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SCIENTIFIC LETTERS

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

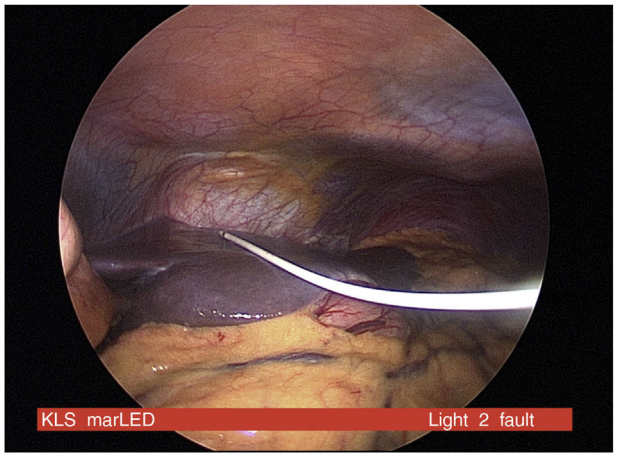

Figure 1 DiaPort catheter change via laparoscopy. Image during the procedure.

are not suitable for CIPII because have been associated 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.

References

1. Giacca A, Caumo A, Galimberti G, Petrella G, Librenti MC, Scavini M, et al. Peritoneal and subcutaneous absorption of insulin in type I diabetic subjects. J Clin Endocrinol Metab. 1993;77:738–42.
2. Broussolle C, Jeandidier N, Hanaire-Broutin H. French multicentre experience of implantable insulin pumps. The EVADIAC Study Group. Evaluation of Active Implants in Diabetes Society. Lancet (London, England). 1994;343:514–5.
3. Hanaire-Broutin H, Broussolle C, Jeandidier N, Renard E, Guerci B, Haardt MJ, et al. Feasibility of intraperitoneal insulin therapy with programmable implantable pumps in IDDM. A multicenter study. The EVADIAC Study Group. Evaluation dans le Diabète du Traitement par Implants Actifs. Diabetes Care. 1995;18:388–92.
4. Schaepelynck Bélicar P, Vague P, Lassmann-Vague V. Reproducibility of plasma insulin kinetics during intraperitoneal insulin treatment by programmable pumps. Diabetes Metab. 2003;29:344–8.
5. Gin H, Renard E, Melki V, Boivin S, Schaepelynck-Bélicar P, Guerci B, et al. Combined improvements in implantable pump technology and insulin stability allow safe and effective long term intraperitoneal insulin delivery in type 1 diabetic patients: the EVADIAC experience. Diabetes Metab. 2003;29:602–7.
6. Liebl A, Hoogma R, Renard E, Geelhoed-Duijvestijn PH, Klein E, Diglas J, et al. A reduction in severe hypoglycaemia in type 1 diabetes in a randomized crossover study of continuous intraperitoneal compared with subcutaneous insulin infusion. Diabetes Obes Metab. 2009;11:1001–8.
7. van Dijk PR, Logtenberg SJJ, Groenier KH, Haveman JW, Kleefstra N, Bilo HJG. Complications of continuous intraperitoneal insulin infusion with an implantable pump. World J Diabetes. 2012;3:142–8.
8. Spaan N, Teplova A, Stam G, Spaan J, Lucas C. Systematic review: continuous intraperitoneal insulin infusion with implantable insulin pumps for diabetes mellitus. Acta Diabetol. 2014;51:339–51.
9. Schaepelynck P, Riveline JP, Renard E, Hanaire H, Guerci B, Baillot-Rudoni S, et al. Assessment of a new insulin preparation for implanted pumps used in the treatment of type 1 diabetes. Diabetes Technol Ther. 2014;16:582–9.
10. Spaan N, Teplova A, Renard E, Spaan J. Implantable insulin pumps: an effective option with restricted dissemination. Lancet Diabetes Endocrinol. 2014;2:358–60.

