Effect of intravenous versus subcutaneous insulin delivery on the intensity of neuropathic pain in diabetic subjects

Porównanie dożylnego i podskórnego podawania insulin na intensywność bólu neuropatycznego u chorych na cukrzycę

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Abstract

Introduction: The effectiveness of treatment of painful diabetic polyneuropathy remains unsatisfactory. The aim of this study was to compare effects of intravenous *vs.* subcutaneous insulin delivery in patients with diabetic symmetric sensorimotor polyneuropathy on pain relief, the quality of life, sleep disturbance, and the nerve conduction.

Material and methods: Thirty-four patients with diabetic polyneuropathy (mean age 62 ± 10 years, duration 17 ± 10 years), who reached a pain score over 40 mm on the VAS scale, HbA_{1c} 7.5–10%, were randomly assigned to continuous intravenous insulin infusion (examined group) and multiple injections (control subjects). Before and after five days of the insulin treatment the effects on pain relief (SFMPQ-VAS), the quality of life improvement (EuroQol EQ-5D), and sleep disturbances (AIS) were assessed.

Results: Both groups experienced significant pain reduction, improvement of the quality of life, and reduction of sleep disturbances, i.e. a VAS in the study group of 69 ± 14 mm before treatment *vs.* 40 ± 19 mm after treatment ($p < 0.001$), and in control subjects 66 ± 16 mm *vs.* 47 ± 17 mm ($p < 0.001$).

No difference in level of pain intensity reduction between the groups studied was found.

Conclusions: Intensification of insulin treatment applied for five days results in improvement of the physical condition of patients with painful diabetic polyneuropathy, through pain relief, and improvement of the quality of life and sleep quality. The efficacy of insulin intravenous infusion and multiple injections is comparable. **(Endokrynol Pol 2015; 66 (3): 237–243)**

Key words: *diabetes mellitus; diabetic complications; painful diabetic polyneuropathy; insulin treatment; insulin intravenous infusion*

Streszczenie

Wstęp: Skuteczność leczenia bólowej polineuropatii cukrzycowej jest niesatysfakcjonująca. Celem badania była ocena wpływu dożylnej lub podskórnej podaży insuliny u chorych z symetryczną bólową polineuropatią czuciowo-ruchową na: stopień nasilenia bólu, poprawę jakości życia, ilościową i jakościową ocenę snu oraz przewodnictwo czuciowo-ruchowe w nerwach strzałkowym i łydkowym.

Materiał i metody: 34 chorych z cukrzycową polineuropatią (średni wiek chorych 62 ± 10 lat, czas trwania cukrzycy 17 ± 10 lat), z nasileniem bólu > 40 mm w skali VAS i HbA_{1c} 7,5–10% zostało losowo przydzielonych do grupy otrzymującej dożylny wlew insuliny (grupa badana) lub podskórne wstrzyknięcia insuliny w modelu wielokrotnych wstrzyknięć (grupa kontrolna). Oceniono wpływ leczenia na nasilenie bólu (SFMPQ-VAS), jakość życia (EuroQol EQ-5D) i zaburzenia snu (AIS).

Wyniki: Zaobserwowano znamienne zmniejszenie nasilenia bólu, poprawę jakości życia oraz snu. VAS w grupie badanej 69 ± 14 mm przed i 40 ± 19 mm po leczeniu ($p < 0,001$), w grupie kontrolnej odpowiednio 66 ± 16 mm i 47 ± 17 mm ($p < 0,001$). Nie obserwowano różnic pomiędzy grupami.

