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Intraperitoneal insulin therapy in patients with type 1 diabetes. Does it fit into the current therapeutic arsenal?

Infusión continua de insulina intraperitoneal en pacientes con diabetes tipo 1. ¿Encaja en el arsenal terapéutico actual?

Achieving an optimal glycaemic control without hypoglycaemia is the main treatment objective for patients with type 1 diabetes (T1D). Over the last years, improvements in diabetes education, intensified insulin therapy, continuous subcutaneous insulin infusion (CSII), and continuous glucose monitoring (CGM) have supported people with T1D to achieve this goal. In spite of all these advances, still barriers exist to obtain an ideal control in the majority of patients.

Continuous intraperitoneal insulin (CIPII) administration may be considered as a treatment modality for both adults and children with T1D using optimised intensive insulin therapy for whom subcutaneous insulin has failed due to subcutaneous insulin resistance or skin conditions (lipoatrophy/hypertrophy, skin reaction or local allergy). Failure of subcutaneous insulin may result in recurrent or unexplained hypoglycaemia or hyperglycaemia.[1] It has also been considered as a treatment modality for adults with T1D with severe needle phobia, and for those being considered for islet cell/pancreatic transplantation, or where transplantation is not available. It has been reported than CIPII has comparable glucose outcomes with less hypoglycaemia and less insulin dose than the obtained by CSII.[2–4]

There are two different technologies developed in CIPII: implanted intraperitoneal pumps (MiniMed MIP2007C, Medtronic, Northidge, USA) and implanted catheter as the DiaPort system (Roche Diabetes, Germany). CIPII pumps are implanted surgically over the rectus abdominus muscle fascia and contains a reservoir that can be filled every 6 weeks with U400 insulin and a catheter extended into the peritoneal space. On the other hand, the DiaPort system consists of a surgically established intraperitoneal catheter connected to a percutaneous port implanted in the anterior abdominal wall. In this case, the Roche Accu-Chek Combo pump (Roche Diagnosis, Basilea, Switzerland) filled by U100 human insulin is connected to the port and operates as it was a CSII pump.[5,6]

Here we present data from a 52-year-old man with T1D diagnosed in 1974 at the age of 11. He started treatment with CSII (Accu-Chek Combo) in 2013 because of repeated severe/non severe hypoglycaemia/hypoglycaemia unawareness at Charing Cross Hospital, London. At the same time, CGM through a Dexcom G4 platinum (Dexcom, CA, USA) system was started. In 2014, he presented active retinopathy with recurrent photocoagulation due to continuous proliferative changes. His HbA_{1c} was 48 mmol/mol (6.5%) and his creatinine was 84 μmol/L. The same year, he started developing problems with subcutaneous insulin absorption. It was reported that delivered insulin was not acting appropriately with a delayed insulin absorption and late episodes of hypoglycaemia.

An individualised programme for optimising his glycaemic control was then started. Structured education revised, insulin use checked and the patient was closely monitored to improve his metabolic control. Addison's disease, presence of autoantibodies against insulin and other endocrinopathies were excluded during the study. Finally, different types of insulin, injection sites and cannulae were tried to solve the situation.

A subcutaneous insulin absorption test was performed in order to complete the study. All subcutaneous insulin was stopped at midnight. IV aspart insulin was administered in a sliding scale overnight. During the morning, IV insulin was stopped to give a subcutaneous bolus of 0.3 UI/kg of insulin aspart. Glucose (mmol/L) and insulin (mu/L) were measured at times −60, 0, 30, 60 and 90 min. C-peptide was undetectable (<3 pmol/L). Measurements of glucose/insulin were 11.0/14.1, 11.8/68.7, 10.4/75.1 and 8.9/78.6 at 0, 30, 60 and 90 min respectively. The test was considered abnormal as the glucose lowering was delayed to 90 min with serum insulin still rising.

The presence of active microvascular complications, hypoglycaemia unawareness, insulin requirements >0.8 UI/-kg/24 h, variable insulin absorption, significant psychological impact and being on an intensified regimen supported by technology forced the team to rethink his treatment.

