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NOCTURNAL HYPOGLYCEMIA – THE MAIN INDICATION FOR INSULIN PUMP THERAPY IN ADULTHOOD

Maja Baretić, Ivana Kraljević and Ivana Pavlić Renar

Department of Endocrinology, Clinical Department of Internal Medicine, Zagreb University Hospital Center, Zagreb, Croatia

SUMMARY – The aim was to determine which adult type 1 diabetic patient receiving multiple daily injection therapy is the most appropriate candidate for insulin pump therapy, while taking into consideration limited insulin pump affordability in Croatia. A total of 145 type 1 diabetic patients (52% diagnosed in adult age) were monitored at the Department of Endocrinology, Clinical Department of Internal Medicine, Zagreb University Hospital Center from 2009 to 2014. Twenty-one patients started insulin pump therapy in adulthood (seven men and 14 women, median age 27). Five patients had chronic complications (retinopathy in two, polyneuropathy in one, and both nephropathy and retinopathy in two patients). The median HbA1c at the initiation of pump therapy was 6.95% *versus* 6.5% after 1 year of pump therapy. Patients were stratified according to indications for insulin pump therapy (frequent and/or severe hypoglycemia, specific lifestyle, having not reached glycemic goals despite adherence/labile diabetes, and preconception). Patients could meet more than one criterion. Initially, the occurrence of hypoglycemia was analyzed by 6-day continuous glucose monitoring, while re-evaluation was done after collecting history data at 1 year ± 3 months. Initially, all patients had a median of 5 hypoglycemias/6 days (30% nocturnal) *versus* 1 hypoglycemia/6 days (without nocturnal) after 1 year. The Wilcoxon signed-rank test yielded a statistically significant difference in hypoglycemic events, nocturnal hypoglycemia and HbA1c. Patients commencing insulin pump therapy due to hypoglycemia initially had median HbA1c of 6.7% with 7 hypoglycemia/6 days (50% nocturnal). After one year, median HbA1c was 6% with 1 hypoglycemia/6 days (without nocturnal). In conclusion, the main indication for insulin pump therapy in adults is the frequency of hypoglycemia, especially nocturnal ones.

Key words: *Diabetes mellitus, type 1 – complications; Hypoglycemia prevention and control; Insulin – pump administration and dosage; Insulin infusion systems; Insulin pump; Adult*

Introduction

According to the most recent report of the Croatian National Institute of Public Health from 2013, there were 241,990 adult persons suffering from diabetes registered with their general practitioners. Of these cases, 6.96% were classified as type 1[1]. The International Diabetes Federation (IDF)-Europe Access survey conducted in Croatia showed that most patients treated with insulin were using insulin analogues and insulin pens. This type of therapy is available across the country[2]. Only 611 patients with type 1 diabetes in Croatia were treated with insulin pumps, of which 384 were children and 227 adults (data from the sole distributor as of October 2014). The survey[2] claims that the use of insulin pumps in Croatia is limited, and that the pumps are more widely available in the capital than in other areas. They are primarily given to children and pregnant women.

Type 1 diabetes is a condition where insulin replacement therapy is life-saving. The standard basal-

Correspondence to: *Maja Baretić, MD, PhD*, Department of Endocrinology, Clinical Department of Internal Medicine, Zagreb University Hospital Center, Kišpatićeva 12, HR-10000 Zagreb, Croatia
E-mail: maja.simek@zg.t-com.hr

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bolus treatment administering multiple daily injections is sometimes associated with practical problems and requires an alternative solution. The use of insulin pump moderately improves glycemic control as revealed in meta-analyses[3,4], as well as in multicenter observational studies[5]. Patients that do not reach glycemic goals despite being compliant with multiple daily injections or have problems such as too frequent or unrecognized hypoglycemia, i.e. dawn phenomenon, are candidates for continuous subcutaneous insulin infusion (CSII), e.g., insulin pumps. Those who exhibit allergy to prolonged acting insulin are also candidates for CSII[6]. There is no strict evidence that CSII treatment in pregnancy is superior to a multiple injection regimen in lowering hypoglycemia rates (lack of randomized trials). Though, it is clear that patient satisfaction is an acceptable indication for pump therapy during pregnancy[7]. Beyond childhood, preconception and pregnancy, the indications for insulin pump are brittle diabetes with many glycemic excursions, frequent severe hypoglycemia and/or hypoglycemia unawareness, dawn phenomenon, high insulin sensitivity and a specific lifestyle (e.g., shift work, travel and sports). A small observational study confirmed the beneficial effect of CSII in post-exercise hypoglycemia[8]. Not every patient showing the mentioned indications is suitable for this kind of demanding and sophisticated technology. Selecting an optimal candidate is not easy, especially when the number of devices is limited. Although there are no published local guidelines, Croatian diabetologists generally follow the American Association of Clinical Endocrinologists (AACE) and National Institute for Health and Clinical Excellence (NICE) guidance in selecting patients for pump treatment.