Wnioski: Intensyfikacja insulinoterapii stosowana przez 5 dni powoduje poprawę stanu klinicznego chorych na cukrzycę powikłaną bólową polineuropatią poprzez: zmniejszenie nasilenia bólu, poprawę jakości życia, poprawę parametrów snu. Zastosowanie wlewu dożylnego insuliną ma porównywalną skuteczność jak iniekcje podskórne. **(Endokrynol Pol 2015; 66 (3): 237–243)**

Słowa kluczowe: *cukrzyca; powikłania cukrzycy; bólowa polineuropatia cukrzycowa; insulinoterapia; dożylna podaż insuliny*

Introduction

Diabetic neuropathy is a heterogeneous group of symptoms and/or signs of dysfunction of the peripheral nervous system resulting from diabetes mellitus, provided that other possible causes are ruled out [1]. Symmetric chronic sensorimotor polyneuropathy that usually develops slowly and insidiously is the most common clinical form of diabetic neuropathy. It is a serious problem in modern diabetology. Pain is the

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basic clinical problem in patients with advanced diabetic polyneuropathy. Patients usually report symmetric pain in the lower extremities, occurring spontaneously, without any discernible cause. Studies have demonstrated that patients with such pain experience significantly reduced quality of life. Therefore, if the treatment effectiveness is assessed, one should consider subjective patient's experiences related to intensity of pain and improvement of quality of life. The drugs used in the treatment of diabetic neuropathy include agents that act on the causes of the neuropathy and symptomatic agents. Drugs that are directed at the pathogenesis of diabetic polyneuropathy and recommended by the Polish Society of Diabetology in line with international guidelines include -lipoic acid, benfotiamine, and angiotensin converting enzyme inhibitors (ACE-I) [2]. Among the symptomatic drugs, tricyclic antidepressants (amitriptyline) and anticonvulsants including carbamazepine, gabapentin, and pregabaline exhibit the highest effectiveness [3, 4]. Many patients use analgesics, most commonly paracetamol and other non-steroidal anti-inflammatory drugs (NSAIDs) that exhibit good analgesic properties.

Due to the complex and multifactorial pathogenesis of diabetic neuropathy in which hyperglycaemia is an aetiological factor, the best metabolic control of diabetes is the basic causative effect. Insulin formulations are the principal group of drugs used in the treatment of patients with poorly controlled diabetes mellitus. Insulin directly and indirectly affects intracellular metabolism in the majority of cells in the body. Physiological effects of insulin differ with regard to the time of their appearance. These effects can be classified as follows: rapid, e.g. glucose, amino acid transport; intermediate — that appear after a few minutes, e.g. the effect on the activity of enzymatic proteins; and delayed, which manifest after a few hours or days, e.g. stimulation of cellular proliferation and growth [5].

Based on multiple randomised, multicentre clinical trials, e.g. DCCT (Diabetes Control and Complication Trial), that assessed patients with type 1 diabetes mellitus, and the UKPDS (United Kingdom Prospective Diabetes Study), which enrolled patients with type 2 diabetes mellitus, it is known that metabolic control is a crucial element of treatment of painful diabetic polyneuropathy [6, 7]. In this picture insulin is a tool for the achievement of normal blood glucose concentration. Concurrently, due to the effect of insulin on the above-mentioned processes, it can be a drug affecting neuropathic pain. It is unknown whether intravenous insulin delivery in patients with poorly controlled diabetes mellitus is superior to subcutaneous delivery in patients with symmetric painful sensorimotor polyneuropathy. The aim of this study was to assess the effects

of intravenous *vs.* subcutaneous insulin administration in patients with diabetes mellitus accompanied by symmetric painful sensorimotor polyneuropathy on the following parameters: pain relief, improvement of quality of life, and quantitative and qualitative sleep assessment. These aims were assessed based on a randomised, patient-blinded study.

Material and methods

The study enrolled 34 patients (16 men and 18 women) with uncontrolled diabetes mellitus with sensorimotor polyneuropathy after ruling out other causes of polyneuropathy, who at the study start scored at least 40 mm on a 100-mm visual analogue scale (VAS), a part of the Short-Form McGill Pain Questionnaire (SFMPQ) [8]. Exclusion criteria included other than diabetic causes of polyneuropathy and $HbA_{1c} < 7.5\%$ and $> 10\%$. The study was conducted in in-patient conditions. Patients were fully informed of the aim and conduct of the study. All study subjects provided written consent. The study was approved by the Ethics Committee of the Silesian Medical University in Katowice. Table 1 presents the clinical characteristics of the study subjects.

