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THE ROLE OF PROPRIOCEPTIVE FACILITATION AND ITS APPLICATION AS AN INDISPENSABLE PART OF PRACTICAL PHYSIOTHERAPY

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Abstract: The essence of proprioceptive neuromuscular facilitation consists in the application of specific reinforcement techniques to enhance central arousal by volitional movements to improve active capacity of the affected muscle and muscles groups. This is a method of rising the muscle reaction and volitional impulses, which can be reached during stimulation of proprioceptive nerve endings. Proprioceptive neuromuscular facilitation consists is a philosophy and a concept treatment (Kabat, 1950) and for the first time the method was applied in physiotherapy practice in 1947. Dr. Kabat and Maggie Knott was the founders which started and continued to expand the development of techniques. Nowadays patients with traumatic as well as orthopaedic symptoms are treated with this concept successful. Development of PNF concept followed some specific techniques and patterns responsible to the neuromuscular facilitation. Movements are our natural way to interact with our environment. Interactions are directed by the mechanism of motor learning principles includes a progression from hands-on to hands-off treatment strategy. The mean goal is functional oriented activities and independence. The physiotherapy should be focussed always to mobilize the reserves to reach the highest point of function. Especially in the first and cognitive stage of motor control, the therapists manual facilitation will be a helpful tool in reaching this goal (Adler et. al, 2007).

Keywords: PNF, neuromuscular facilitation, muscles.

Introduction

Our goal is to reach the highest functional level and maximal independence in activities of daily living, to increase the quality of life for each patient. On the level of participation, the patient should take a part in normal activities again. The physiotherapist will always integrate principles of motor learning and motor control in his PNF treatment to reach this highest functional level. (https://www.ipnfa.org/for-patients/)

Without denying the importance of passive movement of the treatment methodology, which aim is to preserve and increase joint's range of motion, Kabat et al support the thesis that passive movements with nothing they contribute directly to the volitional activity in motor units of muscles. When applying passive movements with help there are active only the small part of motor units in the relevant muscles or muscles groups (Kabat, 1958).

Kabat (fig. 1) and his school are directing their own scientific interest looking for physiological phenomena, to facilitate and strengthen the muscular response in weakened volitional movement (International PNF association, 2013).

As is known, the force of contraction of a muscle is determined by the number of active motor units (Гранит,1957).

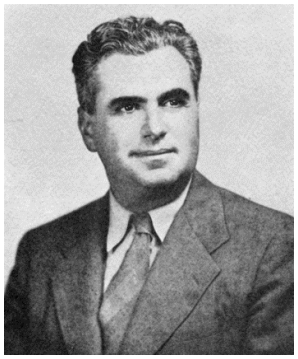

Fig 1. Dr. Herman Kabat - 1947, (Sandel, 2013)

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For greater precision the method of PNF can be defined as a means of increasing muscles reaction, relating to volitional impulses, which is achieved through proprioceptive nerve endings (Levine, Knott, Kabat, 1952).

"Noticebal muscle contraction is reached during contraction of more than 20% from motor units in one muscle", (Levine, Kabat, 1953) that's why PNF affects the impulses reaching central nerve system from the nerve ends in muscles, joints, and the labyrinth (Knott, Voss, 1956).

Materials and methods

A search was performed on PubMed, ScienceDirect, Google scholar, Researchgate et al.

Discussions

Facilitation means one muscle increasing response through the mechanisms of central nerve system (Kabat, McLeod. 1959).

For example, by hypotrophy some muscles groups, one systematic repetition to facilitate volitional contraction, can lied to a gradual decrease in synaptic resistance and the strengthening of volitional conduction pathways to these muscle groups. Later, because the result of PNF applying direct volitional contraction of the muscles is observed without any need for additional stimulation to facilitate it (Sirtori, Corbetta, Moja, Gatti, 2009).

As a common problem in the postoperative physiotherapy is the pathological increased muscle tone especially by the flexor muscles around elbow joint at the expense of weakened extensors, or as well as known muscle disbalance. Sherington studies reciprocal innervation and successive induction and found that reflex volitional contraction of a muscles leads to relaxation of antagonist muscles. The phenomenon is called reciprocal innervation. This is basic phenomenon of muscles activity allowing the performance of smooth and coordinated movements (Licht, 1984). Sherrington draws attention to the fact that immediately after triggering a reflex for example, the extensibility of the opposite is suppressed. It turns out that an active contraction of the motor muscle facilitates the subsequent volitional movement of the agonist (Sherrington, 1947).

The work of Sherrington was important in the development of procedures and techniques of PNF patterns. (Adler, Beckers, Buck, 2000).

It was found that with increasing of muscle elongation his willingness to respond to a standard cortical stimulus increase. Because of that reason in the developed by Nikolova (2019) methodology in the presence of flexion contracture in elbow joint stretching is not recommended. Interesting is the fact that any contraction or stretching of a muscle affects neighbouring muscles in a certain way. Experiment contributed by Gerhorn and Loofbarow (Ayres, 1959) about proprioceptive stimuli related to passive movements in the elbow joint or resistance of triceps brachii muscle indicates that in flexion from 115 in elbow joint m.triceps brachii, m.extensor carpi ulnaris and radialis have a significantly reduced threshold of irritability. In extension in elbow joint respectively opposite relations are observed, obvious activity of m.biceps brachii, m.extensor carpi radialis and m.brachioradialis. From these and further experiments of the authors it is proved that between some muscle groups there is a close functional connection. Thus, two or more muscles working together can be considered as a form/model of movement or a form of muscular joint activity. Experiments show that more activity can be created in one muscle with proprioceptive impulses caused in a muscle other than one's own. Hence the conclusion that each muscle of one limb is significantly affected in its activity from the proprioceptive impulses created by other muscles in the same limb. This is fundamental to the muscle's activity itself and for the targeted impact of certain muscles. From the above data can be stablished, that in their activity muscles do not work in isolation from each other and are in close functional relationships fixed in certain patterns of movement within in which one element creates favourable conditions for others, that means that facilitates their action. This is done mainly through proprioceptive mechanisms. Afferent impulses in one muscle facilitate the contractions of his synergists (Voight, Hoogenboom, Cook, 2008). Electro myographic research (EMG)of Levin and Kabat on patients shown that the position of joints facilitates muscles activity not only because of the factor "impact of stretching". If the forearm is in supination, m.biceps brachii is facilitated although in this position it is shortened (Levine et. al 1954).

