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Clinical outcomes with MiniMed™ 780G Advanced Hybrid Closed Loop Therapy in 2- to 6-year-old children with Type 1 diabetes

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Abstract

Advanced hybrid closed loop (AHCL) therapy with the Medtronic MiniMed™ 780G system improves glycemia, however the clinical outcomes in younger children remain less established. This pilot study aimed to explore the CGM metrics while on AHCL in very young children. Children between two and seven years of age and on insulin pump therapy were recruited. A 2-week phase in Manual Mode was followed by a 6-week AHCL phase. CGM metrics were analyzed to review glycemic outcomes. Out of 11 participants enrolled [mean (SD) age 5.3 (0.8) years), 10 completed the study. Time in closed loop was 96.7 (3.9)%. In AHCL, participants had a mean (SD) time in range of 72.6 (7.4)% and spent 3.0 (1.74)% and 0.63 (0.46)% in time < 70 mg/dl and < 54 mg/dl respectively . AHCL is a feasible option for management of young children with type 1 diabetes.

INTRODUCTION

The management of type 1 diabetes in young children presents a combination of challenges to parents/caregivers and to health care professionals. Achieving healthy glycaemia is a challenge given the unpredictable eating, activity and behaviour patterns, small insulin doses and the organization required to manage diabetes in young children which place a considerable burden on parents [1] The fear of nocturnal hypoglycemia is common in parents[2], known to increase anxiety, impact sleep and their overall well-being. To avoid hypoglycemia, maladaptive behaviours may emerge which lead to hyperglycemia with resultant impact on glycemic management. Not surprisingly, they are known to spend a substantial amount of their time in hyperglycemia while on insulin injections/pumps[3].It is also known that the early age of diagnosis also increases the risk of diabetes-related complications[4]. Hence it is vital to explore strategies that can increase time in target glucose range in this young age group.

Although advanced hybrid closed loop (AHCL) therapy is proposed as standard care for children with type 1 diabetes[5], the availability of these devices in younger children remains limited with most systems approved for use with age and total daily insulin limits. The Medtronic Minimed™ 780G insulin pump is currently not approved for children under the age of seven years and the use of the pump in the younger age is largely restricted to off-label use. The AHCL algorithm in this system has a choice of glucose targets, an automated correction bolus up to every 5-minutes, and an improved user interface with Bluetooth connectivity which permits remote monitoring.[6] As the AHCL system has been shown to be beneficial in improving glycemic outcomes in children and adults in clinical trials[7,8] and real-world studies[9], there is a focus in reviewing these outcomes in young children who have been previously excluded from these trials due to their young age. Hence, this study aimed to explore the clinical outcomes following the commencement of AHCL with 780G insulin pump. The study sought to explore the clinical outcomes and experiences while using AHCL.

MATERIALS AND METHODS

This was a prospective single-arm observational study conducted in an outpatient setting in Perth, Australia. Ethics approval was received for the study (RGS0000003688). Written informed parental consent was obtained for all participants. The study recruited children aged between two and seven years of age, with type 1 diabetes diagnosed for at least > 12 months, utilising insulin pump therapy and continuous glucose monitoring (CGM) systems for at least three months with total daily insulin requirement of ≥ eight units/day for the last two weeks, willing to perform the prerequisite finger prick blood glucose measurements for the study period and living in an area with internet and cellular coverage. Participants on any other automated insulin delivery systems were excluded from the study.

Participants had a 2-week run-in phase (±1 week) during which participants used the 780G system in Manual Mode followed by 6-weeks (±1 week) of AHCL. A minimum 7-day run-in period was required to collect baseline glycemic data[10]. During this period, all participants utilised 'Suspend before/on low' features and no adjustments were made to the pump settings. With commencement of AHCL, the target glucose was set at 6.7 mmol/l (120 mg/dl) and the active insulin time was set at 4 hours at the start of the study. Families were advised to follow general recommendation of pre-meal insulin bolus, with insulin administered at or just after meals for fussy eaters. However, if there was a delay in insulin bolus following meal, caregivers were advised to enter only 50% of the carbohydrates consumed if insulin bolus was after half an hour of meal consumption or to administer a correction dose if more than an hour later.

