Clinical Experience with the Hybrid Closed-Loop Insulin Delivery System (Minimed™ 670G) compared to Sensor Augmented Therapy (MiniMed™ 640G) and standard care

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Abstract

Background: This real-world clinical study compared the efficacy of a hybrid closed-loop system (HCL) to a sensor integrated pump (SIP) system and usual care.

Methods: Twenty-four subjects aged 8 to 65 years were randomly selected from 6 clinical centers to take part in this prospective study. Subjects were on a variety of standard care programs at base-line (Phase 1) and then used SIP for two months (Phase 2) followed by two months on HCL (Phase 3).

Results: Compared with baseline, the mean HbA1c for the cohort reduced by 0.37% after 2 months of SIP therapy and by 0.7% after 2 months of HCL therapy. At study end, the mean HbA1c for the cohort was 7.2%. Time in severe hypoglycemia reduced to 0.4% (0.7% at baseline) for both SIP and HCL therapies. Time below 70 mg/dl reduced progressively between Phase 1 (baseline therapy), Phase 2 (SIP) and Phase 3 (HCL) (6%, 2.5% and 1.5% respectively) of the study. In the study intervention arms, less time was spent above 180 mg/dl (32.1% with SIP and 25.5% with HCL) versus 37% at baseline. The mean time-in-range (TIR) achieved was 72.5% with HCL, versus 65.2% with SIP (58.3% at baseline). Similarly, 50% of the subjects achieved a TIR of over 70% on HCL versus 33% on SIP (8% at baseline).

Conclusions: This small, prospective, real-world study demonstrated that irrespective of the starting parameters, SIP therapy reduced mean HbA1c levels, TIR and hypoglycemic events. Implementation of an HCL system enhanced these outcomes further.

Key Words: Type 1 diabetes; Continuous glucose monitoring; Hybrid closed loop system; Sensor integrated pump; Glucose time-in-range; Automated insulin delivery;

Introduction

The advent of Continuous Glucose Monitoring (CGM) has opened a new paradigm for people with diabetes on insulin therapy. The use of CGM with Insulin pump therapy (CSII) is well established[1], but increasingly has been promoted for use with individuals on Multiple Insulin Injection Regimens (MIR)[2-4]. Of interest, the COMISAIR study[3] suggested that individuals using CGM with MIR could do as well as those on CSII with regard to HbA1c reductions. The GOLD study[5] demonstrated that individuals on CGM also had less severe hypoglycemia than those using conventional finger-prick blood glucose monitoring, despite lower HbA1c levels. The efficacy of CGM in reducing hypoglycemia in individuals with severe hypoglycemia unawareness has recently been confirmed[6].

While most studies comparing CGM (with or without CSII), to conventional finger-prick testing traditionally utilize the A1C as a primary end-point, these studies have also better delineated the limitations of the HbA1c. This test does not reflect intra- and inter-day glycemic excursions that may lead to acute events (such as hypoglycemia), postprandial hyperglycemia and glycemic variability[7]. New metrics to better assess glycemic control have been identified and include estimated mean glucose, time-in-range (TIR), and percentage of time in both hyperglycemic (glucose >180 mg/dl) and hypoglycemic ranges (glucose <70 mg/dl.) [8]. International Societies have subsequently endorsed these new metrics and recommended the appropriate targets that should be achieved [9].

Sensor-integrated pump therapy (SIP) has demonstrated improved HbA1c levels[10-11], less glycemic variability[12-13] and reduced hypoglycemia[3,14]. Subsequently, the first hybrid closed-loop system (HCL) that automatically adjusts basal insulin delivery every 5 minutes based on sensor glucose data has become commercially available. This system has been shown to be safe and effective in improving glycemic control[15-16].

This study compares the sequential effects of standard therapy versus the use of SIP using the MiniMed™ 640G and then HCL with the MiniMed™ 670G system (both devices manufactured by Medtronic MiniMed, Inc., Northridge, CA) in a group of subjects with type 1 diabetes. The purpose was to determine and quantify any difference in glycemic parameters in the same subjects on the 3 different forms of therapy. More particularly, we sought to

identify whether there was any advantage to HCL versus SIP in a same-subject cohort in a real-world situation.

