

# Management of pain in outpatients with critical limb ischemia

## Leczenie bólu w warunkach ambulatoryjnych u chorych z krytycznym niedokrwieniem kończyn

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### ABSTRACT

**Introduction:** Critical limb ischemia (CLI) is a condition resulting from chronic impaired limb perfusion by arterial blood, which is always accompanied by rest pain. The key objectives of treatment are to prevent high-level amputations and to manage pain. Currently there are no strong recommendations regarding pharmacotherapy for pain in patients with CLI.

The aim of the study was to evaluate analgesics currently used in patients with CLI on an outpatient basis and to assess their effectiveness in pain treatment.

**Materials and methods:** The study included 88 patients diagnosed with CLI, who declared taking a painkiller in the past 12 h. Patients were asked for the name of the drug. The truth of the declaration was verified by the presence of the drug in the serum of 45 randomly selected patients. All patients rated pain intensity on a numerical scale (NRS) before and after treatment. Their mental state was evaluated by Mini-Mental State Examination (MMSE) test.

**Results:** The most commonly used analgesics were ketoprofen, ibuprofen and acetaminophen. Pain management was successful in 11.4% of patients. Average pain intensity before taking the drug was 8.34 points (SD 1.27) and 5.85 (SD 1.57) after. In only 11 patients the presence of the declared drug was confirmed in serum. In 22 patients other drugs were found. For patients who reported that analgesic medication was ineffective, MMSE value averaged 22.1 (SD 4.95) and 25.1 (SD 4.25) for the group reporting effective treatment,  $p = 0.07$ . Patients reporting ineffectiveness of medications had suffered for an average duration of 8.2 weeks (SD 1.39), while the effective group average 5.2 weeks (SD 5.13),  $p = 0.06$ .

**Conclusions:** Treatment of pain in patients with CLI in an outpatient setting is ineffective because it is based on medications used in the treatment of nociceptive pain and not neuropathic pain. There is an urgent need to improve the treatment of pain in patients with CLI by educating family doctors.

**Keywords:** critical limb ischemia; pharmacotherapy of pain.

### ABSTRAKT

**Wstęp:** Kluczowymi elementami leczenia krytycznego niedokrwienia kończyn (CLI) są: zapobieżenie wysokim amputacjom oraz walka z bólem. Aktualnie nie ma rekomendacji dotyczących stosowania leków przeciwbólowych w tym przypadku.

Celem pracy była ocena skuteczności leczenia bólu w warunkach ambulatoryjnych.

**Materiały i metody:** Do badania włączono 88 chorych z rozpoznaniem CLI, którzy deklarowali stałe przyjmowanie leku przeciwbólowego od momentu pojawienia się bólu spoczynkowego. Chorych proszono o podanie nazwy leku, a prawdziwość deklaracji zweryfikowano testami na jego obecność w surowicy krwi losowo wybranych 45 osób. U wszystkich chorych, przed i po zastosowaniu ostatniej dawki leku, oceniono natężenie bólu w skali numerycznej (NRS). Określano także ich stan psychiczny za pomocą testu Mini-Mental State Examination (MMSE).

**Wyniki:** Najczęściej stosowanymi lekami przeciwbólowymi były ketoprofen, ibuprofen i paracetamol. Leczenie przeciwbólowe

było skuteczne u 11,4% chorych. Średnie natężenie bólu przed przyjęciem leku wyniosło 8,34 pkt. (SD 1,27), zaś po zażyciu go – 5,85 (SD 1,57). Tylko u 11 chorych potwierdzono obecność w surowicy deklarowanego leku, a w 22 przypadkach znaleziono ślady innego. Dla chorych, którzy twierdzili, że działanie leków przeciwbólowych było nieskuteczne, wartość MMSE wyniosła średnio 22,1 (SD 4,95), dla grupy twierdzącej przeciwnie – 25,1 (SD 4,25),  $p = 0,07$ . W grupie chorych deklarujących nieskuteczność przyjmowanych leków czas trwania dolegliwości wynosił średnio 8,2 tygodni (SD 1,39), dla drugiej grupy – 5,2 (SD 5,13),  $p = 0,06$ .

**Wnioski:** Leczenie bólu u chorych z CLI w warunkach ambulatoryjnych jest nieskuteczne, gdyż błędnie wykorzystuje się do niego leki stosowane w leczeniu bólu receptorowego, a nie neuropatycznego. Należy poprawić leczenie bólu u chorych z CLI poprzez edukację lekarzy.

