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**Dear readers,  
Dear colleagues and friends,**

*It is my honor and great privilege to welcome all scientists, physicians and readers of our medical journal to share their thoughts and novel findings with us. The academic journal “Acta Medica Bulgarica” is a peer-reviewed journal, which represents the progress in clinical judgment and scientific research in Bulgaria over the last years. Recently, the journal gained some international attention and numerous manuscripts are received from writers outside the country, so we are now publishing scientific papers from all around the world. This highlights our continuing efforts in improving the quality of our academic journal – Acta Medica Bulgarica, the official journal of Medical University – Sofia. In light of the increasing interest in the journal, it will be published three times per year, starting in 2019. We hope to present the recent advances in medical and basic research. We would also like to successfully address the unmet needs of young investigators and scientists from the academic community and from around the world. Our goal is to steadily improve the scientific standards and quality of research in Bulgaria and contribute to the improvement of patient care on an international level. The Open Access option is a major advantage allowing fast dissemination of research data. Original research articles, case reports and practical reviews are welcome from all fields of Medicine, Dentistry, Pharmacy, and Health Management. We also accept letters to the editor, short communications and provocative comments on hot topics, such as the latest breakthroughs and discoveries in the field of medical science, contradictory results from clinical trials or clinical guidelines that have changed the face of clinical practice.*

*Looking forward to high quality submissions,*

  
Prof. V. Zlatkov, DM, PhD  
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## COMPREHENSIVE ANALYSIS OF PAIN SYNDROME IN PATIENTS WITH MANDIBULAR FRACTURES TREATED WITH NUCLEO CMP FORTE

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**Abstract.** *The objective of this study was to perform a comprehensive evaluation of major indices of pain syndrome in patients with mandibular fractures accompanied by damage of inferior alveolar nerve using conventional therapeutic regimen supplemented by the administration of drug product Nucleo CMP Forte. Operative and post-operative treatment of 50 patients with angular fractures of the mandible, accompanied by clinical manifestations of inferior alveolar nerve damage, was performed. The severity of pain syndrome and neuropathy symptoms was evaluated using the LANSS pain scale, DN4 questionnaire, the Visual Analogue Scale (VAS) and Neuropathy Total Symptom Scores (NTSS-9). Decrease of pain syndrome was revealed in both groups but with different dynamic pattern. In the treatment group pain syndrome manifestations and neuropathy symptoms decreased quicker than in the comparison group. As LANSS, DN4, VAS and NTSS-9 scales characterize pain syndrome from various perspectives, the results were different but similar tendency was shown. At the beginning of the study LANSS scale indices were nearly identical in both groups, while on the 7th and 14th day they were 1.35 and 2.03 times lower, respectively, in the treatment group compared to the control group. On the first day NTSS-9 scale values did not practically differ in between the studied patients, being somewhat higher in the treatment group. On the 7th and 14th day the values increased 1.24 and 3.82 times, in the treatment group and in the group of comparison, respectively. Thus, the patients in the treatment group showed significantly greater pain relief than those in the comparison group. The analysis of dynamic pattern of complaints as well as the objective findings in angular fractures of the mandible, accompanied by the damage of inferior alveolar nerve, demonstrated that the administration of drug product Nucleo CMP Forte led to a more pronounced improvement of pain syndrome in the course of treatment. Because of the fact that neuropathic pain can develop in orthodontic treatment, as well as when partial and complete removable dentures are used, the administration of drug product Nucleo CMP Forte is warranted in combined therapy of both mandibular fractures followed by the clinical manifestations of inferior alveolar nerve damage, and neuropathic pain management in orthodontics and orthopedic stomatology.*

**Key words:** mandibular fracture, Nucleo CMP Forte, pain, allodynia, VAS, NTSS-9, LANSS, DN4

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## INTRODUCTION

Injuries of the facial bones hold a special place among mechanical skeletal injuries due to their anatomic features, and because of high incidence of severe functional and cosmetic disorders which follow them. In recent years an increase of traumatism in general is seen both in Ukraine and abroad, including the incidence of dentofacial injuries. It should be noted that persons with dentofacial injuries make 20-40% of all dental surgery in-patients, and mandibular bone injury is considered to be the most common pathology (72-91.9% of all cases of facial bone fractures in peacetime) [3, 7].