Patient Population

During a 5-year period (2009-2014), 164 patients with type 1 diabetes were monitored at the Department of Endocrinology, Clinical Department of Internal Medicine, Zagreb University Hospital Center. The proportion of patients diagnosed in adult age was 52%. For the remaining 48% that developed diabetes in childhood, transition from a pediatric diabetologist to adult one was performed. Over a 5-day period, 84 patients attended a structured education program that included daily consultations with a multidisciplinary healthcare team. The team was led by an endocrinologist-diabetologist and included a nurse-educator, nutritionist, physical medicine specialist and psychiatrist who provided psychological support. Of the 164 patients, 26 (15%) patients (eight male and 18 female) were treated with insulin pump. All of them went through the structured (re)education program. They were subsequently capable of self-management in administering both multiple daily injections, instructed for optimal usage of CSII technology and taught to count carbohydrates and determine insulin doses correctly. Five patients started using CSII before the age of 18 at Clinical Department of Pediatrics, whereas 21 adult patients did the same at the Department of Endocrinology. The median age when commencing pump therapy was 27 (age range 21-39) years. Five patients had chronic complications, i.e. retinopathy in two, polyneuropathy in one, and both nephropathy and retinopathy in two patients.

Data on 21 patients previously treated with multiple daily injections who commenced insulin pump therapy in adulthood were retrospectively analyzed. Finally, 20 patients were analyzed because one of them had started insulin pump therapy only recently and had no closing data. Data were analyzed using descriptive statistics, after which nonparametric Wilcoxon signed-rank test and correlation analysis were performed. Statistical analysis was performed using SPSS 15.0 (SPSS, Chicago, IL, USA), with the level of statistical significance set at $p<0.05$.

Results

The median HbA1c upon commencing insulin pump therapy was 6.95% (5.3%-11.4%). After 1 year ± 3 months of CSII therapy, the median HbA1c was 6.5% (4.9%-8.4%). The Wilcoxon signed-rank test ($p=0.0006$) confirmed a statistically significant difference between the initial median and one-year value of HbA1c.

The indication for insulin pump therapy was determined by the diabetologist-endocrinologist on the basis of personal judgment, and documented in the patient's medical records. There were four main indication groups for CSII: 1) frequent and/or severe hypoglycemia; 2) specific lifestyle, e.g., shift work, sports; 3) the patient did not reach glycemic goals despite adher-

ence and/or labile diabetes; and 4) preconception, e.g., planned pregnancy with expected complications.

A patient could meet more than one criterion. The most frequent indication was hypoglycemia found in 57% of cases, followed by specific lifestyle indication 47%, failure to reach glycemic goals despite good compliance in 29% of patients, and planned pregnancy with expected complications in 29% of female patients.

Initial occurrence of hypoglycemia was analyzed using 6-day continuous glucose monitoring. The next evaluation took place after one year with the hypoglycemia incidence estimated using history data. The initial median number of hypoglycemic events during the 6 days was 5 (0-6) in all patients. Hypoglycemic events that occurred during the night were expressed in percentages with an initial median value of 30% (0-100%). After one year, 20 patients were analyzed again. The second evaluation resulted in a median value of 1 (0-7) hypoglycemic event during a 6-day period, with 0% of all hypoglycemias being nocturnal. The total number of hypoglycemias was significantly lower after one year (p=0.000). The median percentage of nocturnal hypoglycemia after one year of CSII therapy was 0. There was no correlation between the initial level of HbA1c and the number of hypoglycemias (Spearman's rank correlation coefficient was equivalent to -0.3, p value in the test was not significant, p=0.392), and after one year there was no significant correlation (Spearman's rank correlation coefficient was equivalent to -0.18, p=0.307).