Materials and Methods

Six Diabetes Centers with extensive experience in insulin pump therapy were identified. These included 4 Adult centers and 2 pediatric centers. Each center was asked to randomly select 4 type 1 subjects for the study. Thus 24 subjects were enrolled into the study. Subjects were on a variety of therapies for their diabetes. Subject demographics and therapies prior to inclusion in the study are listed in Table 1. Subjects were eligible for recruitment if they were 7 years of age or older, not pregnant, and using a minimum of 8 units of insulin per 24 hours. Subjects with any other systemic disease or any therapy other than insulin were excluded.

Table 1: Treatment options and demographics of the subjects

Baseline Therapy	Number of Subjects	Gender (M/F)	Age Range (years)
MIR ^a & SMBG ^b	11	5-Jun	12 to 58
MIR & FGM ^c	1	0/1	15
MIR & CGM ^d	2	1-Jan	25,49
CSII ^e & SMBG	9	3-Jun	Jul-65
CSII & FGM	1	Jan-00	16
Total	24	14/10	Jul-65
^a MIR = Multiple Daily Injection Regimen			
^b SMBG=Self-Monitoring of Blood Glucose (Finger prick)			
^c FGM= Flash Glucose Monitoring (Abbott Libre Personal)			
^d CGM= Real-time Continuous Glucose Monitoring			
^e CSII=Continuous Subcutaneous Insulin Infusion (Insulin Pump Therapy)			

4 children (aged 7 - 10 years), 6 adolescents (aged 10 - 18 years) and 14 adults (over 18 years of age) were included in the study.

Following the signing of informed consent, the subjects underwent 3 Phases of management, namely:

- In Phase 1, on their current therapy, the subjects underwent 2 weeks of CGM, utilizing Abbott Libre personal flash monitoring. The glycaemic data generated was downloaded and analyzed.
- In Phase 2, the subjects were provided with a MiniMed™ 640G pump and Medtronic Guardian™ Sensor 3 sensors and trained in their use. They were instructed to utilize the fully-integrated system (SIP) and were expected to achieve at least 80% sensor utilization. After 2 months, the last 2 weeks of CGM data was downloaded and analyzed.
- In Phase 3, subjects were converted to HCL using the MiniMed™ 670G pump and were instructed to aim for 100% sensor usage on Auto Mode. After 2 months, the last 2 weeks of CGM data was downloaded for analysis.

Blood was drawn for HbA1c analysis at the end of each Phase.

Statistical Analysis

The data in this study was analyzed in an exploratory manner, as the sample size was not determined using power analysis. Quantitative data was summarized using number of observations - mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum. Categorical data was summarized using counts and frequencies. Given the small sample size and the presence of outlying observations, HbA1c changes from baseline to Phase 2 and to Phase 3, and from Phase 2 to Phase 3 were analyzed using Wilcoxon signed rank tests with Bonferroni correction. p values <0.05 were considered statistically significant. CareLink™ software was utilized to calculate mean glucose, estimated HbA1c (eA1C), time-in-range, and time in hypoglycemia (<70 mg/dl and <54 mg/dl) for each subject.

Results

CGM data was not available for 4 of the 24 subjects at baseline, leaving 20 subjects for baseline analysis. CGM data was available for the end of Phases 2 and 3 for all 24 subjects. Changes in HbA1c are depicted in Figure 1. After 2 months of SIP, the median HbA1c had reduced by 0.1% overall and mean HbA1c by 0.37%. Following a further 2 months on HCL, the median HbA1c reduced

0.4% from baseline with a 0.7% reduction in mean HbA1c. Despite the small number of subjects, this reduction in median HbA1c was statistically significant ($p=0.006$). The mean HbA1c for the entire cohort at the end of the study was 7.2%.

12 of the subjects were excluded from analysis of other metrics because of missing data points, no baseline data (4 subjects) or because the TIR had been calculated on parameters other than 70 to 180 mg/dl.

Figure 1: Changes in HbA1c during the study Phases

Phase 1: Standard Therapy

Phase 2: Automated pump therapy (MiniMed™ 640G)

Phase 3: Hybrid Closed Loop system (MiniMed™ 670G)

Figure 2 depicts analyses of all parameters of glycemic control for the remaining 12 subjects where full data was available. For all parameters measured, a progressive improvement was seen with each phase of therapy. Of clinical importance, the reduction in percent time in severe hypoglycemia (<54 mg/dl) was the same for SIP and HCL therapies (0.4%), and reduced from 0.7% in Phase 1. However, the percent time below 70 mg/dl reduced

progressively between Phase 1 (baseline therapy), Phase 2 (SIP) and Phase 3 (HCL) (6%, 2.5% and 1.5% respectively). Also, less time was spent above 180 mg/dl (37% at baseline, 32.1% with SIP and 25.5% with HCL). As a result, the mean percent TIR achieved was 72.5% with HCL, 65.2% with PIC and 58.3% at baseline. Similarly, 50% of the subjects achieved a percent TIR of over 70% on HCL versus 33% on SIP and only 8% at baseline.