„Diagonal/Spiral models of Kabat“ what is their purpose?

Kabat pays special attention to combined primary movements called motion patterns. The models are from simpler to more complex involving several joints and components. Kabat concludes that the diagonal-spiral models are the most effective. This is due to the close relationship with the spiral and rotational characteristics of the skeletal system-bones, joints, and ligaments structures. This type of movements is in harmony with their topographic location of the muscles from their initial and final insertion and with a structural characteristic on the individual muscles. The diagonal/spiral model of volitional movement is mean this movement which involve several joints simultaneously and three components: flex./ext./abd./ add./ ext./int. rotation (Kabat, 1958; Surburg, P. R., & Schrader, J. W. (1997). Each diagonal consists of two models of movements, and they are antagonistic each other, having one main component of flexion or extension. These basic components should be always combined with abduction/adduction or rotation. The diagonal/spiral patterns of movement using in PNF provide optimal opportunities for contraction of the main muscles performing the movement (Лиментал, 1963), (fig.2). One model of movement which is optimal for one whole “chain” of muscles, allows them to contract from their extended starting position to the point of maximum shortening, when the model is performed during full range of motion (Kabat, 1958).

PNF patterns can be used depending on the indications for the exercises like:

- free active movements
- passive movements for determine the range of motion or active movements with help
-active movements against resistance

Fig.2 Maggie Knott and Herman Kabat demonstrated diagonal/spiral models of movements,1950, Institute Vallejo, California, (Sandel, 2013).

Most popular and useful are the following models:

“switching antagonists“ - if it used in his full range of motion it’s working like proprioceptive facilitation also by the tensile factor at the time of the change of direction and by the applied resistance. It’s recommended the exercise with resistance to be repeated several times for the strongest antagonist and after that to perform the resistance movement for the weak agonist (Knott & Voss, 1956).

There are several varieties of pattern **“switching antagonists“** which are widely used in kinesitherapy practices

„slow reversal“- isotonic contraction of antagonists followed by isotonic contraction of agonists. Movements are performed slowly against the respective maximum resistance in accordance with the recovery stage. The movement with the stronger antagonists is done first, and then with the weakest which we want to strengthen.

„slow reverse-hold“- the difference here is that the patient must “hold” the isometric contraction. Immediately after detention is done isotonic contraction in opposite way, and by the end of the movement should repeat the same procedure.

„rhythmic stabilization“ – starting with one active isotonic contraction against resistance on agonists muscles , and in the strongest position of the volume of movement the patient must “hold” isometric. Follows one isometric contraction on weakness agonists against appropriate maximum dosing resistance. Followed by alternation of isometric contractions against maximum resistance on antagonists and agonists – rhythmic. Simultaneous strengthening of both movements is achieved. After the last isometric contraction on weakness muscles, the patient continued movement in one isotonic contraction. This model can be applied at any point of range of motion and is particularly suitable when patient experiences pain when performing movements. The described varieties on switching agonists are used

for strengthening of active movements add to increase the range of motion (ROM) in affected segment.

The following varieties are used as relaxing techniques to relax muscles with pathological increased tone.

„slow reversal-hold-relax“ – Isotonic contraction of the muscles that restrict movements is performed followed by isometric contraction on the same and then a short period of volitional relaxation of their antagonists. Relaxation must take place at the point from which the ROM of the antagonist muscles is further limited.

„hold-relax” - isometric contraction is performed against maximum resistance on muscle with increased tone according to the stage of treatment. Following by volitionally relaxation on those muscle, which can be performed with isotonic contraction on agonists. Patients with pain during stretching of the muscles with increased tone, this pattern can be just optional. For example, patients after immobilization because the fracture of radial head, often we can see the limitation of extension. The pattern applied on m.biceps brachii accompanied with slowly increased resistance can provide relaxation on the biceps, and in the same time stimulation on m. triceps brachii. Precise decision of suitability is required in cases where is vicious imbalance on antagonists.

PNF exercises are not allowed when the muscles are tired, because if one muscle does not respond maximum adequately as possible, the exercises will lose their original purpose (Розенблат, 1961, Kabat et. al, 1995). Otherwise they will be ineffective without satisfaction from patient's position (Банков ,1967).

“Contract-relax” Another technique is the contract-relax. It is almost identical to hold-relax, except that instead of contracting the muscle without moving, the muscle is contracted while moving. This is sometimes called isotonic stretching (Surburg & Schrader, 1997). Proprioceptive neuromuscular facilitation contract relax antagonist stretching technique was better than Proprioceptive neuromuscular facilitation hold-relax stretching technique in improving the hamstring muscle flexibility (Ramachandran et. al, 2018).

Conclusion

With great respect to priceless scientific contribution of dr. Herman Kabat, who continuous until nowadays and reaching the methodises increases the possibilities of physiotherapy where it is a major way of recovering. The goal of proprioceptive neuromuscular facilitation techniques is to promote functional facilitation, inhibition, strengthening and relaxation of muscle groups (https://www.slideshare.net/). The principles are based on concentric, eccentric, and static muscle contractions. These muscle contractions with properly graded resistance and suitable facilitatory procedures are combined and adjusted to fit the personal needs of each patient. (Adler, Beckers & Buck, 2007). We have grouped the PNF techniques so that those with similar functions or actions are together. Proprioceptive neuromuscular facilitation philosophy consist of positive approach: no pain, achievable tasks, set up for success, highest functional level, motor learning and mobilize potential. The effect of neurophysiological stimulus continues after stimulus stops. The feeling of increased power and ROM that comes after a maintained static contraction is a result different pattern. Last, but not least the treatment approach is always positive, reinforcing and using that which the patient can do, on a physical and psychological level. The primary aim of all treatment is to help patients to achieve their own highest level of function. To reach this highest level of function, the therapist integrates principles of motor control and motor learning (https://www.slideshare.net/). The proprioceptive neuromuscular facilitation concept provides us with many tools such as verbal and visual input, tactile information, and techniques like rhythmic initiation, combining of isotonic and replication to give the patient information about these activities. (Springer, Berlin, Heidelberg, 2008). But the therapist must decide when and how much external information the patient needs. With proprioceptive neuromuscular facilitation philosophy in mind, the physiotherapists will always give the best facilitation. At the end the patient must fulfil all activities independently and without our help (https://www.slideshare.net/).