Eleven patients that commenced insulin pump therapy due to an indication of hypoglycemia were analyzed separately. Upon commencing pump therapy, their median HbA1c was 6.7% (5.3%-9.4%), with a median of 7 (4-21) hypoglycemias over a period of 6 days, and a median of 50% (0-100%) nocturnal hypoglycemia events. After one year, the median HbA1c was 6.0% (4.0-8.4%), and a median of 1 (0-7) hypoglycemia in 6 days, again with 0% of all hypoglycemias being nocturnal. There was a statistically significant difference between the HbA1c value before and after CSII therapy (p=0.050), between the initial number of hypoglycemic events and their number after one year (p=0.003). There was also a statistically significant difference between the initial number of nocturnal hypoglycemic events and the number of nocturnal events after one year of CSII therapy (p=0.011).

In nine patients, the indication for insulin pumps was a specific lifestyle. Of these, four patients worked in shifts, four patients were sporting enthusiasts performing high-intensity exercises on daily basis, and one was mother with type 1 diabetes having specific needs. Only two of the patients with an indication were from the hypoglycemia group. Their initial median HbA1c was 7.4% (6.8%-11.4%), and after one year it decreased to 6.75% (6%-7.8%; p=0.035).

Six patients did not reach glycemic goals before commencing CSII therapy despite good adherence, or had brittle diabetes. Three of them also had an indication in the hypoglycemia group, another three of these young patents already had chronic complications of the disease, two of them suffering from both severe kidney disease and retinopathy and one having painful polyneuropathy. Two patients had dawn phenomenon, one with extreme labile diabetes including frequent ketoacidosis and hypos. The initial median value of their HbA1c was 8.9% (6%-11.4%), and after one year it decreased to 7.14% (6%-8.4%), yielding a statistically significant difference (p=0.028). The initial median value of all hypoglycemic events was 7 (0-20) over a 6-day period, and after one year it was 1 (0-7) hypoglycemia in 6 days, but the difference was not statistically significant (p=0.068). When analyzing the CSII basal rate levels of these patients, large discrepancies of insulin needs during various periods of the day became apparent.

Five female patients had an indication for the use of insulin pump due to anticipated high-risk planned pregnancy (diagnosis such as chronic renal failure grade IV with nephritic syndrome, previous intrauterine fetal demise and spontaneous miscarriages, labile diabetes with frequent hypoglycemia followed by epileptic seizures, severe retinopathy, and allergic reaction to insulin analogues). An indication of hypoglycemia was shown in three of these five patients. Five patients gave birth (one of them twice, so there were 6 pregnancies) and one patient without an initial indication of preconception care is currently pregnant. The median age at conception was 26 (25-31) years. On average, they wore an insulin pump for 10 months before conception. Their initial median HbA1c when initiating pump therapy was 6.15% (6%-8.9%), at the time of conception the median HbA1c was 5.31% and for all 6 pregnancies the median HbA1c in the third tri-

mester was 5.28%. All deliveries were performed using elective cesarean section at 38±2 weeks, and only one child briefly stayed in the neonatal intensive care unit for observational purposes (Apgar 10/7). The median weight of the newborns was 3.255 (2.670-4.870) g and median length 48.5 (47-55) cm.

Discussion

According to large studies, estimates show that 5% of type 1 patients optimally treated with multiple daily insulin injections suffer from severe hypoglycemia. At least another 5% undergo hypoglycemia to such an extent that they experience significant disability on a daily basis. Furthermore, 15% of type 1 diabetic patients have elevated HbA1c with extensive fluctuations in blood glucose and unpredictable, moderate hypoglycemia. A small proportion of these have dawn phenomenon[9-12]. Presumably, 15%-20% of type 1 patients would significantly benefit from the use of insulin pump[13], with a similar percentage of 12% as suggested by the NICE TA151 guidelines[14].

If patients have the option of deciding for themselves whether to take CSII therapy without primary medical indication, the number could be much bigger. The percentage of pump users among type 1 diabetics differs significantly among countries[15]. The highest incidence is in the USA (37.8% in 2009, significantly higher than 17% five years earlier)[16]. It should also be noted that, although NICE estimates the need of pump therapy in 12% of type 1 diabetics, a 2011 audit in the UK revealed that there were significantly less (around 6%) users[17]. In Croatia during 2013, there were approximately 16,800 adult type 1 diabetic patients[1]. In October 2014, there were 611 insulin pumps in use for both pediatric and adult type 1 diabetics, yielding approximately 3.4% (including around 1000 children with type 1 diabetes) of patients with type 1 diabetes treated with CSII therapy. However, there is the issue of estimating the actual number of persons with type 1 diabetes. For example, the Swedish National Diabetes Registry has reported 18,168 persons with type 1 diabetes (15% of them pump users)[18] in a country with a population roughly double that of Croatia (9,640,000 *vs.* 4,290,000). The Swedish Registry considers type 1 insulin-requiring diabetes the one appearing before the age of 35. The Croatian Registry does not specify the age at onset.

