the RCT, with the exception of age, height, weight, duration of diabetes and HbA1c data which were updated at the commencement of this sub-study (Table 1). During this sub-study, participants were sent an identical safety questionnaire every 14 days which was timed to coincide with the day each sensor change was due. Each participant received 6 questionnaires per intervention phase and 6 questionnaires per control phase, totaling 12 questionnaires over the 6-month (24-week) period. After the first three-month phase of this study, questionnaire timing was

Table 1 Participant characteristics

Variable, *n* (%)	Participants (*n* = 34)	Eligible participants who declined participation (*n* = 30)	*p* value[g]
Age (years), mean (± SD)	17.0 (2.2)	17.2 (1.89)	0.620
Male, *n* (%)[a]	20 (59)	13 (43)	0.316
Prioritized ethnicity, *n* (%)[a]			0.800
New Zealand European/European	21 (62)	16 (53)	
Māori[b]	8 (24)	8 (27)	
Pacific Islander	5 (15)	5 (17)	
Asian	0 (0)	1 (3)	
Deprivation (NZDep2013), n (%)[a]			0.252
Low deprivation (score: 1–3)	11 (32)	8 (27)	
Medium deprivation (score: 4–7)	16 (47)	10 (33)	
High deprivation (score: 8–10)	7 (21)	12 (40)	
BMI z-score[c], median (IQR)	0.81 (0.04–1.44)	0.93 (0.05–1.56)	0.783
Duration of diabetes (years), mean (± SD)	8.8 (3.6)	9.5 (3.3)	0.372
HbA1c (mmol/mol), mean (± SD)	89 (16)	89.5 (17.5)	0.988
HbA1c (%), mean (± SD)	10.3 (1.4)	10.3 (1.6)	0.965
Insulin regimen, *n* (%)[a]			1.000
MDI	29 (85)	26 (87)	
CSII	5 (15)	4 (13)	
Previous skin problem, *n* (%)[a, d]			0.255
Non-specific eczema or dermatitis	9 (26)	5 (17)	
Adhesive reaction[e]	1 (3)	0 (0)	
Other	1 (3)	1 (3)	
Current or past history of atopy[f]	13 (46)	9 (50)	1.000

[a]Data obtained from the primary study. [b]Māori are the indigenous population of New Zealand. [c]BMI z-score calculated using Centre for Disease Control Guidelines; two participants from each group unable to generate BMI z-score as over 20 years of age at the commencement of this study. [d]Previous skin problem was self-reported. [e]One participant reported a non-specific skin reaction to a surgical dressing. [f]Current or past history of atopy was self-reported and includes allergic rhinitis, asthma and atopic dermatitis; data are missing from 6 participants included in this study and 12 eligible participants who declined participation. [g]*p*-values for continuous variables were calculated using a paired t-test and *p*-values for categorical variables were calculated using Fisher's exact test

SD standard deviation, *NZDep2013* New Zealand deprivation index 2013, a marker of socioeconomic status, *BMI* body mass index, *HbA1c* glycated hemoglobin A1c, *NZ* New Zealand, *MDI* multiple daily injections, *CSII* continuous subcutaneous insulin infusion

adjusted to account for previous sensor loss and changes to the scheduled study visit time. Thus, no washout period was required between study arms. Each safety questionnaire included questions regarding use or non-use of an adhesive patch (to report adherence to the study protocol), if the participant experienced a sensor loss before the expected 14 days (loss prior to 14 days defined the primary outcome), and any FGM or adhesive patch-related cutaneous AEs the participant experienced and the corresponding severity. Information was collected electronically and managed using the survey administration tool REDCap™ (Research Electronic Data Capture) [19, 20]. Up to three contact attempts were made to non-responders. Participants were also asked to send photographs of cutaneous AEs to research staff to aid in documenting and describing AEs.

Statistical analyses

Appropriate summary statistics were calculated for all variables of interest (means and standard deviations for normally distributed continuous variables, medians with 25th and 75th percentiles for non-normally distributed continuous variables, and counts and percentages for categorical variables). A linear mixed binomial model with sensor loss (defined as loss prior to day 14) as the response variable was fitted. For the intention-to-treat analysis, the predictor of interest was patch allocation. For the per-protocol analysis, we removed all questionnaires where patch use differed from patch allocation. A model with patch use as a predictor was also used with sex, the NZ deprivation index (a measure of socioeconomic status [21]) and study phase as fixed effects,

in addition to a random intercept for each participant. The odds ratio (OR) was estimated for all coefficients, and all confidence intervals (CI) are 95%. *P*-values for continuous variables were calculated using a paired t-test, and *p*-values for categorical variables were calculated using Fisher's exact test. A *p*-value below 0.05 was considered statistically significant. Baseline demographic and clinical characteristic statistical analyses were performed using Stata® v15.1 (StataCorp LLC, TX, USA). All other statistical analyses were performed using R version 3.6.0 [22].

