Does the blood glucose control have an effect on the success of the painful diabetic neuropathy treatment?

Da li kontrola glukoze u krvi ima efekta na uspeh terapije bolne dijabetesne neuropatije

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Abstract

Background/Aim. Diabetic neuropathy (DN) is the basic complication of diabetes, associated with impaired glucose regulation, metabolic disturbances, microvascular vessel damage and increased cardiovascular risk. We monitored the impact of glucose control on the efficacy of painful diabetic neuropathy (PDN) treatment, when all pharmaceutical treatment options were exhausted.

Methods. Patients (n = 53, both gender, average age 68.3 ± 12.6) with PDN resistant to the pharmacotherapy were treated with the ultrasound-guided local anesthetic (0.5% procaine hydrochloride, 1% lidocaine, 0.25% levobupivacaine) blocks. Neuropathy was confirmed in accordance with the applicable European Federation of Neurological Societies (EFNS) criteria. Glycosylated hemoglobin (HbA1C) and blood glucose levels were monitored before and after therapy and one month after the treatment. Neuropathic pain was confirmed by Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) or Douleur neuropathique (DN4) or pain DETECT scales. The pain intensity was assessed by Visual analog scale, Neuropathic pain symptom and Neuropathic pain symptom inventory (VAS, NPS, and NPSI, respectively) scales before and after therapy and one month after the treatment. The efficacy of the therapy was assessed as: excellent result (> 50% of pain loss), good result (30%–49% of pain loss and the therapy does not work (< 30% of pain loss). The correlation between glucose control and the outcome was examined. Results. Because the values of glycemia and HbA1C were not different among patients treated with different local anesthetics, they were presented together. All patients had elevated blood glucose and HbA1C levels before (8.23 ± 2.77 mmol/L and 8.53% ± 2.48% respectively), after (8.43 ± 2.461 mmol/L and 8.85% ± 2.87%, respectively) and one month after the treatment (8.49 ± 2.22 mmol/L and 8.51% ± 2.09%, respectively). The loss of the pain was not result of the decrease in blood glucose and HbA1C blood levels. VAS, NPS, NPSI values were the following before the therapy: 81.53 ± 11.62 mm; 62.00 ± 13.04; 53.40 ± 17.63, respectively; after the therapy: 29.00 ± 9.23 mm; 13.79 ± 6.65; 11.83 ± 7.93, respectively; and one month later: 26.15 ± 8.41 mm; 12.68 ± 6.03; 9.81 ± 7.64, respectively. There was no correlation between glucoregulation and excellent outcome.

Conclusion. Even though the disturbance of glucose control is the key factor for the progression of PDN, it is not significant for the outcome of the pain treatment. New investigations are required.

Key words: diabetic neuropathies; blood glucose; blood chemical analysis; surveys and questionnaires; anesthetics, local; nerve block; pain measurement; treatment outcome.

Apstrakt

Uvod/Cilj. Dijabetesna neuropatija (DN) je osnovna komplikacija dijabetesa, udružena sa poremećajem glikoregulacije i metabolizma, ostecenjem malih krvnih sudova i povišenim kardiovaskularnim rizikom. U istraživanju je praćen uticaj glikoregulacije na efikASNOST LEĆENJA BOLNE DIJABETESNE NEUROPATIJE (BMĐN) REZISTENTNE NA MEDIKAMENTNO MINIMALNO INVAZIVNOJ TERAPIJOM. Metode. Kod bolesnika (n = 53, oba pola, starosti 68,3 ± 12,6) sa BMDN primenjena je minimalno invazivna terapija – lokalnim anesteticima (0,5% prokain hidrohlorid, 1% lidokain, 0,25% levobupivakain) ultrazvučno vodeni blokovi. Neuropatija je potvrđena u skladu sa važećim kriterijumima Evropske federacije neuro-loškog udruženja (EFNU). Glikoregulacija je preko vrednosti glikemije i glikozilirani hemoglobina (HbA1c), pre lećenja,

