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Complex Analgesia (Infiltrations and Deep Oscillation) in Patients with Stump Pain and Phantom Pain after Lower Limb Amputation (Double-blind Randomised Controlled Trial of Efficacy)

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Authors' contributions

This work was carried out in collaboration between all authors. Author IBK designed the study, managed the literature searches and wrote the protocol. Authors BRI and RDY managed the analyses of the study. Author RDY performed the statistical analysis. All authors wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Most of amputees feel residual limb (stump) pain, phantom sensations and phantom pain. Our purpose was to remind the wide public of the impact of rehabilitation (including the modern physical modality Deep Oscillation - DO) in the pain management of amputees.
Goal: Comparative evaluation of drug, physical (including DO) and combined analgesia in the complex rehabilitation of patients after femoral amputation suffering from stump pain and phantom pain. In the current article we tested the ***hypothesis*** that a preformed modality (Deep Oscillation) is able to provide an analgesic effect, to relieve reactive depression and to ameliorate the quality of life of amputees.

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Materials and Methods: During last years a total of 63 amputees with stump pain and phantom pain were observed and investigated. The investigation was conducted with consideration for the protection of patients, as outlined in the Declaration of Helsinki, and was approved by the appropriate institutional review boards and ethic commissions. All patients gave written informed consent before undergoing any examination or study procedure.
A simple randomization was used. Patients were sequentially numbered and randomized into three treatment groups of 21 each one.
All patients received a complex rehabilitation programme including physical therapy and patients' education. In group 1 we applied too drug therapy – paravertebral infiltrations with steroids, lidocaine and B vitamins. Patients of groups 2 received a complex rehabilitation programme, including DO. In group 3 we applied drug and physical analgesia techniques (infiltrations and DO).
For statistical evaluation we used t-test (ANOVA) and Wilcoxon rank test (non-parametrical correlation analysis), performed using SPSS package. The treatment difference was considered to be statistically significant if the *P value* was < *0.05*.
Results: The comparative analysis of results shows a significant improvement of the symptoms of the patients, concerning: pain relief (visualized by the analysis of results of Visual analogue scale, evaluation of stump tenderness), and depression (scales of Zung and McGill Quality of life questionnaire). In all cases we detected reduction of pain sensation and depression; amelioration of the independence in ADL. The drug analgesia in group 1 was fast, but short; the efficacy in group 2 is slow, but stable, and durable. We received best results in group 3.
Discussion: The drug therapy is efficient but with short duration. The physical analgesia with DO initiates its effect slowly, but the results are stable. Best efficacy was observed in case of combination of medication with physical modalities – in the beginning due to the steroid injection, toward the moment of effective «input» of the physical modalities.
Current paper proposes personal opinions on some contemporaneous theories of pain and therapeutic concepts of analgesia, including physical analgesia. We mentioned principal natural and preformed physical modalities, with effectiveness in clinical practice. Authors suggest a conception of mechanisms of physical analgesia, especially in case of application of Deep oscillation.
Conclusion: We could recommend the complex program for treatment of the pain in amputees.

Keywords: Stump pain; phantom pain; analgesia; physical modalities; deep oscillation; pathogenetic mechanism.

ABBREVIATIONS

ADL : Activities of daily living
ANOVA : Analysis of variances
A.Th. : After therapy
B.Th. : Before therapy
DO : Deep Oscillation
GABA : Gamma (γ) amino-butyric acid
HIVAMAT: Histological (HI) Variable (VA) Manual (MA) Technique (T)
IASP : International Association for the Study of Pain
ICF : International Classification of Functioning, Disabilities and Health
NMDA : N-methyl D-aspartate (NMDA) receptor antagonists
NSAIDs : Nonsteroidal anti-inflammatory drugs
PRM : Physical and Rehabilitation Medicine
QoL : Quality of life
TENS : Transcutaneous electro-neurostimulation
Zung-D : Self-Rating Depression Scale of Zung

1. INTRODUCTION

1.1 Amputation

According the medical definitions the amputation is ''the intentional surgical removal of a limb or body part; performed for the following reasons: to remove malignant tumors, after severe trauma, and to remove tissues without adequate blood supply, because of injury to the blood vessel, hardening of the arteries, arterial embolism, impaired circulation, repeated severe infection that leads to gangrene, severe frostbite, Raynaud's disease, or Buerger's disease'' [1,2]. More than 90% of amputations, performed in Europe and in United States, are consequences of complications of the diabetes mellitus: diabetic angiopathy, neuropathy, diabetic foot ulcers, arthropathy [1,3,4], with considerable medical and economic impact.

Most investigators evaluate principal problems in amputees: alteration of the body image, gait and

mobility difficulties, limitations of the independence in activities of daily living (ADL), and reduction of the quality of life of persons with lower limb amputation [3,5,6]. Some authors are oriented to psychological problems of post-amputation life - sense of grief, loss and shock post operatively [7], or related conditions (anxiety, depression, etc.) [4, 8, 9].

We decide to investigate the pain in amputees: pain in the residual limb (stump pain), pain in the missing part of the body (the phantom limb pain) and the relationship of these types of pain with problems of the amputee – depression and quality of life.

1.2 Pain

Pain is one of the most frequent sensations, formed in the nervous system. It's a subjective experience, provoked by nociceptive activation, by changes in sensory nerves and roads, or by cerebral centers – regulators of stress, affects and motivation. By definition, pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [10].

1.3 Post-amputation Pain

The Declaration of Montréal of the International Pain Summit of the International Association for the *Study of Pain* (IASP) identifies that chronic pain is a serious chronic health problem and access to pain management is considered as a fundamental human right [11,12].

Most of amputees feel residual limb (stump) pain, phantom sensations and phantom pain [8,13,14].

Post-amputation pain is a challenge for professionals. In the pain management of amputees various medications and physical modalities are applied.

1.4 Physical Analgesia (and Its Clinical Rationale)

We proposed the notion ***physical analgesia*** for the application of physical factors for pain management [3,5]. By our opinion the anti-pain effect of physical modalities is very important, with a high level of efficacy. Physical analgesia has not adverse effects and side consequences, and may be applied in combination with other therapeutic factors (promoting medication's analgesic effect).

In physical analgesia a lot of **physical modalities** are applied [3,5]:

- ***Preformed modalities*****:** Low frequency currents and low frequency modulated middle frequency currents (sinusoidal-modulated, interferential, Kots currents); Transcutaneous electroneurostimulation (TENS); High frequency currents (*diathermy, ultra-high frequency currents, decimeter and centimeter waves);* Ultra-sound and phonophoresis with NSAIDs; Low frequency magnetic field; Deep Oscillation;
- ***Natural modalities*****:** Cryo-factors *(ice, cold packs, cold compresses);* Thermo-agents *(hot packs, hot compresses),* Hydro- and balneo-techniques (*douches, baths, piscine);* hydro and balneo-physiotherapy techniques (*underwater massage, under water exercises, etc.);* Peloidotherapy (*fango therapy, thermal mud, sea lye compresses*); Physiotherapy techniques - stretching, post-isometric relaxation, manual therapy (traction, mobilization, manipulation); massages (manual and with devices; periostal, connective tissue massage, etc.);
- ***Reflectory methods*****:** Electrotherapy, thermotherapy and physiotherapy in reflectory points and zones; acupuncture, laserpuncture, acupressure, etc.

