Endocrinol Nutr. 2016;63(3):103–105

ENDOCRINOLOGÍA Y NUTRICIÓN

www.elsevier.es/endo

EDITORIAL

Benefits of continuous subcutaneous insulin infusion in type 1 diabetes. Is there any doubt?☆

Beneficios del tratamiento con infusión subcutánea continua de insulina en la diabetes tipo 1. ¿Queda algún lugar para la duda?

María Asunción Martínez-Brocca

Unidad de Gestión Clínica de Endocrinología y Nutrición, Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/Consejo Superior de Investigaciones Científicas/Universidad de Sevilla, Sevilla, Spain

The favorable impact of intensive therapy on cardiovascular risk in patients with type 1 diabetes mellitus (T1DM) is well-known.[1] However, even with adequate control according to current clinical practice guidelines ($HbA_{1c} \leq 6.9\%$), cardiovascular mortality in T1DM is two times higher than the mortality seen in the general population after adjusting for socioeconomic and clinical variables.[2] Both the treatment strategies available and HbA_{1c} are imperfect elements for achieving and reflecting, respectively, optimum metabolic control, understood as the normalization of blood glucose levels, their variability, and hyperglycemic and hypoglycemic events.

Steineck et al. recently addressed in the *British Medical Journal* the interesting issue of the impact of the treatment of T1DM with continuous subcutaneous insulin infusion (CSII) or insulin pumps on cardiovascular mortality. For this, they analyzed the rates of cardiovascular and all-cause mortality in 18,168 patients with T1DM included in the Swedish Diabetes Registry monitored for a mean of 6.8 years. A comparison of the cohort on CSII therapy (n = 2441) with the cohort treated with multiple dose insulin (MDI) (n = 15,727) showed a clinically relevant decrease in the risk of death from cardiovascular disease, coronary artery disease, and all-cause mortality favoring CSII.[3] These long-awaited results allow it to be stated that an association exists between CSII and lower cardiovascular mortality in patients with T1DM.

This study has had a considerable clinical impact, but its limitations have also been recognized. The results seen cannot be attributed to the therapy itself, to the clinical management of patients given CSII, or to the diabetes education received. On the other hand, although a cause and effect relationship cannot be established due to the observational design of the study, this potent health outcome is plausible from the pathophysiological viewpoint. Thus, severe hypoglycemia has been shown to be four times less common in patients with T1DM on CSII as compared to MDI, with greater benefits in patients with higher event rates.[4] Severe hypoglycemia has been recognized as a risk factor for cardiovascular events, especially in high-risk patients,[5,6] and recently as a risk factor for decreased survival after a cardiovascular event in T1DM.[7] In addition, different meta-analyses have shown that in T1DM, CSII significantly decreases HbA_{1c} as compared to MDI, with a mean difference in HbA_{1c} ranging from −0.3% to −0.6%;[4,8–11] it should be noted that this effect is the greater the higher the HbA_{1c} level, which makes CSII particularly effective in patients with poorer chronic control and, thus, at a greater risk of secondary complications.[4] It has not been elucidated yet whether other favorable effects of CSII, such as decreased glycemic variability, may contribute to decreased cardiovascular mortality.

CSII may be particularly effective in children because it allows for the adaptation to the low insulin requirements and the variable intake and physical activity characteristic of this age group. Thus, data from European and US registries

☆ Please cite this article as: Martínez-Brocca MA. Beneficios del tratamiento con infusión subcutánea continua de insulina en la diabetes tipo 1. ¿Queda algún lugar para la duda? Endocrinol Nutr. 2016;63:103–105.

E-mail address: masuncion.martinez.sspa@juntadeandalucia.es

have related CSII therapy to improved metabolic control in this population.[12,13]

In addition to its clinical benefits, CSII therapy has been shown to be cost-effective in economic evaluation studies conducted in neighboring countries, and also in the Spanish health system.[14] The available evidence warrants the inclusion of CSII in clinical practice guidelines such as those issued by the National Institute for Health and Care Excellence (NICE), which are usually restrictive because they take into consideration not only efficacy criteria, but also cost-effectiveness.[15] Despite this strong evidence, the use of CSII in Spain is surprisingly low and has not substantially increased in recent years. National experts have previously expressed their concern about this situation.[16,17] Thus, the proportion of Spanish patients with T1DM treated with CSII ranges from 3%–4%,[18] much lower than the 15%–20% reported in countries from North and Central Europe. There is also a worrying variability between the different autonomous communities, and between the different hospitals within the communities, in both pediatric and adult populations. This has resulted in a serious problem of accessibility and of unequal opportunities in our health system. The economic recession in recent years may have contributed to slowing down the introduction of CSII implementation programs, a situation to which the suppliers of this technology have also had to adapt, but this cannot be considered as the main or only cause of this technological gap, which is similar to others that have historically occurred in the care of diabetic patients in Spain. From the organizational viewpoint, the work teams required are not especially complex,[17] but need to be adequately trained, highly motivated and, above all, stable. Institutionally, the existence of CSII programs with evaluable results should be recognized as a quality criterion for the care of patients with T1DM. Above all, it is our own barriers, those of the healthcare professionals, which should be removed in order to overcome this worrying therapeutic inertia, which denies effective and efficient therapy to a significant proportion of our patients. Some of the professionals in charge of patients with T1DM or responsible for their care still underestimate the clinical benefits of therapy both in terms of HbA_{1c} reduction and in other metabolic control and quality of life parameters (beyond HbA_{1c}), and question its efficiency. This has an impact on CSII expansion, because it affects the most critical issue, the professional confidence which is based on the best scientific knowledge. This represents the true engine of the organization. On the other hand, patient motivation is also recognized as a limiting element, which indeed it is. It is also usually regarded as an intrinsic patient characteristic that we have no possibility of changing. However, with adequate training, CSII improves treatment flexibility and the quality of life of patients, and this is their preferred option also.[11] For these reasons, working in a real environment of shared decision-making with realistic expectations[19] could in many cases overcome our own skepticism and promote in the patient the motivation and implication required by the therapy when clinically indicated.