At Department of Endocrinology, Clinical Department of Internal Medicine, Zagreb University Hospital Center, 15% of adult type 1 diabetic subjects were treated with insulin pumps. This fact confirms the above IDF statement about the disproportionate use of insulin pumps across the country[2].

An essential indication for the use of CSII is hypoglycemia, a side effect of the life-saving insulin therapy. Hypoglycemias occur even when insulin is administered in the best possible manner using multiple daily injections, analogues and pens in a compliant and trained patient. Other indications for CSII are of great importance for everyday life, although they are not immediately threatening; however, they are threatening at long term due to the inability to reach the HbA1c target and prevent the onset of chronic complications. Some indications are a matter of personal choice (shift work, sports, or pregnancy planning). Hypoglycemic events are noted in all guidelines as a key indication for CSII therapy[6,14,19]. When taking this into consideration, it is no wonder that a diabetologist's personal judgment in most indications for CSII includes hypoglycemia.

In all study patients, there was a significantly lower incidence of hypoglycemia after one year of insulin pump therapy (5 events in 6 days *vs.* 1 event in 6 days), along with a significantly lower HbA1c (6.95% at the beginning *vs.* 6.5% after one year). Their initial HbA1c showed a weak negative correlation with hypoglycemic events, confirming that some diabetic patients are prone to hypoglycemia despite more flexible HbA1c goals (the mean HbA1c upon commencing pump use was not very low), e.g., some of the patients had severe and frequent hypoglycemia despite undergoing suboptimal glycemic control.

The group of patients with hypoglycemia as a specific indication for insulin pump had about 7 hypoglycemic events in 6 days, with about 50% of them being nocturnal. They actually had a hypoglycemic event every other night. After one year of therapy, hypoglycemic events became rare (1 event in 6 days), and virtually no nocturnal events. This was accompanied by a strict goal of HbA1c value of 6.0%. A typical patient with type 1 suffers on average two episodes of symptomatic hypoglycemia *per* week, and one episode of severe hypoglycemia *per* year[20]. After one year of CSII, patients that had previously had frequent hypoglycemic events became 'average type 1 patients'.

The lifestyle indication is not a crucial one, and the consequences of insulin pump therapy are not easy to describe in numbers alone. Physical activity is extremely important for some young patients with type 1 diabetes mellitus. Survey of a small group of 28 patients completing 5 days of structured education at the Department of Endocrinology, Clinical Department of Internal Medicine, Zagreb University Hospital Center, showed that 87.5% of patients undergoing moderate to high intensity activities achieved a minimum of 600-1500 MET (Metabolic Equivalent of Task) minutes/week as scored by the International Physical Activity Questionnaire (IPAQ)[21]. Two patients managed to go bike riding from the northern to the southern end of the Croatian coast, cycling about 850 km with no hypoglycemia, ketoacidosis or larger glycemic excursions. One of the patients had a lifestyle indication and was a medical doctor working shifts in the emergency ward 3-5 times a month. Another patient was a nurse working a similar schedule and did not experience any larger excursions. One of the patients was mother of a child with type 1 diabetes, experiencing frequent nocturnal glycemic excursions. After one year of CSII therapy, these patients had no hypoglycemia, but most important is that they were able to perform their duties and physical exercises almost without any limitations posed by diabetes, and experienced HbA1c improvement (7.4% *vs*. 6.75%).

For patients who did not reach the glycemic goal with multiple daily injections, or had labile diabetes, insulin pump was also a good choice. Their final HbA1c was 7.14% as a result of frequent diurnal basal rate fluctuations, whereas such variations were not possible using conventional therapy.