CGM metrics for all participants were reviewed on a weekly basis (video or phone call) and modifiable pump settings (Target glucose, Insulin Carbohydrate Ratio (ICR), Active insulin time (AIT)) were adjusted as required. For safety purposes, all participants were followed in real-time during the entire study duration by the research nurse (diabetes educator) via the CareLink™ Connect app (Medtronic).

Outcomes measured included CGM metrics according to the international recommendations[11]. Safety endpoints included serious adverse events which included severe hypoglycemia and diabetic ketoacidosis events. Clinical and glycemic data are reported using descriptive statistics expressed as mean (SD) and/or median (IQR).

RESULTS

11 participants [73% female, mean (SD) age 5.3 (0.8) years, diabetes duration 3.3 (0.7) years, pump therapy 3.0 (0.8) years, total daily insulin 17.2 (4.7) units/day, HbA1c 7.1 (0.5)%, CGM use 92 (13)%, Time in range 58.1 (14.1)%] were enrolled in the study. Children were previously on Medtronic pumps [MiniMed™ 640G (n=7), 670G (n=1), 770G (n=1), 780G (n=1)] and Omnipod (n=1). Eight participants were on Dexcom G6 with three on Guardian™ sensor 3 (GS3) utilising suspend before low feature. The mean (SD) run-in period was 11.4 (4.6) days. One participant was withdrawn from the study by the investigator after three weeks of being in AHCL due to concerns of high levels of variability in diabetes management which could potentially increase the risk of hypoglycemia. Ten participants continued to use the device for the 6-week study period.

Mean (SD) CGM use and percent time in closed loop was 94.4 (4.7)% and 96.7 (3.9)% respectively. The mean (SD) time in range (TIR) 70-180 mg/dl was 64.9 (10.4)% in Manual Mode and 72.6 (7.4)%in AHCL. Likewise, time in tight range 70 – 140 mg/dl was 41.7 (10.4)% in Manual Mode and 51.4 (7.2)% in AHCL. Participants spent 3.0 (1.74) and 0.63 (0.46)% of the time < 70 mg/dl and < 54 mg/dl of respectively in AHCL. Glycaemic variability as measured by Coefficient of variation was 37.1 (6.1)% and 37.6 (5.4)% in Manual Mode and AHCL respectively. Table shows the CGM metrics in Manual Mode and AHCL in each week.

All participants stayed on the target glucose of 6.7 mmol/l (120 mg/dl) during the 6-week study. AIT was reduced from 4 hours to 2.3 hours in five participants, 2.45 hours in four participants and remained at 4 hours in one participant. At study entry, the mean (SD) ICR at breakfast, lunch and dinner were 13.6 (3.6), 17 (4.7) and 14.5 (3.4) respectively. During the study, ICR was strengthened to optimize glucose levels. At six weeks, the mean (SD) ICR at breakfast, lunch and dinner were 11 (2), 14 (5) and 12 (2).

. Eight of the ten participants upgraded to the 780G AHCL following the study with approval of their clinical teams for off-label continued use. While one participant was not due for their pump upgrade, another participant reverted to Dexcom G6 sensor as they preferred calibration-free sensor and did not trust the algorithm.

There were no episodes of severe hypoglycemia or diabetic ketoacidosis. There was one hospital admission for gastroenteritis with poor fluid intake and vomiting which

required treatment with parental fluids. Participant remained in AHCL during admission, according to the discretion of the treating clinician.

DISCUSSION

This feasibility study demonstrated the clinical outcomes from a 6-week use of 780G AHCL in very young children with type 1 diabetes. The study contributes to the growing interest in the use of closed loop therapy in this vulnerable age group. The recognition of improved safety of these devices in older children have led clinicians and researchers to trial and use these closed loop systems in young children. There have been early reports of safety and efficacy with the first-generation algorithm in the 670G in very young children.[12,13] AHCL in this age group with the 780G was investigated in a 12-week prospective Finnish study in 35 children which reported the system to be safe with improvements in glycemic control.[14] Time in range had improved from 58% at baseline to 66.6% at 12 weeks with reduction in hyperglycemia and no increase in hypoglycemia. More recently, the performance of the 780G system in 12 children was reported in a retrospective study in which families had chosen to use the system.[15] In our study, the mean TIR was 58% at enrolment and 64.9% in Manual Mode highlighting the Hawthorne effect in a research study[16]. Overall TIR was 72.6% in AHCL, meeting the recommended target goal. The increase in TIR was immediate and maintained throughout the 6-week AHCL period. Time spent in hypoglycemia also remained within the clinical recommended acceptable cut-offs. The results of our study align with the previous studies and highlight the glycemic outcomes with AHCL in very young children with type 1 diabetes. The cohort represents a group of early adopters of technology utilising pump and CGM optimally in the daily care of their child. Post study, families collaborated with their clinical team to upgrade their pumps to enable off-label use of AHCL.