All study subjects completed the following questionnaires twice (before and on day 5 of the study):
— Short-Form McGill Pain Questionnaire (SFMPQ);
— quality of life questionnaire EuroQol EQ-5D VAS Worksheet;
— sleep disturbance questionnaire AIS (Athens Insomnia Scale).

At the time of hospital admission all study subjects were questioned about the duration of their diabetes mellitus and its type, previous antidiabetic therapy and treatment of painful polyneuropathy, co-morbidities, and the presence of other late diabetic complications. Anthropometric parameters were collected and venous blood samples were withdrawn for laboratory tests: HbA_{1c}, lipid profile. A five-item neurological examination of the feet was performed involving assessment of perception of touch, vibrations, pain, temperature, and deep reflexes to confirm diabetic polyneuropathy. Furthermore, sensorimotor conduction was assessed by measuring conduction velocity, amplitude, and latency of F wave in peripheral motor and sensory nerves in the lower extremities: peroneal nerve (a motor nerve) and sural nerve (a sensory nerve). During the study the patients continued their previous therapy. No other drugs were added that might have affected neuropathic pain. Patients received intravenous insulin infusion (the study group) or multiple subcutaneous insulin injections (the control group) for five days. Patients were randomised into study groups using block-four randomisation. Blood glucose concentration was measured

Table I. *General characteristics of the study group classified into subgroups treated with intravenous or subcutaneous insulin. Data are presented as means ± SD*

Tabela I. *Ogólna charakterystyka badanych grup leczonych insuliną dożylnie i podskórnie (Dane podano jako średnie ± SD)*

	All patients n = 34	Examined group n = 17	Control subjects n = 17
Age (years)	62 ± 10	60 ± 9	63 ± 10
Sex (M/F)	16/18	10/7	6/11
Disease duration (years)	17 ± 10	19 ± 12	15 ± 8
Duration of insulin therapy (years)	12 ± 12	11 ± 14	12 ± 9
BMI [kg/m²]	32.5 ± 4	32.8 ± 4	32.2 ± 5
HbA$_{1c}$	8.7 ± 1.3	8.8 ± 1.2	8.5 ± 1.3
Mean blood glucose concentration on day 1 [mg/dL]	176 ± 36	189 ± 42	163 ± 24†
Mean glucose concentration on day 5 [mg/dL]	135 ± 26	143 ± 27	128 ± 24

†$p < 0.05$ *vs.* the study group

Figure 1. *Individual values of pain intensity (VAS score) in patients treated with intravenous insulin (examined group) and subcutaneously (control subjects)*

Rycina 1. *Indywidualne wartości nasilenia bólu (wg skali VAS) u chorych leczonych dożylnie insuliną (grupa badana) i insuliną podskórnie (grupa kontrolna)*

at least eight times per day. Target glucose concentration values were: fasting 70–110 mg/dL (3.9–6.1 mmol/L), and 2 hours after a meal < 140 mg/dL (7.77 mmol/L). The study group receiving intravenous insulin received an infusion of 50 mL 0.9% NaCl + 50 units of aspart insulin using an infusion pump Ascor 22 with adjustable flow depending on blood glucose concentration. The insulin dose was adjusted based on serum glucose concentration, according to the protocol that was prepared based on the Yale protocol [9]. Patients treated with subcutaneous insulin received insulin aspart sc before each meal at a dose titrated to blood glucose concentration and a slow intravenous infusion of 0.9% NaCl (as a placebo). If blood glucose concentration two hours after a meal was higher than the target value (< 140 mg/dL (7.77 mmol/L)), additional subcutaneous insulin was administered to correct hyperglycaemia. After five days of intensive treatment the following were repeated: five-item neurological examination of the feet and examination of sensorimotor conduction.