The clinical benefits of this ''new-old'' technology in T1DM have already been amply shown, and are confirmed by the associated decrease in mortality. The continued questioning of CSII effectiveness or efficiency as a reason for slowing its implementation is not a scientifically solid argument and also limits the introduction of other advanced technologies to which our patients may have delayed and marginal access. The currently available scientific evidence should be regarded as definitive and lead to its unanimous acceptance by professionals and to resolute institutional action. We should therefore focus on the identification and removal of barriers that limit the expansion of CSII in T1DM in our working environment.

Conflicts of interest

M.A. Martínez-Brocca has participated as an investigator in research projects wholly or partially funded by Medtronic and Roche, and has received fees for papers and participation in work groups funded by Medtronic.

References

1. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005;353:2643–53.
2. Lind M, Svensson AM, Kosiborod M, Gudbjörnsdottir S, Pivodic A, Wedel H, et al. Glycemic control and excess mortality in type 1 diabetes. N Engl J Med. 2014;371:1972–82.
3. Steineck I, Cederholm J, Eliasson B, Rawshani A, Eeg-Olofsson K, Svensson AM, et al. Insulin pump therapy, multiple daily injections, and cardiovascular mortality in 18,168 people with type 1 diabetes: observational study. BMJ. 2015;350:h3234.
4. Pickup JC, Sutton AJ. Severe hypoglycaemia and glycemic control in type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous insulin infusion. Diabet Med. 2008;25:765–74.
5. Zoungas S, Patel A, Chalmers J, de Galan BE, Li Q, Billot L, et al. Severe hypoglycemia and risks of vascular events and death. N Engl J Med. 2010;363:1410–8.
6. Mellbin LG, Rydén L, Riddle MC, Probstfield J, Rosenstock J, Díaz R, et al. Does hypoglycaemia increase the risk of cardiovascular events? A report from the ORIGIN trial. Eur Heart J. 2013;34:3137–44.
7. Lung TW, Petrie D, Herman WH, Palmer AJ, Svensson AM, Eliasson B, et al. Severe hypoglycemia and mortality after cardiovascular events for type 1 diabetic patients in Sweden. Diabetes Care. 2014;37:2974–81.
8. Pickup JC, Mattock MB, Kerry S. Glycaemic control with continuous subcutaneous insulin infusion compared to intensive insulin injection therapy in type 1 diabetes: meta-analysis of randomised controlled trials. BMJ. 2002;324:705–8.
9. Weissberg-Benchell J, Antisdel-Lomaglio J, Seshadri R. Insulin pump therapy: a meta-analysis. Diabetes Care. 2003;26:1079–87.
10. Jeitler K, Horvath K, Berghold A. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. Diabetologia. 2008;51:941–51.
11. Misso ML, Egberts KJ, Page M, O'Connor D, Shaw J. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. Cochrane Database Syst Rev. 2010;1:CD005103.
12. Blackman SM, Raghinaru D, Adi S, Simmons JH, Ebner-Lyon L, Chase HP, et al. Insulin pump use in young children in the T1D Exchange clinic registry is associated with lower hemoglobin A1c levels than injection therapy. Pediatr Diabetes. 2014;15:564–72.

13. Maahs DM, Hermann JM, DuBose SN, Miller KM, Heidtmann B, DiMeglio LA, et al. Contrasting the clinical care and outcomes of 2,622 children with type 1 diabetes less than 6 years of age in the United States T1D Exchange and German/Austrian DPV registries. Diabetologia. 2014;57:1578–85.
14. Conget Donlo I, Serrano Contreras D, Rodríguez Barrios JM, Levy Mizrahi I, Castell Abat C, Roze S. Cost-utility analysis of insulin pumps compared to multiple daily doses of insulin in patients with type 1 diabetes mellitus in Spain. Rev Esp Salud Publica. 2006;80:679–95.
15. National Institute for Health and Care Excellence [Internet portal]; ©2008 [published 23 Jul 2008; updated Dec 2014; accessed 1 Oct 2015]. Available from: http://www.nice.org.uk/guidance/TA151.
16. Conget I, Giménez M, Ampudia-Blasco FJ. Posibles causas de la infrautilización de la infusión continua de insulina en España. Av Diabetol. 2013;29:1–3.
17. Botella M, Álvarez J. Sobre el zorro y las uvas ii. Posibles causas de la infrautilización de la infusión continua de insulina en España. Av Diabetol. 2013;29:112–3.
18. Renard E. Insulin pump use in Europe. Diabetes Technol Ther. 2010;12 Suppl. 1:S29–32.
19. Joshi M, Choudhari P. Multiple daily injections or insulin pump therapy: choosing the best options for your patient – an evidence-based approach. Curr Diab Rep. 2015;8:1, http://dx.doi.org/10.1007/s11892-015-0644-z.