Weaker settings for AIT were used at the time of AHCL commencement in our study. This was subsequently strengthened during the study period to improve TIR without increase in time spent in hypoglycemia. Active insulin time was reduced from 4 hours to 2.5 to 2.75 hours in most children and the target glucose was maintained at 6.7 mmol/l (~120 mg/dl). CHO ratios were strengthened, guided by the post-prandial glucose levels. Temporary target of 8.3 mmol/l (~150 mg/dl) was also advised for young children, especially with low TDI, to reduce the risk of hypoglycemia with re-siting of pump cannula. Setting

expectations at the start and goals of achieving TIR closer to 70% should be discussed and is a key step in commencing and maintaining AHCL therapy.

The system used the GS3 which required finger-prick blood glucose readings for calibration and for maintenance in closed loop. Our cohort was predominantly on Dexcom G6 prior to commencing the study and hence finger-pricks were seen as an added burden during the study period. The availability of the Guardian™ 4 sensor with no requirement for calibrations makes the system more favourable and suitable to younger children.

Safety and performance of different algorithms have increasingly been studied in the younger population. The CamAPS system is approved in UK, EU and Australia for children above one year of age and more than five units of total daily insulin following the establishment of its safety and efficacy in a 16-week period of a cross-over RCT in children between one and seven years of age with a mean adjusted increase in TIR of 8.7 percentage points between control and intervention groups.[17] More recently, the PEDAP trial investigated the safety and efficacy of the CONTROL IQ system in young children between two and six years of age and reported an increase in TIR by 12.5 percentage points in a 13-week RCT.[18] The Omnipod 5 Automated Insulin Delivery System also increased TIR by 10.9% in a single-arm 13-week study in this age group.[19] The various algorithms studied in this age group will provide increased options for families to tailor their choice according to their needs.

The limitations of this study include the small numbers, the short duration single-arm study with the lack of a control group and participant-reported outcomes. Weekly contact with the research nurse with adjustments to pump settings could potentially influence the reported clinical outcomes. Nevertheless, the strength of the study is in its ability to provide guidance to health care professionals around the feasibility to use the device in this age-group in clinical care. In conclusion, MiniMed™ 780G AHCL is a feasible therapeutic option for management of young children with type 1 diabetes.

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AUTHOR CONTRIBUTIONS

MA contributed to the study design, supervised the study, collected data, conducted analysis and wrote the manuscript. JD conducted the research visits, recorded data, followed participants in real-time and reviewed the manuscript. GS provided statistical input. ED and TJ contributed to the study design and reviewed the manuscript. TJ is the guarantor of this work and had access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

CONFLICT OF INTEREST

Nil

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ETHICS STATEMENT

Ethics approval was received for the study (RGS0000003688). Written informed parental consent was obtained for all participants.

REFERENCES

1. Chetty T SF, Browne-Cooper K, Davis E. Young Children with Type 1 diabetes. Australian Diabetes Educator 2018;21(1):1-8

2. Van Name MA, Hilliard ME, Boyle CT, et al. Nighttime is the worst time: Parental fear of hypoglycemia in young children with type 1 diabetes. Pediatric diabetes 2017, doi:10.1111/pedi.12525

3. DiMeglio LA, Kanapka LG, DeSalvo DJ, et al. Time spent outside of target glucose range for young children with type 1 diabetes: a continuous glucose monitor study. Diabetic medicine : a journal of the British Diabetic Association 2020;37(8):1308-1315, doi:10.1111/dme.14276

4. Mauras N, Buckingham B, White NH, et al. Impact of Type 1 Diabetes in the Developing Brain in Children: A Longitudinal Study. Diabetes care 2021;44(4):983-992, doi:10.2337/dc20-2125

