

EDITORIAL

Automated insulin delivery systems: Myths, legends and management of the Holy Grail



Sistemas automáticos de administración de insulina: mitos, leyendas y gestión del Santo Grial

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For centuries, the most intrepid explorers searched the entire face of the earth for the Holy Grail, hoping to find a relic with miraculous healing powers. In the same way, since the discovery of insulin 100 years ago, the scientific community has been searching for a device capable of automatic blood glucose control in patients with type 1 diabetes (T1D), without the risk of hypoglycaemia, which would help them cope with the eventualities typical of day-to-day life (exercise, meals, intercurrent illnesses, etc.), the so-called artificial pancreas (AP). In the last decade, there have been exponential advances in this direction, accentuated after the marketing of the first Automatic Insulin Delivery (AID) system five years ago. In light of the above, we ask ourselves, what is true and what is merely a myth about that Holy Grail known as the AP? And which patients can most benefit from its use?

In the absence of biological cure for T1D in the medium term, after the marketing of the first AID system in 2017, there was hope for a technological solution that would mean a true revolution in the management of this disease. Continuous subcutaneous insulin infusion (CSII) incorporates a

control algorithm capable of automating infusion by integrating continuous glucose monitoring (CGM) data. The most advanced of these infusers not only adjust the basal insulin administered, but are capable of automatically administering corrective boluses to maintain blood glucose levels within the preset targets. Under this premise, expectations were inevitably high. However, the reality of currently marketed systems is that they still have limitations and challenges that must be considered and communicated to patients. To begin with, this system's controller is based on interstitial glucose values (a lag of 5–25 min compared to venous glucose measurements) and its action is delayed due to the delay in the absorption of the subcutaneous insulins that are currently available (peak at 45–60 min). For this reason, the marketed systems are still hybrid, which means they require the participation of the patient to announce intakes and count carbohydrates, while they also offer improved performance when undertaking physical exercise. Although some AID systems offer the option to increase the blood glucose target and even make the algorithm less aggressive, exercise planning is still essential with these settings. It should also be borne in mind that users of AID systems must have technical knowledge about how they operate and know how to return to the use of non-automated

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systems in the event of a malfunction. A final and equally important limitation is that they are expensive.

If we analyse the results reported in randomised clinical trials comparing the use of AP with sensor-augmented pump (SAP) therapy, these devices decrease HbA1c by 0.15–0.33% and increase the time in range (TIR) 70–180 mg/dl by 9–11%, achieving an average TIR close to 70% (65.0–71.2%).^{1–4} Even so, almost half of patients still do not achieve the established glycaemic control targets.⁵ The results obtained in real life are similar.^{6,7} However, we must keep in mind the clear superiority of AP in terms of glycaemic control compared to standard T1D treatment in Spain (multiple doses of insulin and flash glucose monitoring), where it has been shown to reduce HbA1c by 1.4% in patients with poor previous glycaemic control.⁸ In addition, for the first time we have a device that improves glycaemic control and, at the same time, decreases the risk of hypoglycaemia (or does not increase it).

The bulk of the evidence in terms of glycaemic control suggests that patients with suboptimal control are set to benefit the most from this type of therapy.^{9,10} In addition, the decrease in time in hypoglycaemia in most clinical trials also points to a benefit for the population with recurrent hypoglycaemia, although the specific evidence is scarce in this high-risk subgroup.^{11,12} Further, multiple studies have already confirmed its safety and efficacy in populations of all ages, from children one year of age¹³ to older adults.¹⁴ Despite the fact that the glycaemic targets pursued during pregnancy are lower than those offered by most AID systems on the market, there is also a device approved in the European Union for use in pregnant women.¹⁵ Consequently, the most recent clinical practice guidelines recommend considering starting this treatment in any T1D patient trained in its use, especially in those individuals with suboptimal glycaemic control, as well as in the population with recurrent hypoglycaemia.^{16,17} Finally, the notable benefit in terms of quality of life and relief from the drawbacks of T1D self-management in patients with good glycaemic control should also be an aspect to take into account.^{18,19} However, with one very recent exception,²⁰ clinical guidelines, consensus, expert recommendations or recommendations that come directly from a public health system that help us to discern, against a backdrop of limited financial resources, for which patients and scenarios we should prioritise the initiation of therapy with AP after standard treatment with multiple doses of insulin and CGM, are anecdotal. If such an important decision is left to arbitrariness and the situation specific to each individual centre and teams of professionals, the door to inequity remains open.

There are currently no comparative studies between the different hybrid AID systems, so there is no evidence as to the superiority of one over the others in terms of glycaemic control beyond anecdotal preference, often based on self-fulfilling prophecies. In fact, the dizzying rate of technological development results in enormous difficulty in generating comparative scientific evidence between devices of the same generation. Therefore, the availability or technical preferences (previous CSII or associated CGM system, control screen from mobile phone vs CSII, degree of complexity of use or parameters adjustable by the user) should prevail when choosing between AID systems. It must be taken into account that on many occasions the preferences

of the user and the professional for one AP device over another are based on different criteria. Patients may prioritise usability, portability, convenience and ease of use, while the professional is generally more interested in features related to device performance and achievement of clinical goals. In this sense, we should also be able to help those patients who choose to use open source or do-it-yourself systems, which have already demonstrated their safety and efficacy, to optimise their glycaemic control.^{4,21,22}

While we await the arrival of even faster insulins and a fully automatic AP system, in the not too distant future we will have increasingly portable systems, CSII devices without tubes,²³ and that are more automated, circumventing, for example, the need for carbohydrate counts²⁴; as well as bihormonal systems that incorporate glucagon²⁵ for better prevention of hypoglycaemia, or pramlintide²⁶ to optimise postprandial control. We will even have the option of using adjuvant treatments such as sodium glucose co-transporter 2 (SGLT2) inhibitors to increase TIR.^{27,28} The arrival of multiple AID systems with probably increasingly differentiated benefits should help us to better personalise treatment. Consequently, and as professionals, all this will also force us to update our knowledge so we can offer the best and most sustainable treatment to our patients.

In summary, although far from being perfect at present, AID systems have already broken paradigms and offer T1D patients the possibility of obtaining a degree of glycaemic control achievable to date with other treatments, without increasing the risk of hypoglycaemia, and improving their quality of life. Without overlooking the continuation of the task of seeking the Holy Grail and its miracles, it would be beneficial if we now concentrated on the more mundane management of all the good progress that we have already made and make AP treatment available in the fairest and most sustainable way possible to all T1D patients who need it.

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