Results

Participant characteristics

A total of 34 of 64 participants who completed 6 months of the *'Managing Diabetes in a Flash'* trial were recruited into this study. There were 17 participants randomized to receive the adhesive patches first, and 17 were randomized to the control group, before crossing over after 3 months. Baseline demographic and clinical data are summarized in Table 1. There were no statistical differences between participants who participated in this study and those who declined. Among the individuals who participated in this study, 21% (7/34) self-reported a previous non-sensor related skin reaction or issue, with one participant reporting a non-specific skin reaction to a surgical dressing. Additionally, 46% (13/28) study participants reported a previous history of atopy (allergic rhinitis, asthma and/or atopic dermatitis).

Intention-to-treat analysis

The response rate of completed questionnaires was 77% (314/408). There was no significant difference in response rate between the first three-month phase and the crossover phase of this study. Overall, premature sensor loss (loss prior to day 14) was reported in 18% (58/314) of questionnaires, involving 62% (21/34) of participants. Twelve percent (4/34) of participant's experienced 1 premature sensor loss, 35% (12/34) participants experienced 2–3 premature sensor losses and 15% (5/34) participants experienced ≥ 4 premature sensor losses. Regardless of allocation, among participants that reported sensor loss, 50% (11/22) participants had the same proportion of premature sensor loss with and without patch use, 27% (6/22) participants had a higher proportion of premature sensor loss with patch use, and 23% (5/22) participants had a lower proportion of premature sensor loss with patch use compared to no patch.

Sensor loss was reported in 17% (26/152) of questionnaires from participants allocated to control and 20% (32/162) of questionnaires from participants allocated to intervention (OR = 1.20, CI = 0.65–2.21, $p = 0.56$) (Table 2, Fig. 2). With regard to actual use of the adhesive patch, regardless of allocation, 21% (23/112) of questionnaires that used a patch reported sensor loss, whereas 17% (35/202) of questionnaires which did not use the patch reported sensor loss. There was no significant difference in sensor loss between these two groups (OR = 1.23, CI = 0.65–2.30, $p = 0.54$). The linear mixed model showed the unadjusted estimate of the odds ratio for patch loss, under intention to treat, was 1.28 (CI = 0.66–2.47, $p = 0.46$). Similarly, when adjusted for sex, NZ deprivation and study phase, this was also not significant (OR = 1.04, CI = 0.31–3.45, $p = 0.26$), nor if patch use (rather than allocation) was the predictor (OR = 1.04, CI = 0.32–3.43, $p = 0.79$).

Per-protocol analysis

Overall, 38% (118/314) questionnaires were non-compliant to the allocation of use or non-use of an adhesive patch. 22% (34/152) of questionnaires of participants allocated to control reported using a patch. Comparatively, 52% (84/162) of questionnaires from participants allocated to the intervention did not use the adhesive patch.

A per-protocol analysis was therefore completed, with all questionnaires that were non-compliant with allocation and adhesive use or non-use excluded, leaving 196 questionnaires available for analysis. Premature sensor loss was reported in 15% (18/118) of questionnaires compliant with no adhesive patch use and 19% (15/78) of questionnaires compliant with the adhesive patch use (OR = 1.49, CI = 0.60–3.75, $p = 0.38$) (Table 2, Fig. 2). When controlled for sex, deprivation and study phase, this comparison was also not significant (OR = 1.49, CI = 0.48–4.62, $p = 0.26$).