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nakon ciklusa terapije i posle jednog meseca od završetka terapije. Neuropatski bol potvrđen je skalam na Leeds assessment of neuropathic pain signs (LANS) ili Duplom neuropatique (DN4) ili pain DETECT skale za utvrđivanje bola. Intenzitet bola je ocenjeni su vizualnom analognom skalom, neuropatskom skalom simptoma bola i listom simptoma neuropatskog bola. Primjenjena je perineuralna blokada lokalnim anestetikima, pod kontrolom ultrazvuka. Efikasnost terapije određivana je procentom smanjenja bola: > 50% – odličan rezultat, 30%–49% – dobar rezultat i < 30% – terapija ne deluje. Ispitana je korelacija glikoregulacije (glikemije i nivoa HbA1C) na početku lečenja (8,23 ± 2,77 mmol/L i 8,53% ± 2,48%, redom), na kraju terapije (8,43 ± 2,46 mmol/L i 8,85% ± 2,87%, redom) i posle meseca praćenja (8,49 ± 2,22 mmol/L i 8,51% ± 2,09%, redom). Prenasan bol nije bio u vezi sa smanjenjem glikemije [skale za procenu bola redom pre terapije: 81,53 ± 11,62 mm; 62 ± 13,04; 53,40 ± 17,63; jedan mesec posle terapije: 29 ± 9,23 mm; 13,79 ± 6,65; 11,83 ± 7,93; i jedan mesec kasnije: 26,15 ± 8,41 mm; 12,68 ± 6,03; 9,81 ± 7,64]. Nije bilo korelacie između poremećaja glikoregulacije i odličnog terapijskog odgovora.

Kljucne reči: dijabetesne neuropatije; glikemija; krv, hemijske analize; upitnici; anestetici, lokalni; blokada živca; bol, merenje; lečenje, ishod.

**Introduction**

Diabetic neuropathy (DN) is the basic complication of diabetes that was first described by Dyck et al. in 1880 as symmetrical sensorimotor polyneuropathy. For the first time, it was associated with impaired glucose regulation, metabolic disturbances, microvessels damage and increased cardiovascular risks. Hyperglycaemia is the essential disorder in the pathogenesis of the DN development in both types of diabetes. It increases the polyol pathway activity, the development of DN (DN4) or pain DETECT scale for the assessment of neuropathic pain. The intracellular decrease of NADPH level leads to the depletion of nitric oxide formation and blood supply to the nerves because the nitric oxide is a very strong vasodilator. All this causes the nerve damage and leads to ectopic electrical discharges and the Nav hyperexcitability and the increased bursts of electrical impulses in the nociceptive system at the dorsal corn of the spinal cord. Such bursts damage the antinociceptive gate-control mechanism and the P substance expression. The Nav accumulates at the damaged sites of axons what leads to ectopic electrical discharges and the Nav hyperexcitability and the increased bursts of electrical impulses in the nociceptive system at the dorsal corn of the spinal cord. Such bursts damage the Nav hyperexcitability and the Nav involvement in the development of this process equalize the pathophysiology of chronic pain with epilepsy.

Local anesthetic agents (LA) block the Nav canals. Over the last seven to ten years, the LA application has been introduced into the chronic neuropathic pain therapy. Over the last seven to ten years, the LA application has been introduced into the chronic neuropathic pain therapy. Therefore, intracellular hyperglycaemia damages the mitochondrial function and leads to over-activity of the hexosamine pathway: reactive nitrogen species and the peroxynitrite in particular are very toxic. The results of clinical application of antioxidants are contradictory as well: alpha-lipoic acid can have light beneficial therapeutic effect or ensure positive prospects for the improvement.

Diabetic neuropathy is commonly manifested as the loss of sensitivity with the chronic neuropathic pain: pain lasting for more than three months accompanied by allodynia and hyperpathia. The development of chronic neuropathic pain is also explained by disturbances of action potentials. The central nervous system (CNS) interprets it as a pain (allodynia and hyperpathia). The up-regulation of voltage-dependent Na-canals (Nav) is confirmed in neuropathic pain models. The Nav accumulates at the damaged sites of axons what leads to ectopic electrical discharges and the Nav hyperexcitability and the increased bursts of electrical impulses in the nociceptive system at the dorsal corn of the spinal cord. Such bursts damage the Nav hyperexcitability and the Nav involvement in the development of this process equalize the pathophysiology of chronic pain with epilepsy.

