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Comparative analgesic efficacy of ultrasound-guided nerve blocks induced by three anesthetics with different duration of action in the treatment of resistant neuropathic pain in the lower extremities

Poređenje analgetske efikasnosti blokova nerava pod kontrolom ultrazvuka pomoću tri anestetika različite dužine dejstva u lečenju rezistentnog neuropatskog bola donjih ekstremiteta

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Abstract

Background/Aim. The neuropathic pain (NP) treatment is a big medical and socioeconomical problem. The new sorts of the NP treatment was developed and are applied in case of a medical treatment failure. The aim of this work was to investigate the efficacy of the ultrasound-assisted treatment of the resistant and chronic peripheral neuropathic pain with the local anesthetic nerve blocks. Due to the inefficacy of conventional treatment, three local anesthetics (short-acting, medium-term and long-acting) were administered in a series of the same minimal dose on a daily basis. Complications, side effects, the execution time of procedure and the onset time of local anesthetic were also investigated. **Methods.** In this prospective, randomized and double-blinded study, 108 patients (of which 53 were diagnosed with diabetes and 55 with radiculopathy) with the resistant and chronic peripheral neuropathic pain in the lower extremities were treated with a series of ultra-sound assisted peripheral nerve blocks. The conventional treatment was exhausted. The presence of this neuropathic pain was confirmed by, at least, one of the three scales – the Leeds Assesment of Neuropathic Simptoms and Signs (LANSS) scale, the Dolour Neuropathic 4 questions (DN4) scale and the pain DETECT(PD-Q) scale. Other therapies were not applied. The nerve blocks were administered on a daily basis until the relief of pain (visual analogue scale – VAS < 30), and after that, two additional nerve blocks were given. The three local anesthetics of the different duration of therapeutic effect were given at the same minimal dose: the schort-acting (1% procaine-chloride solution), medium-term (1% lidocaine-chloride solution) and long-acting (0.25% levobupivacaine-chloride solution) local anesthetics were used. The therapeutic efficacy was measured with the percentage reduction in the pain intensity on the VAS scale before and after the therapy and one month after the treatment: > 50% – excellent results; 31–49% – good results; < 30% the therapy did not work. The side effects, complications, the execution duration of procedure, the onset time of numbness, the number of corrections of the needle direction were recorded as well. **Results.** For all three groups: nerve blocks took 5.4 ± 1.48 minutes to do (withouth difference among the groups), the onset of numbness occured, on average, within 3.75 ± 2.62 minutes (withouth differences among the groups), and the need for corrections of needle direction was minimal (1.03 ± 0.17 corrections). All the patients experienced a loss of pain sensation (VAS < 30); when a long-acting anesthetic was used, the number of required nerve blocks was significant ($p < 0.001$) smallest (4.33 ± 0.63 blocks), than in other two groups, and the percentage pain reduction was highest (73.13%) ($p < 0.001$). The pain relief lasted one month after the therapy without the application of any other therapy. Neither complications nor side effects were observed. **Conclusion.** The procedure dercibed is a safe, efficient and easy-to-perform and does not lead to any complications and side effects. The pain relief is achieved most effectively and rapidly with the long-acting local anesthetics, and maintained even for one month without the introduction of any additional therapy.

Key words:
neuralgia; nerve block; ultrasonography; lower extremity.