Our purpose is to emphasize on the analgesic capacities (and the safety) of some contemporaneous non-traditional techniques: paravertebral infiltrations (local anaesthetics) and Deep Oscillation (a contemporaneous physical factor, based on the influence of the electrostatic field on tissues in profundity).

2. OBJECTIVE

The GOAL of current study was to realize a comparative evaluation between the efficacy of pure drug therapy, physical analgesia and combined anti-pain therapy (drug and physical analgesia) on the stump pain and the phantom pain in patients after lower extremity amputation.

In the current article we tested the ***hypothesis*** that a preformed modality (Deep Oscillation in this case) is able to provide an analgesic effect, to alleviate reactive depression and to ameliorate the quality of life of amputees.

3. DESIGN OF THE STUDY, MATERIALS AND METHODS

3.1 Study Design

Our controlled prospective randomized double-blind investigation was effectuated during last years (April 2005-March 2017) on a total of 63 patients, divided into 3 groups (21 patients for each one), in eight *Physical and Rehabilitation Medicine (PRM) departments & clinics* in *two* Bulgarian cities *(*Sofia and Pleven):

- *In-patients* of three *PRM Clinics in multi-profile University hospitals for active care (*one – in *Pleven /2007-2011/*, two – in *Sofia*: Hospital 'Saint Ivan Rilsky' /2012-2014/ and the Hospital 'Sainte Anna' /2015-2017*/);*
- *In-patients* of two *Specialized Rehabilitation Hospitals* (National Rehabilitation hospital of Ovtcha kupel /2005-2006/ and 'Yasen' in Bankia /2014-2015/);
- *Out-patients* in *PRM Departments of three medical centres (MC):* in Pleven (MC 'Pleven" /2007-2011/), and in Sofia (MC 'St Ivan Rilsky' /2012-2015/ and MC 'Saint Thomas' /2014-2017/).

3.1.1 Outcome measures

During the period of the study we checked all amputated patients, hospitalized in mentioned hospitals. A detailed clinical and functional examination was performed for every patient, including history of the disease, date and cause of amputation, presence of stump and phantom pain; functional status, pathokinesiological analysis, manual muscle test, goniometry, centimetry. Special attention was paid to pain evaluation, presence of muscular or articular contractures; clinical signs and symptoms of neuropathy or angiopathy in the contralateral limb; depression.

3.1.2 Eligibility criteria for participants

After detailed analysis of potential participants and with the objective to assure data uniformity, we decided to put strong inclusion and exclusion criteria, as follows:

3.1.2.1 Inclusion criteria

All patients with trans-tibial amputation, effectuated during last 12 months, due to diabetic complications, with signs and symptoms of diabetic polyneuropathy in the contra-lateral lower limb, and suffered by stump and phantom pain (duration of 1 to 6 months).

3.1.2.2 Exclusion criteria

We excluded patients without stump or phantom pain, with amputation of the upper limb or other level of lower limb (trans-femoral, disarticulations, etc.); amputations due to traumatic of other conditions, very 'old' amputations (executed more than 1 year ago).

According the CONSORT (Consolidated Standards of Reporting Trials) 2010 statement [15], we present patients' distribution and flow in the *Table 1 (Flow diagram*).

All patients were investigated according to an examination *Protocol* - before (B.Th.), during (Day 8) and after (A.Th.) therapy, and one month after the end of the rehabilitation (1 month later - follow-up).

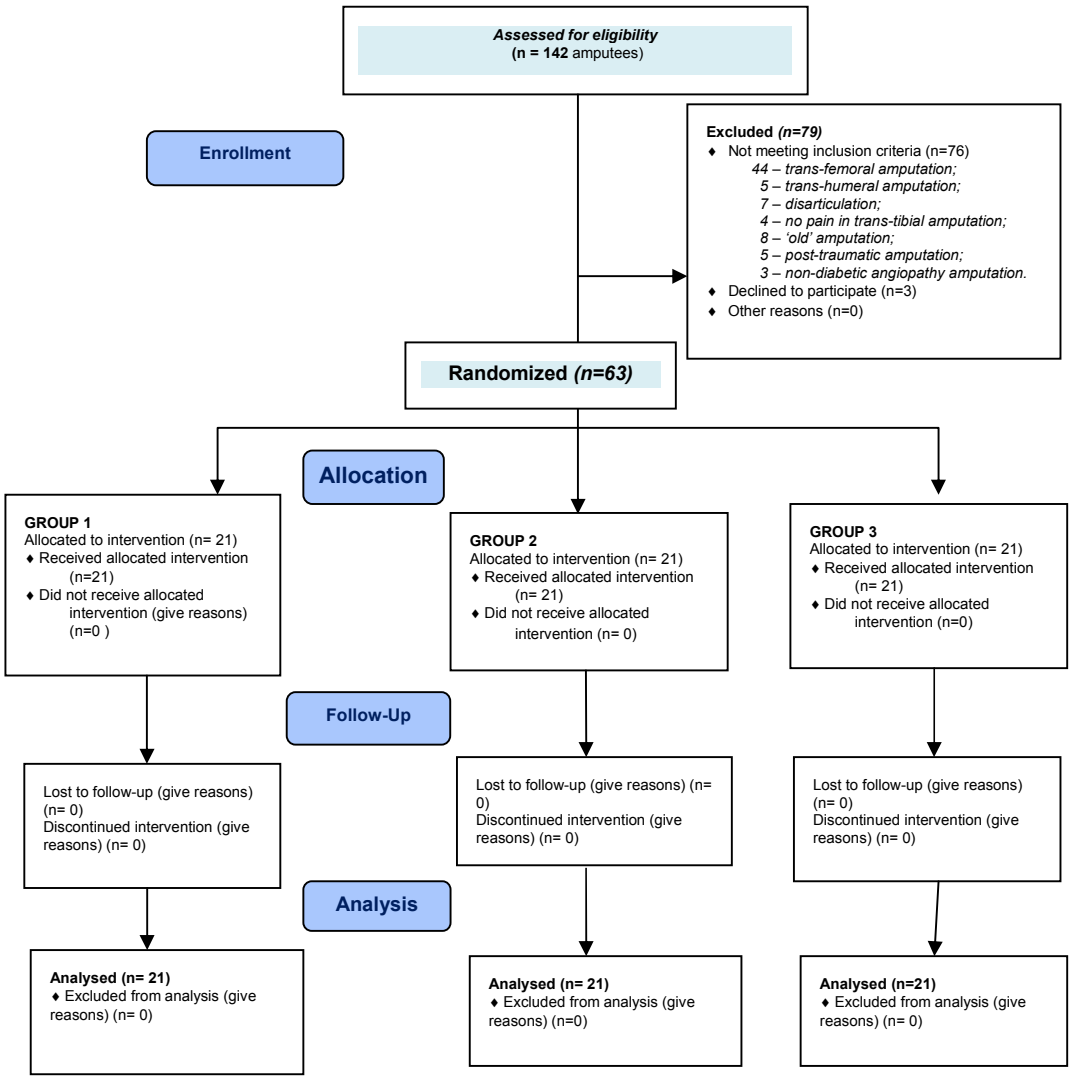
All patients received a complex PRM program of 3 weeks (15 procedures).