The clinical team finally decided to proceed for individual funding approval for DiaPort CIPII system. Human insulin U100 in combination with a stabilising agent was chosen instead of rapid acting insulin analogues as they are not suitable for CIPII because have been associated

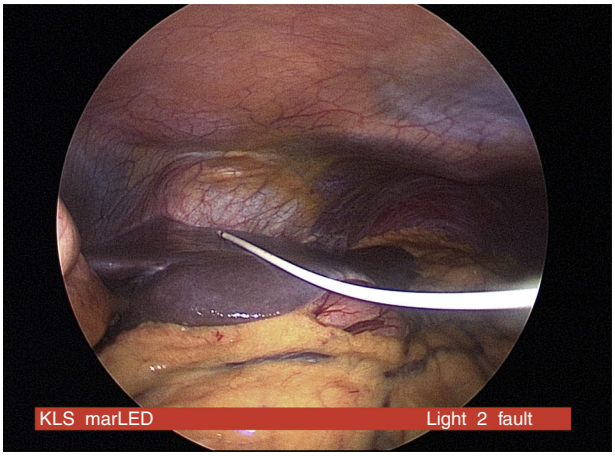

Figure 1 DiaPort catheter change via laparoscopy. Image during the procedure.

with catheter occlusion. CGM through Dexcom G4 platinum was continuously used before and after the procedure. During the 2-years follow-up there were neither severe hypoglycaemia nor ketosis/ketoacidosis episodes presented. Retinopathy remained stable and hypoglycaemia awareness was not completely restored. Two catheters replacements due to blockage were performed during the follow-up.

CIPII devices require a surgical procedure for insertion with associated risks of the anaesthesia, bleeding, infection and discomfort (Fig. 1). The commonest complications of CIPII use are catheter occlusion, pump dysfunction, pain and local infection. However, 80% of people using CIPII had no reported complications over a 15-month period. Peritonitis is rare (0.4/100 patient year) and no mortality related to peritonitis has been reported with CIPII.[7] In a prospective randomised trial using CIPII through catheter, the more frequently reported adverse event was infection/inflammation around the port affecting 21%/10% of the patients after 6/12-months of follow-up, respectively. The median time from implantation to the occurrence of the first complication requiring surgical intervention was 3.6 years (95%CI: 2.2–5.0 years).[8]

The cost between both CIPII techniques differ substantially. While DiaPort implantation kit cost is around €5000 excluding the costs of insulin and surgical implantation, the cost for an implantable pump is close to €30 000 with an expected battery life of 8 years (the cost of additional visits for pump reservoir filling and U400 insulin are not included).[9]

CIPII seems to be a valuable option for people with T1D who are unable to safely or effectively manage their diabetes with subcutaneous insulin due to skin issues. Until now, it has been also a good choice for those people with T1D and severe hypoglycaemia, and for whom transplantation options were either unavailable or unsuitable.[10] Moreover, given the reversible nature of CIPII and its comparatively low risks and costs when compared with transplantation, it may be a treatment modality to consider as an alternative to islet cell/pancreas transplantation. Nevertheless, as new technological options appear on the market (like sensor-augmented pump with low/predictive suspend or hybrid closed-loop systems) it is difficult to value the paper that CIPII is going to have in the next future. In this scenario, it is very likely that it will eventually only become an alternative for those with skin problems or extreme insulin resistance.

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Linfomas primarios tiroideos. Experiencia en hospitales de Castilla-La Mancha

Primary thyroid lymphomas. Experience in hospitals of Castilla-La Mancha

El linfoma primario tiroideo (LPT) es una entidad rara que se define por la afectación única de la glándula tiroides y de los ganglios linfáticos locorregionales, debiéndose descartar la afectación en otra ubicación en el momento del diagnóstico[1]. Representa menos del 2-5% de las neoplasias de tiroides y menos del 2,5% de los linfomas extranodales[2]. Presenta una mayor prevalencia en mujeres con una relación 4:1 y se desarrolla en la mayoría de los casos entre los 60 y 75 años, con una edad media de 67 años[3]. La forma de presentación clínica más habitual es una masa de crecimiento rápido, que puede ser dolorosa, y que ocasiona síntomas por compresión (disnea, disfagia, afonía, estridor y tos). El 10-20% de los LPT desarrollan un cuadro sistémico asociado (fiebre, sudoración nocturna y pérdida de peso)[4,5]. Lo habitual es que los sujetos se encuentren eutiroideos en el momento del diagnóstico aunque un 10% pueden presentar un hipotiroidismo primario.