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Apstrakt

Uvod/Cilj. Lečenje neuropatskog bola (NB) je veliki medicinski i socioekonomski problem. Kada se iscrpe medikamentozne metode lečenja, razvijaju se novi pravci u lečenju NB. Cilj rada bio je ispitivanje efikasnosti lečenja hroničnog, rezistentnog perifernog NB blokovima lokalnih anestetika pod kontrolom ultrazvuka. Zbog neefikasnosti konzervativnog lečenja, primenjivene su svakodnevne serije blokada tri lokalna anestetika (kratkog, srednjedugog i dugog dejstva), u istoj minimalnoj dozi. Beležene su komplikacije, neželjeni efekti, vreme potrebno za izvođenje procedure i započinjanje delovanja lokalnog anestetika. **Metode.** U ovom prospektivnom, randomizovanom i dvostruko-slepom istraživanju, 108 pacijenata (53 sa dijagnostikovanim dijabetesom i 55 sa radikulopatijom) sa rezistentnim i hroničnim perifernim NB u donjim ekstremitetima lečeno je serijom blokada perifernih nerava lokalnim anesteticima, pod kontrolom ultrazvuka. Konzervativno lečenje je bilo iscrpljeno. Postojanje NB je potvrđeno najmanje jednom od tri skale – the *Leeds Assesment of Neuropathic Simptoms and Signs* (LANSS) skala, *the Dolour Neuropathic 4 questions* (DN4) skala i *the pain DETECT questionnaire* (PD-Q) skala. Drugo lečenje nije primenjivano. Blokade nerava su davane svakodnevno do postizanja obezboljavanja [Vizuelno-analogna skala (VAS) < 30], i još dve blokade nakon toga. Primenjena su tri lokalna anestetika različite dužine dejstva u istoj minimalnoj dozi: kratkog dejstva (1% rastvor prokain-hlorida), srednjedugog dejstva (1% rastvor lidokain-hlorida) i dugog dejstva (0,25% rastvor levobupivakain-hlorida). Terapijska efikasnost je merena procentom smanjenja bola merenog VAS pre i posle lečenja i jedan mesec nakon završetka terapije: odličan rezultat > 50%; dobar rezultat 31–49%; terapija ne deluje < 30%. Beleženi su i neželjeni efekti, komplikacije, trajanje procedure, vreme potrebno za razvoj trnjenja i broj korekcija pravca igle. **Rezultati.** Za sve tri grupe izvođenje nervnog bloka je trajalo 5,04 ± 1,48 min (bez razlike između grupa), početak trnjenja je nastajao u proseku posle 3,75 ± 2,62 min (bez razlike između grupa), a potreba korekcije pravca igle bila je minimalna (1,03 ± 0,17 korekcije). Svi pacijenti su bili obezboljeni (VAS < 30) kada je primenjen anestetik dugog dejstva; broj potrebnih blokada za taj efekat bio je visokoznačajno ($p < 0,001$) manji (4,33 ± 0,63 blokada), nego u druge dve grupe, i procenat smanjenja bola bio je visokoznačajno veći (73,13%) ($p < 0,001$). Gubitak bola se održavao mesec dana nakon završetka lečenja bez primene bilo kakve druge terapije. Nije bilo komplikacija, niti neželjenih efekata. **Zaključak.** Opisana procedura je bezbedna, efikasna i laka za izvođenje, nije praćena komplikacijama niti neželjenim efektima. Obezboljavanje se postiže efikasnije i brže sa anesteticima dugog dejstva, i održava se jedan mesec bez bilo kakvog dodatnog lečenja.

Ključne reči:
bol, neuropatski; blokada živca; ultrasonografija; ekstremiteti, donji.

Introduction

The neuropathic pain (NP) is a pain arising as a consequence of the damage affecting the somatosensory part of the central nervous system (CNS) or peripheral nervous system. There are two types of the NP – central and peripheral [1, 2]. By its nature, it is chronic (it lasts longer than three months, or could even last for years [2]), and it is commonly seen in the clinical practice (5% up to 20% of the general population suffer from the NP) [2–4]. The Canadian Association for the Study and Treatment of the Neuropathic Pain thinks that the annual amount of around 11 200 Canadian dollars is spent for the treatment of only one patient with the NP [5].

The years 2014–2015 were declared as the Global Year Against the Neuropathic Pain to stress the importance of prevention, identification, tretament and socieconomical severity of this problem [6].

The neuropathic pain may occur in a single, or more often, in a mixed form [7, 8]. The neuropathic pain component is diagnosed in up to 35% of all pain syndromes [3, 4]: radiculopathy, the Failed Back Surgery Syndrome (FBSS), the pain in malignant diseases (particularly in bronchus), systemic and rheumatic diseases, the pain following the treatment with certain medications (for instance, chemotherapy), a part of the central pain (following an injury, surgery, ischemia, or the CNS infection), metabolic disorders (for instance, thyroid diseases), etc. It is essential to be familiar with specific questionnaires and ways to identify the neuropathic component of a mixed pain [9–14].