All patients present at the beginning of the study, finished the rehabilitation, and were investigated before, during and after treatment.

3.1.3 Details of organization of the study, randomisation and blinding

According recommendations [16,17,18,19] the investigation was realized by a multi-professional team; including: a medical doctor – specialist in Physical and rehabilitation medicine (PRM) and in Neurology, with sub-specialization in Pain medicine. The physical therapy complex was performed by a physical therapist, with sub-specialization in the fields of Neurological and Orthopedical Rehabilitation, and in Pain therapy. The statistical analysis was performed by a mathematician – specialist in Information Technologies. The medical doctor provided the exams of patients (before, during and after treatment) without information concerning the rehabilitation complex. The physical therapist oriented every first patient to gr 1, every second patient – to gr 2, etc. The mathematician had not information about patients' personal data and PRM complex; he had only investigations' results. The details of the series were revealed to investigators after the end of the study.

Table 1. Flow diagram



3.2 Ethic Aspects

The study satisfies legal and ethical norms.

The investigation was effectuated with consideration for the protection of patients, as outlined in the *Declaration of Helsinki (1964)*.

The study was approved by the appropriate institutional review board and ethic commission.

All patients signed a *written* informed consent for participation in the investigation, before undergoing any examination or study procedure.

3.3 Materials

All patients suffered from trans-femoral amputation, effectuated 6 months to 1 year before the admission in our clinic. All patients suffered from stump and phantom pain, gait difficulties, altered body image and limited activities of daily living (ADL), and reduced quality of life. All patients had diabetic neuropathy and angiopathy, with diabetic foot, before the amputation. The declared origin (cause) of the amputation of our patients was diabetic angiopathy.

The distribution of patients is presented in Figs. 1 and 2 (by sex - Fig. 1; by age – Fig. 2).

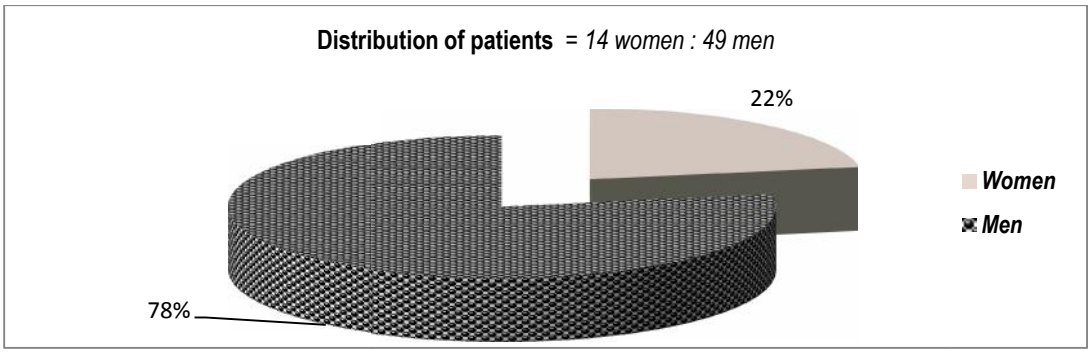


Fig. 1. Distribution of patients *(M:W)*

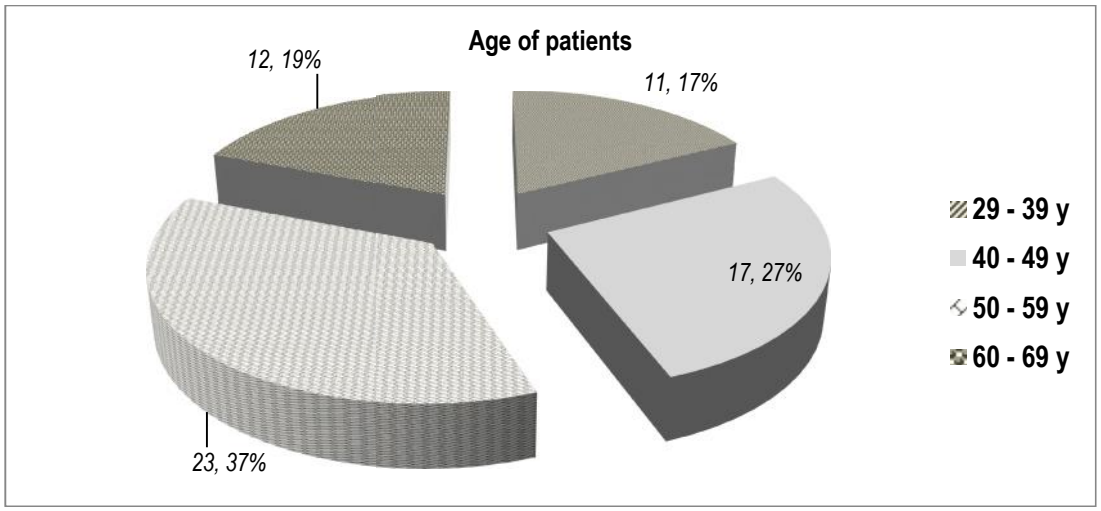


Fig. 2. Distribution of patients *(age)*

3.4 Examination Protocol

A detailed functional examination was performed for every patient (before and after therapy, and one month after the end of rehabilitation), including functional status, pathokinesiological analysis, pain evaluation, manual muscle test, goniometry, centimetry, depression [20]. Finally, global testing was applied – evaluation of the quality of life (QoL) and testing according the International Classification of Functioning, Disabilities and Health (ICF, 2001) [21]. During the treatment (day 8) we effectuated only clinical analysis, incl. dolorimetry, VAS and Zung-D test.

An important part of the examination protocol was the detailed description of the stump and phantom pain, including excitatory sensitive signs and symptoms: feelings of cramping, burning, aching, paresthesia, dysesthesia, sensations of heat or cold in the limb (residual or phantom). For quantitative pain evaluation we used the Visual analogue scale [VAS with values from 0 (no pain) to 10 (worst pain imaginable)]; Faces scale [series of faces with expressions from smiling (0 = “no hurt”) to tearful (10 = hurts worst)] and exam of the tenderness of the stump [pressure dolorimetry - values from 0 (no pain) to 3 (very important pain)].

The psychological battery included two tests – the scale for depression of William Zung [22] and the correspondent question (concerning depression) of the Mc Gill Quality of life questionnaire [23].

The analyzed scores of the Self-Rating Depression Scale [Zung-D] were from 20 (norm) to 80 (depression - D), distributed in 4 ranges: normal (20-44), mild depression (45-59), moderate D (60-69) and severe D (70 and above) [24].

