Insulin pump therapy in children and adolescents with type 1 diabetes: the italian viewpoint

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Abstract. *Background and Aim:* A panel of experts of the Italian Society of Paediatric Endocrinology and Diabetology translated into Italian the international insulin pump therapy recommendations in children and adolescents with type 1 diabetes. *Methods:* After an extensive review of the literature using evidence-based recommendations, several issues were taken into account, such as patient selection, advantages and disadvantages, instrument choice, insulin type, therapy planning and follow-up, emergencies, nutrition, particular occasions (like parties, holidays, sick days, travels), exercise, continuous glucose monitoring and integrated system, neonatal diabetes. The panel evaluated the cost-effectiveness of insulin pump therapy compared to multiple daily injection therapy, analysing the cost-benefit ratio. *Results:* Some tweak was needed due to the Italian dietetic singularity, meal schedule, climate and lifestyle. Insulin pump therapy in neonatal diabetes is a new issue and no guidelines have been published yet for this age-group. Moreover, legal issues according to the Italian law have been added and are peculiarity of our recommendations. An "informed therapeutic agreement" between the patient and his/her family and the diabetic team has to be signed before starting insulin pump therapy. *Conclusions:* We think that nowadays the need for clinical guidelines is important and worth the effort that all countries develop faithful adaptation into their local languages taking into account specific contexts and local peculiarities, without making substantial modifications to the original text. (www.actabiomedica.it)

Key words: Children, adolescents, type 1 diabetes mellitus, insulin pump therapy, CSII recommendation

Introduction

The current goals for the treatment of children and adolescents with type 1 diabetes mellitus (T1DM) include achieving near-normal glycaemia, minimizing the risk of hypoglycaemia, optimizing quality of life, and preventing or delaying long-term microvascular and macrovascular complications (1, 2). Continuous subcutaneous insulin infusion (CSII), provides a treatment option that may assist in the attainment of all of these goals in children of all ages (3, 4). In paediatric patients, CSII has been demonstrated to reduce both glycosylated haemoglobin (HbA1c) levels and frequency of severe hypoglycaemia, without

sacrifices in safety, quality of life, or weight gain, particularly together with the use of new insulin analogs and improvements in pump technology (5-9).

However, there is still a worldwide debate among diabetologists concerning the advantages of CSII over multiple daily injections (MDI), especially in terms of cost-effectiveness ratio (10), stable reduction in HbA1c levels, occurrence of severe hypoglycaemic events, episodes of diabetic ketoacidosis (DKA), and frequency of hospitalizations in young patients (11).

Even if it appears that CSII remains an effective way of intensive insulin therapy, it may be challenged in patients with stable basal insulin needs. Nevertheless, individual factors seem to be decisional in the choice between CSII and MDI using long-acting analogues, among which patient/family ability and skills and will to use an insulin pump are critical.

Consensus Statement from International Societies

In the issue of June 2007 of Diabetes Care (12) a Consensus statement from the European Society for Paediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes was published, endorsed by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes about the use of CSII therapy in the paediatric age-group. For each major topic area, clinical experts were chosen to review the literature and provide evidence-based recommendations according to the criteria used by the ADA.

In their paper (12) the authors concluded that very few long-term studies on pump use in children and adolescents have been published, and almost all of them are observational ones. The vast majority of the studies use a multidisciplinary trained team that usually is not available to the general paediatrician or nonacademic paediatric endocrinologist. This may be a caveat to prescribing CSII. However, based on the available evidence and the experience of the expert panel, CSII therapy may be appropriate for children and youth of all ages provided that appropriate support personnel is available. CSII use in children and adolescents may be associated with improved glycaemic control and improved quality of life (13) and poses no greater, possibly less, risk than MDI. Minimizing the risks of CSII entails the same interventions that promote safety in all patients with type 1 diabetes, including proper education, frequent blood glucose monitoring, attention to diet and exercise, and the maintenance of communication with a diabetes team. Additional risk reduction may be possible with current continuous glucose sensors and will almost certainly decline further with advances in this technology and the eventual development of "closed-loop" insulin delivery systems (14).

The Italian Viewpoint

A panel of experts of the Italian Society of Paediatric Endocrinology and Diabetology (ISPED) translated into Italian the international insulin pump therapy recommendations for children and adolescents with T1DM (12). Some tweak was needed due to the Italian dietetic singularity, meal schedule, climate and lifestyle.