The fractures of mandibular body are associated with the damage of inferior alveolar nerve – the largest branch of mandibular nerve, passing in the mandibular bone canal of the same name. This nerve is the peripheral branch of trigeminal nerve, and its injury causes a number of physiologic and morphologic changes in facial tissues and oral cavity organs. The damage of this branch of trigeminal nerve in mandibular fractures can over time be manifested by severe paroxysmal facial pains. Peripheral nerve injury is accompanied by different sense disorders in the corresponding innervation zone, the development of pain syndrome of various intensity as well as frequent emotional and stress disorders [2, 6, 9].

Most of the injuries are associated with pain syndrome of various degree of severity. The diagnostics of neurodental diseases is a great challenge in maxillofacial surgery, the main clinical manifestation of them being pain syndrome and neurologic disorders in dentofacial region [4, 5].

Neuropathic pain (NP) develops due to the damage of different divisions of the somatosensory nervous system. It can also be caused by the damage of afferent somatosensory system at any level, from peripheral sensory nerves to cerebral cortex, as well as by disturbances in descending antinociceptive systems. Neuropathic component is thought to support long-term pain in traumas, when the pain itself is caused by inflammatory changes in the local region. NP develops due to the damage or dysfunction of the system transmitting pain signal in the normal condition. Disorders associated with NP development belong to heterogeneous group of diseases with the involvement of peripheral and central nervous systems. Pathophysiologic basis for neuropathic pain is neuron hyperexcitation occurring as a result of plastic changes in the structures involved in transmission and processing of nociceptive signals. NP can greatly influence the person's quality of life. It often poorly responds to treatment because of its resistance to

many drugs and is followed by side effects despite effective drug therapy. Neuropathic pain, developing due to the damage or dysfunction of peripheral and central nervous system structures, as opposed to nociceptive (physiologic) pain in body tissue injury, is not protective by character, but it is chronic desadaptive state accompanied by sensor, vegetative and trophic disorders [1, 5, 10].

The patients hospitalized with mandibular fractures do not usually receive adequate drug therapy, aimed at the rehabilitation of the damaged inferior alveolar nerve, or its administration is rather delayed, thus being ineffective. Taking into consideration the rather high prevalence of pain syndrome, its influence on working capacity, activity, quality of life, disability and great economic expenditures, the need for a study on this urgent problem becomes obvious [8].

Neuropathic pain can develop in orthodontic treatment, as well as when partial or complete removable dentures are used. The study of new methods of treatment of this pathology and their introduction into clinical practice seem to be one of the promising directions of research in dentistry.

The **objective** of this study was to perform a comprehensive assessment of major indices of pain syndrome in the patients with mandibular fractures accompanied by the damage of inferior alveolar nerve in conventional therapeutic regimen supplemented by administration of drug product Nucleo CMP Forte.

## MATERIAL AND METHODS

To achieve the target goal, operative and postoperative treatment was performed to 50 patients (46 males and 4 females) with angular fractures of the mandible accompanied by the clinical signs of inferior alveolar nerve damage. The study was carried out at the Department of Maxillofacial Surgery of Vinnytsia City First Aid Hospital and Dentofacial Department of Vinnytsia Regional Clinical Hospital named after M. I. Pirogov from September, 2015 to October, 2017.

The patients with angular fractures (isolated unilateral or combined bilateral) with no clinical manifestations of contralateral nerve damage were selected for adequate processing of the data obtained. There was either no bone dislocation in the patients or it was not greater than 1 cm. Due to its elasticity and mobility, no complete rupture of inferior alveolar nerve in non-ballistic angular mandibular fractures occurred.

The patients were divided into two clinical groups – treatment group and comparison group. The treatment group consisted of 25 patients (23 males and 2 females) 18 to 31 years of age (average age 24.9



years). Those patients underwent conventional range of therapeutic measures including an operation for bone fragment reposition and splinting of both jaws, 10 day parenteral (i.v./i.m.) administration of a broad-spectrum antibiotic (ceftriaxone) and a non-steroid anti-inflammatory drug (diclofenac), as well as additional administration of 10 parenteral injections of drug product Nucleo CMP Forte in the dose of 3 ml once a day. The average duration of in-patient treatment was 13.5 days.

The subjects of the comparison group were 25 patients (23 males and 2 females), 19 to 30 years of age (average age 24.6 years). Those patients underwent conventional management including bone fragment reposition and splinting of both jaws, 10 day parenteral (i.v./i.m.) administration of broad-spectrum antibiotic (ceftriaxone) and non-steroid anti-inflammatory drug (diclofenac). The average duration of hospital stay was 14.4 days.