According to the International Association for the Study of Pain (IASP) classification, one of typical forms of the NP is the peripheral neuropathy [13]. More than 100 types of peripheral neuropathy have been identified [13], of which the diabetic neuropathy is very common – 60%–80% of patients with both type of diabetes may develop this form of the NP [3, 13].

The diabetic neuropathy is very similar to the nerve pain occurring after the Failed Back Surgery Sindrome (FBSS); when combined, they represent the most common form of the chronic peripheral neuropathic pain [15].

Therefore, the painful diabetic neuropathy and radiculopathy with the neuropathic component is chosen as the model of chronic, localized peripheral NP for the, better understanding and identification of the NP as a component of a mixed pain.

The NP is diagnosed on the basis of the following: the confirmation that the nerve system was damaged by some agent; the overt manifestation of the damage and the identification of the typical somatosensory symptoms [16, 17]. The presence of symptoms or signs only (for instance, allodynia or hyperpathia), does not justify the use of the term and diagnosis of the neuropathic pain [15, 16–18].

In practice, the presence of neuropathic pain component is the most easily identified by using several questionnaires such as the Leeds Assessment of Neuropathic Symptoms and Signs-LANSS scale [12], *Douleur Neuropathique en 4 Questions* (DN4) scale [9], Pain DETECT (PD-Q) scale [14], which can detect the component of the NP. The questionnaires are the

most often used together in order to increase the accuracy of the NP detection in the course of the pain analyses.

The treatment efficacy is most often measured by the Visual Analogue Scale (VAS): the excellent result – > 50% pain reduction; a good result –31%–49% pain reduction, the unsatisfactory result – < 30% pain reduction [19].

All the pharmacological treatments were found to be ineffective in 20% to 40% of patients (non-responders) due to the common development of unacceptable side effects [15, 20, 21]. There is a great number of protocols for the neuropathic pain treatment that are recommended by the leading associations of the countries, pain societies and federations. The primary treatment of the NP is non-surgical – it is treated with a combination of several medications in 3–4 steps [5, 22, 23]. The first-line treatment involves the application of antidepressants and anticonvulsants, the local application of drugs often in combination with opioids that are most often considered the second or third-line treatment [5, 24, 25]. There is neither unique way for the NP treatment nor unique combination of medications for the same type of pain.

When the medical therapy is exhausted, the minimally invasive, interventional therapy is applied. It is any procedure requiring a small incision or a procedure during which the instruments are inserted into the body cavity reducing in that way the tissue damage to a minimum [26, 27]. The Special Interesting Group on Neuropathic Pain (NeuPSIG) was established within the framework of the International Association for the Study of Pain (IASP). According to the NeuPSIG definition, the interventional procedure is „an invasive procedure involving the delivery of drugs into the target location“ [15, 24]. The high vitamin D doses, local anesthetics (LA), magnesium, gentamicin with or without corticosteroids are currently most commonly used in the NP treatment [28–32]. The success of the neuropathic pain management is the most frequently limited by the development of the unwanted effects [29]. Therefore, the local application of medications such as gels, plasters or injections has a significant place in the NP treatment [17, 24, 25, 31, 32]. During the application of a gel or plaster to the skin, a medication penetrates only 5 mm below the skin's surface; lidocaine and capsaicin can only be used in that way [24]. The USA and Germany have the longest experience in the application of LA in the form of gel or a plasters – eight years, and their application in the NP treatment was officially approved in some 50 countries [24]. On the other side, there is a much greater number of LA that can be used at any dose and dilution for the peripheral nerve blocks in the area where the NP is localized.

In addition to the needle prick, as disadvantages of the methods, the following were mentioned: the damage of a nerve or a blood vessel, nonselective effects of LA – the development of transient motor weakness, and, when very high doses are applied, cardiovascular and side effects of the CNS [24, 31].

The recommendation of the NeuPSIG Group is to conduct investigations that could contribute to the precise refining of the nerve block protocols. This study was done in the accordance with this recommendation. The aim of the study was to investigate the efficacy of the ultrasound-guided treatment of the resistant chronic localized peripheral NP in the lower extremities (LE) with three different local anesthetics – schort-acting, medium-term and long-acting.