The Quality of life (QoL) was evaluated using the McGill Quality of life questionnaire [23] – using a scale from 0 (minimum) to 10 (maximum). For the needs of current article we analyzed only three questions: Part A – global evaluation (*Considering all parts of my life over the past two days the quality of my life has been: from very bad /0/ to excellent /10/),* Part B – Physical Problems – question 1 *(Over the past 2 days, one troublesome symptom has been pain – answers from 0 /no problem/ to 10 /tremendous problem/)* and Part C – question 5 *(Over the past two days, I have been depressed – answers from 0 /not at all/ to 10 /extremely/).*

3.5 Characteristics of Patients before the Treatment

All patients had diabetes mellitus of type 2 (non-insulino-dependent = NID-DM), diabetic polyneuropathy (DPNP) and diabetic angiopathy, important pain and stump tenderness (P), phantom sensations (PhP), signs of reactive depression (D) and altered quality of life (QoL). A lot of patients had too arterial hypertension (art-HT), different level of ischemic heart disease (IHD), dyslipidemia; some of them – cardiac insufficiency (card-insuff). All patients present lower limb weakness and hypotrophy of the femoral muscles. Table 2 presents detailed information about clinical characteristics of patients before treatment (baseline).

3.6 Physical and Rehabilitation Medicine (PRM) Programme of Care

As declared, a simple randomization was used. Patients were sequentially numbered and randomized into three treatment groups.

Table 2. Baseline clinical characteristics of patients

Patients' characteristics	Number (and percentage) of patients from the correspondent group			
	Group 1	Group 2	Group 3	All patients
Presence of DM - NID	21 (100%)	21 (100%)	21 (100%)	63 (100%)
History of the disease NID-DM (years=y)				12,1 y, SD=3,7
Presence of DPNP	21 (100%)	21 (100%)	21 (100%)	63 (100%)
History of DPNP				9,6 y, SD 2,4
Presence of Diab Angiopathy	21 (100%)	21 (100%)	21 (100%)	63 (100%)
History of Diab Angio				4,3 y, SD=1,2
Presence of art-HT	20 (95,24%)	21 (100%)	19 (90,48%)	60 (95,24%)
History of art-HT				13,4 y, SD=2,4
Ischemic heart disease (IHD)	16 (76,19%)	20 (95,24%)	17 (80,95%)	53 (84,13%)
History of IHD				9,3 y, SD=1,9
Dyslipidemia (dys-Lip)	19 (90,48%)	12 (57,14%)	16 (76,19%)	47 (74,60%)
History of dys-Lip				11,7 y, SD=1,8
Cardiac insufficiency (card-insuff)	20 (95,24%)	13 (61,90%)	21 (100%)	54 (85,71%)
History of Card Insuff				10,1 y, SD=1,4
Presence of pain (P)	21 (100%)	21 (100%)	21 (100%)	63 (100%)
Intensity of P (0-10)	9,7	9,6	9,8	9,7
Stump tenderness (0-3)	2,4	2,6	2,5	2,5
Phantom pain (PhP)	21 (100%)	21 (100%)	21 (100%)	63 (100%)
Depression – presence	21 (100%)	21 (100%)	21 (100%)	63 (100%)
Level of D (Zung-D) – moderate & mild D	51,3	51,5	50,9	51,23
Altered Quality of life	21 (100%)	21 (100%)	21 (100%)	63 (100%)
McGill QoL (0-10)	1,4	1,6	1,8	1,6
Centimetry (10 cm above the patella – difference between the amputee and non-amputee limb)	4,8 cm	5,3 cm	4,9 cm	5,0 cm

Used abbreviations in the Table 1: NID-DM: Non-insulino-dependent Diabetes mellitus; DPNP = Diabetic polyneuropathy; DiabAngio = Diabetic angiopathy; art-HT = Arterial hypertension; IHD = Ischemic heart disease; dys-Lip = Dyslipidemia; Card-Insuff = Cardiac insufficiency; P = Pain; PhP = phantom pain; D = depression; QoL = quality of life

All patients received a complex rehabilitation programme including physical therapy and patients' education (stump care, putting-on prosthesis). We accentuate on: analytic exercises (including isometric exercises) for hip muscles, post-isometric relaxation for ilio-psoas muscle, stretching of the lumbar fascia, strengthening exercises for the paravertebral and abdominal muscles and for the 'healthy' limb; manual massage; balance training and gait training (with the provisory or the definitive prosthesis) [3,17].

In group 1 we added drug therapy: *paravertebral infiltrations with cortico-steroids* (Hydrocortisone), *B vitamins* (B1, B6, B12) *and local anaesthetic* (Lidocain 2%).

In patients of groups 2 we included the *preformed physical modality DO* (DO - fibromyalgia programme).

In group 3 we applied *combined drug and physical analgesia techniques* (infiltrations and DO).

3.7 Statistical Analysis

Statistical analysis was performed with SPSS electronic package, version 11.5. We applied options for two samples comparison) with parametrical analysis of variances ANOVA: *t-test (t-criterium, p value), Signed test, Signed rank test.*

The treatment difference was considered to be statistically significant if the *P value* was < 0.05. In some cases we received lower results of the P-value ($p<0.01$).

There was no statistical significance in principal characteristics of different groups before treatment.

4. RESULTS AND ANALYSIS

For us, the primary endpoint was change in pain intensity. Secondary efficacy endpoints included changes in the level of depression and in the quality of life of amputees.

The comparative *analysis of results* shows a significant improvement of the symptoms of the patients in all groups, concerning: *pain (Fig. 3), diminution of stump tenderness (Fig. 4), depression (Zung-D scale – Fig. 5); and quality of life (McGill questionnaire - Figs. 6, 7 and 8).*

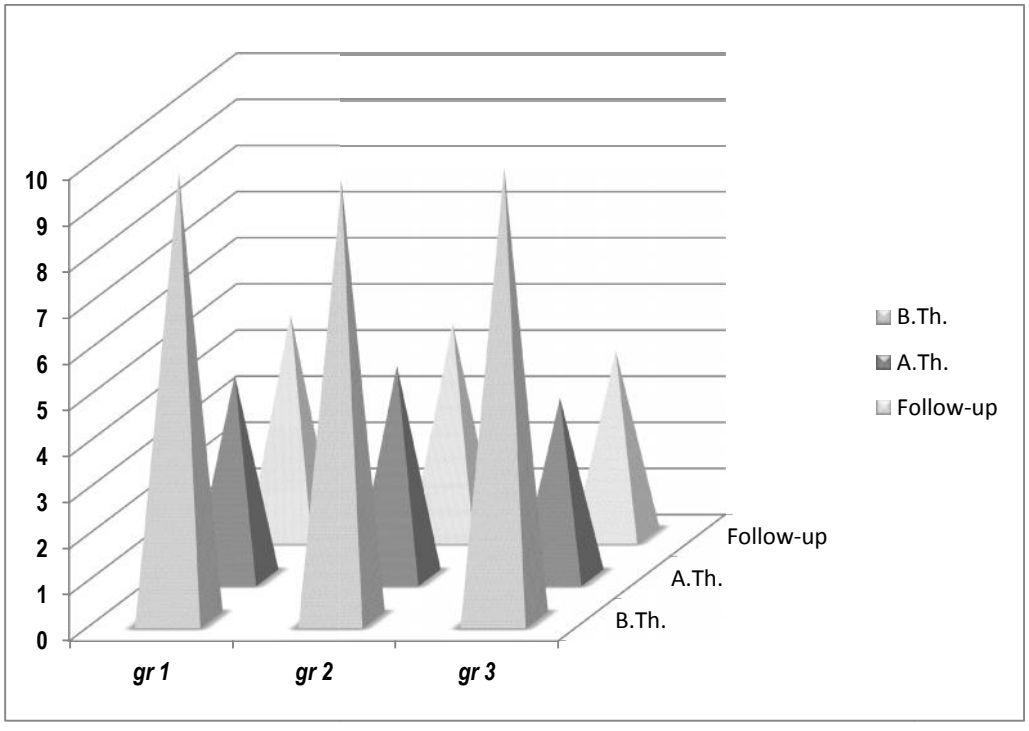


Fig. 3. Pain relief (*VAS 0-10*; *no pain, to worst pain*)