The effects of PNF have been addressed in many studies, a systematic review of which has been made, for example, by Opplert et al. (2017). Proprioceptive neuromuscular facilitation can be a promising intervention, and severalstudies have investigated this subject in the past fiftheen years (Lazarou et. al, 2017; Padua et al., 2004 ; Takasaki, Okubo & Okuyama, 2020).

It may be possible that PNF contributes to enhancement of the JPS, but the effect of PNF on the JPS is hypothesized to different with different techniques, body regions, and physical problems (Takasaki, Okubo & Okuyama, 2020).

In this publication, we tried to emphasise the broad-spectrum application and the neurophysiological

foundation of Proprioceptive neuromuscular facilitation to be of maximum assistance to practicing colleagues in the various fields of Physiotherapy and Medicine.

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MICROBIOLOGICAL ISOLATES AND IT'S RESISTOTYPE FROM CLINIC OF VASCULAR SURGERY FOR THE FIRST QUATER OF 2022

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Abstract: One of the most common complications of surgical exposures is the surgical site infection (SSI). Although it varies between different surgical profiles, it can reach up to one third of all complications. In vascular surgery patients ischemic ulcers are very common, as well as factors, compromising the immune system such as diabetes, chronic kidney disease etc. One of the main surgical exposures in vascular surgery is inguinal, providing access to the femoral artery and its bifurcation. Although it allows a wide range of reconstructions, implanting different types of prosthetic materials, stents and providing anastomosis site, it contains lymph nodes, which can contaminate the reconstruction and cause SSI with severe consequences. Patients, prone to SSI due to concomitant diseases, are threatened by sepsis, limb loss and even death, which makes prevention of those type of complications essential.

Aim: To investigate etiological spectrum of microbiological isolates and their resistance against most common antimicrobials among vascular surgery patients.

Materials and methods: The study is retrospective, conducted in the period 01 January 2022 – 31 March 2022. All of the samples were obtained from patients of Clinic of Vascular Surgery. After isolation of pure culture from the samples, the strains were identified by MALDI TOF MS and Vitec – 2 Compact. Antibiotic resistance was determined with Bauer-Kirby disk diffusion method.

Results: From all 419 of the patients, hospitalized in the Clinic of Vascular surgery for this period, 28 isolates from 26 (6,21%) patients were obtained, of which Gram-negative were 19 (67,86%) and Gram-positive - 9 (32,14%). From Gram-negative - enterobacteria – 14 (73,68%), and non-fermenting gram-negative bacteria (NFGNB) were 5 (26,32%). Only 3 (21,43%) from all enterobacteria were extended spectrum beta-lactamases producing strains (ESBLs). No strains, resistant to carbapenems (RCP) were isolated. Five (55,55%) of the Gram-positive isolates were Staphylococcus aureus, 4 (80%) of which were methicillin resistant Staphylococcus aureus (MRSA). Two of the Gram-positive species isolated were Enterococcus faecalis, of which 1 with a high-level aminoglycoside resistance (HLAR). No Vancomycin resistant enterococci (VRE) were discovered. There were no colistin-resistant Acinetobacter baumannii and Pseudomonas aeruginosa strains.

Conclusion: From all 28 isolates 8 (28,57%) were with acquired types of antimicrobial resistance. With almost one third of the isolates that are problematic in terms of antibiotic susceptibility, treatment of those patients can be challenging. Prevention of in hospital contamination with polyresistant strains, associated with medical care it is crucial for reducing the number of severe complications, decreasing of hospital stay and cost for treatment.

Keywords: Vascular surgery, Surgical site infection, Microbiological isolates, Resistotype

Introduction

The prevalence of peripheral artery disease (PAD) is reaching almost 15% in patients above 45 years of age and up to 20% in patients aged above 70 years (Andras, 2014; Cacoub, 2009; Norgren, 2007; Ohman, 2006; Olin, 2010; Beaumier, 2020). A recent study of the general population in Germany revealed an increase in the prevalence of PAD among the general population from 1,85% in 2009 to 3,14% in 2018 with annual prevalence of Rutherford class 5-6 (Critical limb ischemia and tissue loss) varying between 4,5-7% (Rammos, 2021). One of the most common complications of surgical exposures is the surgical site infection (SSI). Although it varies between different surgical profiles, it can reach up to one third of all complications (WHO GGPSSI, 2019; PHE, 2019; GIVE, 2021). Main causes for SSI in vascular surgery are break in the aseptics, contact of the graft with patient's flora harboured in lymphatic nodes injured intraoperatively (Back, 2005; Bandyk, 1991). In addition, concomitant diseases such as diabetes, kidney failure etc. are independent factors for decreasing local immunity and can lead to SSI (Inui, 2015; Trinidad, 2019; Wiseman, 2015; GIVE, 2021). Considering the possibility for bacterial lymphatic metases in animal models (Siggins, 2020) and the reported frequencies of infections associated with vascular

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prosthesis varying between 0.2 and 5% depending on the vascular exposure (Bandyk, 1991; Dean, 1978; Fry, 1966; Liekweg, 1977; O'Hara, 1986; Calligaro, 1992; Campbell, 1994; Durham, 1986; Goldstone, 1974; Lorentzen, 1985; Naylor, 2002; Ohki, 2001; Rosenthal, 1990; Szilagyi, 1972; Hallett, 1977)

Aim

To investigate etiological spectrum of microbiological isolates and their resistance against most common antimicrobials among vascular surgery patients.

Materials and methods

The study is retrospective, conducted in the period 01 January 2022 – 31 March 2022. All of the samples were obtained from patients of Clinic of Vascular Surgery with wet gangrene, ulcers or clinical suspicions of surgical site infection after vascular reconstruction. The specimens were immediately placed in Amies transport medium. After delivery in Department of Microbiology, samples were cultured on 5% sheep blood agar, eosin methylene blue (EMB) agar, chocolate agar and chromagar candida. The incubation was performed on 35-37oC for 24-48 hours. The isolated pure cultures were identified by MALDI TOF MS and Vitec – 2 Compact. Antibiotic resistance was determined by EUCAST 2022 protocol.