Methods

A prospective, randomized, double-blinded, clinical study was conducted. The study included 108 patients divided into three groups. Three types of randomly chosen LA with the different duration of therapeutic effect were used for the nerve blocks: short-acting (1% procaine-chloride solution); medium-acting – (1% lidocaine-chloride solution), and long-acting a (0.25% levobupivacaine-chloride). The solutions of LA were prepared in the Military Medical Academy Pharmacy Sector, and were marked as the X1, Y1, Z1 layers – for double-blinded condition.

The inclusion criteria in the study were: the both genders; age > 18 years; the pain lasting longer than three months and shorter than six years; the presence of a resistant, chronic and localized peripheral NP in the lower extremities arising as a consequence of diabetes mellitus or as a neuropathic component of radiculopathy; the NP was confirmed by the scores on the LANSS pain scale: ≥ 12 scores or the pain DETECT scale: ≥ 19 scores or the DN4 scale: ≥ 4 scores; each patient filled-up each scale; the painful, lower-extremity diabetic neuropathy confirmed by a neurologist according to the valid recommendations of the 2010 European Federation of Neurological Societies (EFNS) guidelines [15]. The glycemic values were measured four times a day; in cases with this type of pain and radiculopathy in the lower extremities, radiculopathy was confirmed by the clinical, neurological and EMNG examinations; the previous pharmacological treatment was ineffective (VAS > 30), or side effects were unacceptable. All patients were mentally healthy and intellectually capable of understanding their participation in the study, and gave their informed consent.

The patients that were excluded from the study were those with ischaemic cerebral and/or myocardial diseases; metabolic mitochondrial diseases; liver diseases; acidosis; arrhythmias; hemorrhagic diathesis; psychiatric illnesses; epilepsy; organic CNS diseases confirmed by the magnetic resonance imaging (MRI); the allergic reaction to LA; the unregulated arterial hypertension. Other types of peripheral neuropathy detected through the adequate analyses, additional testings and examinations were also excluded.

The single nerve block therapy per day for the NP therapy was applied. Only one type of randomly chosen LA was given to one patient during the entire course of therapy. The nerve blocks were administered on a daily basis until the pain was released (VAS < 30 mm), two additional nerve blocks were given to determine therapeutic effects, but no more than ten nerve blocks were used. The subgluteal sciatic nerve blocks [33] (always with 5 mL of LA) and the lower inguinal lumbar plexus blocks [33] (the “3-in-1 block” always with 3 ml of LA) were used to pain therapy in the entire extremity, i.e., only the nerve block administered in the painful region, in the radiculopathy pain distribution with the same dose of LA.

The treatment efficacy was evaluated by the VAS scores before and after the pain relief and one month after the

completion of treatment. The evaluation was done in the following way: firstly, the VAS scores were measured before the therapy, at the end of therapy, and one month after the treatment. Then, the percentage of pain reduction was determined. The therapy results were scored as: excellent –50% of initial pain reduction; good – 31%–49% of initial pain reduction; the therapy does not work – < 30% of initial pain reduction.

In addition to the VAS scores measured before and after the therapy as well as one month later, the onset of numbness (occuring simultaneously with the pain releif), were recorded by each patient (after daily examination of each patient, during the treatment and with the ultrasound examination before the new block).

The 8–18 MHz high frequency linear probe of the ultrasound machine, the screening program for peripheral nerves, and the B- and Color Doppler mode (on the Toschiba Aplio 500 Ultrasound Maschine) were used [33]. The blocks were performed by a specialist, trained for the ultrasound examination of the periferal nerves, with the assistance of nurses. The execution duration of procedure, all side effects and complications, the number of corrections of the needle direction were recorded as well.

The Ethical Committee of the Military Medical Academy, Belgrade, Serbia, approved all the study procedures (Ethical Committee meeting dated November 30, 2015.).

Statistical analysis

The number of patients included into the study was based on the expected difference in the satisfactory pain relief results of three anesthetics. The minimally satisfying degree of analgesia was 30%, the statistic test power was 80% (0.08). Taking this into consideration (with statistic errors type 1) we calculated that the number of patients should be 36 per group making the total of 108 patients. The commercial statistical program GPower 3.1. was applied for the calculations.

Normality of the data was assesed by the Kolmogorov-Smirnov test. After that, the Friedman test, Wilcoxon Signed-Ranks test, the χ^2-test, Mann-Whitney or Kruskal-Wallis test were used.