The severity of pain syndrome and neuropathy symptoms was evaluated using the LANSS pain scale, questionnaire DN4, the Visual Analogue Scale (VAS) (assessment of subjective feelings of pain intensity) and Neuropathy Total Symptom Scores (NTSS-9).

**The LANSS Pain scale (Leeds Assessment of Neuropathic Symptoms and Signs, M. Bennett, 2001) – the grading scale of neuropathic symptoms and signs**

According to this scale the patient is asked 5 questions concerning the intensity and character of his pain; the signs of allodynia and impaired sensitivity in the innervation zone are detected as well. Every question has the corresponding value in scores. To receive the total value, the parameters of sensor descriptors and sensitivity tests are summarized. The maximal value is 24. If the sum is < 12, neuropathic mechanisms of pain development are unlikely. If the sum is > 12, neuropathic mechanisms of pain formation are probable.

**DN4 Questionnaire – for diagnostics of neuropathic pain, Bouhassira D, et al., 2005**

According to DN4 questionnaire method, assessment interview with the patient is conducted. The questionnaire consists of two blocks of questions: the first one (7 items) is filled in by the examiner after interviewing the patient, and the second one (3 items) – after clinical examination of the patient. The first part of the questionnaire evaluates such positive sensory symptoms as spontaneous pain (burning sensation, sensation of coldness, electric shock sensation), paresthesia and dysesthesia (“skin crawling”, tingling, numbness, pruritus). The second part helps to reveal allodynia and negative sensory symptoms (Table 1).

If the score is 4 or higher, the pain is of neuropathic origin. If the score is less than 4, the pain is unlikely to be neuropathic pain. Maximal score is 10.

**Table 1. DN4 Questionnaire**

Does the pain have one or more of the following characteristics?		
	yes	No
1. Burning		
2. painful cold		
3. electric shock		
Is the pain associated with one or more of the following symptoms in the same area?		
	yes	No
4. tingling, crawling sensation		
5. pins and needles		
6. numbness		
7. itching		
Examination of the patient		
Is the pain located in the same area where physical examination reveals one or more of the following characteristics?		
	yes	No
8. Reduced sensation (hypoesthesia) to touch		
9. Reduced sensation (hypoesthesia) to prick		
Can the pain be caused or increased in the painful area by:		
	yes	No
10. Brushing in this area?		

**The Visual Analogue Scale (VAS) (Huskisson E. C., 1974)**

This is a subjective assessment method of pain severity when the patient is asked to mark with a pen the point on the non-graded 10 cm line that best describes his pain intensity. The left boundary corresponds to “0” (absence of pain), the right one – to “10” (unbearable pain). Usually 10 cm paper, cardboard or plastic ruler is used for this purpose. On the back of the ruler centimeter divisions are made, by which the doctor registers the values obtained in the examination chart. One of the major advantages of this scale is its ease of administration. In dynamic assessment the change in pain intensity is considered objective and significant, if the actual VAS value differs from the previous one by more than 13 mm. The Visual Analogue Scale reflects the intensity of pain experienced by the patient at the time of examination. Pain intensity is marked by the patient himself (Table 2). As to its disadvantages, VAS scale is a uni-

dimensional measure of pain intensity, i.e. only pain intensity can be determined by this scale. Because of this, other methods of pain assessment are usually used in studies as well.

**Table 2.** Visual Analogue Scale (VAS)

1	2	3	4	5	6	7	8	9	10

**Neuropathy Total Symptom Scores (NTSS-9)**

NTSS-9 scale measures symptoms for the previous 24 hours (Table 3). The scale can be used to evaluate a number of symptoms developing in patients with traumatic damage of inferior alveolar nerve. The severity and frequency of such symptoms as shooting pain, burning sensation, aching pain, allodynia (a painful response to normally innocuous stimulus), static hyperalgesia, tingling, numbness, sensation of coldness in the zone of inferior alveolar nerve inner-

vation, cramps (mimic muscle twitching) can be assessed both separately and in combination. The sum of all symptom indices is used for comprehensive evaluation of neuropathy symptoms by NTSS-9 scale.

The investigations were carried out for three times during the period of treatment: on admission (the first day), on the 7<sup>th</sup> and 14<sup>th</sup> days of treatment. The patients were required to undergo a course of treatment without analgesics because of analgesic effect of diclofenac, which could confound the study results. The examination was carried out in the following way: at the day of admission – within the shortest possible time prior to drug prescription, on the 7<sup>th</sup> and 14<sup>th</sup> days of treatment – in the morning prior to medicinal manipulations (not less than 6 hours after the previous drug administration).