Results

For the observed period 419 patients were hospitalized in the Clinic of Vascular surgery.

Table 1

Twenty-eight isolates from 26 (6,21%) patients were obtained. Isolated microorganisms originated from 13 geniuses. Most of the isolates were presented by Order Enterobacteriales, followed by NFGNB and Staphylococcus spp. No fungal isolates for the period were found (Table 1).

Microorganism	Isolates number
Acinetobacter baumanii	2
Citrobacter freundii	2
Enterobacter cloacae	1
Enterococcus faecalis	2
Klebsiella oxytoca	2
Klebsiella pneumoniae	3
Morganella morganii	2
Proteus vulgaris	1
Pseudomonas aeruginosa	2
Raoutella ornitholytica	1
Serratia liquefaciens	2
Staphylococcus aureus	5
Coagulasa negative staphylococci	2
Stenotrophomonas maltophilia	1
Total	28

Among the isolated microorganisms in the period Gram-negative bacteria were prevalent almost three times fold to Gram-positive. Most isolated bacteria from Gram /+/ group were Staphylococcus spp. - Staphylococcus aureus was 5 (55,6%) and Coagulase-negative Staphylococci 2 (22,2%). Other isolated Gram-positive cocci were Enterococcus faecalis. (Figure 1)

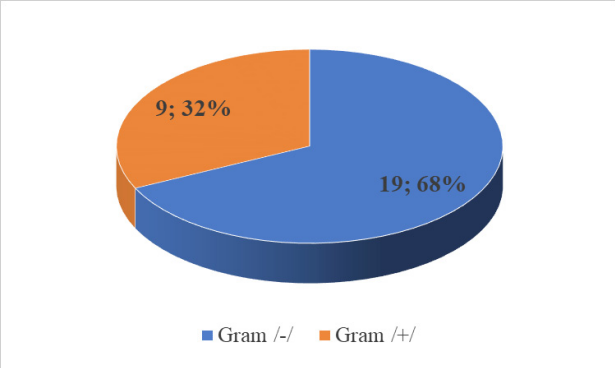

Figure 1

Gram-negative isolates consisted from two major groups – Order Enterobacteriales and non-fermenting gram-negative bacteria, as enterobacteriales were found in ¾ from all of the Gram/-/ isolates. (Figure 2)

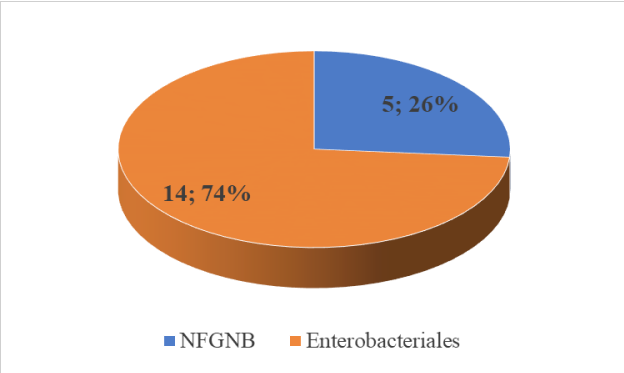

Figure 2

Most isolated species from all positive cultures was Staphylococcus aureus - 5 (17,6%). Methicillin sensitive Staphylococcus aureus was found in one (20%) of the cases and MRSA in four (80%). (Figure 3). Three (60%) of the strains were resistant to Clindamycin, but all 5 were susceptible Trimethoprim-sulfamethoxazole and Ceftaroline.

High-level of aminoglycosides resistant (HLAR) strain of Enterococcus faecalis was found in one case (50%).

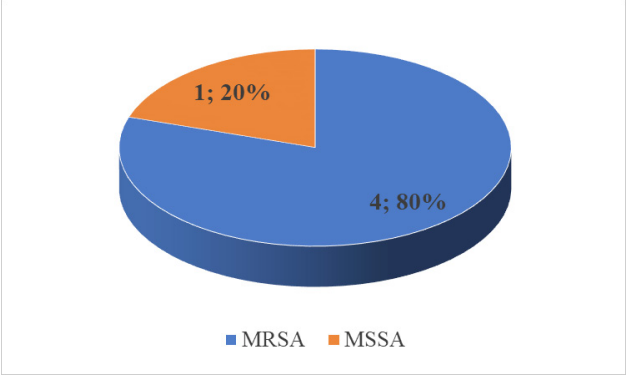

Figure 3

From all of the Enterobacteriales orders, ESBLs producing strains were found in 3 (21%), the other 11 (79%) strains were susceptible to penicillines and cephalosporines. (Figure 4)

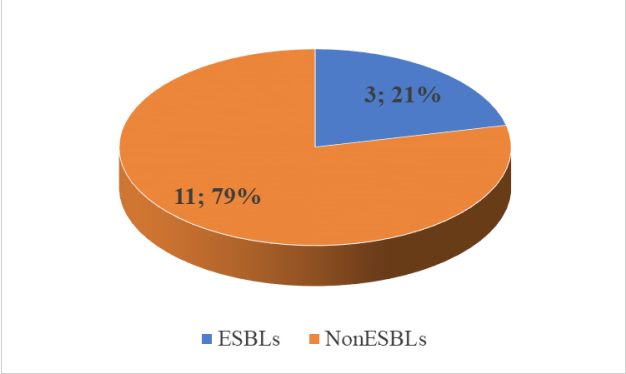

Figure 4

Overall, 20 (71%) of the isolated strains were highly susceptible to tested antimicrobials. In 8 (29%) of the positive cultures showed different mechanisms of an acquired resistance. (Figure 5)