After an extensive review of the literature using evidence-based recommendations (12), several issues were taken into account, such as patient selection, advantages and disadvantages, instrument choice, insulin type, therapy planning and follow-up, emergencies, nutrition, particular occasions (like parties, holidays, sick days, travels), exercise, continuous glucose monitoring and integrated system, neonatal diabetes. The panel evaluated the cost-effectiveness of insulin pump therapy compared to multiple daily injection therapy, analysing the cost-benefit ratio.

The draft of final paper has been shared with all members of the ISPED and gained their approval before submitting it to the executive committee of the ISPED for the final consent.

Patient Selection

The decision to begin pump therapy should be jointly made by the child, parent(s)/guardians, and diabetes team (12). All paediatric patients with T1DM are potential candidates for CSII, and there is no low-

er age limit for initiating CSII (15-18). Due to its cost, however, a careful evaluation has to be done in order to select the "right" patients for CSII therapy and avoid drop-outs.

Moreover, the Italian National Health Service guarantees to all children with diabetes the best care free of charge. The cost of treating diabetes is borne by the Local Health Organizations. So it was necessary to establish the minimum criteria for qualifying and licensing hospitals to prescribe pumps in order to make the criteria uniform throughout the country.

According to international recommendations (12), the indications to start CSII therapy represent: recurrent severe hypoglycaemia, wide fluctuations in blood glucose levels regardless of HbA1c, suboptimal diabetes control, microvascular complications and/or risk factors for macrovascular complications, good metabolic control but insulin regimen that compromises lifestyle. In our recommendations we considered specific indications according to patient age (Table 1). In fact, we think that the criteria to qualify a patient as a candidate for pump therapy may differ depending on age, because every period has different metabolic characteristics. In very young children the main risk is hypoglycaemia, while in adolescents it is the dawn phenomenon and/or insulin resistance (18-22).

Beyond patients indications, both diabetes team (Table 2) and patient/family prerequisites (Table 3) have to be taken into great account. In Italy, it is essential that all hospitals show these characteristics and are integrated into the Italian Health Organisation in order to start insulin pump therapy.

Table 1. Indications for the use of the pump in children of different ages

Pre-school and school age children
• Recurrent hypoglycaemia
• Wide fluctuations in blood glucose levels
• Very low insulin needs and difficulty of splitting the dose
• Needle phobia
Puberty and adolescence
• Dawn phenomenon
• Insulin resistance
• Recurrent hypoglycaemia
• Impaired metabolic control
• Improvement of quality of life

Table 2. Characteristics qualifying and licensing hospitals to prescribe CSII in Italy

1. Paediatric Diabetes Team specialized in using and teaching CSII therapy
2. Medical availability 24/7
3. Collaboration among all the medical figures involved in the care of a child with pump (i.e, general practitioner, family paediatrician, ER doctors, physician, etc)

Table 3. Patient/family characteristics qualifying patients as candidates for pump therapy

1. Consent to wear the pump
2. Motivation of patient and family
3. Education about therapy and glycaemic control
4. Willingness to check blood sugar levels often

The main counter-indication to CSII therapy is the lack of one of the characteristics indicated in the Table 2 and 3, regardless of the indications.

The timing of pump initiation remains an important consideration for the family and health care team in optimizing the likelihood of successful implementation and outcomes. Considering the total free of charge system of the Italian Health Organisation, it is important to avoid drop-outs. Thus, it is useful that patients who are candidates for pump therapy go through an appropriate period of MDI therapy before starting with the pump. In fact, there is no scientific evidence of any advantages in the use of CSII therapy at the onset of T1DM.

Discontinuation of CSII should be considered if counter-indications arise during the treatment.

Nutritional Issues

Although Italy, over the last several decades, has suffered from some negative effects of excessive "westernisation" in dietary habits, it still remains the cradle of the Mediterranean diet, the ideal one for patients with T1DM, as stated by most guidelines (23-25).

A balanced diet containing 55-60% of carbohydrates from cereals, fruit and vegetables is a well recognised cornerstone. It is not only the quantity of carbohydrates that matters, but also their type or source, the composition of the meal (macronutrients

and fibre content), digestibility and the cooking method that influence post-prandial glucose levels.

Therefore, insulin therapy using CSII must be adjusted to the dietary plan. Since most recent pumps have several features like special boluses (simple, square and double-wave), bolus calculator, insulin on board, it is necessary more than ever before, especially in Italy, due to our kind of diet, to use all these advanced functions. In fact, it is possible to take into account the quantity and type of carbohydrates and fibres, the glycaemic index of the meal and the duration of intestinal absorption of carbohydrates and other nutrients.