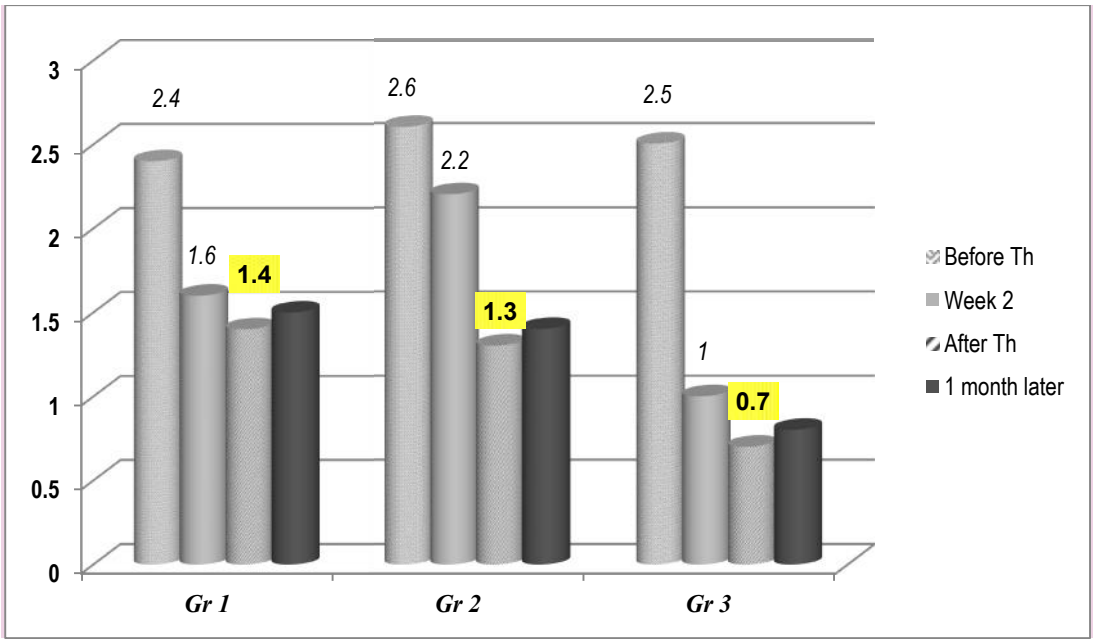


Fig. 4. Pressure dolorimetry – stump tenderness
(From no pressure pain /0/ – to extreme sensibility /3/)

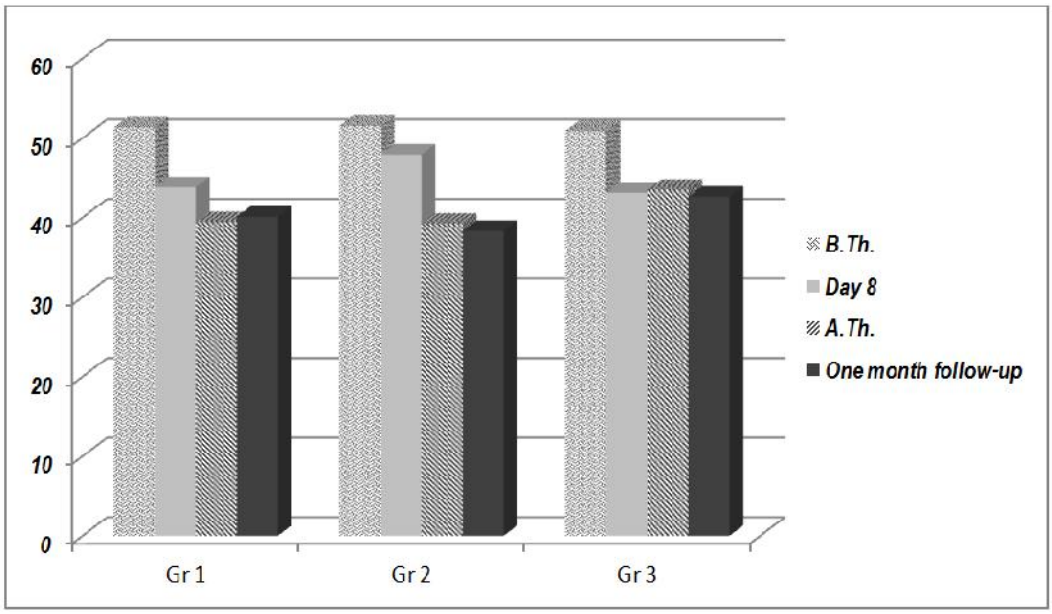


Fig. 5. Psychological tests: Express scale of ZUNG – Depression
(Transition from moderate or mild depression /50-52 points/ to norm /under 44 points/)

4.1 Reduction of Pain Intensity and Diminution of Stump Tenderness

The reduction of pain sensation is visualized by the Visual analogue scale (VAS 0-10), presented in Fig. 3, and the diminution of stump tenderness – by dolorimetry (Fig. 4). The analgesic effect is significant in all groups (comparison before and after therapy), but is most expressed (significance < 0.05) in group 3 (combination of medication and physical analgesia).

A very interesting fact is the fact that the drug analgesia has a fast beginning but for an insignificant period. The physical analgesia begins its efficacy slowly (no significance between values before Th and the second week), but has a long duration including one month after the end of rehabilitation (significance during comparisons B.Th. and A.Th.; and B.Th. and one month later).

4.2 Reduction of Level of Reactive Depression

The decrease of points according to the express scale of Zung for depression (Zung – D), presented in Fig. 5, shows the reduction of the reactive depression, that is typical for the first months after amputation. We observed significant reduction of the depression level in all groups, more expressed in group 3. A statistical significance in all groups comparing points before and after therapy was shown. No statistical significance was shown between the results of the second and the third group.

4.3 Quality of Life of Amputees

The influence of the rehabilitation complex is visualized in the answers to McGill's questionnaire presented in Figs. 6, 7 and 8.

Practically, the complex question (global evaluation) can be considered like satisfactory concerning the QoL – presence of statistical significance comparing values before and after therapy (Fig. 6).

In the current study we decided to include some elements of McGill questionnaire as controls of the primary outcomes: Part B: Physical problems - Evaluation of the troublesome symptom - in this case 'Pain' (presented in Fig. 7); and Part C: Feelings and thoughts, Question 5 - Depression (presented in Fig. 8).