As the antimicrobial drug included in the therapeutic regimen had no influence on the study results, it was used according to conventional treatment regimen equally in the treatment group and in the group of comparison.

**Table 3.** NTSS-9 scale

Symptom	Severity				Frequency		
	You would assess severity as				You would assess frequency as		
During the previous 24 hours you had	absent	weak	moderate	severe	rare	frequent	constant
Shooting pain	0	1	2	3	0	0.33	0.66
Burning sensation	0	1	2	3	0	0.33	0.66
Aching pain	0	1	2	3	0	0.33	0.66
Allodynia (aberrant pain)	0	1	2	3	0	0.33	0.66
Static hyperalgesia	0	1	2	3	0	0.33	0.66
Tingling	0	1	2	3	0	0.33	0.66
Numbness	0	1	2	3	0	0.33	0.66
Sensation of coldness	0	1	2	3	0	0.33	0.66
Cramps (twitching)	0	1	2	3	0	0.33	0.66

**RESULTS**

The following data were obtained after analyzing the study results:

The signs of allodynia, impaired sensitivity in the innervation zone as well as the intensity and character of the pain were established using the LANSS pain scale. Scale indices decreased in both groups indicating reduction of the pain syndrome. This is not surprising, as acute period (1-3 days) is followed by regeneration in the fracture zone, if no inflammatory complications develop, leading to the decrease of pain syndrome. However, the reduction of pain inten-

sity was not the same in the two groups (Fig. 1). At the beginning of the study the indices were nearly equal in both groups, but on the 7<sup>th</sup> and 14<sup>th</sup> days they were 1.35 and 2.03 times lower, in the treatment group and in the group of comparison, respectively.

The analysis of DN 4 questionnaire data found the following pattern of relationship (Fig. 2). At the beginning of the study practically no differences between the two groups' indices were revealed, moreover, they were somewhat higher in the treatment group. On the 7<sup>th</sup> day the difference was insignificant (the values were 2.03 times lower in the treatment group).



However, on the 14th day there was a significant difference in the indices – 2.23 times lower in the treatment group than in the group of comparison.

The next diagram (Fig. 3) shows the tendency of VAS (Visual Analogue Scale) indices to decrease both in the treatment group and in the group of comparison. Significantly more rapid decrease of pain was revealed in the treatment group. On admission the in-

dices in that group were similar to those in the group of comparison, they were 1.15 times lower on the 7th day, being insignificantly different. But on the 14th day VAS indices were 2.9 times lower than those in the comparison group.

Examination data obtained by Neuropathy Total Symptom Scale (NTSS-9) are presented in Table 4 and Fig. 4.