Every diabetes team must include the figure of a skilled dietician (26) to accomplish well-planned nutritional services, and provide: 1) an initial phase of structured nutritional education furnishing fundamental information about diet and nutritional requirements, guidelines for nutritional management of the diabetic patient and a guide for putting into effect the initial dietary changes regarding the choice of foods, with particular attention to the carbohydrate content; 2) an advanced phase, during which the nutritional action becomes more dedicated and structured, according to the needs of the patient, his/her lifestyle and the therapeutic goals.

Even if within certain limitations, there are some instruments that can be useful to achieve the best results: 1) carbohydrate counting, 2) dietary diary, and 3) recipes and cookbooks.

Carbohydrate counting represents the gold standard for those patients using insulin pumps who have irregular dietary habits and require extreme flexibility. Anyway, carbohydrate counting should not be used in an uncritical manner (27,28), but it can be a useful instrument to adjust and adapt the dose and distribution of the insulin with respect to the absorption times of the carbohydrates in a single meal.

Both insulin sensitivity factor and insulin-carbohydrate ratio are important for finding the most effective insulin dose for each meal (or even just for correcting hyperglycaemia). These correcting factors are difficult to be determined in paediatric age. Therefore, it is very important to personalise and find the right factors establishing on empirical rules (29), but mainly by trial and error.

Exercise

A major challenge in managing insulin therapy is the lean reproducibility of the metabolic effects of the subcutaneously injected insulin. CSII reduces the intra-individual variability of absorption, since insulin is administered in the same site for the duration of the subcutaneous cannula (i.e., 2-3 days) and may prevent exercise-linked hypoglycaemia and hyperglycaemia (30,31) (Table 3).

The Italian approach to exercise and CSII aims at giving detailed indications about the insulin infusion modifications during and/or after exercise in order to prevent acute and/or post-exercise hypoglycaemia and hyperglycaemia (32-37).

We suggest to check blood sugar readings before exercise, and when possible also during it. It is very important to check glycaemia also after exercise in order to prevent post-exercise hypoglycaemia (37). Knowing the glycaemic trends to physical activity enables the patient to modify the therapy accordingly.

Low intensity exercise does not generally affect the blood glucose level unless activities are performed for more than 30 min; for extended exercise, adjustments may involve basal infusion rate, bolus doses or both (37).

Accurate adjustments of the insulin dose have to take into account: time, exercise intensity and duration, training and last but not least the individual's response to exercise. These adjustments might be made on a trial and error basis (Table 4).

Some indications for a fine-tuning of CSII therapy are listed below:

- reduce the pre-meal bolus, if exercise starts within 1-3 hours of meal;
- it may be useful to reduce the insulin dose before the next meal;
- decrease the basal rate by 50% during exercise;
- it may be useful to decrease basal rate 30-60 min before starting exercise;
- sometimes, instead of reducing basal rate, the pump may be switched off or disconnected;
- if suspension lasts over 2 hours, take extra bolus before and/or during suspension of CSII;
- reduce overnight basal insulin delivery by 10-30% to avoid late onset hypoglycaemia;

Table 4. Advantages and disadvantages of CSII therapy during exercise

Advantages	Disadvantages
Decrease glycaemic variability	Visibility of the pump
Management of hypoglycaemia and hyperglycaemia	"Forget" diabetes
Unplanned exercise	Need for prolonged disconnection
Management of unexpected event	Risk of detachment of catheter
	Blockage in the infusion set

- take extra carbohydrate every 30-60 minutes during exercise;
- for unplanned exercise, often seen during paediatric age, stop insulin administration by simply disconnecting the pump;
- in the presence of hyperglycaemia (over 250 mg/dl) and ketosis, exercise is not recommended;
- in the presence of hyperglycaemia alone, check glycaemic trend and administer insulin if necessary;
- if pre-exercise glycaemia is <100mg/dl, feed some carbohydrate before starting exercise.

This advice may be a starting point from which each patient could find the optimal practice for his/her individual situation. The exact adjustments of the insulin dose need to be made on an individual basis, learning by trial and error.

Cost-effectiveness

We have reviewed the cost-effectiveness of CSII in children in the context of possible improvement of percentage of HbA1c and of other clinical benefits over MDI. Cost-effectiveness depends on clinical efficacy but reported clinical efficacy parameters may overlook definite benefits perceived by children and parents using CSII. There are few detailed reports on cost comparisons between CSII and MDI in adults (38), even less in children or adolescents (10, 38, 39).