Table 2 Comparison of premature sensor loss and cutaneous adverse event reports

Analysis	Variable	Questionnaires from no patch group, *n* (%)	Questionnaires from patch group, *n* (%)	*p* value[a]
Intention to treat	Premature sensor loss	26/152 (17)	32/162 (20)	0.56
	Cutaneous adverse event	10/152 (7)	9/162 (6)	0.81
Per protocol	Premature sensor loss	18/118 (15)	15/78 (19)	0.38
	Cutaneous adverse event	3/118 (3)	5/78 (6)	0.27

[a]*p*-values calculated using Fisher's exact test

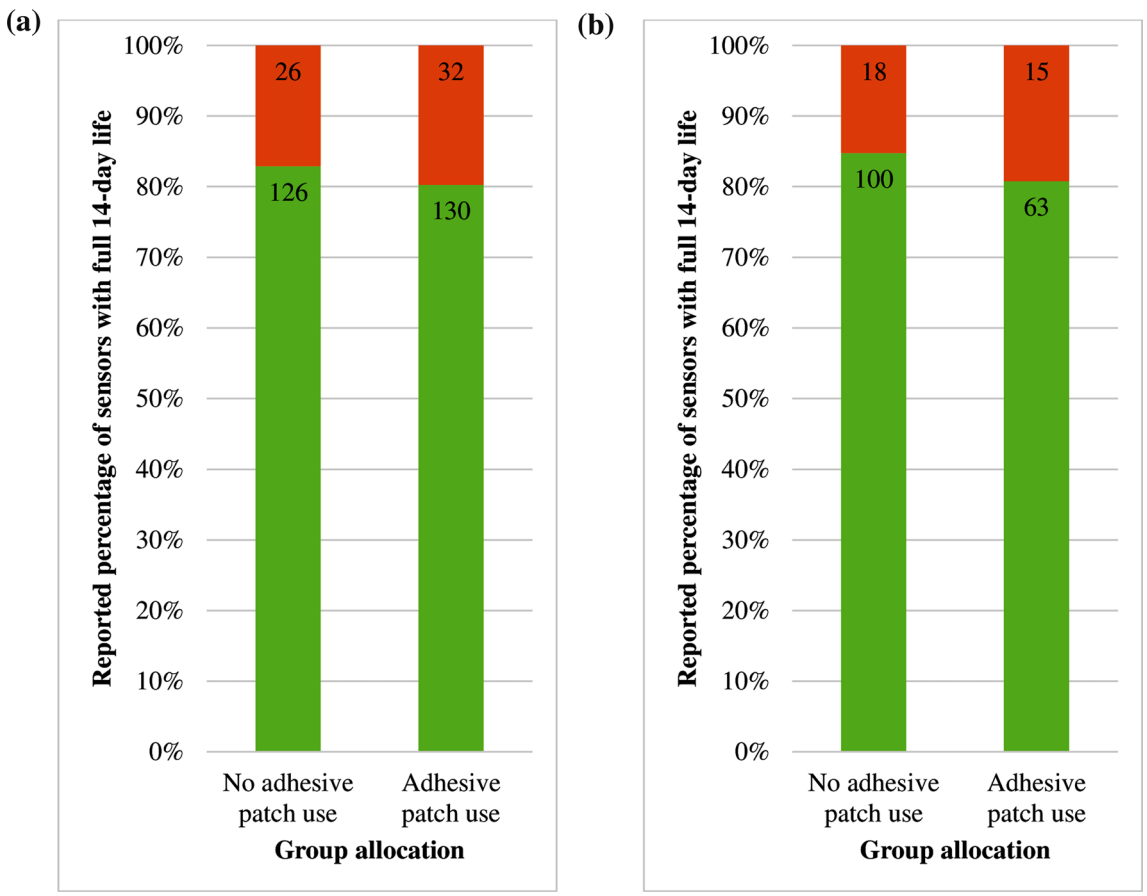

Fig. 2 Reported sensor longevity by intervention group: **a** intention-to-treat analysis (comprised of all completed questionnaires); **b** per-protocol analysis (comprised of completed questionnaires compliant with patch allocation); green represents sensors with full 14-day sensor life; orange presents sensor loss prior to day 14

Cutaneous adverse events

Overall, there were 19 cutaneous AEs, involving 26% (9/34) participants. One cutaneous AE was reported for every 33 weeks of use. With regard to severity, 58% (11/19) reports of cutaneous AEs were rated as mild, 42% (8/19) were rated as moderate, and no AEs were rated as severe. There was no significant difference between reports of cutaneous AEs between the control and intervention group (7% [10/152] and 6% [9/162], respectively, $p = 0.81$) nor for the per-protocol analysis between the control and intervention group allocation when participants reported being compliant (3% [3/118] and 6% [5/78], respectively, $p = 0.27$).