Figure 2: Continuous Glucose Monitoring results comparing the last two weeks sensor data at each Phase of the study (12 subjects)

Discussion

Utilizing metrics recommended by the International Consensus on Use of Continuous Glucose Monitoring[8-9], the comparison between standard therapy, SIP therapy and HCL is clear. On all parameters, SIP is better than standard therapy and this is improved further with HCL. This small cohort of subjects had a wide age-range and the subjects had multiple variations of

therapy at baseline. While the uncontrolled nature of the subject selection could be criticized, this is a real-world study and the results might suggest that irrespective of the subjects' baseline therapy, they are likely to benefit from sensor augmented pump therapy, particularly HCL. This is in line with the findings of Cordero et al[18] who, with a much larger cohort of subjects, reported that individuals without prior CGM experience,

and those already using CGM, similarly benefitted from the MiniMed™ 670G HCL system.

The reductions in time spent in hypoglycemia (blood glucose <70 mg/dl) and particularly <54 mg/dl are striking. It is perhaps not surprising that no difference was seen in the percentage of documented severe hypoglycemia incidences <54 mg/dl between the SIP and HCL systems, since both have the 'low glucose suspend' functionality. However, the advanced system employed by the HCL appears to be more effective in reducing the number of episodes below 70 mg/dl. While this might not have a major effect on long-term outcomes, it can be expected to improve subject confidence and quality of life.

All long-term outcome studies have relied on the HbA1c as a surrogate marker of glycemic control and the HbA1c remains the gold standard. However, the HbA1c is not without problems as comprehensively reviewed in the publication by the "Beyond HbA1c writing group"[7]. With the ability to measure other glycemic parameters, the use of the HbA1c in assessing glycemic control can be enhanced by taking TIR into account. To date there have been no outcome studies supporting the perception that TIR or glycemic variability may be as good or better a marker of long-term outcomes than HbA1c, and it is unlikely that such data will be forthcoming in the near future. Nevertheless, studies have indicated that by addressing these parameters, HbA1c levels can be reduced, and that this can be achieved with reductions in hypoglycemia using sensor-augmented insulin pump therapy [9,10,16-18]. Expert opinion suggests that these parameters should be considered as important aspects in the assessment of glycemic control[7-9].

This was not constructed as a formal clinical study but is rather a report on real-world experience in the use of the Hybrid Closed-Loop Insulin Delivery System (Minimed™ 670G) compared to Sensor Augmented Therapy (MiniMed™ 640G) and standard care. There are therefore several weaknesses inherent in this report, which include the absence of data on some of the patients. Further, if constructed as a formal study, it may have been advantageous to institute a cross-over design, but this is not standard practice in a real-world setting. We also did not formally canvas the patients with regard to their experience on the two different systems. Nevertheless, this small cohort demonstrates that in a largely unselected and disparate group of patients visiting a routine diabetes clinic, the use of the Sensor Augmented Therapy (MiniMed™ 640G) pump improves parameters of glycemic control, and this is further enhanced by the Hybrid Closed-Loop Insulin Delivery System (Minimed™ 670G).

Conclusions

This small prospective study was performed in a real-world clinical situation and involved a wide variety of subjects with respect to both age and levels of glycemic control. Irrespective of the starting parameters, SIP reduced mean HbA1c levels, TIR and hypoglycemic events, and implementation of the HCL system resulted in further improvements.

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Conflict-of-interest disclosure

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Abbreviations

CGM:	continuous glucose monitoring
HCL:	Hybrid closed loop system insulin pump (MiniMed™ 640G),
SIP:	Sensor integrated pump system (MiniMed™ 640G),
CSII:	Continuous subcutaneous insulin infusion - Insulin pump therapy,
MIR:	Multiple Insulin Injection Regimen,
eA1c:	Estimated HbA1c,
TIR:	Percent time-in-range.