Results were presented as means ± SD, and if their distribution was not normal — as medians and interquartile ranges. The following were used to assess the differences: *t*-Student test, and if the distribution was not normal: Mann-Whitney U test or Wilcoxon signed-rank test.

Results

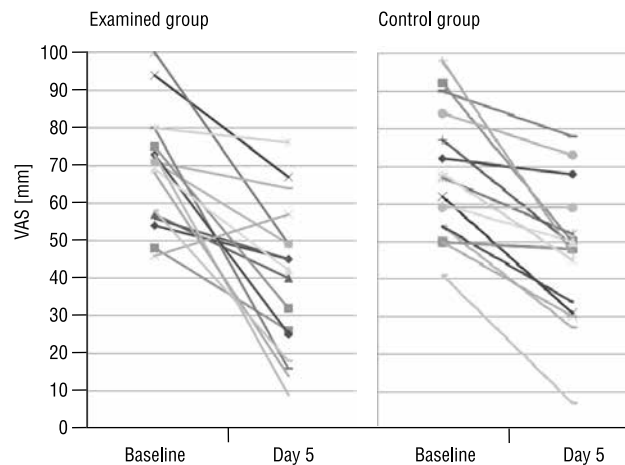Table I presents characteristics of the study groups. Patients qualified to intravenous therapy (the study group) had significantly higher average blood glucose concentration at the start of the study when compared to patients treated with subcutaneous insulin (the control group). The other parameters did not differ between the groups.

Figure 1 presents individual values in pain intensity before and after five days of therapy. The baseline values of VAS were 69 ± 14 mm in the examined group and 66 ± 16 mm in control subjects, respectively (ns). After five days of treatment a significant ($p < 0.001$) similar reduction of pain intensity was observed in both groups, respectively 40 ± 19 mm *vs.* 40 ± 17 mm. No difference in the level of decrease was observed between the groups studied (ns). Pain intensity did not differ between the groups. Table II presents evaluation of quality of life on day one and day five of the therapy, based on the EuroQol EQ-5D VAS Worksheet. At baseline the examined group reported statistically significantly better quality of life compared to control subjects ($p < 0.05$). After five days of therapy a significant improvement of quality of life was observed only in control subjects ($p < 0.001$). A statistically significant improvement of sleep disturbances was observed on day five both in the examined group and in control subjects ($p < 0.01$; $p < 0.05$, respectively) (Table III).

Sensorimotor conduction was evaluated in 30 study subjects (16 from the study group and 14 from the control group). Evidence of polyneuropathy in this investigation was not found in 3 of 4 patients excluded from the evaluation of conduction, while one patient was an outlier. Table IV presents values of sensorimotor conduction. Before treatment initiation both groups demonstrated reduced amplitude of evoked potentials

from investigated nerves and prolonged end latency. Reduced conduction velocity in the sural nerve was found both in the examined group and in control subjects, while in the peroneal nerve – only in control subjects. No significant differences were found between the groups with regard to any of the parameters of sensorimotor conduction. Improved conduction velocity in the sural nerve versus the pretreatment values was found after five days of intravenous insulin therapy ($p < 0.05$). Improved conduction velocity after therapy was not found in control subjects in the sural nerve or in the peroneal nerve.

Discussion

This randomised, patient-blinded study demonstrated that intensification of insulin therapy results in improved general condition in patients with painful diabetic polyneuropathy, through reduction of neuropathic pain and improvement of sleep parameters. Intravenous insulin delivery exhibits comparable efficacy to subcutaneous injections.

Available literature data indicates that it is the first study to compare the effects of intravenous and subcutaneous insulin delivery on the intensity of neuropathic pain in diabetic subjects.