Discussion

While simple in design, this is the first randomized crossover trial to evaluate if FGM sensor life can be prolonged by adding an additional adhesive patch. The main finding is that there is no difference in rate of premature sensor loss before the expected 14-day sensor session life, whether or not an adhesive patch is used. Overall premature sensor loss was reported in 18% of sensor sessions. In addition, minimal cutaneous AEs were experienced by both groups, suggesting the use of additional adhesive patches is not harmful and does not appear to contribute to the burden of cutaneous AEs.

Premature sensor loss is an important issue, occurring in approximately 7–32% of CGM use among adults [8] and 24% of FGM sensors among youth [9]. Importantly, one observational study found when all FGM sensors are secured by an additional plaster, premature sensor loss was numerically lower and occurred in 20% of sensors [23]. As sensors are a considerable cost to health care, a simple cheap patch (approximately 1 USD) is an attractive concept to prolong sensor life. Although the overall percentage of FGM sensors which ended prematurely in this study was lower compared to previous studies [9, 23], data from this study were not supportive of routine use of the adhesive patches investigated. However, this study found that at an individual level, 23% of people may have experienced the benefit of

fewer reported premature sensor with patch use, compared to no patch use, suggesting that it remains possible there is a cost–benefit for certain individuals.

Importantly, cutaneous AEs, common among FGM use [4, 9, 12–14], were minimal and similar between groups in this study. Notably, the rate of AEs in this study was lower, at a rate of 1 cutaneous AE per 33 weeks of FGM use, compared to a recent study which reported a rate of 1 cutaneous AE per 18 weeks of FGM use [9]. Previous studies have shown isobornyl acrylate present in the adhesive component of the sensor [11] has been identified as the probable cause for some FGM-associated cutaneous AEs [11, 14, 24–26]. Thus, given there is a clear need for measures to prevent premature sensor loss, consideration regarding skin safety for patches with additional adhesives is important. The RockaDex adhesive patches used in this study do not contain isobornyl acrylate which may provide a possible reason why an increase in cutaneous AEs was not associated with patch use. In addition, study participants were actively managed by research staff and recommendations for the prevention and management of cutaneous AEs, which could also suggest a reason for the minimal AEs reported. However, it is possible if participants experienced a FGM-associated AE, they chose not to use or continue to use an adhesive patch when allocated.

The key strength of this study is data collected from an independent, non-industry-sponsored randomized crossover trial, with a systematic methodology and approach to data collection. The adjustment of questionnaire timing prior to crossover enabled previous sensor loss to be accounted for and ensured questionnaires were both timed to coincide with each 14-day sensor and consistent throughout the trial. The novel comparison between the use of an additional patch compared with no additional measures to prolong sensor life is also important.

However, as this study focused on a small group of youth from a wider study with high-risk glycemic control, and a specific patch type, the generalizability of these findings remains unclear. This study's relatively small sample size is a limitation, given the study was powered based on the original primary RCT outcome. Given this, the possibility for a type II error for this sub-study remains possible. Past studies have also found youth have reduced adherence to T1D management [27, 28], including misreporting of SMBG [29, 30]. As premature sensor loss and RockaDex patch use data were self-reported by participants, it is possible that participants falsely reported sensor loss or patch use. This could suggest why similar rates of sensor loss were reported with and without patch use and the non-adherence seen. Despite this, it is reassuring that the premature sensor loss rate was not higher than the general population of FGM users. In addition, the exact duration in days of each sensor was not collected in this trial which is a weakness. Thus, it is possible that the use of an additional adhesive patch prolonged sensor life, but not for the entire 14-day period. Moreover, as this study only focused on one brand of adhesive patches, further research regarding the effect of other patches or cohesive tape, a product that is wrapped around the arm to secure the sensor, is needed.

In conclusion, this randomized crossover trial provides no evidence that an additional adhesive patch has any significant advantage for the prevention of premature FGM sensor loss compared to no additional adhesive. Importantly, this study also found the use of a RockaDex adhesive patch did not contribute to additional cutaneous AEs. Ultimately, while the results of this trial do not contribute to support for routine patch use, given their low risk and cost, with some possible benefits in some individuals, an individualized approach to their use is still warranted.

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Compliance with ethical standards

Conflicts of interest The authors declare no conflicts of interest.

Ethics approval Ethics approval was granted by the Southern Health and Disability Ethics Committee (17/STH/240) and conforms to the provisions of the Declaration of Helsinki. The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618000320257p; https://www.anzctr.org.au/ACTRN12618000320257p.aspx and was issued a Universal Trial Number (U1111-1205-5784) by the World Health Organization International Clinical Trials Registry.

Informed consent Informed consent was obtained from all participants for inclusion in the study.

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