All the data were collected and processed using the SPSS program for Windows. They were presented in the standard way as the mean values with the standard deviation.

The value of < 0.05 was considered statistically significant, and the value of < 0.001 as highly significant and used for the multiple comparison tests.

Results

There were 3 groups of the patients treated with local anaesthetics, each consisted of 36 randomly chosen patients: the group 1 – the patients treated with 1% procaine-chloride solution (X1); the group 2 – the patients treated with 1% lidocaine-chloride solution (Y1) group and the group 3 – the patients treated with 0.25% levobupivacaine-chloride solution (Z1) group. The groups included roughly the same number of men and women ($p = 0.65$), with similar mean age ($p = 0.83$) and the neuropathic pain lasting, on average, for about 3 years ($p = 0.74$). There was no significant differences ($p = 0.75$) between the number of patients in the subgroups with diabetic neuropathy (DN) and radiculopathy with the neuropathic component (R) in all groups (Table 1).

There was a very significant difference among the groups in the number of nerve blocks (N) for the pain relief (VAS < 30): Kruskal-Wallis test, $p < 0.001$; comparison of the N between the pairs performed by the Mann-Whitney test was $p < 0.001$ in all cases. There was no difference between N for DN and R subgroups treatment in any of the groups (Wilcoxon test; for all results $p > 0.05$). The very significant difference in N for the pain relief was found between all DN subgroups and all R subgroups, when different anesthetics were applied (the Kruskal-Wallis test and Wilcoxon test in all cases $p < 0.001$).

The efficacy of anesthetics was measured by a level of pain with the VAS scale, before (VASp) the treatment, after the treatment (VASpp) and one month after treatment was completed (VASm). There was a very significant difference for all anesthetics ($p < 0.001$). The positive trend in the pain relief continued in the groups 2 and 3 as well; in all cases the Friedman test showed statisticali significant ($p < 0.001$).

Table 1

The efficacy of treatment with different anestethics: the number of the blocks (N) for groups and subgroups treatment and level of the pain measured by Visual Analogue Scale (VAS) before the treatment (VASp), immediatelly after the treatment (VASpp) and one month after the treatment (VASm)

Group/diagnosis	Blocks mean ± SD	VASp mean ± SD	VAS pp mean ± SD	VASm mean ± SD
Group 1	9.86 ± 0.54	80.06 ± 12.35	30.47 ± 9.26	27.08 ± 7.48
subgroup1 DN	10 ± 0	83.31 ± 8.65	34.31 ± 8.44	28.94 ± 8.61
subgroup1 R	9.75 ± 0.72	77.45 ± 14.35	27.40 ± 8.92	25.6 ± 6.28
Group 2	7.31 ± 2.28	76.53 ± 13.23	28.19 ± 7.60	27.75 ± 6.28
subgroup2 DN	7.33 ± 2.54	77.83 ± 14.18	30.22 ± 9.31	28.89 ± 6.05
subgroup2 R	7.28 ± 2.05	75.22 ± 12.48	26.17 ± 4.87	26.61 ± 6.47
Group 3	4.33 ± 0.63	80.17 ± 17.56	21.06 ± 7.35	19.14 ± 7.7
subgroup3 DN	4.37 ± 0.68	80.11 ± 15.87	19.16 ± 6.71	17.53 ± 7.27
subgroup3 R	4.29 ± 0.58	80.24 ± 19.78	23.18 ± 7.65	20.94 ± 7.97
Total DN	7.08 ± 2.76	80.30 ± 13.4	27.49 ± 10.33	24.83 ± 9.06
Total R	7.25 ± 2.58	77.58 ± 15.54	25.69 ± 7.48	24.49 ± 7.2

DN – diabetic neuropathy; R – radiculopathy.

Group 1 – patients treated with short-acting local anesthetic; Group 2 – patients treated with midium-acting local anesthetic; Group 3 – patients treated with high-acting local anesthetic.