**Rezultati.** Svi bolesnici su imali povišenu vrednost glikemije i HbA1C na početku lečenja (8,23 ± 2,77 mmol/L i 8,53% ± 2,48%, redom), na kraju terapije (8,43 ± 2,46 mmol/L i 8,85% ± 2,87%, redom) i posle meseca praćenja (8,49 ± 2,22 mmol/L i 8,51% ± 2,09%, redom). Prenasan bol nije bio u vezi sa smanjenjem glikemije i HbA1C na početku terapije, 30%–49% – dobar rezultat i < 30% – terapija ne deluje. Ispitana je korelacija glikoregulacije (glikemije i nivoa HbA1C) na početku lečenja (8,23 ± 2,77 mmol/L i 8,53% ± 2,48%, redom), na kraju terapije (8,43 ± 2,46 mmol/L i 8,85% ± 2,87%, redom) i posle meseca praćenja (8,49 ± 2,22 mmol/L i 8,51% ± 2,09%, redom). Prenasan bol nije bio u vezi sa smanjenjem glikemije [skale za procenu bola redom pre terapije: 81,53 ± 11,62 mm; 62 ± 13,04; 53,40 ± 17,63; jedan mesec posle terapije: 29 ± 9,23 mm; 13,79 ± 6,65; 11,83 ± 7,93; i jedan mesec kasnije: 26,15 ± 8,41 mm; 12,68 ± 6,03; 9,81 ± 7,64]. Nije bilo korelacie između poremećaja glikoregulacije i odličnog terapijskog odgovora.

**Kljucne reči:** dijabetesne neuropatije; glikemija; krv, hemijske analize; upitnici; anestetici, lokalni; blokada živca; bol, merenje; lečenje, ishod.
it is recommended to control the blood glucose level four times a day, and the blood HbA1C level once a month. Considerably less important risk factors for the DN development are hyperlipidemia, hypertension, smoking, alcohol abuse, obesity, age, and the duration of diabetes.

Does the poor glucose control have the impact on the DN therapy outcome? Can the chronic pain be relieved by the suppression of basic pathophysiological mechanisms involved in chronic neuropathic pain, regardless of the glucose control? It is about the pain that disturbs all aspects of life, not only of the patient but also of his/her family members. That is the main issue this study deals with.

Methods

Patient selection

This study included 53 adult patients of both genders (24.5% males and 75.5% females), average age 68.4 ± 12.6 years with chronic painful diabetic neuropathy in the lower extremities. The duration of the pain was longer than three months and less than six years (3.2 ± 1.78 years). All patients had poor glycemic control (it was measured four times a day) and elevated HgA1C values. The 84.9% of the patients were smokers with mildly elevated values of arterial pressure (96.2%) controlled using only one type of medicine given at a low dose. None of the patients abused alcohol. Medical therapy benefits were exhausted: ineffective (the pain measured by VAS scale was > 30 mm) or side-effects were intolerable, and the therapy was discontinued (at the patient's request or the physician's judgment that vital functions or normal daily activities of the patient are seriously threatened). The neuropathic pain in lower extremities was confirmed by the LANSS (LANSS ≥ 12 points), or pain DETECT scale (≥ 19 points) or DN4 scale (≥ 4 points). All the scales were used for each patient. The diabetic neuropathic pain was confirmed in accordance with the EFNS recommendations: clinical and neurological examination, the electromyoneurographic examination of lower extremities. All patients were mentally healthy and intellectually capable of understanding their participation in the study and gave their informed consent for it. The exclusion criteria were: ischaemical cerebral and/or myocardial diseases; metabolic mitochondrial diseases; liver diseases; respiratory or metabolic acidosis; arrhythmias; hemorrhagic diathesis; psychiatric illnesses; epilepsy; CNS diseases confirmed by magnetic resonance imaging (MRI); three or more evidence-based risk factors for stroke or acute myocardial infarction; evidence-based allergic reaction to local anesthetics; unregulated arterial hypertension.