**Słowa kluczowe:** krytyczne niedokrwienie kończyn; leczenie farmakologiczne bólu.

## INTRODUCTION

Critical limb ischemia (CLI) is an extreme condition resulting from chronic impairment of limb blood perfusion mostly caused by atherosclerosis. This term was introduced over 30 years ago [1]. According to the current definition, it covers patients with resting pain, ulceration or necrosis of limbs, with systolic pressure in foot arteries <50 mmHg or finger <30 mmHg [2]. Some researchers argue that this definition needs to be broadened to include cases of local infection [3]. It is estimated that the prevalence of CLI among the European population aged 40–69 is around 0.24% and this prevalence increases significantly with age [4]. At the moment of diagnosis, 20–25% of patients require primary limb amputation, 50–60% undergo revascularization (surgical or endovascular) and 25% undergo conservative treatment. After one year, 20–25% of patients from the last group die, most frequently due to coronary heart disease and stroke [2, 5]. Treatment of CLI patients includes pain management, prevention of high-level amputation, improvement and prolongation of quality of life and reduction of risk factors for cardiovascular diseases [2, 6]. The Trans-Atlantic Inter-Society Consensus suggested the use of acetaminophen or non-steroidal anti-inflammatory drugs as first-line medications in the treatment of pain, noting that they are ineffective in a high percentage of cases [2].

The aim of the study was to find out which drugs are used to treat pain in CLI patients in ambulatory conditions, to assess their efficacy and to identify factors that may affect their effectiveness.

## MATERIALS AND METHODS

The study was conducted after obtaining the consent of the Bioethical Committee of the Pomeranian Medical University in Szczecin no. KB-0012/81/13, in accordance with the principles of good medical practice and the Helsinki Declaration.

The study included 88 consecutive CLI patients admitted to the Department of Vascular Surgery between September 2013 and December 2015. The criteria for inclusion in the study included: critical ischemia of lower limbs diagnosed on the basis of a clinical examination, supplemented by a current angio-CT or Doppler ultrasonography, declaration of consumption of analgesics during the entire period of resting pain (the last dose taken within 12 h before inclusion), and consent to participate in the study. The criterion for exclusion was the documented diagnosis of a neurological disorder.

Demographic and clinical characteristics of patients are presented in Table 1.

During the survey, patients were asked to indicate the name of the painkiller taken and whether the drug was taken as needed or according to a schedule. Pain relief was rated on a Numerical Rating Scale (NRS) before and after the last dose, where 0 is the absence of pain and 10 is the most severe. The drug was considered effective when the final value was at least 50% lower than the initial value [7].

TABLE 1. Demographic and clinical characteristics of the study group

Age (years)	68.23
Men	60 (68.18%)
Women	28 (31.82%)
Smoking cigarettes	41 (46.59%)
Ischemic heart disease	35 (39.77%)
Arterial hypertension	42 (47.73%)
Cardiomyopathy and cardiac insufficiency	21 (23.86%)
Chronic obstructive pulmonary disease	9 (10.23%)
Diabetes mellitus	28 (31.82%)
Planned primary revascularization	64 (72.73%)
Planned reoperation	24 (27.27%)
Higher education	1 (1.14%)
Secondary education	24 (27.27%)
Basic education	63 (71.59%)
Arterial obstruction in the aortoiliac segment	33 (37.50%)
Arterial obstruction in the femoro-popliteal section	55 (62.50%)
Rest pain without ulcers or necrosis	35 (39.77%)
Presence of ulceration or necrosis	53 (60.23%)

In order to verify the truthfulness of the declarations of analgesic consumption, in 45 randomly selected patients, a blood sample was taken in the morning to determine the presence of the following drugs: paracetamol, diclofenac diclofenacum, ibuprofen, ketoprofen, naproxen, tramadol, hydrochloride, metamizol. The analysis was performed using solid phase extraction (SPE) and high-performance liquid chromatography with diode detector (HPLC-DAD) in the Department of Clinical and Forensic Toxicology of the Pomeranian Medical University in Szczecin.

The next step was to assess patients' mental state using the Mini-Mental State Examination (MMSE). The examination took place in an isolated room allowing for concentration and was conducted by one of the researchers trained by a psychologist. In patients with higher and secondary education the cut-off point was 26 points, and in patients with primary education 23. Values below these indicate the probability of cognitive disorders [8].

Statistical analysis was performed using commercial software (Statistica; StatSoft, Inc. USA). Shapiro–Wilk's test was used to check the distribution. Comparisons of quantitative variables were made using t or Kolmogorov–Smirnov tests for non-normal distribution. Comparisons of qualitative variables were made using the Yates patched  $\chi^2$  test.

## RESULTS

Out of 88 patients, 43 (49%) declared that they were taking ketoprofen, 17 – ibuprofen, 15 – paracetamol, 14 – tramadol, 4 – diclofenac, 1 – naproxen. Among the respondents 85% of the medications were prescribed by a doctor. No patient had been consulted by a neurologist or psychologist before taking

analgesic treatment, nor had taken advantage of a pain counselling centre.

