ORIGINAL ARTICLE

UDC: 616.379-008.64-06:616.8-009.7-08
https://doi.org/10.2298/VSP160613367J

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 impared glucoregulation, metabolic distrurbances, microvascular vessel damage and increased cardiovascular risk. We monitored the impact of glucoregulation 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 glucoregulation and the outcome was examined. **Results.** Because the values of glycenia 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, oštećenjem malih krvnih sudova i povišenim kardiovaskularnim rizikom. U istraživanju je praćen uticaj glikoregulacije na efikasnost lečenja bolne dijabetesne neuropatije (BMDN) rezistentne na medikamentno minimalno invazivnom 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 vođenim blokovima. Neuropatija je potvrđena u skladu sa važećim kriterijumima Evropske federacije neurološkog udruženja (EFNU). Glikoregulacija je preko vrednosti glikemije i glikozilirani hemoglobina (HbA1c), pre lečenja,

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nakon ciklusa terapije i posle jednog meseca od završetka terapije. Neuropatski bol potvrđen je skalama *Leeds assessment of neuropathic symptoms and signs* (LANSS) ili *Dopleur neuropathique* (DN4) ili *pain DETECT* skale za utvrđivanje bola. Intenzitet bola je ocenjeni su vizuelnom analognom skalom, neuropatskom skalom simptoma bola i listom simptoma neuropatskog bola. Primenjena je perineuralna blokada lokalnim anesteticima, 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) i ishoda lečenja. **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). Prestanak bola 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 korelacije između poremećaja glikoregulacije i odličnog terapijskog odgovora.

Ključne 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 impared glucoregulation, metabolic disturbances, microvessels damage and increased cardiovascular risks [1, 2]. Hyperglycemia is the essential disorder in the pathogenesis of the DN development in both types of diabetes [2–15]. It increases the polyol pathway activity [1, 4, 6, 16]: glucose is transformed into sorbitol, catalyzed by aldose reductase, with the oxidation of nicotinamide adenine dinucleotide phosphate (NADPH) to $NADP^+$ [4, 6]. Sorbitol oxidizes to fructose with the reduction of nicotinamide adenine dinucleotide (NAD^+) to NADH. Long-lasting hyperglycemia elevates the affinity of aldose reductase for glucose. Inhibitors of aldose reductase activity are very effective in preventing the DN development in animal model, but clinical application is limited by a dose-dependent toxicity [16]. The sorbitol is accumulated in a cell and leads a cell in to the osmotic stress because it cannot pass through the cell membrane, but it does not cause the damage to neurons [17–19]. Toxicity of hyperactive polyol pathway is in the increased turnover of NADPH to NAD^+, in the decreased reduction and regeneration of glutathione, in the increase of advanced glycation end products (AGEs), and in the activation of protein kinase C (PKC) isoforms [17–19]. 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 vasodilatator [4, 6, 20]. All this causes the nerve damage and leads to the progressive and ascendant development of the distal-to-proximal diabetic neuropathy in an extremity [21].

Cellular glutathione depletion increases toxic products [17] and the level of oxidative stress [1, 4, 6] what is another basic biochemical mechanism for the DN development confirmed in diabetic animal models [22]. Intracellular hyperglycemia causes the autoxidation of glucose and its metabolites, an increased formation and expression of receptors for AGEs and its activating ligands. The accumulation of AGEs products is associated with the activation and proliferation of microglia and astrocytes-morphological changes in the central nervous system, six years after the presence of continuous neuropathic pain [1–6]. Intracellular hyperglycemia damages the mitochondrial function and leads to over-activity of the hexosamine pathway [23–25]: reactive nitrogen species and the peroxynitrite in particular are very toxic [26–29]. The results of clinical application of antioxidants are contradictory as well: alpha-lipoic acid can have light beneficial therapeutic effect [30, 31] or ensure positive prospects for the improvement [32, 33].

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 [4, 6]. The development of chronic neuropathic pain is also explained by disturbances of action potentials [4, 6, 34, 35]. The central nervous system (CNS) interprets it as a pain (allodynia and hyperpathia) [4, 7, 36]. The up-regulation of voltage-depended Na-canals (Nav) is confirmed in neuropathic pain models [37]. 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 [38]. Such bursts damage the antinociceptive gate-control mechanism and the P substance expression [38]. Disturbances in the Nav expression, structure and function cause the neuronal hyperexcitability or the development of neuropathic pain [39]. The CNS hyperexcitability and the Nav involvement in the development of this process equalize the pathophysiology of chronic pain with epilepsy what is confirmed by therapeutically used antiepileptic drugs [40].