5. Sherr JL, Schoelwer M, Dos Santos TJ, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Diabetes technologies: Insulin delivery. Pediatric diabetes 2022;23(8):1406-1431, doi:10.1111/pedi.13421

6. McVean J, Miller J. MiniMed(TM)780G Insulin pump system with smartphone connectivity for the treatment of type 1 diabetes: overview of its safety and efficacy. Expert Rev Med Devices 2021;18(6):499-504, doi:10.1080/17434440.2021.1926984

7. Bergenstal RM, Nimri R, Beck RW, et al. A comparison of two hybrid closed-loop systems in adolescents and young adults with type 1 diabetes (FLAIR): a multicentre, randomised, crossover trial. Lancet 2021;397(10270):208-219, doi:10.1016/s0140-6736(20)32514-9

8. Collyns OJ, Meier RA, Betts ZL, et al. Improved Glycemic Outcomes With Medtronic MiniMed Advanced Hybrid Closed-Loop Delivery: Results From a Randomized Crossover Trial Comparing Automated Insulin Delivery With Predictive Low Glucose Suspend in People With Type 1 Diabetes. Diabetes care 2021;44(4):969-975, doi:10.2337/dc20-2250

9. Arrieta A, Battelino T, Scaramuzza AE, et al. Comparison of MiniMed 780G system performance in users aged younger and older than 15 years: Evidence from 12 870 real-world users. Diabetes, obesity & metabolism 2022;24(7):1370-1379, doi:10.1111/dom.14714

10. Smith GJ, Abraham MB, de Bock M, et al. Impact of Missing Data on the Accuracy of Glucose Metrics from Continuous Glucose Monitoring Assessed Over a 2-Week Period. Diabetes technology & therapeutics 2023;25(5):356-362, doi:10.1089/dia.2022.0101

11. Battelino T, Danne T, Bergenstal RM, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes care 2019;42(8):1593-1603, doi:10.2337/dci19-0028

12. Forlenza GP, Pinhas-Hamiel O, Liljenquist DR, et al. Safety Evaluation of the MiniMed 670G System in Children 7-13 Years of Age with Type 1 Diabetes. Diabetes technology & therapeutics 2019;21(1):11-19, doi:10.1089/dia.2018.0264

13. Salehi P, Roberts AJ, Kim GJ. Efficacy and Safety of Real Life Usage of MiniMed 670G Automode in Children with Type 1 Diabetes Less than 7 Years Old. Diabetes technology & therapeutics 2019, doi:10.1089/dia.2019.0123

14. Pulkkinen MA, Varimo TJ, Hakonen ET, et al. MiniMed 780G™ in 2- to 6-Year-Old Children: Safety and Clinical Outcomes After the First 12 Weeks. Diabetes technology & therapeutics 2023;25(2):100-107, doi:10.1089/dia.2022.0313

15. Tornese G, Carletti C, Lanzetta MA, et al. Safety of Real-life Usage of Advanced Hybrid Closed-Loop System MiniMed 780G in Children With Type 1 Diabetes Younger Than 7 Years Old. Diabetes care 2023;46(6):e123-e125, doi:10.2337/dc22-2046

16. Abraham MB, Nicholas JA, Crone M, et al. The Importance of the Hawthorne Effect on Psychological Outcomes Unveiled in a Randomized Controlled Trial of Diabetes Technology. Journal of diabetes science and technology 2018;12(3):735-736, doi:10.1177/1932296817747293

17. Ware J, Allen JM, Boughton CK, et al. Randomized Trial of Closed-Loop Control in Very Young Children with Type 1 Diabetes. The New England journal of medicine 2022;386(3):209-219, doi:10.1056/NEJMoa2111673

18. Wadwa RP, Reed ZW, Buckingham BA, et al. Trial of Hybrid Closed-Loop Control in Young Children with Type 1 Diabetes. The New England journal of medicine 2023;388(11):991-1001, doi:10.1056/NEJMoa2210834

19. Sherr JL, Bode BW, Forlenza GP, et al. Safety and Glycemic Outcomes With a Tubeless Automated Insulin Delivery System in Very Young Children With Type 1 Diabetes: A Single-Arm Multicenter Clinical Trial. Diabetes care 2022;45(8):1907-1910, doi:10.2337/dc21-2359

Table 1: Glycemic outcomes following commencement of AHCL.