In all cases we obtained statistical significance comparing results before and after therapy, and comparing values before therapy and one month after the end of rehabilitation ($p<0.05$).

There's no measured statistical significance between groups concerning the QoL.

In all cases we detected reduction of pain sensation and depression; amelioration of the independence in ADL and quality of life. The drug analgesia in group 1 was fast, but short; the efficacy in group 2 is slow, but stable, and durable. Best results were obtained in patients of group 3.

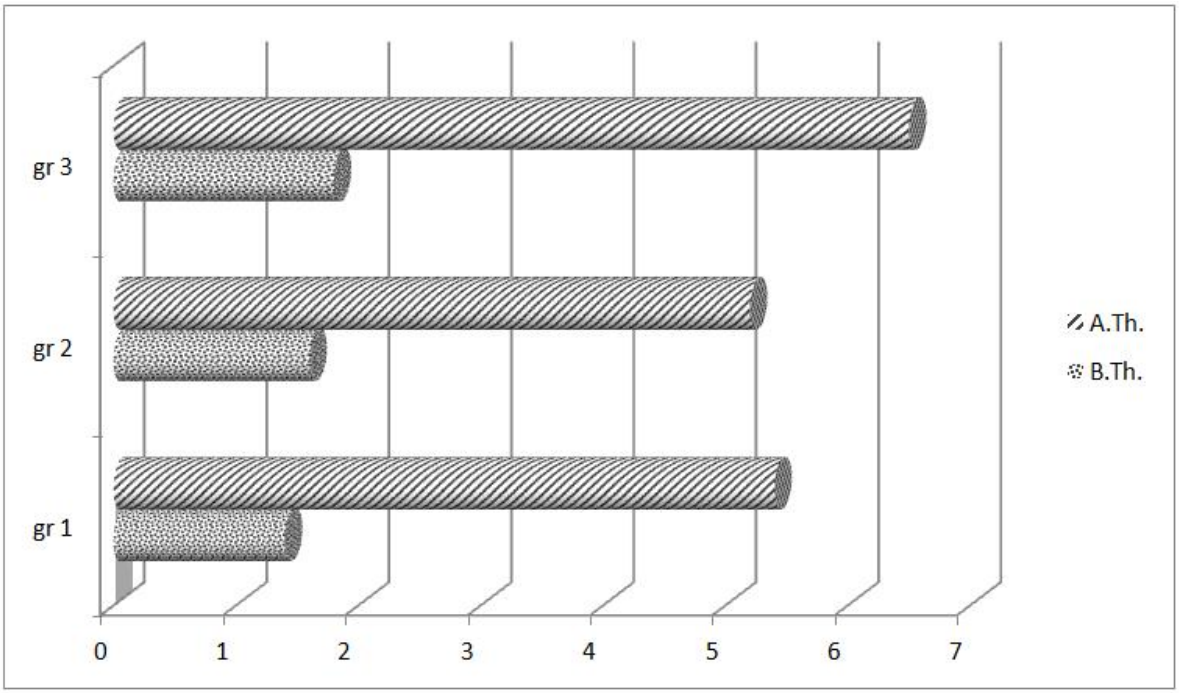


Fig. 6. McGill quality of life questionnaire – global evaluation
(Amelioration of the global evaluation of all parts of own life – from bad /0/ to excellent /10/)

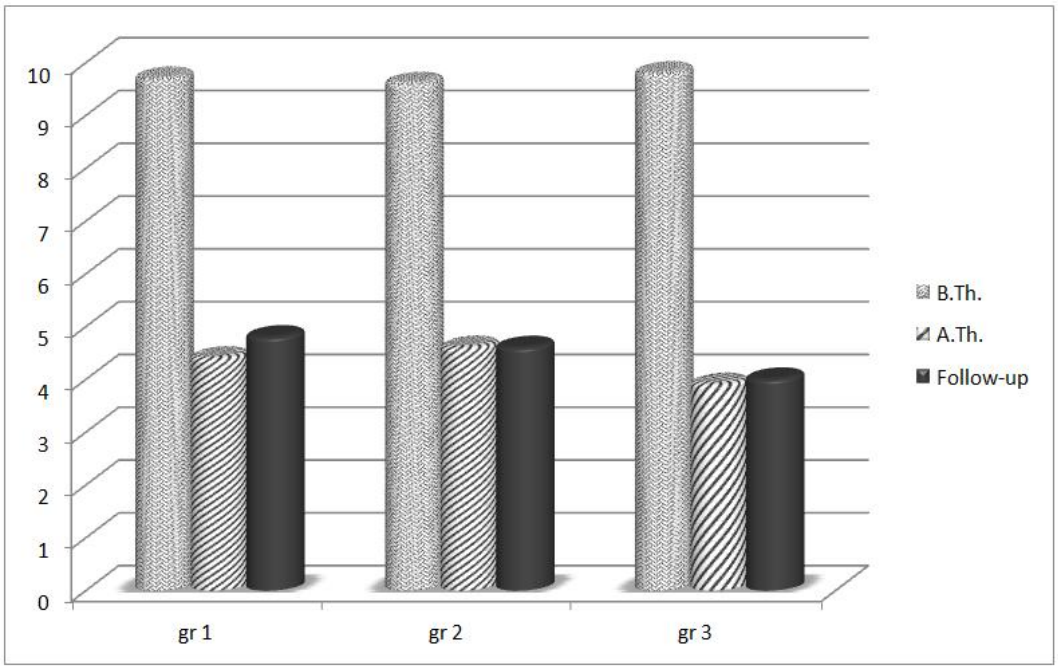


Fig. 7. McGill quality of life questionnaire – Part B: Physical problems: Pain
(Reduction of the troublesome symptom – evaluation from no problem /0/ to tremendous problem /10/)