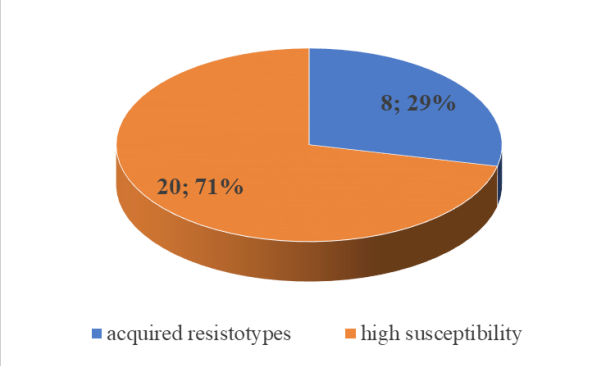

Figure 5

Discussions

From all of the isolated strains problematic resistotype was found in eight of the cases for the period. Methicillin-resistant *Staphylococcus aureus*, ESBLs producing strains and HLAR reach almost 1/3 of the isolates. No Vancomycin-resistant enterococci (VRE) and resistant to carbapenems strains were isolated for the period. According to the world literature the etiological spectrum of SSI in vascular surgery is very broad, with prevalence of *Staphylococcus aureus* and *Enterobacteriales*, which can lead to an increase of acqired antimicrobial resistance in those microorganisms (Back M.R., 2019). Broad spectrum-beta-lactamases producing strains also are in major consideration, reaching 21% of all of the *Enterobacteriales*, which approximate other autors observations (Jolivet, 2018). Surgical site infection (SSI) can be found in 2% to 5% of all surgeries, performed in the United States (Martone, 1998). Known risk factors for MRSA contamination include diabetes, chroniodialysis, peripheral vascular disease, prolonged antibiotic exposure, and extended length of stay in the ICU (Drinka, 997; Ibelings, 1998). The overall compromised local and systemic immunity in vascular patients can allow a local opportunist infection evolve in systemic one. (Inui, 2015; Trinidad, 2019; Wiseman, 2015; GIVE, 2021; WWIWP Canada, 2022).

Conclusions

From all 28 isolates 8 (28,57%) were with acquired types of antimicrobial resistance. With almost one third of the isolates that are problematic in terms of antibiotic susceptibility, treatment of those patients can be very challenging in terms of costs and final outcome. Prevention of in hospital contamination with polyresistant strains, associated with medical care it is crucial for reducing the number of severe complications, decreasing of hospital stay and cost for treatment.

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FIBROMYALGIA - CHARACTERISTICS AND PROOF OF PAIN

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Abstract: Fibromyalgia is a disease that remains unrecognized due to ignorance and misinterpretation of symptoms. This article presents a clinical case from the medical practice of Fibromyalgia, while characterizing the pain syndrome and the necessary tests to prove the diagnosis.

The clinical case concerned a patient with lumbar pain syndrome who did not respond to non-steroidal anti-inflammatory drugs. No connection has been established with the diseases provided for in the differential diagnosis, such as disc herniation, acute arterial insufficiency, rheumatoid arthritis. The laboratory tests performed are normal, except for a slight increase in AST of about 200 U / l, as well as high CRP values. No instrumental studies such as endophotonic emission computed tomography (SPECT), positron emission tomography (PET), magnetic resonance imaging (MRT) and electroencephalogram (EEG) were performed.

The case describes a modified symptom in the elderly. Modified symptoms are experienced differently by patients. In this case, our own (from the doctor's experience) paradigm was used for diagnosis. The paradigm consists of four main steps, which are: description of the specifics of each symptom; two aspects of the diagnosis: what is and what is not; the symptoms form a whole which represents the diagnosis with a logical connection and sequence and analysis of small deviations and nuances - a way of accurate diagnosis.

The burning nature of the pain, the presence of painful nodules in the lumbar and scapular areas bilaterally, point to myositis. Various non-steroidal anti-inflammatory drugs have been administered in various forms (oral, topical and injectable), with no effect. As a last resort, a tricyclic antidepressant, amitriptyline, was included, which showed that the pain disappeared within a month. The presence of a mental component in the field of rheumatic disease, the effect of amitriptyline pain and the presence of sore spots at the predilection sites, led to the disease "Fibromyalgia". Diagnosis of fibromyalgia is necessary to comply with two conditions clinical analysis of pain with the detection of painful points and instrumental nuclear magnetic resonance imaging to demonstrate dysfunction of the central nervous system and electroencephalogram for sleep disorders.

To improve the diagnostic process, it is necessary in practice to apply tests of hormones and neurotransmitters.

Keywords: fibromyalgia, amitriptyline, muscle pain, endophotonic emission computed tomography, positron emission tomography.

Field: Medical Science and Health

Introduction

Fibromyalgia is a common disease characterized by chronic widespread pain, sleep problems (including unrefreshing sleep), physical exhaustion, and cognitive impairment. The definition, pathogenesis and treatment are controversial, and some even dispute the existence of this disease (Roberto, E. H., & Marcelo, C. F., 2010). There is ignorance, misinterpretation of the symptoms, which remains undiagnosed. This article presents a clinical case from the medical practice of the disease "Fibromyalgia", while at the same time characterizing the pain syndrome and the necessary tests to prove the diagnosis.

Medical case

History: After a stressful moment, the patient complains of acute pain in the lumbar region, bilaterally, without irradiation to the limbs. The pain is sharp, cutting even when moving, and at the slightest movement it is provoked. Objective status: This is a woman of sixty-one years. Afebrile and hemodynamically stable: RR 140/90, Pulsus 72 / min. Expressed anxiety, to panic attack. Move both limbs in bed. Neurological status normal, with deep and superficial sensitivity preserved. Presence of pulsations on a. poplitea billateralis, a. dorsalis pedis billateralis and a. femoralis billateralis. The lower limbs are warm and mobile. There is no morning stiffness of the limbs (Enrico et al., 2013). A neurologist was consulted and diagnosed with Radiculitis lumbosacralis. Prescribed medications - NSAIDs and B

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vitamins - had no effect. The patient remained in bed for six months. After administration of amitriptyline for about a month, the pain disappea

Discussion

Theoretical statement

It is believed that in the etiology of the disease Fibromyalgia (Clauw DJ., 2009), factors such as:

• Dysfunction of the Central and autonomic nervous system - spontaneous nervous activity and increased excitability of neurons in the spinal cord;

• Neurotransmitters - serotonin, norepinephrine, dopamine, endorphins substance P, methenkephalins whose levels are high;

• Hormones: cortisol - increased under stress; growth hormone, which is reduced during sleep;

• Immune system - activated glial cells release cytokines;

• External stressors;

• Psychiatric aspects;

These factors determine the non-specific clinical picture, as well as the type of laboratory and instrumental tests, namely:

Fibromyalgia syndrome is characterized by three main symptoms (Clauw DJ., 2009): pain, fatigue and sleep disturbance. The diagnosis is clinical because there are no laboratory abnormalities. To make a diagnosis, it is necessary to emphasize the characteristics of pain. The patient should be asked about additional symptoms such as Raynaud's syndrome, irritable bowel syndrome, sleep disturbance and chronic fatigue. By its nature, the pain is diffuse, deep, burning, can irradiate. Presence of painful musculoskeletal pain at points in specific areas of the body. It is characteristic of them that they are painful under pressure (Figure 1).