The last indication for CSII was planned pregnancy in association with some anticipated complications not necessarily related to diabetes. The outcome of such a high-risk pregnancy is not easy to predict. A recent multicenter study in women using insulin pumps during pregnancy, just like in our small group, indicated a lower HbA1c without an increased risk of severe hypoglycemia[22]. All the patients wore insulin pump before becoming pregnant and started their pregnancy well prepared (were well educated and informed about lower targets). The preconception HbA1c was 5.31%, and in the third trimester it was of a similar value of 5.28%, with a low incidence of hypoglycemia. The general result of other pregnancy outcomes is not possible to statistically evaluate in only 6 cases; however, in those pregnancies CSII therapy was effective and safe.

Conclusion

Despite administering insulin basal bolus therapy using multiple daily injections, insulin analogues, pens, undergoing intensive education and re-education, hypoglycemia is still a major clinical problem for patients with type 1 diabetes. While awaiting the development of other therapeutic choices, insulin pump provides an effective option for patients experiencing severe, frequent hypoglycemic events, especially nocturnal ones. For patients with a specific lifestyle, CSII alleviates the limitation set by insulin dependent diabetes. For those who do not reach glycemic targets or have labile diabetes, insulin pump can improve glycemic control. In pregnant women with type 1 diabetes, it provides a safe way to adhere strictly to glycemic targets.

The modest experience acquired in our center confirms that hypoglycemia is the major reason for pump therapy. All patients improved their blood glucose regulation, indicating that the current patient selection process seems to work. However, local guidelines on further development would be of help. Additionally, reimbursement policy as well as education for patients and professionals could help overcome the disproportional use of pumps in various parts of the country.

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Sažetak

NOĆNA HIPOGLIKEMIJA – VODEĆA INDIKACIJA ZA TERAPIJU INZULINSKOM CRPKOM U ODRASLIH

M. Baretić, I. Kraljević i *I. Pavlić Renar*

Cilj studije bio je istražiti koji su odrasli bolesnici s tipom 1 dijabetesa liječeni s više dnevnih doza inzulina najbolji kandidati za liječenje inzulinskom crpkom, uzimajući u obzir njihovu ograničenu dostupnost u Republici Hrvatskoj. Na Zavodu za endokrinologiju Interne klinike Kliničkoga bolničkog centra Zagreb praćeno je 145 bolesnika s tipom 1 dijabetesa (kod 52% njih je bolest dijagnosticirana u odrasloj dobi) u razdoblju od 2009. do 2014. godine. Kod 21 bolesnika (7 muškaraca i 14 žena, medijan dobi 27 godina) liječenje crpkom započelo je u odrasloj dobi. Petoro bolesnika je imalo kronične komplikacije (dvoje retinopatiju, jedan polineuropatiju, a dvoje je imalo i retinopatiju i neuropatiju). Medijan HbA1c prije započinjanja liječenja inzulinskom crpkom je bio 6,95%, a nakon godine dana terapije crpkom 6,5%. Bolesnici su bili razvrstani prema indikaciji za liječenje crpkom (učestale i/ili teške hipoglikemije, specifičan stil života, nepostizanje željenih ciljeva glikemije unatoč suradljivosti/nestabilan dijabetes te pretkoncepcija). Bolesnici su mogli ispunjavati i više od jedne indikacije. Na početku liječenja učestalost hipoglikemija se analizirala kontinuiranim praćenjem glukoze tijekom 5-6 dana, a reevaluacija je učinjena iz anamnestičkih podataka nakon 1 godine ± 3 mjeseca. Na samom početku liječenja bolesnici su imali 5 hipoglikemija/6 dana (30% noćnih), a nakon godine dana 1 hipoglikemiju/6 dana (bez noćnih). Wilcoxonov *signed-rank* test pokazao je statistički značajnu razliku u broju i učestalosti noćnih hipoglikemija te u HbA1c. Kod onih bolesnika u kojih je liječenje započelo inzulinskom crpkom s indikacijom hipoglikemije prije crpke medijan HbA1c je bio 6,7% sa 7 hipoglikemija/6 dana (50% noćnih). Nakon godinu dana medijan HbA1c je bio 6% s 1 hipoglikemijom /6 dana (bez noćnih). Kao zaključak, vodeća indikacija za liječenje inzulinskom crpkom u odraslih bolesnika je učestalost hipoglikemija, osobito noćnih.

Ključne riječi: *Dijabetes melitus, tip 1 – komplikacije; ; Hipoglikemija – prevencija i kontrola; Inzulin – primjena i doziranje; Inzulin, sustavi za infuziju; Inzulinska crpka; Odrasla osoba*