El objetivo de este trabajo es presentar nuestra experiencia en el manejo de los LPT en 3 hospitales de Castilla-La Mancha. Para ello se seleccionaron aquellos pacientes con diagnóstico histológico de LPT o con ese diagnóstico codificado en el informe de alta hospitalaria desde 1990 hasta la actualidad, y se realizó un análisis retrospectivo de las historias clínicas. Siete pacientes, todas mujeres con una edad media de 59 años, cumplían estas características. En todos los casos el LPT se presentó como un nódulo tiroideo no doloroso asociado a sintomatología compresiva de rápido crecimiento (1-12 semanas de evolución). En 6 casos (85,7%), las pacientes presentaban una tiroiditis crónica autoinmune asociada y en 4 casos (57%) un hipotiroidismo primario. Los resultados de las pruebas de imagen se muestran en la tabla 1. En 6 casos (85,7%) se realizó una punción aspiración con aguja fina (PAAF) guiada por ecografía; el resultado citológico se muestra en la tabla 1. En 2 pacientes, en uno de ellos tras PAAF, se realizó biopsia con aguja gruesa (BAG). Se realizó tratamiento quirúrgico en el 71% de los casos: tiroidectomía total (TT) en 4 pacientes y hemitiroidectomía en un caso. En todos los casos se administró quimioterapia (QT) sistémica; los esquemas de tratamiento se resumen en la tabla 1. Tres pacientes (42,8%) recibieron también radioterapia (RT). Por último, en ningún caso se ha producido muerte o recidiva del LPT.

Los LPT son neoplasias infrecuentes. La mayoría de los LPT son linfomas no Hodgkin (LNH). El 50-80% son linfomas difusos de células grandes B (LDCGB) y el 20-30% son de tejido linfoide asociado a mucosas (MALT), mientras que otros subtipos histológicos como el folicular, linfocítico de célula pequeña, Burkitt (LB), Hodgkin o linfoma T son extremadamente infrecuentes[6]. En nuestra serie, una paciente presenta un LB y en dos casos coexistían además carcinomas papilares de tiroides (CPT). Aunque el CPT representa el 85% de los cánceres del epitelio folicular del tiroides, la asociación de LPT y CPT es excepcional y hay pocos casos descritos en la literatura[7,8]. El riesgo de presentar un LPT se multiplica por 80 en presencia de una tiroiditis crónica autoinmune, aunque la evolución de esta entidad a linfoma es infrecuente[1]. Por otra parte, la relación de la tiroiditis crónica autoinmune con el CPT sigue siendo objeto de controversia aunque su coexistencia representa una realidad clínica cuyo significado aún desconocemos[9]. El diagnóstico de certeza de los LPT a menudo requiere una biopsia quirúrgica, ya que la mayoría de las exploraciones citológicas presentan una baja sensibilidad[10]. El papel de la PAAF en el diagnóstico del LPT es limitado por la dificultad en realizar el diagnóstico diferencial entre linfoma y la infiltración linfocitaria tiroidea. Sin embargo, la sensibilidad de la PAAF ha aumentado considerablemente al introducir otras técnicas como la citometría de flujo, estudios inmunohistoquímicos o técnicas moleculares. En nuestra serie, únicamente en un caso se obtuvo el diagnóstico de certeza tras PAAF (caso 2); se trataba de una paciente con un LB, que supone una variante más agresiva. En el caso 1 se realizó citometría de flujo en el material obtenido de la PAAF y esta técnica ayudó a completar el diagnóstico de LNH B, aunque finalmente también se realizó una biopsia ganglionar para obtener el diagnóstico anatomopatológico definitivo. En los casos 3 y 5 se realizaron técnicas de biología molecular en la muestra obtenida por BAG, confirmando así el diagnóstico anatomopatológico sin requerir cirugía. La estadificación se realiza según la clasificación de Ann Arbor: IE (enfermedad limitada al tiroides), IIE (afectación de tiroides y ganglios locorregionales), IIIE (afectación de ganglios a ambos lados del diafragma) e IVE (afectación difusa). El 90% de los LPT se diagnostican en estadios tempranos de la enfermedad[11], tal y como sucede en nuestra serie.

Tradicionalmente, el tratamiento de los LPT era la cirugía. En nuestra serie en cinco casos se optó por tratamiento quirúrgico. En todos los casos, el tratamiento