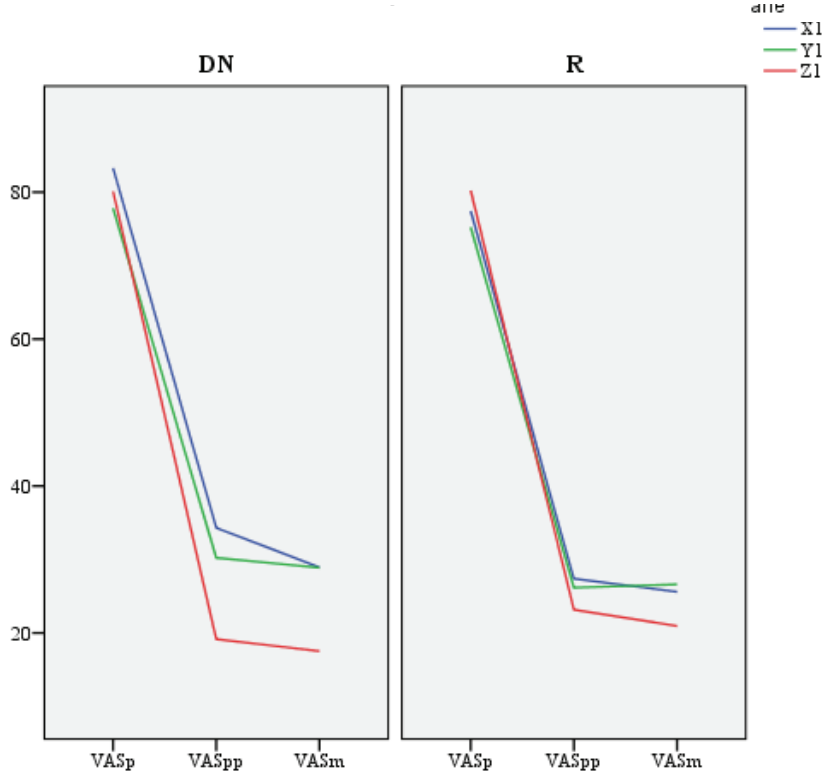

Fig. 1 – The eficacy of anestetics in the subgroups with diabetic neuropathy (DN) and the subgroups with radiculopathy (R). X1 – short-acting local anesthetic; Y1 – medium-acting local anesthetic; Z1 – long-acting local anesthetic. For other abbreviations see under Table 1.

There was no difference (measured by the VAS score) between the results of treatment subgroups DN and R within the same group, the Wilcoxon test showed $p > 0.005$, except for the group 3, immediatelly after the treatment ($p = 0.039$); after one month, this difference dissapeared ($p > 0.05$) (Figure 1).

The very significant differences in the value of the VAS scores, were found between the same subgroups (DN and R) in all groups, when the different anesthetics were aplied (Friedman and Wilcoxon test, in all cases $p < 0.001$). The lowest values of the VAS score was achieved in the group 3. The trend of the excellent results continued one month after the therapy was accomplished in the subgroup with DN after the treatment with 1% procain-cloride solution and in the subgroup R after the treatment with 0.25% levobupivacaine-chloride solution ($p < 0.05$) (Table 2).

The highest percentage in the pain reduction (73.73%) was achieved by the application of long-acting anesthetic in the group 3. The positive trend in the pain relief in relation to the VAS scores measured before the treatment continued in all local anesthetic groups, but the highest trend was noticed in the group of long-acting local anesthetic (76.13%) (Table 3).

The nerve block procedure lasted for some five minutes on average, the onset time of numbness after the completion of procedure was less than four minutes ($p > 0.05$).

Table 2
The average execution duration of procedure (in minutes), and the onset time of nerve block (NB) (in minutes)

Anesthetics*	The duration of NB (mean ± SD)	The onset time of NB (mean ± SD)
Group 1	4.9 ± 1.52	3.78 ± 2.72
Group 2	5.1 ± 1.53	3.82 ± 2.58
Group 3	5.02 ± 1.68	3.65 ± 2.51
Total	5.04 ± 1.58	3.75 ± 2.62

***For explanation see under Table 1.**

Table 3
The percentage of the pain reduction measured by the Visual Analogue Scale (VAS) score: immediately after the treatment completed and immediately and one month after the treatment completed

Anesthetics*	VAS score (% of initial pain reduction)		Assesment of results
	immediately after treatment completed	a month after treatment completed	
Group 1	62.06	66.23	excellent
Group 2	63.02	63.68	excellent
Group 3	73.73	76.13	excellent
Total	67.47	71.69	excellent

***For explanation see under Table 1.**

There were no serious complications (injuries of the nerves or vessels) or unwanted effects recorded even though 7 ± 2.7 nerve blocks on average were administerd to each patient (over 750 nerve blocks/108 patients). The only mild side effect that occured occasionally was the development of subcutaneous hematomas not larger than 1 cm in diameter at the site of the needle insertion into the skin and subcutaneous tissue.