References

1. Rodbard D. Continuous glucose monitoring: a review of successes, challenges, and opportunities. *Diabetes Technol Ther.* 2016;Suppl 2:S3-S13. doi: 10.1089/dia.2015.0417
2. Tamborlane WV, Beck RW, Bode BW, Buckingham B, Chase HP, Clemons R, et al. Juvenile diabetes research foundation continuous glucose monitoring study group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Eng J Med.* 2008;359(14):1464–1476. doi: 10.1056/NEJMoa0805017
3. Šoupal J, Petruželková L, Flekač M, Pelcl T, Matoulek M, Daňková M, et al. Comparison of different treatment modalities for type 1 diabetes, including sensor-augmented insulin regimens, in 52 weeks of follow up: a COMISAIR study. *Diabetes Technol Therap.* 2016;18(9):532–538. doi: 10.1089/dia.2016.0171
4. Distiller LA. Should all patients on insulin be using continuous glucose monitoring? *Journal of Endocrinology, Metabolism and Diabetes of South Africa.* 2018; 23(3):59–63. doi:10.1080/16089677.2018.1515164

5. Lind M, Polonsky W, Hirsch I, Heise T, Bolinder J, Dahlqvist S et al. Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections. The GOLD randomised clinical trial. JAMA. 2017;317(4):379–387. doi: 10.1001/jama.2016.19976
6. Heinemann L, Freckmann G, Ehrmann D, Faber-Heinemann G, Guerra S, Waldenmaier D et al. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. Lancet. 2018;391(10128):1367–1377. doi: 10.1016/S0140-6736(18)30297-6
7. Beyond A1C writing group. Need for Regulatory Change to Incorporate Beyond A1C Glycemic Metrics. Diabetes Care 2018; 41(6):e92–e94. doi:10.2337/dci18-0010
8. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVreis JH, et al. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care. 2017;40(12): 1631–1640. doi: 10.2337/dc17-1600
9. Batelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Giester T, 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
10. Bergenstal RM, Tamborlane WV, Ahmann A, Buse JB, Dailry G, Davis SN, et al. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. N Engl J Med. 2010;363(4):311–320. doi: 10.1056/NEJMoa1002853
11. Hermanides J, Norgaard K, Bruttomesso D, Mathieu C, Frid A, Dayan CM, et al. Sensor augmented pump therapy lowers HbA(1c) in suboptimally controlled type 1 diabetes; a randomized controlled trial. Diabet Med. 2011;28(10):1158–1167. doi: 10.1111/j.1464-5491.2011.03256.x
12. Luo P, Cheng Q, Chen B, Li Y, Wu J, Zhang X, et al. Hypoglycemia and blood glucose fluctuations in the application of a sensor-augmented insulin pump. Diabetes Technol Ther. 2013;15(12):984–989. doi: 10.1089/dia.2013.0078
13. Zucchini S, Scipione M, Balsamo C, Maltoni G, Rollo A, Molinari E, et al. Comparison between sensor-augmented insulin therapy with continuous subcutaneous insulin infusion or multiple daily injections in everyday life: 3-day analysis of glucose patterns and sensor accuracy in children. Diabetes Technol Ther. 2011;13(12):1187–1193. doi: 10.1089/dia.2011.0080
14. Choudhary P, Olsen BS, Conget I, Welsh JB, Vorrink L, Shin JJ. Hypoglycemia prevention and user acceptance of an insulin pump system with predictive low glucose management. Diabetes Technol Ther. 2016;18(5):288–291. doi: 10.1089/dia.2015.0324
15. Bergenstal RM, Garg S, Weinzimer SA, Buckingham BA, Bode BW, Tamborlane WV, et al. Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. JAMA. 2016; 316(13):1407–1408. doi: 10.1001/jama.2016.11708
16. Garg SK, Weinzimer SA, Tamborlane WV, Buckingham BA, Bode BW, Baily TS, et al. Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. Diabetes Technol Ther. 2017;19(3): 155–163. doi: 10.1089/dia.2016.0421
17. Stone MP, Agrawal P, Chen X, Liu M, Shin J, Cordero TL, et al. Retrospective Analysis of 3-Month Real-World Glucose Data after the MiniMed 670G System Commercial Launch. Diabetes Technol Ther. 2018;20(10):689–692. doi: 10.1089/dia.2018.0202
18. Cordero TL, Garg SK, Brazg R, Bailey TS, Shin J, Lee SW, et al. The Effect of Prior Continuous Glucose Monitoring Use on Glycemic Outcomes in the Pivotal Trial of the MiniMed™ 670G Hybrid Closed-Loop System. Diabetes Technol Ther. 2017;19(12):749–752. doi: 10.1089/dia.2017.0208