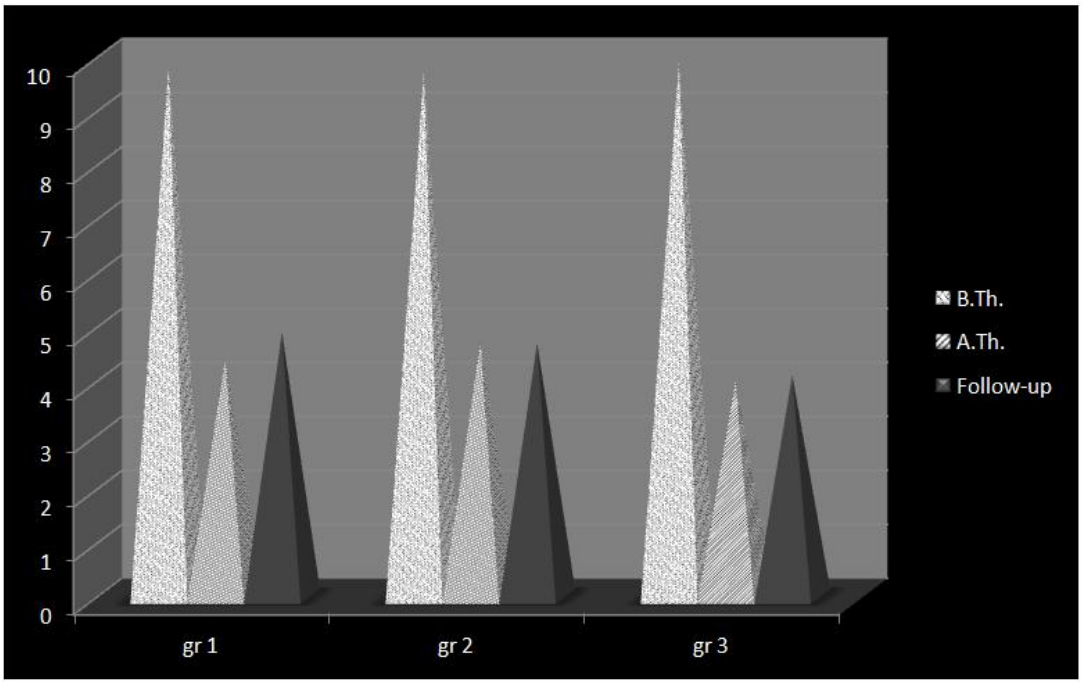


Fig. 8. McGill quality of life questionnaire – Part C: Feelings and thoughts, question 5 - Depression
(Over the past 2 days, I have been depressed; answers: from not at all /0/, to extremely depressed /10/)

The drug therapy is efficient but with short duration. The physical analgesia with Deep Oscillation initiates its effect slowly, but the results are stable. Best efficacy was observed in case of combination of medication with physical modalities – in the beginning due to drugs towards the '*input*' of physical analgesia.

5. DISCUSSION

5.1 Post-amputation Pain

Most of amputees feel residual limb (stump) pain, phantom sensations and phantom pain [8,13,14].

A lot of theories (from neuro-biological to cognitive) try to explain amputees' pain (especially phantom pain). Many authors consider that phantom pain is associated with maladaptive plastic changes along the neuraxis and alterations of the cortical representation of the affected limb, dues to a loss of GABA-ergic inhibition, glutamate-mediated long-term potentiation-like changes and resulting structural shift (e.g. axonal sprouting) [25]. The role of neuroplasticity is considered like very important, as well as cortical reorganization and disturbed body perception [26,27]. According some theories, phantom pain is a descending (top-down) phenomenon, triggered by the loss of sensory input from the amputee limb and caused by maladaptive cortical plasticity [8,13,28]. Other authors defend the alternative hypothesis: the phantom limb pain is an ascendant (bottom-up) processus, due to exaggerated input, generated ectopically in axonotomized (after the nerve section) primary afferent neurons in the dorsal root ganglia, that used to innervate the limb [29].

Post-amputation pain is a challenge for professionals. In the pain management of amputees various medications are applied: oral opioid analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), N-methyl D-aspartate (NMDA) receptor antagonists, muscle relaxers; additional medicines, including antidepressants, anti-epileptic and neuroleptic agents [1]. Surgical management includes thermo-controlled coagulation of the spinal cord, spinal cord stimulation and stereotactic deep brain stimulation [7,26,27]. But almost of the modern scheduled drugs and surgical interventions (applied for treatment of the persistent pain) are associated with limitations, side and even adverse effects [1,3,15,16]. In some cases a lot of other techniques are preferred: correct prosthetic care; physical therapy, exercises; transcutaneous electro-neurostimulation (TENS), acupuncture; relaxation and stress management approaches; biofeedback, cognitive and behavioral therapy [3,5,9,10,30].

5.2 Mechanisms of Physical Analgesia

In some countries, a psychological approach to rehabilitation is imposed [8,9,30]. Traditionally, the Bulgarian rehabilitation school makes efforts to investigate objectively and to explain **pathogenetic mechanisms of physical analgesia**.

In physical medicine we apply the principles of ***gate-control theory***, formulated by the British physiologist *Patrick Wall* and the Canadian psychologist *Ronald Melzack*, in their common article "Pain Mechanisms: A New Theory" [31]. Melzack and Wall suppose the existence of a controlling mechanism in the spinal medulla, which is closed in response to the normal stimulation of fast fibers of tactile sense, but is open if the slow fibers of pain perception transport numerous and intensive sensory signals. The gate is closed if these signals are interrupted by a new stimulation of the fast fibers.

The formulation of the gate-control theory [10,28] for explanation of pain introduced the principle of the "contra-stimulation" – final effect reticence by stimulation of inhibiting systems or else final effect stimulation by embarrassment of inhibiting systems [3]. Investigations of prof. Yordanka Gacheva demonstrate that *the selective electrostimulation of tactile Aβ-nerve fibers (with high velocity of conduction) provokes a previous stimulation of suppressive neurons, they inhibit the tardily arrived nociceptive stimuli of A-δ and C-fibers* (with slower conduction velocity) [citation by 3]. Some authors consider that a closer suppressive transfer mechanism exists at spinal level. At the peripheral level the direct anti-adaptative electrostimulation of the receptors probably provokes a hyperpolarization with a decrease of the sensibility of the nociceptors. A direct low frequency electrical stimulation of the Aδ and C fibers may cause an analgesic effect.

We propose our own theory for explanation of mechanisms of action of physical modalities on the nociceptive and neuropathic pain [3]: *By influence on the cause for irritation of pain receptors* - consequence of stimulation of circulation, metabolism and trophy of tissues (by low and medium frequency electric currents,

magnetic field, ultrasound, He-Ne laser; massages; manual techniques); *By blocking of nociception* (low frequency currents, including transcutaneous electrical nerve stimulation or TENS; lasertherapy); *By inhibition of peripheral senzitization* (low and middle frequency currents, TENS; magnetic field; lasertherapy); *By peripheral sympaticolysis* (low frequency currents like dyadinamic currents, peloids); *By stopping the neural transmission (by C and Aδ delta - fibers) to the body of the first neuron of the general sensibility* (iontophoresis with Novocain in the receptive zone – the region of neuro-terminals); *By input of the gate-control mechanism* (TENS with frequency 90-130 Hz and interferential currents with high resulting frequency - 90-150 Hz); *By activation of the reflectory connections: cutaneous – visceral, subcutaneous-connective tissue-visceral, proprio-visceral, periostal-visceral and motor-visceral* (classic manual, connective tissue and periostal massage, post-isometric relaxation and stretching-techniques); *By influence on the pain-translation in the level of posterior horn of the spinal medulla – using the root of activation of encephalic blocking system in the central nervous system* (increasing the peripheral afferentation) and *influence on the descending systems for pain – control* (TENS with frequency 2-5 Hz and interferential currents with low resulting frequency 1-5 Hz, acupuncture and laserpuncture; reflectory and periostal massage, zonotherapy, acupressure, su-dgok massage; preformed factors in reflectory zones /palms of hands, plants of feet, paravertebral points; zones of Head, of Mackenzie, of Leube-Dicke, of Vogler-Krauss/); *By inhibition of central sensitization* (lasertherapy; peloidotherapy; physiotherapy); *By influence on the psychic state of the patient* – the drug «doctor» and the drug «procedure».

In the case of phantom pain, physical analgesia effectuates an inhibition of the source of ectopic nerve discharge, and this way impedes the functional involvement of primary or successive generators of the phantom limb pain.