Before inclusion in the study the patients were treated with both oral antidiabetic drugs (6 patients), oral drugs in combination with insulin (11 patients), and insulin monotherapy (17 patients). No differences were found between these groups with regard to the analysed parameters of glycaemic control. Previous treatment could have affected the results obtained; however, the aim of the study was to evaluate whether intravenous insulin delivery is superior to subcutane-

Table II. *Evaluation of quality of life — EuroQol EQ-5D VAS Worksheet (0–100 points) at baseline (EQ 0) and day five of the study (EQ 1). Data are presented as means ± SD*

Tabela II. *Ocena jakości życia — skala EuroQol EQ-5D VAS (0–100 punktów) wyjściowo (EQ 0) i po 5 dniach badania (EQ 1). Dane podano jako średnie ± SD*

	Examined group n = 17	Control subjects n = 17
EQ0 — at baseline	57 ± 14†	42 ± 19
EQ1 — day five of the study	63 ± 18	61 ± 15***
Δ EQ	7†	19

†$p < 0.05$ *vs.* the control group
***$p < 0.001$ *vs.* baseline

Table III. *Quantitative sleep evaluation according to Athens Insomnia Scale at baseline (AIS 0) and day five of the study (AIS 1). Data are presented as means ± SD*

Tabela III. *Ocena jakości snu wg Ateńskiej Skali Bezsenności wyjściowo (ASIS 0) i po 5 dniach badania (ASIS 1). Dane przedstawiono jako średnie ± SD*

	Examined group (E) n = 17	Control subjects (C) n = 17	Number of subjects with AIS > 10 n (%) Group E	Number of subjects with AIS > 10 n (%) Group C	E *vs.* C
AIS 0 — at baseline	13 ± 5	12 ± 5	13 (76%)	12 (71%)	ns
AIS 1 — day five of the study	9 ± 5**	9 ± 5*	6* (35%)	5* (29%)	ns

*$p < 0.05$ *vs.* baseline
**$p < 0.01$ *vs.* baseline

Table IV. *Parameters of sensorimotor conduction in peripheral nerves at baseline and after five days of therapy. Data are presented as medians and interquartile ranges*

Tabela IV. *Parametry przewodnictwa czuciowo-ruchowego w nerwach obwodowych wyjściowo i po 5 dniach leczenia. Dane przedstawiono jako mediany i przedziały ufności*

		Before treatment	After 5 days of therapy	Before treatment	After 5 days of therapy	E *vs.* C
		Examined group (E) n = 16		Control subjects (C) n = 14		
Sural (sensory) nerve	Conduction velocity SCV [m/s]	32.5 (26.5–42)	38 (29–45) *	33 (25–38)	36 (31–40)	ns
	Amplitude [μV]	3.4 (1.05–7.45)	2.6 (1.5–6.2)	2.4 (1.3–6.2)	3.3 (1.1–4)	ns
	Latency [ms]	3.85 (3–5.2)	3.4 (3.2–4)	4.4 (3.4–5.9)	3.7 (3.3–4.4)	ns
Peroneal (motor) nerve	Conduction velocity MCV [m/s]	43 (40–46)	43 (39–47)	41 (36–49)	40 (38–47)	ns
	Amplitude [mV]	2.85 (2.35–4.1)	2.8 (1.4–5)	2 (0.8–3.7)	1.9 (0.8–4.8)	ns
	Latency [m/s]	13.8 (11.9–14.65)	13.3 (12.3–15.3)	13 (11.7–15.2)	13.7 (12.4–16.9)	ns

ous injections with regard to the effect on the analysed parameters. Therefore, we can assume that the treatment prior to inclusion in the study had no effect on the obtained results, which supported the fact that no intergroup differences were observed irrespective of the method of insulin administration.

The group receiving intravenous insulin and the group treated with subcutaneous insulin were homogeneous with regard to anthropometric measurements as well as the results of laboratory tests (HbA_{1c}). Mean blood glucose concentration differed between the study groups despite patient randomisation. Higher values of 24-hour mean glucose concentration were found in the examined group, but blood glucose reduction after five days of treatment was similar in both groups (mean reduction of blood glucose concentration was approximately 40 mg/dL — 2.22 mmol/L).

