Low-Blood Glucose Avoidance Training Improves Glycemic Variability in Adults With Type 1 Diabetes Complicated by Impaired Awareness of Hypoglycemia: HypoCOMPaSS Trial

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The Comparison of Optimized MDI Versus Pumps With or Without Sensors in Severe Hypoglycemia (HypoCOMPaSS) trial was a prospective, multicenter, randomized controlled trial examining the restoration of impaired awareness of hypoglycemia (IAH) and the prevention of severe hypoglycemia (SH) in adults with type 1 diabetes using multiple daily injections (MDI) compared with continuous subcutaneous insulin infusion (CSII), with or without adjunctive real-time continuous glucose monitoring (RT-CGM), using a 2 × 2 factorial design (1). Few studies are currently available to compare the difference in glycemic variability (GV) between MDI and CSII and between self-monitored blood glucose (SMBG) and RT-CGM (2–4). These studies showed an improvement in GV in favor of CSII and RT-CGM. However, none of them included participants with IAH or history of SH. The aim of this study is to compare the changes in GV between MDI and CSII and between SMBG and RT-CGM group in this specific patient group with type 1 diabetes with IAH or recurrent SH.

A total of 96 participants were recruited for the study. Each participant undertook 7 days of blinded CGM using Medtronic iPro at baseline and prior to each of the four weekly visits during the 24-week randomized controlled trial period. GV was measured as glucose SD and coefficient of variation (%CV), calculated using available Excel formulas published online (5).

Overall, there were decreases in GV between baseline and week 24 measured by SD (3.9 ± 1.0 vs. 3.4 ± 0.8 mmol/L, P < 0.001) and %CV (41.3 ± 8.0 vs. 36.8 ± 8.1%, P < 0.001).

The MDI group realized improvement in GV from baseline to week 24 as measured by SD (3.8 ± 1.0 vs. 3.3 ± 0.7 mmol/L, P = 0.007) and %CV (42.1 ± 8.4 vs. 36.1 ± 6.7%, P = 0.002). The CSII group realized similar improvement in SD (4.0 ± 1.0 vs. 3.5 ± 0.8 mmol/L, P = 0.005) and %CV (41.7 ± 7.2 vs. 37.5 ± 9.2%, P = 0.01). Thus, CSII and MDI therapy did not differ in SD and %CV at baseline and week 24.

However, using mixed-effects modeling, taking into account GV at each time point and other covariates, CSII appeared to have a more rapid impact in GV improvement compared with MDI, with an estimated average difference of −3.25 ± 0.96% (95% CI −5.15, −1.36) (P = 0.001) in %CV and a trend toward improvement in SD with difference of −0.25 ± 0.13 mmol/L (95% CI −0.50, 0.002) (P = 0.052) (Fig. 1).

The SMBG group realized GV improvement in %CV between baseline and week 24 (41.3 ± 6.9 vs. 37.1 ± 6.5%, P = 0.005). No differences were seen in SD (3.8 ± 0.9 vs. 3.5 ± 0.7 mmol/L, P = 0.069). In the RT-CGM group, GV improvement was seen in both SD (4.0 ± 1.0 vs. 3.4 ± 0.8 mmol/L, P < 0.001) and %CV (42.4 ± 8.5 vs. 36.8 ± 9.4%, P = 0.003). SMBG and RT-CGM groups did not differ at baseline and week 24. Further, these groups did not differ when GV was analyzed using mixed-effects modeling (Fig. 1).

These data suggest that the educational intervention has played an important part...
in improving GV, although there was no specific control group to support this hypothesis.

In conclusion, we have shown that GV can be improved within 24 weeks in adults with long-standing type 1 diabetes complicated by IAH and recurrent SH. This was seen in all four arms of the study, suggesting that the education-based intervention coupled with weekly health care professional input was essential.

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work and, as such, had full access to all the data in
the study and takes responsibility for the in-
tegrity of the data and the accuracy of the data
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Prior Presentation. An abstract containing
some of the reported data was presented at
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Appendix

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References

1. Little SA, Leelarathna L, Walkinshaw E, et al.
Recovery of hypoglycemia awareness in long-
standing type 1 diabetes: a multicenter 2 × 2
factorial randomized controlled trial comparing
insulin pump with multiple daily injections and
continuous with conventional glucose self-
monitoring (HypoCOMPaSS). Diabetes Care 2014;
37:2114–2122
2. Prieto-Tenreiro A, Villar-Taibo R, Pazos-
Couselo M, González-Rodríguez M, Casanueva
F, García-López JM. Benefits of subcutaneous
continuous insulin infusion in type 1 diabetic
patients with high glycemic variability. Endocri-
3. Chimenti EM, de la Morena LH, Vaquero PM,
Sáez-de-Ibarra L, Domínguez MG, Sánchez LF.
Assessing glycaemic variability with continuous
glucose monitoring system before and after
continuous subcutaneous insulin infusion in
people with type 1 diabetes. Diabetes Res Clin
Pract 2010;90:e57–e59
of continuous glucose monitoring in subjects
with type 1 diabetes on multiple daily injec-
tions versus continuous subcutaneous insulin
infusion therapy: a prospective 6-month study.
Diabetes Care 2011;34:574–579
5. Rodbard D. New and improved methods to
characterize glycemic variability using continu-
ous glucose monitoring. Diabetes Technol Ther
2009;11:551–565