The average number of corrections of the needle direction was 1.03 ± 0.17.

Discussion

The treatment of neuropathic pain is often inefficient – most often limited and caused by the development of side effects [3, 5, 15]. Therefore, new methods involving the local application of medications in the areas of the nerve structures that innervates the location where the pain is localized need to be found [25].

The local application of medications in the neuropathic pain treatment may be non-invasive (topical), in a form of a gel or skin patch, and invasive – various nerve structure blocks and the instillation of medications into the body cavity where nerve structures are located [3, 5, 15].

The development of non-invasive methods started in 1998, when a gel and skin patch with the 5% lidocaine-chlorid solution intended for the acute pain management was first produced in the USA. Nowadays, there are gels and skin patches containing the combination of 2.5% procaine-chlorid and 2.5% lidocaine-chlorid [24]. They are the only FDA recommendation for the neuropathic pain therapy in the postherpetic neuralgia. Beside the USA, the Italian and German Chronic Pain Schools have the longest experience in their application (eight years). However, beside in the USA, the skin pathes and gels are registered in 50 other countries. In the EU countries, they have been in use since 2008 [34–36]. In addition to the fact that the patients cannot always access them officially, the patches and gels contain only lidocaine and procaine-type local anesthetic, which penetrate only five millimeters below the skin's surface, and that is why they are almost ineffective in the obese patients or in the areas of the deeper nerve structures [34].

The therapy of chronic neuropathic pain has become more important over the recent years because it allows for the application of a larger number of different medications: higher doses of the vitamins D and D3, various local anesthetics, magnesium, gentamicin with or without corticosteroids, various concentrations, doses with the much greater accuracy and considerably smaller number of complications [33, 37].

The ultrasound guidance for the performance of the nerve blocks allowed for the reduction of applied doses and complications in particular. The description of the nerve structure and the execution of the nerve block procedure take place in real time, and thus, reduce the number of damages to the nerve structures and major blood vessels by some 30% [32, 33, 38]. Although the ultrasound was used for the first time in 1978, only two studies on that issue have been published until 2002, when, in the next year, that number amounted up to 43 [38, 39]. The ultrasound-guided low-extremity nerve block was introduced much later in Germany, the country with one of the strongest associations for the ultrasound clinical application. This method has been used in the low-extremity treatment for the last six to seven years [32, 33, 35]. It is, therefore, not surprising that, in its current recommendation on the interventional treatment of neuropathic pain, the NeuPSIG stresses the need for further and more thorough study of peripheral nerve and plexus block protocols, as well as for defining their place, doses of medications to be used for such purposes and the execution protocols [21].

There are not many studies devoted to this issue, the published series are very rare and insufficient for deriving serious conclusions taking into account that this is a very actual and still developing field.

Despite the fact that local anesthetics have, been used for a long time for the management of the acute pain during surgical procedures, the nerve blocks with local anesthetics have been recently introduced into the treatment of the chronic and neuropathic pain in particular. In the treatment of the acute pain during a surgery, the local anesthetics are also used for developing motor paralyses in the extremities, which explains the use of doses 60–200 times higher than those applied in our study and which proved to be sufficient to treat the outpatients with neuropathic pain [32, 33].

The occurence of the motor paralyses in the outpatients with the neuropathic pain is not desirable, because, it is very disturbing for the patient who is even warned that it might happen and is transient. The motor weakness requires the hospitalization of the outpatients and their close monitoring, and in case of the chest muscle blocks, their vital functions should be monitored for at least two hours. Because of that, the motor weakness is not desirable and represent a side effect or even a complication.