The inclusion criteria were normal values of the following biochemical analyses: complete blood count, sedimentation rate, serum proteins, B12 and D3 vitamin blood level, the blood level of C3 and C4 components of the complement, the blood tumor marker values [β2 microglobulin, carcinoembryonic antigen – CEA, alpha-fetoprotein (α FP), cytokeratin fragment 21 (CYFRA 21), neuron specific enolase (NSE), carbohydrate antigens (CA) 72.4, CA 125, CA 15.3, CA 19.9; for male: prostate specific antigen (PSA), free PSA (fPSA), international normalized ratio (INR) and activated partial thromboplastin time (APTT) values, hepatic enzymes [aspartate aminotransferase (AST); alanine aminotransferase (ALT); gamma-glutamyl transferase (GGT); lactate dehydrogenase (LDH), blood levels of the urea, creatinine, uric acid, the urine levels of amylase, triglycerides, high-density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol blood levels. The urine value of the ketones was always less than two pluses (at the start and the end of the therapy, and one month after the therapy). Based on the examination of the blood vessels of lower extremities by Doppler sonography and multisliced computed tomography (MSCT) angiography, more than 30% stenosis were excluded.

The glycemic values were measured four times a day (the phosphorylation of glucose by the hexokinase method on a Siemens Dade Dimension RxL Max chemistry analyzer), on the basis of which the mean blood glucose level was calculated before the introduction of the therapy, at the end of the therapy, and one month after the treatment. The HbA1C blood level was also measured [by the turbidimetric inhibition immunoassay (TINIA), SIEMENS Dimension RXLMAX analyzer] before the therapy, at the end of the therapy and one month after the completion of the treatment.

The ultrasound-guided treatment (in B-mod and color doppler mod; on the Toshiba Apio 5000 Ultrasound Maschine with linear probe 7–18 MHz, the programe for periferal nerves and muscles) was performed using injections – blocks with local anesthetics (0.5% procaine hydrochloride, 1% lidocaine, 0.25% levobupivacaine), under sterile conditions. The blocks were given five days a week until the pain was lost and two blocks more until the positive therapeutic effects were observed, but no more than ten blocks.

The blocks were administered into the lower extremities: „three in one“ blocks – lower (caudal) lumbar plexus block (always 3 mL of LA only) and subgluteal sciatic nerve blocks (always 5 mL of LA only). Prior to the initiation of the treatment, when the procedure was explained to the patients and informed consents were obtained from them, the pain was assessed by the VAS, NPS, NPSI, and pain DETECT Scale. In the same way, the pain was assessed after the treatment and one month upon the completion of the therapy.

The outcome of the chronic neuropathic pain treatment was assessed by listed scales and numerical values were interpreted as follows: excellent results (the pain intensity is reduced by ≥ 50% as compared to the initial pain evaluation); good results (the pain intensity is reduced by 30%–49% when compared to the initial pain evaluation) and unsatisfactory (the pain intensity is reduced by < 30% as compared to the initial pain evaluation) After that, the correlation with the initial glycemia and HbA1C values was analyzed.

Ethics

All the research procedures were approved by the Military Medical Academy Ethical Committee, Belgrade, Serbia (Ethical Committee Meeting – 30th November 2015.).

**Statistical analysis**

All the data were collected and processed using the SPSS program for Windows. They are presented in the standard way as the mean values and the standard deviation. Regression and correlation analyses between parameters for the blood glucose levels (glycemia and HbA1C values) and the treatment results (VAS, NPS, NPSI and the pain DETECT scale values) were carried out.

**Results**

Because the values of glycemia and HbA1c were not different among patients treated with different local anaesthetics, they were presented together.