	Manual Mode	**AHCL**							
	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Overall	
n	11	11	11	11	10	10	10		
%Time 70-180 mg/dl Mean (SD)	64.9 (10.4)	72.0 (9.7)	72.3 (12.9)	73.2 (7.1)	71.6 (7.7)	74.7 (12.2)	69.7 (6.0)	72.6 (7.4)	
Median (IQR)	61.8 (15.4)	72.2 (17.6)	76.9(18.6)	71.7(7.9)	71.8(11.4)	77.3(13.9)	68.8(5.6)	75(11.8)	
%Time 70-140 mg/dl Mean(SD)	41.7 (10.4)	51.0 (8.5)	51.7 (12.8)	53.2 (6.4)	49.9 (7.6)	54.6 (12.8)	47 (5.9)	51.4 (7.2)	
Median (IQR)	39.8 (13.6)	49.8 (13.8)	55.8 (17.2)	52.6 (7.3)	52.7 (13.4)	58.9 (17.0)	49.9 (9.9)	52.9 (10)	
%Time >180 mg/dl Mean(SD)	32.3 (10.1)	24.2 (10.1)	25.0 (12.7)	23.5 (6.6)	25.6 (7.7)	21.8 (12.4)	27.2 (6.6)	24.4 (7.2)	
Median (IQR)	31.7 (15.2)	26.1 (14.2)	19.9(14.0)	23.4(8.3)	23.7(9.9)	17.9(14.8)	25.9(7.4)	22.1(10.5)	
%Time >250 mg/dl Mean(SD)	9.12(4.60)	5.50 (4.82)	6.82 (6.57)	6.45(4.27)	6.72 (4.26)	5.63 (5.90)	6.13(4.30)	6.19(4.18)	
Median (IQR)	10.09(3.75	5.86(7.59)	4.15(6.20)	6.13(3.17)	5.95(6.71)	3.19(5.16)	5.19(3.19)	5.49(5.04)	
%Time >300 mg/dl Mean(SD)	2.24(2.11)	1.35 (1.82)	2.25(2.88)	2.05(1.85)	1.79 (1.67)	1.54 (2.38)	1.74(2.60)	1.79(1.74)	

Median (IQR)		1.91(1.27)	0.61(1.82)	1.01(3.29)	1.50(2.01)	1.59(3.02)	0.56(1.50)	0.98(1.26)	1.61(1.94)	
%Time <70 mg/dl	Mean(SD)	2.81 (2.16)	3.83 (2.83)	2.70 (1.73)	3.36(2.79)	2.73 (2.10)	3.46(2.22)	3.05(2.84)	3.0 (1.74)	
Median (IQR)		1.91(3.18)	3.32(2.37)	2.49(2.04)	3.80(2.80)	2.36(2.63)	3.22(2.62)	1.99(3.36)	2.98(2.10)	
%Time <54 mg/dl	Mean(SD)	0.61 (0.68)	0.75 (0.56)	0.46(0.46)	0.72(0.88)	0.70 (0.94)	0.64 (0.51)	0.86(0.86)	0.63(0.46)	
Median (IQR)		0.20(1.10)	0.77(0.87)	0.33(0.69)	0.39(0.73)	0.53(0.79)	0.51(0.52)	0.74(1.26)	0.63(0.49)	
Mean SG mg/dl	Mean(SD)	160 (14)	147 (15)	149 (19)	147 (10)	150 (12)	144 (19)	153 (12)	148 (11)	
Median (IQR)		155 (20)	145 (20)	141 (17)	144 (11)	148 (16)	136 (27)	151(14)	144(14)	
CEV	Mean(SD)	37.1(6.1)	36.2(5.0)	36.6(6.0)	39.3(7.3)	37.2(5.8)	36.1(5.6)	36.7(6.7)	37.6(5.4)	
Median (IQR)		36.8(8.0)	33.8(7.3)	35.3(9.0)	40.9(8.7)	37.6(3.3)	36.3(7.5)	34.5(9.7)	37.6(7.1)	
AIT (mins)	Mean(Range)	-	3.3(2,4)	3.1(2.3,4)	2.8(2.3,4)	2.8(2.3,4)	2.5(2.3,4)	2.5(2.3,4)	-	

SG: Sensor Glucose, CEV: Coefficient of variation. AIT: Active Insulin Time