Higher concentrations of LA accelerate onset of effect in the isolated nerve. The duration of the effect depends on the dosage and concentration of local anesthetic, resorption from tissue into the blood, and its building to the membrane receptors (protein-binding activity). To avoid motor weakness of a lower extremity, we applied smaller dose and concentration LA during the pain treatment study. The subgluteal and inguinal region were anatomically poorly vascularized, with low resorption into the blood consequently. The potency *in vitro* (isolated nerve) for procaine (X1), lidocaine (Y1) and levobupivacaine (Z1) is 1, 4, and 16 respectively. The protein binding for X1, Y1 and Z1 is 5.8%; 64%–70% and 97% respectively. The duration of a single-dose injection effect is 0.5–1 h; 2–4 h and 4–7 h for X1, Y1 and Z1 respectively. The duration of anesthesia, after a single–dose injection, is significantly longer with Z1 than with any other LA [32].

Since the minimum dose of the local anesthetics was applied, no complications or side effects were observed in the course of our investigation. The pain relief was achieved by daily repetitive nerve blocks (the cumulative analgetic effect of local anesthetics [32, 33]), the application of the local anesthetic directly to the surface of the nerve structure that caused the pain, and the use of the ultrasound based on the

knowledge of the ultrasound anatomy of the nerve and the nerve block area.

Thus, the patient experienced the pain relief immediately, simultaneously with the clinical sensation of numbness, because the sensitive nerve fibers are always grouped together.

The comparison of the three local anesthetic groups with the various duration of the therapeutic effect showed a greater efficacy of the long-acting local anesthetics: the pain relief was achieved by a smaller number of the nerve blocks, and the decline in the pain intensity was larger as compared with the use of the medium-term and short-acting local anesthetics ($p < 0.001$). This effect is probably a consequence of longer de-excitation of the nociceptive and supraspinal systems and the achievement of balance between the nociceptive systems and activities of the antinociceptive pathways. However, further investigation in that direction is certainly needed [33].

Certainly, we can disscuss about achieving better efficacy of the local anesthetics because there were three groups of patients treated with different local anesthetics which had very similar mean VAS scores at the beginning of the study and they remained similar when compared them regarding the gender, age of patients, the number of patients with diabetes and radiculopathy in each group.

It is well-known that the mechanism of action of local anesthetics and antiepileptics is very similar –the target site of their action are voltage-dependent sodium channels. To fully achieve the effect of antiepileptic drugs, the continuous use of medications for four weeks is required [15], and that is why we, in our study, re-evaluated the treatment efficacy after that period. Therefore, it is not surprising that the effectiveness of therapy in our study was even larger after four weeks, without the introduction of any additional therapy.

Based on this experience, we can stress that disadvantages of this method, without any doubt, are invasiveness and the patient's need for the daily visits which is particularly difficult for the patients living far away. Morover, the method requires specific training – the knowledge about the ultrasound examination of peripheral nerves, the ultrasound anatomy and certain skills, because, if the in-plane technique is used, the one we applied in our study, the needle should always remain within the 1 mm wide beam from the ultrasound probe.

Based on the clinical experience, we suggested the application of the protocol involving daily administration of a minimal local anesthetic dose („3-in-1 block" with 3 mL, i.e., 5 mL of local anesthetic for the subgluteal sciatic nerve blocks), to prevent the possibility of side effects and development of transient paralyses of muscle groups in particular, since it requires the observation and hospitalization of a patient after the nerve block.

By performing the ultrasound-guided nerve blocks, we excluded the possibility of complications (the damage to a nerve or blood vessel). Having compared local anesthetics with different duration of therapeutic effect, we showed that a long-acting local anesthetic was the most effective allowing for the achievement of the pain relief in the patients after the smallest number of nerve blocks. On the other side, this treatment protocol requires patient's visits on a daily basis, represents an invasive and painful procedure that is gladly accepted by the patients for they feel pain relief almost after the first block. Therefore, this method may be applied in the treatment of the neuropathic pain only when all pharmacotherapeutic options are exhausted.

Conclusion

The method that was applied in our study is efficient and easy-to-perform. No complications were observed.

Based on the percentage of the pain reduction and the smallest number of nerve blocks required to achieve the pain relief (VAS < 30), the long-acting local anesthetic was found to be the most efficient. Further investigation is required to highlight the mechanisms of pain relief, the cumulative effect of local anesthetics and the achievemet of full effect for four weeks after initiating the therapy.

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