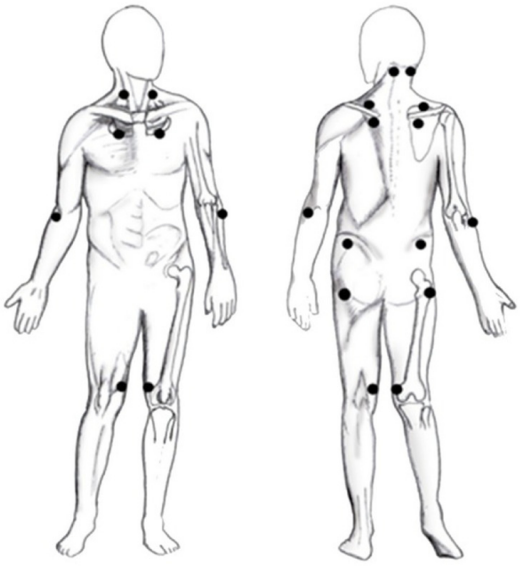

Figure 1 Pre-selection sites of pain in fibromyalgia

In order to be considered a positive point, it must be assessed by digital palpation with about four kilograms of pressure (when the thumb bed fades) and the patient must say that the palpation was "painful" [1]. The duration of musculoskeletal pain is about three months.

The scope of laboratory tests includes: complete blood count, biochemistry, thyroid-stimulating hormone (hypothyroidism may have fibromyalgia-like symptoms or may accompany fibromyalgia) and erythrocyte sedimentation rate and / or C-reactive protein. There are usually no laboratory abnormalities specifically related to this condition. The ANA (antinuclear antibody) test may be positive (Clauw DJ., 2009).

Instrumental research includes (Debra Fulghum, 2021):

1. Endophotonic emission computed tomography (SPECT);
2. Positron emission tomography (PET);
3. Magnetic resonance imaging (MRT);

4. Electroencephalogram (EEG).

Endophoton emission computed tomography demonstrates a reduction in regional cerebral blood flow in the bilateral thalamus and basal ganglia. After treatment with amitriptyline, an increase in regional cerebral blood flow was observed in these structures (Clauw DJ., 2009; Debra Fulghum, 2021).

Positron emission tomography has a higher spatial and temporal resolution than endophotonic emission computed tomography. Demonstrates dysfunction of normal cognitive pain management in patients with fibromyalgia, namely: increase in regional blood flow in the retro splenic cortex and decrease it in the frontal, temporal, parietal and occipital cortex.

Magnetic resonance imaging studies have demonstrated the hypothesis of centrally increased pain management in patients with fibromyalgia (Clauw DJ., 2009; Fibromyalgia, 2020).

Electroencephalographic studies revealed a disturbance in the fourth phase of sleep, a consequence of reduced levels of growth hormone.

Analysis of the medical case

In the clinical case presented above, the patient's life history and family history show a hereditary component for the father's disc herniation, and in childhood - tonsillectomy. There was a slight increase in AST around 200 U / l, as well as high CRP values.

The key point of clinical thought is "low back pain", for which acute arterial insufficiency, stroke, rheumatoid arthritis and disc herniation (closest diagnosis) have been discussed in the differential diagnostic aspect. The onset of pain at rest and the lack of irradiation to the heel or toes of the dermatome, the negative Laseg test, rejects this hypothesis. Given the positive AST values, the differential diagnosis should also include the presence of rheumatoid arthritis, which was ruled out due to lack of stiffness and lack of involvement of small and medium joints. The presence of pulsations of the large and small arteries of the lower extremities, warm and preserved skin color, rule out acute arterial insufficiency (Enrico et al., 2013).

The burning nature of the pain, the presence of painful nodules in the lumbar and scapular areas bilaterally, point to myositis. Various non-steroidal anti-inflammatory drugs have been administered in various forms (oral, topical and injectable), with no effect. As a last resort, a tricyclic antidepressant, amitriptyline, was included, which showed improvement within a month.

The case describes a modified symptom in the elderly. Modified symptoms are experienced differently by patients. In this case, our own (from the doctor's experience) paradigm was used for diagnosis. The paradigm is made up of four main steps, which are

- Description of the specifics of each symptom;
- Two aspects of the diagnosis: what is and what is not;
- Symptoms form a whole that represents the diagnosis with a logical connection and sequence
- Analysis of small deviations and nuances - a way for accurate diagnosis.

In the observed case, a modified symptom is lumbar pain. Its characteristic does not coincide with the characteristics of the symptom of pain from the diseases specified in the differential diagnosis. The presence of a mental component in the field of rheumatic disease, the effect of amitriptyline pain and the presence of sore spots at predilection sites, led to the disease "Fibromyalgia".

Conclusion

Diagnosis of fibromyalgia is necessary to comply with two conditions clinical analysis of pain with the detection of painful points and instrumental nuclear magnetic resonance imaging to demonstrate dysfunction of the central nervous system and electroencephalogram for sleep disorders.

To improve the diagnostic process, it is necessary in practice to apply tests of hormones and neurotransmitters.

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SIGNIFICANCE OF INCREASED D-DIMER VALUES IN FRESH FRACTURES IN ORTHOPEDICS AND CORRELATIONS WITH THROMBOEMBOLIC COMPLICATIONS

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Abstract: Background/aim. At the end of the process of separating clots composed of fibrin we have a D-dimer. This process involves thrombin, which is formed during the process where fibrinogen is converted into fibrin, a factor whose role is to bind the basic units of clots and plasmin, the final participant in the breakdown of fibrin. In medicine, we should not use value of D-dimers as the only parameter for thrombosis. The aims of are research is to investigate correlation between clinical signs of venous thrombosis and D-dimer values in fresh bone fractures and demonstrate, that there is momentous correlation between high values of D-dimers and clinical signs of venous thrombosis, which is often a contraindication for surgical treatment of fractures.