5.3 Deep Oscillation – Principles and Mechanisms of Action

Deep Oscillation® Therapy was originated in Germany in 1988 [15]. Deep Oscillation (DO) is a modern physical modality, based on the influence of the electrostatic field on tissues in profundity, explained with the effect, named after Danish engineers F. A. Johnsen and K. Rahbek [32]. The *Johnsen–Rahbek effect* occurs when an electric potential is applied across the boundary between a metallic surface and the surface of a semiconducting material. Under these conditions an attractive force appears, whose magnitude depends on the voltage and the specific materials involved. R. Atkinson [1969] described a model expressing the attractive force between the contacting materials as a function of the voltage applied across them [33]. The model, which takes into account the presence of surface irregularities, is obtained by an assessment of the effect of field emission on the electrostatic capacitor forces between the contacting surfaces. This model is the base of modern devices: HIVAMAT & Deep Oscillation ®.

The name *HIVAMAT* is an acronym of: (HI) Histological (VA) Variable (MA) Manual (T) Technique [15]. Technically speaking, the HIVAMAT 200™ produces a micro-massage therapy, based on the action of a pulsating, low-frequency, two-phase alternating electrostatic field generated between the practitioner's hands and the patient's skin [15]. At the level of the connective tissue this intermittent electrostatic field produces an intense resonant vibration and the repetition of this phenomenon in rapid succession generates rhythmic deformations of the tissue (skin, connective, and muscular). The resulting effect includes improvement in microcirculation, better tissue nourishment, enhancement of cellular metabolism, promotion of faster healing even on open wounds), anti-oedema, lymph drainage, anti-fibrosis and detoxifying properties, alleviation of pain and swelling, stimulation of collagen production and tissue regeneration. *Deep Oscillation® Therapy* has been proven as an effective treatment for: occupational injuries and conditions associated with pain, inflammation, swelling and scar tissue; sports injuries; general and surgery aftercare; laser re-surfacing rehabilitation; pre-chiropractic adjustment [3,5,34,35].

We consider that the physical modality Deep Oscillation provokes its analgesic effcet by the inclusion of the following **pathogenetic mechanisms***: By influence on the cause for irritation of pain receptors* (due to the stimulation of circulation, metabolism and trophy of tissues); *By blocking of nociception*; *By inhibition of peripheral senzitization*; *By input of the gate-control mechanism*; *By activation of the reflectory connections; By influence on the psychic state of the patient*.

5.4 Drug or / and Non-drug Analgesia? That's the Question…

Our results demonstrated that the combination of drug and non-drug analgesia is most effective.

The influence of physical modalities on the interstitium or **'***milieu intérieur'* of Claude Bernard [36] is the theoretical base for *this combined pain management programme*. The synergy between different physical modalities is the logical base for prescription of *complex program.* The combination of drug and physical analgesia programme is needed, because the mechanism of action of different treatments is diverse [3,5].

5.5 Analgesia Team

For effective pain management the inclusion of a multi-professional therapeutic and rehabilitation team is obligatory [16,17,18]. *Different models of organization of the teamwork* of the staff are applied*:* ***interdisciplinary*** (complex care of the patient from different scientific and professional disciplines); ***multi-disciplinary*** (role of every professional is completely independent from the others); ***transdisciplinary*** (everyone helps the work of the others; role and functions are distributed). We consider that the clinical practice imposes the necessity of transition from a multi-disciplinary to a transdisciplinary model of team work, with a clear definition of the fields of competence and the responsibility of the team members. In Bulgarian rehabilitation practice traditionally a lot of specialists are included: *medical doctors – specialists* in Orthopedics and Traumatology and in Physical and Rehabilitation Medicine (PRM); *bachelors and masters* in Physical Therapy (Kinesiotherapy – according the Bulgarian nomenclature).

5.6 Deductions for the Clinical Practice

Our study proved the beneficial effect of a structured PRM programme on amputee's stump pain, phantom limb pain, depression and quality of life. We consider that the combination of drug therapy (with reduced dosage) and physical therapy (including the pre-formed modality Deep Oscillation) is effective, hasn't important side effects and can be applied in patients with severe co-morbidities and in elderly. The physical therapy and the rehabilitation are a cheap alternative of drug therapy, and can support medical efforts and funds.

We know that amputations in diabetics represent an important cause of incapacity and death [34]. In some European countries, the treatment of diabetic foot complications needs 15 – 25% of resources, designed to the care of diabetics [37,38,39].

From the other side, in old patients we can't apply all medicines and some interventional therapies [7,27,37]. We know that in geriatric patients with an amputated limb and multiple other illnesses, drug therapy may be problematic and invasive techniques may be risky [40]. PRM programme can be a satisfactory alternative for amputees in the elderly.

Further, an early PRM programme can be applied in order to prevent the appearance or aggravation of stump pain and phantom limb pain. Some authors consider that appropriate aggressive pain management is required immediately post amputation in an attempt to avoid chronic PLP [37,41].

5.7 Limitations of Our Study

Our study was carried out on a relatively small group of patients, with trans-tibial amputation due to diabetic angiopathy. All patients suffered from diabetic neuropathy and diabetic foot before the respective amputation. So, now we are sure that the proposed rehabilitation programme, including DO, will be beneficent for this type of patients, but we haven't (at the moment) sufficient experience with amputations due to other causes.

Some of our patients applied too some self-techniques, e.g. self-massage and self-percussion (finger tapping at the point of pain), considering that as a desensitization of the residual limb. In some amputees a modification of prosthesis socket was effectuated (to prevent rubbing at the sensitive part of the limb). These interventions were excluded from the analysis, considering that techniques like insignificant.

Finally, we must underline that all patients, treated by our team, suffered from reactive depression, consequence of the operation (amputation). In all cases, we insisted on the patient education and the dialogue with the amputee and his / her family. We consider that the role of the family members, as co-therapists, is very important for the rehabilitation process. The pain sensation (including stump and phantom limb pain) contains some psycho-

emotional aspects. Unfortunately, we can't add a psychological support to all patients, and we consider that this is an important limit of our rehabilitation programme.

5.8 Practical Issues from Our Study

Physical therapy is a cheap and useful option for increase the amputee's quality of life.

Deep Oscillation is an effective preformed physical modality with significant analgesic effect.

The patient education must be detailed and adapted to the needs of every concrete amputee.

In case of severe depressive reactions, a psychological (or psychiatric) support can be added.

We could recommend our complex programme with physical therapy, patient education, paravertebral infiltrations and Deep Oscillation for treatment of the stump and phantom limb pain in lower limb amputee patients.

The programme can be applied as early or tardive post-op rehabilitation in all cases of amputation.

5.9 Future Directions

We consider that in the future, investigators must observe the efficacy of other preformed physical modalities on stump pain and phantom pain. A comparison between different physical factors can be useful for the pain management in amputees.

6. CONCLUSION

Pain management is an important part of the rehabilitation algorithms in amputated patients with stump and phantom limb pain.

CONSENT

All authors declare that written informed consent was obtained from every patient before any examination or procedure.

ETHICAL APPROVAL

All authors hereby declare that the investigations and treatment of patients have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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