**Table 1**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Before therapy</th>
<th>After therapy</th>
<th>1 month after the treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycemia (mmol/L), mean ± SD</td>
<td>8.23 ± 2.771</td>
<td>8.43 ± 2.461</td>
<td>8.49 ± 2.224</td>
</tr>
<tr>
<td>HbA1c (%), mean ± SD</td>
<td>8.53 ± 2.478</td>
<td>8.85 ± 2.872</td>
<td>8.51 ± 2.090</td>
</tr>
<tr>
<td>VAS (mm), mean ± SD</td>
<td>81.53 ± 11.62</td>
<td>29.9 ± 23.2</td>
<td>26.15 ± 8.413</td>
</tr>
<tr>
<td>NPS (points), mean ± SD</td>
<td>62.0 ± 13.041</td>
<td>13.79 ± 6.649</td>
<td>12.68 ± 6.025</td>
</tr>
<tr>
<td>NPSI (points), mean ± SD</td>
<td>53.4 ± 17.637</td>
<td>11.83 ± 7.932</td>
<td>9.81 ± 7.636</td>
</tr>
<tr>
<td>pain DETECT (points), mean ± SD</td>
<td>25.58 ± 5.891</td>
<td>7.87 ± 3.883</td>
<td>7.53 ± 3.662</td>
</tr>
</tbody>
</table>

HbA1c – glycosylated haemoglobin; VAS – Visual analogue scale; NPS – Neuropathic pain scale; NPSI – Neuropathic pain symptom inventory; SD – standard deviation.

**Table 2**

<table>
<thead>
<tr>
<th>Scales</th>
<th>Glycemia Correlation coefficient</th>
<th>p</th>
<th>HbA1c Correlation coefficient</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VASpp</td>
<td>-0.05</td>
<td>0.698</td>
<td>-0.004</td>
<td>0.978</td>
</tr>
<tr>
<td>VASm</td>
<td>-0.127</td>
<td>0.366</td>
<td>0.062</td>
<td>0.659</td>
</tr>
<tr>
<td>NPSpp</td>
<td>-0.033</td>
<td>0.816</td>
<td>0.076</td>
<td>0.594</td>
</tr>
<tr>
<td>NPSIpp</td>
<td>-0.111</td>
<td>0.431</td>
<td>-0.110</td>
<td>0.431</td>
</tr>
<tr>
<td>NPSIm</td>
<td>-0.089</td>
<td>0.524</td>
<td>-0.116</td>
<td>0.403</td>
</tr>
<tr>
<td>pDETp</td>
<td>-0.081</td>
<td>0.562</td>
<td>0.179</td>
<td>0.199</td>
</tr>
<tr>
<td>pDETM</td>
<td>0.023</td>
<td>0.868</td>
<td>0.158</td>
<td>0.237</td>
</tr>
</tbody>
</table>

Pp – pain after therapy; m – pain one month after therapy; pDET – pain DETECT;
For other abbreviations see under Table 1.

**Discussion**

In the course of the investigation, a group of mostly older (one of the additional risk factor for the DN development) and female patients was formed. The gender changes the pain experience due to differences in psychosocial mechanisms, the hormonal status and activity, the function of the opioid system and the NMDA receptors, all of which required different approaches to the pain therapy in men and women.

The main way to control glycemia in diabetic patients was the measurement of blood glucose and HbA1C levels. To prevent the DN development, the recommended value for HbA1C that should have been maintained was < 7%, while the glycemia level should have been within the range of 0–13 mmol/L or, if it is measured two hours after a meal, it was desirable to be < 18 mmol/L. It was also recommended to measure glycemia four times a day. We formed the group of subjects with metabolic disbalance and poor glucoregulation. Poor glucoregulation leads to the diabetic neuropathy in both types of diabetes, and, the majority of patients in our investigation are with type 2 diabetes (50 out of 53 patients).

In additional to the bad glycemia control, smoking was the factor that contributed to the DN development in all the subjects of our study group, while the hypertension was regulated with minimal dose of only one type of drug. Mild hypertension was recommended for the prevention of hyperglycemic tissue damage, better tissue perfusion, particularly of the CNS tissue, but the values should not exceed 130/80 mmHg.

Other metabolic and vascular neuropathies identified using Doppler sonography or MSCT angiography of lower extremities and on the basis of laboratory results were excluded. There was no correlation between glyceregulation (the values of blood glucose and HbA1C levels) and excellent therapy results with the LA according to the pain scales values. The LA use in the chronic pain treatment is actual again, after ultrasound and Doppler applying for nerve and vascular structure real-time visualization. Local application results with the LA according to the pain scales values. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy and nephropathy in a population-based cohort: The Rochester Diabetic Neuropathy Study. Neurology 1993; 43(4): 817–24.


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