Methods: D-dimer levels of 211 patients with fresh bone fractures. They are classified into groups based on D-dimer values as follows: <250 ng/ml, 250–1000 ng/ml, 1000-5000 ng/ml, 5000-10 000ng/ml.

Results: D-dimer values are not statistically significant with clinical symptoms of venous thrombosis in recent fractures in orthopedics.

Discussion: D-dimer is an indicator related to fibrin degradation that has been used in the past as a prevalence in patients with chances of venous thrombosis. In inflammatory processes, we also have increased values of this parameter, which suggests the existence of some inflammatory change in the body or infection. Our research is among the first to compare D-dimer values in recent fractures in orthopedics and thromboembolic complications. In our research, we showed that there is no significant correlation between elevated D-dimer values in hospitalizations of fresh fractures with clinical signs and a diagnosis of vascular thrombosis. We showed that there is no significant correlation between elevated D-dimer values in hospitalizations of fresh fractures with clinical signs and a diagnosis of vascular thrombosis. With this study, we proved that elevated D dimer is a consequence of trauma and disruption of the continuity and integrity of bone blood vessels, both endosteal and periosteal, which results in thrombosis of small blood vessels.

Conclusions: There is no momentous correlation between elevated D-dimer values in fresh fractures and venous thrombosis. High values of D-dimer are not a contraindication for surgical treatment of fresh fractures.

Keywords: D-dimer, thromboembolism, fractures, prediction.
Field: Medical sciences and Health

INTRODUCTION

At the end of the process of separating clots composed of fibrin we have a D dimer. This process involves thrombin, which is formed during the process where fibrinogen is converted into fibrin, a factor whose role is to bind the basic units of clots and plasmin, the final participant in the breakdown of fibrin. (Wang et al., 2019). In medicine, various diseases give increased values of D-dimer (Tripodi et al., 2011). Laboratory increased values can be used both for the diagnosis and treatment of diseases in which we have venous blood vessel thrombosis (Bounameaux et al., 1994, Hansrani et al., 2017), DIC (Palareti et al., 2002), conditions with reduced heart function and cerebral palsy. However, there are some diseases that do not have points of contact with vascular thrombosis and in which we have increased values of D-dimer, so we can say that it is not trombotically specific. Today, acute infections of the organism caused by the coronavirus known as COVID-19, give laboratory increased values of D-Dimer and these patients

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have a higher percentage of thromboembolic complications of venous blood vessels (Atzrodt et al., 2020, Rabi et al., 2020,). The higher the values of D-dimer, the higher the percentage of worse outcomes per patient, and this isa bad sign for the prognosis of the patient's further condition (Li Y et al., 2020, Li C et al. 2020, Kollias et al., 2020, Artifoni et al., 2020, Vidali et al., 2020, Hunt et al., 2020). Many studies have shown that in orthopedic patients there is no statistically significant difference in laboratory values of D-Dimer between COVID-positive and COVID-negative patients. Therefore, non-adjustable laboratory measurement of D dimers is not recommended in patients who underwent orthopedic surgery (Jungwirth-Weinberger et al., 2021). Also, as a consequence of fractures, the continuity and integrity of arterial and venous blood vessels, both endosteal and periosteal, are interrupted. Consequently, microthrombosis of small blood vessels occurs in the first days of fracture healing as a consequence of the organization of hematomas caused by bone rupture, as well as activation of the healing system in terms of organization of dead cells at the ends of bone fragments.

Aim: This study shows that there is no momentous correlation between increased levels of D dimers and clinical signs of venous thrombosis, which is often a contraindication for surgical treatment of fractures.

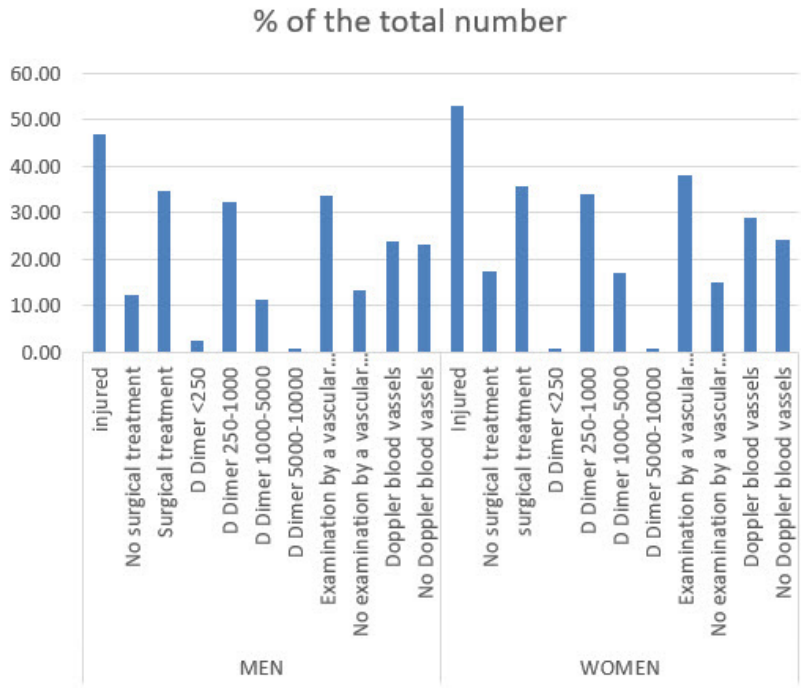
MATERIALS AND METHODS

Patients

The presented retrospective study was approved by the Ethics Committee of KBC Kosovska Mitrovica, in which 211 patients participated, of which 63 were treated non-operatively and 148 were treated operatively between August 2020 and August 2021. Of course, all patients gave their consent to participate in the study. They are classified into groups depending on: gender, age, laboratory values of D-dimer at the hospital, consultation with a vascular surgeon, results of blood vessel Doppler. Each patient was given a laboratory D-dimer value due to the administration of thromboembolic prophylaxis. All fractures in which there were no clear indications for surgical treatment were treated non-operatively. In contrast, those patients who had fractures with clear indications set by the AO group were treated surgically and AO techniques were used to address them.