In the randomly selected group (45 patients), the declared drug was found in the blood serum of 11 patients. In 22 blood samples a different drug was detected than that reported by patient. All the patients were taking painkillers when necessary. No patient had ever taken his medication at the recommended dosages or intervals.

The mean pre-treatment NRS value was 8.34 (SD 1.27), and 5.85 (SD 1.57) after painkiller administration. Only 10 patients (11.4%) reported a significant reduction in symptoms.

For patients who reported that analgesics were ineffective prior to medication, the mean NRS was 8.37 points (SD 1.29), for patients who claimed the contrary – 8.1 (SD 1.19). The difference between these groups was not statistically significant;  $p = 0.52$ .

The mean value in the MMSE questionnaire was 22.44 (SD 4.94). The mean value was 22.1 (SD 4.95) for the patients who reported that analgesics were ineffective, and 25.1 (SD 4.25) for the effective group. In this case, a difference is visible, but not statistically significant;  $p = 0.07$ .

The mean duration (in weeks) of pain in CLI patients was 7.87 (SD 4.94). In the group of patients declaring ineffectiveness of the taken drugs, the mean value was 8.2 weeks (SD 5.13), and in the effective group 5.2 (SD 1.39). The difference found here was also not statistically significant;  $p = 0.06$ .

## DISCUSSION

Pain in the course of CLI affects patients before diagnosis and treatment, patients with persistent pain after successful revascularization of the limbs, patients in whom there is no possibility of improving blood supply to the limbs and those who do not agree to the proposed treatment. Pain accompanies patients at every stage of chronic obstructive peripheral artery disease (COPAD) [9, 10, 11, 12]. In COPAD almost 83% patients have neuropathic pain resulting not only from chronic ischemia but also from coexisting diabetes mellitus or radiculopathy [9]. The pathomechanism of rest pain in CLI is very complex and has not yet been fully elucidated. It has been reported that the nature of pain changes with the progress of limb ischemia, from nociceptive in character during the phase of intermittent claudication to neuropathic in character during CLI [13, 14, 15, 16]. It is indicated that we are dealing here with sensory neuropathy [17, 18]. Pain in CLI patients meets the criteria for chronic neuropathic pain [9]. The treatment of neuropathic pain is not within the traditional WHO pain pyramid; it is different from the treatment of nociceptive pain [19, 20]. In the treatment of neuropathic pain, drugs should be selected individually based on full neurological diagnostics. Tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors, pregabalin or gabapentins may be used [19, 20]. The choice is based on assessment of the nature and basis of pain and may vary depending on the recommendations adopted in a given country.

The collected material highlights the fact that in outpatient settings, pain management in patients with CLI is mainly

based on non-steroidal anti-inflammatory drugs (NSAIDs) and to a much lesser extent on paracetamol and opioid receptor agonists. Only 11% of patients considered their use to be effective. This indicates that the current treatment diametrically differs from the standards of neuropathic pain treatment, which results from the ignorance of those who prescribe these medications. Another important observation is that in a significant number of patients, on the basis of the MMSE test, one can suspect a different type of cognitive impairment, although MMSE is a screening test and as such can never be the basis for diagnosis. In patients over the age of 65, the incidence of dementia is estimated at approximately 10–11%, including a significant group of patients with vascular dementia [21]. In a situation where the pain lasts a long time and the current treatment is ineffective, patients increase the dose of medicines or reach for other drugs, which may lead to drug overdose and side effects. This is very likely considering the change in pharmacokinetics and pharmacodynamics in the elderly and the common choice of polypharmacy. An important problem is the lack of self-discipline in the use of drugs by some of the patients. Effective analgesic treatment requires regular dosing. Difficulties in accessing pain counseling centers means that care for this group of patients rests with primary care physicians. Treatment of pain, especially neuropathic pain, should be performed by teams and be based primarily on diagnosis of the type of pain set by the neurologist.

## Limitations

Limitations of the study result from the relatively small size of the study group. The variety of drugs and coexisting diseases make it impossible to assess the interaction of these drugs with painkillers. The thesis on the neuropathic nature of pain was based on a review of the literature. In the study group, no adequate screening tests to indicate the nature of the pain were performed. For this reason, it cannot be ruled out that some of the patients may have had mixed pain.

## CONCLUSIONS

The treatment of pain in patients with CLI in outpatient settings is ineffective because it is incorrectly based on drugs for the treatment of nociceptive pain and not neuropathic pain.

There is an urgent need to improve the pain management system in patients with CLI by educating physicians caring for these patients.

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