Actually in Italy, review of direct extra costs for CSII over MDI, suggests an extra-cost of about 3600 EUR, and with a rough cost of CSII per patient per year of about 4237,4 EUR that can be reduced to 4046,5 EUR per patient per year breaking-up the cost of devices exclusive for MDI therapy (Table 6). Randomized comparisons between CSII and MDI in childhood and adolescence show few marked clinical effects, but non-randomized comparisons favour CSII. Quality of life parameters fall short in such comparison in children and adolescents alike. There is a dire need for better parameters to assess the well-being of diabetic children treated by CSII or MDI. Only then is it warranted to estimate the cost-effectiveness of CSII vs. MDI in childhood and adolescence (10).

Neonatal Diabetes

Neonatal diabetes is now growing and face the diabetes team with many therapeutic challenge. CSII therapy provides more flexibility to adjust to rapid increases and variability of caloric and food intake. Moreover, the risk of severe hypoglycaemia in newborns requires fine tuning of insulin dosage (12, 40).

A low total insulin requirement (1-3 U/day) needs insulin dilution. This requires a very low hourly insulin basal rate (< 0,015 U/h) and the need for dilution U4, U10 (40-43). Insulin Lispro (Humalog®, Eli Lilly®) can be diluted with Lilly sterile diluent ND-800® (Ely Lilly®) (42). In vitro Aspart® (Novorapid®, Novo Nordisk®) had been shown at U10 and U50 concentration with sterile diluent for NPH (Protaphane, Novo Nordisk®). No significant degradation of biological potency was found after 7 days (44).

Table 5. Insulin adjustments during exercise

Intensity of exercise	Bolus %	Basal infusion %	
Low	- 25-50	- 10-30	These adjustments could be combined and also personalized
Moderate	- 50-75	- 10-30	
High	- 75-100	- 40-50	

Table 6. Extra-cost estimation of CSII vs MDI therapy

	Cost (*) (€)	Need	Need per year (n)	Cost per year (€)
Extra-cost estimation of CSII therapy				
Pump	5226,5		0,25	1306,6
Infusion set	22,0	1 every 3 days	121,7	2675,8
Battery	2,5	1 every 30 days	12	30,0
Cartridges / Adaptators / Syringes	3,1	1 every 3-5 days	73,0	225,0
Total (of extra-cost)				4237,4
Estimation of cost reduction with CSII therapy				
Pen's needles	0,08	4,5/day	1642,5	131,4
Insulin (cost per U)	0,043	-3 UI/day	730	47,5
Pens	24	1 every 2 years	0,5	12,0
Total (cost saving)				190,9
Total (extra-cost less cost-saving)				4046,5

* Cost estimation based on the prices declared by the three Companies now operating in Italy (Animas, Medtronic, Roche) at January 30th 2007

The total daily dose could widely vary. A daily requirement of 0,2-1,4 U/Kg/day was used (40, 41, 43). The basal rate usually represented 20-50% of the total dose given (40, 41, 43). Some authors argue a basal rate of 0,3 U/kg/h. Other ones used an initial dose of 0,01 U/h with subsequent adjustement on the basis of glycaemic values or they determined the initial basal rate on the basis of pre-CSII need (40, 41, 43).

Rapid bolus or square bolus (30-60') were used (40, 43, 45). Sometimes the bolus was delivered after meals (42). Pre-meal bolus of 0,05-0,2 U/meal (40, 42, 43, 45) or 0,01-0,1 U every 10-15 g of carbohydrate (42, 43).

We propose a correction factor of 0,1 U every 100 mg above 150 mg/dl of glycaemia (43).

Legal Issues

We decided to add a part about legal issues to our recommendations in order to fulfill the Italian most recent law indications. In fact, in our legal order it is stated that "none may be obliged to undergo any given medical treatment except under the provisions of the law" (Italian Constitution, art. 32). From this regulation it follows that when a patient gives his consent to medical treatment, he is not legitimising damage to an existing right, but exercising a constitutional right of his own.

The right to self-determination in medicine does not mean only the right to health, but is connected to the general right to freedom of the individual (Constitutional Court, October 22nd 1990, n 471).

Another important juridical foundation of informed consent is the new Italian Deontological Code (December 2006), in particular at the art. 35 where it is stated: "The doctor must not begin diagnostic and/or therapeutic treatment without the patient's explicit and informed consent. The consent is supplementary to, and does not replace information". It is important to say that the previous deontological code used the expression "informed consent", whereas the new one has substituted it with "explicit and informed consent": this means that presumed consent, either tacit or implicit, is no longer acceptable.

Therefore, taking legal medical advice into account, we decided to propose an "informed therapeutic agreement" about the use of insulin pump therapy between the patient and his/her family and the diabetic team.

Conclusions

We think that nowadays the need for clinical guidelines is important and worth the effort that all countries develop faithful adaptation into their local

languages taking into account specific contexts and local peculiarities, without making substantial modifications to the original text.

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