Local anesthetic agents (LA) block the Nav canals [41]. Over the last seven to ten years, the LA application has been introduced into the chronic neuropathic pain therapy [42–45]: locally as a plaster gel or injection-solution, it is applied into the area near the damaged nerve structure [44]. The minimally invasive application of the injection (block) into the area around the nerve structure is extremely safe if done in a real-time and was ultrasound-guided. The minimal LA dose is used because it is applied into the area immediately surrounding the damaged structure. The LA application on a daily basis blocks the changed Nav, and interrupts the increased bursts of electrical impulses passing down to the dorsal corn of the spinal cord [45, 46].

Strong glycemia control reduces the development and progression of diabetic neuropathy up to 64% [1–6]. Therefore,

it is recommended to control the blood glucose level four times a day, and the blood HbA1C level once a month [4, 6]. Considerably less important risk factors for the DN development are hyperlipidemia, hypertension, smoking, alcohol abuse, obesity, age, and the duration of diabetes [1–6].

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%) contolled 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 [47]: clinical and neurological examination, the elecromyoneurographic examination of lower extremities. All patients were mentally healthy and intelectually 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 anasthetics; 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 ensimes [aspartate aminotransferase (AST); alanine aminotrasferase (ALT); gamma-glutamil transferase (GGT); lactate dehydrogenase (LDH), blood levels of the urea, creatinine, uremic 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 allways 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 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 moth 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 Toschiba Aplio 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 [48] 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) [47]. 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 glycenia and HbA1c were not different among patients treated with different local anesthetics, they were presented together.

Glycemia and HbA1C values and numerical values of the VAS, NPS, NPSI and pain DETECT scales before and after the therapy, and one month after the treatment are presented in Table 1.

The mean value of the VAS scale was 29 ± 9.232 after the therapy and 26.15 ± 8.413 one month after the treatment - excellent outcome (more than 50% of pain disappeared).

Table 2 presents the correlation between glycemia and HbA1C value and the numerical values on the pain scales (pain was measured by VAS, NPS, NPSI, and pain DETECT scale). The intensity of pain was measured after therapy and one month after therapy finished.

There was no correlation between glycemia as well as HbA1C values and numerical values of the pain scales (p > 0.5 Friedman's ANOVA).

Table 1

The values of the glycemia, HbA1c and pain scales

Parameters	Before therapy	After therapy	1 month after the treatment
Glycemia (mmol/L), mean ± SD	8.23 ± 2.771	8.43 ± 2.461	8.49 ± 2.224
HbA1c (%), mean ± SD	8.53 ± 2.478	8.85 ± 2.872	8.51 ± 2.090
VAS (mm), mean ± SD	81.53 ± 11.62	29 ± 9.232	26.15 ± 8.413
NPS (points), mean ± SD	62 ± 13.041	13.79 ± 6.649	12.68 ± 6.025
NPSI (points), mean ± SD	53.4 ± 17.637	11.83 ± 7.932	9.81 ± 7.636
pain DETECT (points), mean ± SD	25.58 ± 5.891	7.87 ± 3.883	7.53 ± 3.662

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

Table 2

Correlation between glycemia and glycosylated haemoglobin (HbA1c) and numerical values on the pain scales

Scales	Glycemia		HbA1c		p
	Correlation coefficient	p	Correlation coefficient		
VASpp	-0.05	0.698	-0.004	0.978	
VASm	-0.127	0.366	0.062	0.659	
NPSpp	-0.033	0.816	0.076	0.594	
NPSIpp	-0.111	0.431	-0.110	0.431	
NPSIm	-0.089	0.524	-.116	0.403	
pDETpp	-0.081	0.562	0.179	0.199	
pDETm	0.023	0.868	0.158	0.257	

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 [1–6] 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 [49].

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 [1–6]. It was also recommended to measure glycemia four times a day [4].

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 addition 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 [1, 4, 6].

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 glycoregulation (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 [50]. Local application was safe and easy, required minimal LA doses and avoided the gastrointestinal tract. Administration of a single-shot LA dose on a daily basis resulted in the loss of the pain within few months, frequently without the need to introduce any other type of medication for the neuropathic pain. The Food and Drug Administration (FDA) recommendation is that local anesthetics should be only used for the postherpetic neuralgia pain treatment [51]. The ultrasound-guided block allows local anesthetics to spread along the nerve proximally and distally, which was confirmed by the MRI images taken immediately after blocks were given [52].

Conclusion

The therapy of the medicine-resistant pain in the diabetic neuropathy by the Nav canals block with local anesthetics proved to be effective in our investigation, regardless of the increased blood glucose and HbA1C levels. It may lead to the assumption that they are the only mechanisms involved in the DN development while other mechanisms are responsible for the maintenance of the chronic pain. New investigations are required to provide answers to many pathophysiological enigmas in this chronic pain.

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Received on June 13, 2016.
Revised on August 15, 2016.
Accepted on August 22, 2016.
Online First December, 2016.