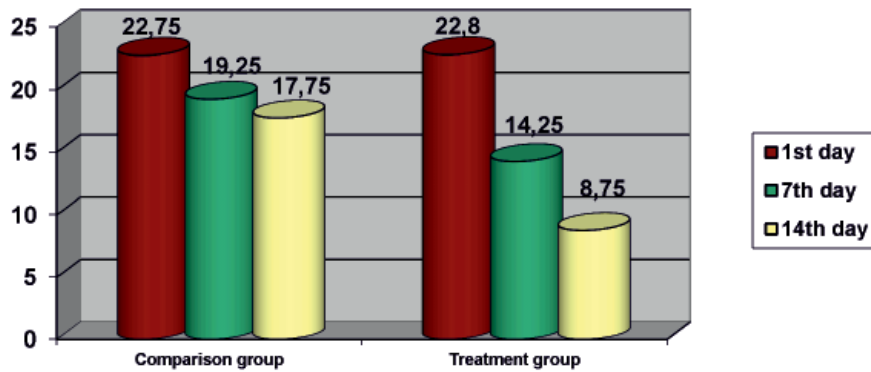


Fig. 1. LANSS pain scale indices

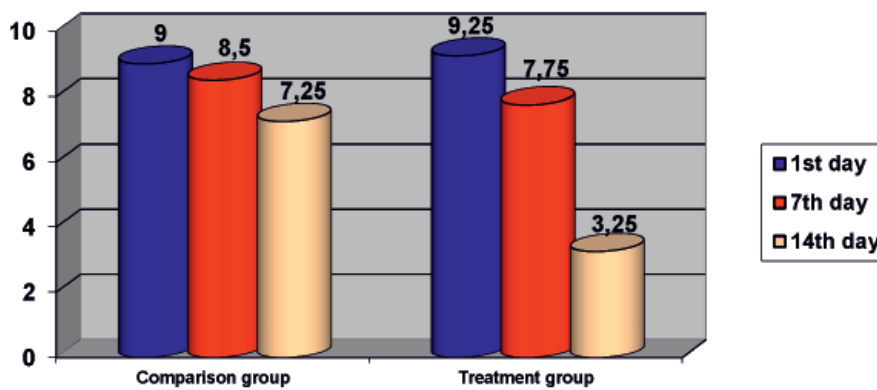


Fig. 2. DN 4 questionnaire indices

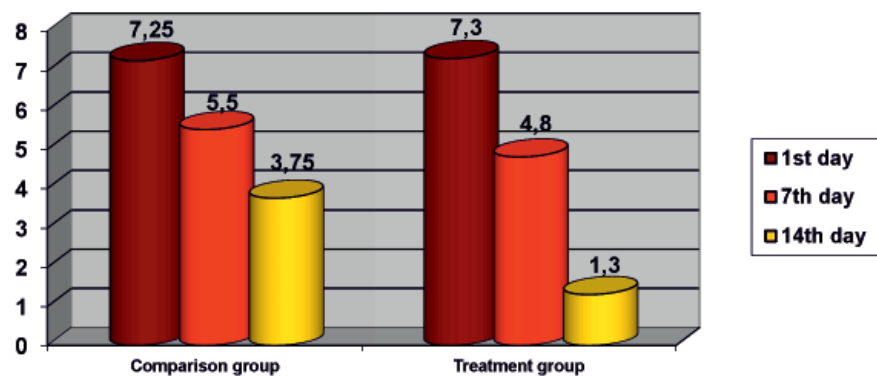


Fig. 3. Dynamic pattern of VAS indices

Table 4. Neuropathy Total Symptom Scale (NTSS – 9)

	Group of comparison	Treatment group
First day	21.97 ± 0.98	22.04 ± 0.95
7th day	17.72 ± 3.39	14.25 ± 1.55
14th day	14.65 ± 2.89	3.83 ± 0.53

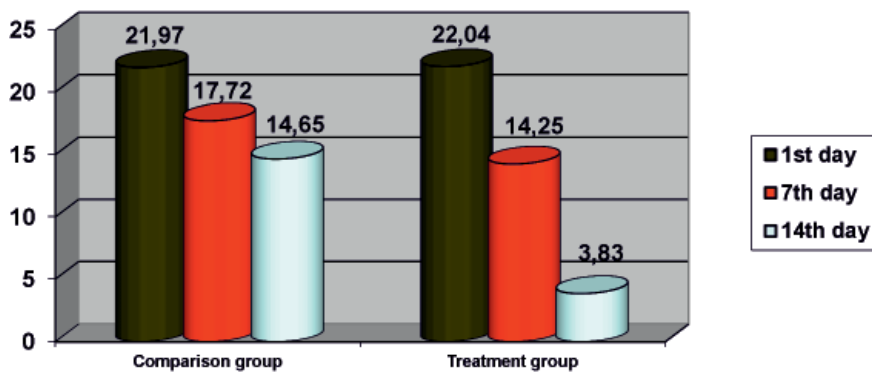


Fig. 4. NTSS – 9 scale indices

Clear-cut differences between the groups were seen in the improvement of the patients' state. It is obvious, that on the first day the indices were similar, being even somewhat higher in the treatment group. On the 7th day the indices were 1.24 times lower and on the 14th day – 3.82 times lower in the treatment group than in the group of comparison.

Since LANSS, DN4, VAS and NTSS-9 scales characterize pain syndrome from various perspectives, the results were different, the tendency, however, was quite similar.

### CONCLUSIONS

**Thus**, having analyzed the dynamics of patients' complaints as well as the objective data in angular fractures of the mandible accompanied by inferior alveolar nerve damage, the administration of drug product Nucleo CMP Forte was found to accelerate the regression of pain syndrome in the course of treatment. The preparation significantly decreased the severity of all neuropathy manifestations, associated with the damage of the inferior alveolar nerve: shooting pain, burning sensation, aching pain, allodynia (aberrant pain), static hyperalgesia, tingling, numbness, sensation of coldness, cramps (twitching). So, the patients benefited subjectively and clinically from the treatment with Nucleo CMP Forte.

Because of the fact that neuropathic pain can develop in orthodontic treatment, as well as when partial or complete removable dentures are used, the administration of drug product Nucleo CMP Forte is warranted in combined therapy of both mandibular fractures, followed by clinical signs of inferior alveolar nerve damage, and neuropathic pain in orthodontics and orthopedic stomatology.

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