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

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

Primary thyroid lymphoma (PTL) is a rare disorder circumscribed to the thyroid gland and locoregional lymph nodes. Disease involvement of other locations should be discarded at the time of diagnosis.[1] It accounts for less than 2–5% of all thyroid gland neoplasms and less than 2.5% of all extranodal lymphomas.[2] Primary thyroid lymphoma shows a greater prevalence in women (a 4:1 proportion), and in most cases develops between 60 and 75 years of age, with a mean age of 67 years.[3] Clinical presentation most often is in the form of a rapidly growing mass that may be painful, and which causes compression symptoms (dyspnea, dysphagia, aphonia, stridor and cough). Associated systemic manifestations (fever, nocturnal perspiration and weight loss) are observed in 10–20% of all cases of PTL.[4,5] The patients usually show a euthyroid profile at the time of diagnosis, though 10% can present primary hypothyroidism.

The present study describes our experience with the management of PTL at three hospitals in Castilla-La Mancha (Spain). We selected those patients with a histological diagnosis of PTL or who presented that diagnosis in the hospital discharge report in the period between 1990 to date, and a retrospective analysis was made of the case histories. Seven patients – all women – with a mean age of 59 years met these characteristics. In all cases PTL presented as a rapidly growing (evolutive course 1–12 weeks), painless thyroid nodule associated with compressive symptoms. Six of the patients (85.7%) presented associated chronic autoimmune thyroiditis, and four (57%) had primary hypothyroidism. The results of the imaging studies are shown in Table 1. Fine needle aspiration biopsy (FNAB) under ultrasound guidance was performed in 6 cases (85.7%). The cytological findings are reported in Table 1. Two patients (including one after FNAB) underwent a core needle biopsy (CNB). Surgical treatment was decided upon in 71% of the cases: total thyroidectomy (TT) in four patients and hemithyroidectomy in one case. Systemic chemotherapy (CT) was provided in all cases. The treatment schemes are shown in Table 1. Three patients (42.8%) also received radiotherapy (RT). No cases of death or PTL relapse were recorded.

Primary thyroid lymphomas are infrequent. Most PTLs are non-Hodgkin lymphomas (NHLs). In turn, 50–80% are diffuse large B cell lymphomas (DLBCLs) and 20–30% are mucosa-associated lymphoid tissue (MALT) lymphomas. Other histological subtypes such as follicular lymphoma, small cell lymphocytic lymphoma, Burkitt's lymphoma (BL), Hodgkin's lymphoma or T cell lymphoma are extremely infrequent.[4] In our series, one patient presented BL, and in two cases coexisting papillary thyroid carcinoma (PTC) was also observed. Although PTC accounts for 85% of all thyroid follicular epithelial cell cancers, the association of PTL and PTC is exceptional, with very few cases reported in the literature to date.[6,7] The risk of suffering PTL increases 80-fold in the presence of chronic autoimmune thyroiditis, though the progression of this disorder to lymphoma is infrequent.[1] On the other hand, the relationship between chronic autoimmune thyroiditis and PTC remains subject to controversy, though the coexistence of both conditions is a clinical reality of still uncertain meaning.[8] A firm diagnosis of PTL often requires surgical biopsy, since most of the cytological explorations show low sensitivity.[4] The role of FNAB in the diagnosis of PTL is limited by the difficulty of establishing a differential diagnosis between lymphoma and lymphocytic infiltration of the thyroid gland. However, the sensitivity of FNAB has increased considerably with the introduction of other techniques such as flow cytometry, immunohistochemical studies or molecular techniques. In our series, a firm diagnosis after FNAB was only obtained in one case (case 2). This was a patient with BL, which represents a more aggressive variant. In case 1 we performed flow cytometry of the FNAB material, and this technique helped to complete the diagnosis of B cell NHL, although lymph node biopsy was also finally performed to establish the definitive histopathological diagnosis. In cases 3 and 5 we performed molecular biological techniques with the CNB material, with confirmation of the histopathological diagnosis without the need for surgery. Staging is made based on the Ann Arbor classification: IE (disease limited to the thyroid gland), IIE (involvement of the thyroid and locoregional lymph nodes), IIIE (lymph node involvement on both sides of the diaphragm) and IVE (diffuse disease). Ninety percent of all PTLs are diagnosed in early stages of the disease,[9] as was confirmed in our series.

Surgery has been the traditional treatment for PTL. Surgery was decided upon in 5 of our patients. In all patients,

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