The patients were qualified to treatment based on clinical data and five-item neurological examination. According to literature data, the presence of at least two pathologies in this examination indicates peripheral polyneuropathy with sensitivity exceeding 87% [10]. All study subjects met this criterion. Some authors believe that simple diagnostic tests are sufficient to diagnose diabetic neuropathy [11], while others suggest expansion of the diagnostic work-up and addition of electroneurophysiological investigations to evaluate amplitude, latency, and velocity of conduction in sensory and motor nerves. To confirm the presence of sensorimotor polyneuropathy and to evaluate the efficacy of provided treatment, all subjects underwent investigation of sensorimotor conduction both before and after five days of insulin therapy. At baseline 31 of 34 study subjects qualified to the investigation, exhibited pathological sensorimotor conduction, and a neurologist diagnosed them with diabetic polyneuropathy. No other pathologies were found in the electroneurophysiological examination in the remaining three patients. Therefore sensitivity of the five-item neurological examination in this study (91%) was close to that reported in the literature.

Before the commencement of the study, potential study subjects underwent very careful selection, and particular emphasis was put on the nature of pain of the lower extremities and time of the day at which the pain was most severe. Besides clinical symptoms, scoring by patients at least 40 mm on the VAS scale, which was a part of the SFMPQ questionnaire, was a key inclusion criterion [8]. No superiority of either method of treatment was found with regard to evaluation on the VAS scale. Lack of differences between patients may have resulted from a very significant factor of therapeutic efficacy, i.e. the placebo effect. Commonly observed analgesic efficacy of agents that do not exhibit such

properties results, for example, from patient expectations of analgesic effects that are converted into a typical conditional reflex ("a drip infusion always results in pain resolution"). Pain-related behaviour is an effect of patient views and reactions on pain and furthermore can be modified by the environment [12]. A similar effect of reduction of pain intensity irrespective of the provided treatment was observed in most of the studies that evaluated various forms of therapy [3, 4, 13].

The analysis of the effects of the provided treatment should not overlook a subjective evaluation of quality of life by patients themselves. A quality of life questionnaire EuroQol EQ-5D VAS Worksheet was used in this study. Intergroup differences in quality of life were found even before the treatment initiation. Patients from the study group had better quality of life than patients from the control group and this difference was statistically significant. Since both groups were homogeneous with regard to age, sex, disease duration, and level of metabolic control, these parameters did not affect the evaluation of the quality of life. Furthermore, this evaluation could not have been affected by the use of antidepressants because tricyclic antidepressants were used only by one person from the study group and three subjects from the control group, and the treatment remained unchanged during the study. Analysis of other variables indicated that 70% of patients from the control group and only 41% patients from the study group had a history of attempts of treatment of painful sensorimotor polyneuropathy. However, these attempts were inadequately effective to improve the quality of life. On the basis of observations of patients with chronic pain it is known that treatment failures markedly impair mood and generate negative emotions in patients such as anger, anxiety, and aggression, which result in impaired quality of life [14]. It is possible that a factor of failed therapy that was more prevalent in the control group contributed to initially worse quality of life in this group. Evaluation of the quality of life after five days of therapy demonstrated a significant improvement in patients receiving subcutaneous insulin, while patients from the study group also exhibited improvement in this regard; however, probably due to better quality of life at baseline this change did not reach statistical significance.

The Athens Insomnia Scale was used to evaluate sleep disturbances [15]. Before the study onset 76% of patients from the study group and 71% of patients from the control group reported significant sleep disturbances, scoring more than 10 points on the AIS scale. Numerous studies emphasise the widespread problem of sleep disturbances, in particular in patients with chronic somatic disorders [16]. Patients with painful sensorimotor polyneuropathy very often complain of

sleep disturbances, which have been confirmed in the presented study. Evaluation of sleep changes demonstrated a significant improvement in the quantitative evaluation of sleep that correlated with reduction of pain complaints and improvement of quality of life. The obtained results were similar for both patients in the intravenous and subcutaneous insulin groups. After five days of therapy significant sleep disturbances were observed only in six patients in the study group (35%) and in five patients from the control group (29%). Despite the fact that patients were woken up at least twice during each night to measure their blood glucose concentration, they considered their night's rest as satisfactory. One can conclude that improvement of sleep was significantly associated with reduction of neuropathic pain.

Available literature data indicates that insulin affects peripheral nerves not only indirectly, through reduction of hyperglycaemia, but also directly. Studies in rats with diabetes induced by streptozotocin have documented the presence of insulin receptors in neuronal cell bodies and in axons. Small insulin concentration delivered subarachnoidally did not result in hyperglycaemia reduction, but it improved velocity of conduction in the peripheral nerves [17]. Most probably direct stimulation of insulin receptors and IGF receptors results in beneficial effects on neurofilament synthesis (involved in impulse conduction in the axon), protects the neuron from apoptosis induced by hyperglycaemia, and improves optimal mitochondrial function. Mitochondria are the source of most adenosine triphosphate (ATP), which is the source of energy for highly metabolically active neurons [17, 18].

The process of impulse conduction in nervous fibres requires normal generation of resting potential, which in turn is a prerequisite for electrical changes termed action potentials. The membrane potential is affected by passive diffusion of K^+, Na^+, Cl^-, and other ions through the plasmatic membrane and their active transport using sodium-potassium pump based on a special transporting enzyme — adenosine triphosphatase activated by ions Na^+ and K^+ (Na^+K^+ATP-ase) [5]. Reduced activity of the sodium-potassium pump was found in diabetic patients [19]. Hyperglycaemia is one of the factors that negatively affect the above-mentioned physiological processes. Insulin not only reduces hyperglycaemia, but it possibly also indirectly affects, through activation of receptors in the neurons and axons, physiological generation of resting, action potential, and conduction in the neurons. Effect of insulin on ionic transport is rapid and provides immediate effect. Furthermore, continuous intravenous insulin infusion guarantees its activity throughout the 24 hours, removes factors resulting in insulin resistance, and facilitates dosage adjustment depending on current serum glucose concentration.

Parameters of sensorimotor conduction in the nerves: peroneal (a motor nerve) and sural (a sensory nerve) were analysed to more objectively evaluate the effects of intravenous insulin on diabetic polyneuropathy. A significant improvement of conduction velocity in the sural nerve was observed after intravenous insulin therapy. Literature data indicates that long-term glycaemic control reduces progression of impairment of conduction velocity both in sensory nerves and in the motor ones. The eight-year Oslo Study conducted by Amthor et al. demonstrated beneficial effects of normal glucose concentration on peripheral nerve function, since improvement of both conduction velocity and amplitude in sensory nerves was found. Parameters of sensorimotor conduction were improved in all study groups in patients with type 1 diabetes mellitus, but the greatest benefits were found in patients receiving continuous subcutaneous insulin infusion (versus conventional therapy and multiple subcutaneous injections) [20]. Consequently, the mode of insulin delivery affects the conduction velocity in the peripheral nerves. Observed improvement of conduction velocity in the sural (sensory) nerve after five days of treatment in patients receiving intravenous insulin correlated with results of clinical and experimental studies.

In summary, even short-term intensification of hypoglycaemic therapy reduces complaints related to diabetic polyneuropathy. The mode of insulin delivery is of secondary importance. Improvement of the patient's clinical condition depends on normalisation of blood glucose concentration and, as it seems, on the placebo effect.

Conclusions

Intensification of insulin therapy used for five days results in improvement of the clinical condition of patients with diabetes mellitus complicated by painful polyneuropathy, through:
— pain relief,
— improvement of quality of life,
— improvement of sleep parameters.

Intravenous insulin infusion has comparable efficacy to subcutaneous injections.

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