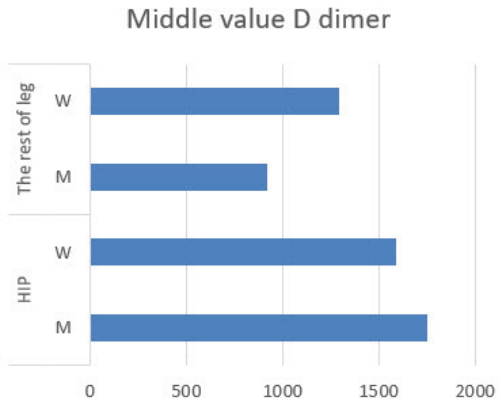
RESULTS

Out of the total number of patients, 53.08% were females and 46.92% were males. From grapf 1, we can see that the largest number of women was between 61-80 years of age, 57 of them, and 35 of them with D-dimer values between 250-1000 ng/ ml. Of the total number of injured - 112, in 80 patients we have consultation I examination by a vascular surgeon, as well as 60 performed Doppler blood vessels. 75 patients or 35.55% were treated surgically. As for men, the largest number of injured, 36 of them were between 61-80 years old, with D-dimer values between 250-1000 ng / ml of 21. Of the total number of injured, ie. 99 patients, in 71 patients a consultation with a vascular surgeon and 50 Doppler blood vessels were performed. 73 patients or 34.60% were treated surgically.



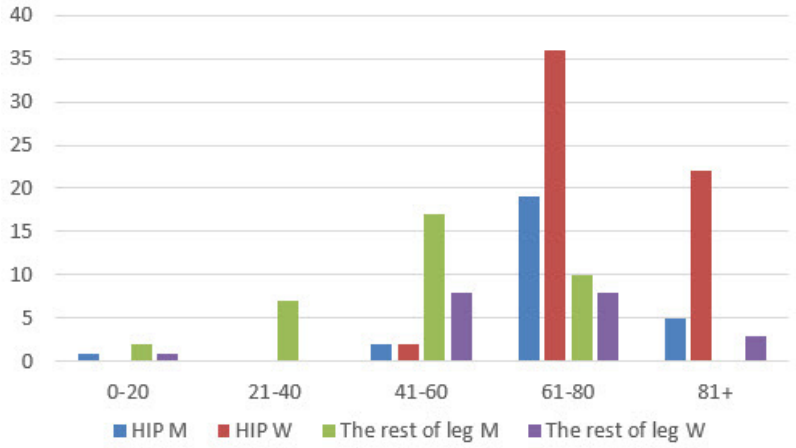
*The D value of the dimer is expressed in ng / ml, and is normal <250 ng / mL
Graph 1. Summary chart of all patients who participated in the study

The largest number of patients have fresh leg fractures, 179 of them. Considering the graph 2 values of D dimers, we came to the data that the middle value of D dimers in men with fractures of hip is 1754 ng / ml, and in women the mean is slightly lower and it is 1587 ng / ml We can conclude that in women the largest number of hip fractures was 60, and as for men, 27 of them had hip fractures



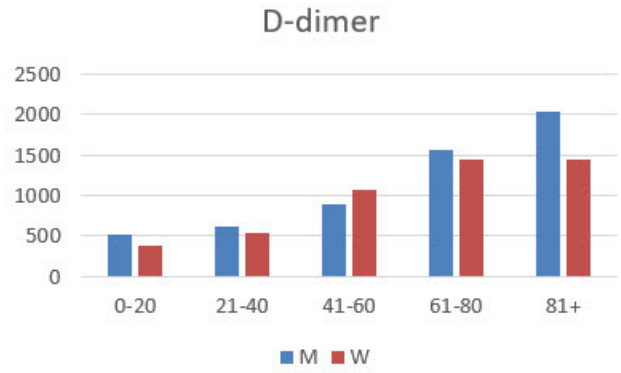
* The D value of the dimer is expressed in ng / ml, and the normal value is <250 ng / mL
Graph 2. Middle value of D dimer in male/female with leg fractures

Graph 3 shows that the largest number of male patients with hip fractures is between 61-80 years old, 19 of them. Also in women, 36 of them were between 61-80 years old.

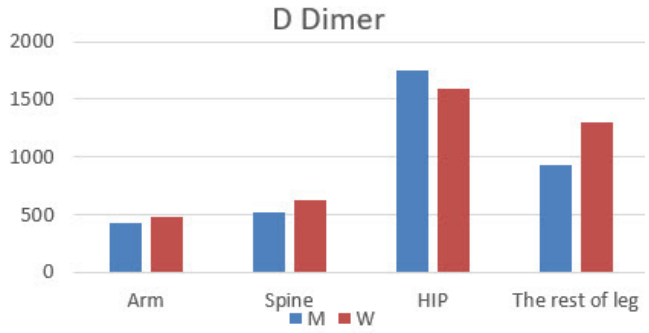


Graph 3. Number of patients with hip fracture in relation to age

In relation to age, the highest mean value of D dimers is in patients aged 81 years and older. In men aged 81+, the mean value of D dimer is 2024 ng / ml, and in female patients this value is 1445 ng / ml. (Graph 4).



*The value of D dimer is expressed in ng / ml, the normal value is <250 ng / mL
Graf 4.Mean value of D dimer in relation to age



*The value of D dimer is expressed in ng / ml, the normal value is <250 ng / mL
Graph 5: Mean value of D dimer in relation to fractures of the upper, lower extremity (hip and other part of the leg) and spine

What is most important to us is that all 211 patients who participated in the study did not have clinical signs of venous thrombosis, as well as a confirmed diagnosis of venous thrombosis. Which means that there is no statistically momentous correlation between increased values of D dimer and venous thrombosis in fresh fractures. Comparing our retrospective study with the latest research conducted by Wang ZI et al., Palareti et al., As well as in the light of Covid infection where D dimers are measured daily by Atzrodt et al. tissue trauma itself as well as natural fracture organizations and not a consequence of venous thrombosis. Given that we had the largest number of patients with hip fractures, we conclude that increased D-dimer is not a contraindication for surgical treatment of hip fractures, any method according to the AO classification and fractures and the choice of surgical treatment.

DISCUSSION

D-dimer is an indicator related to fibrin degradation that has been used in the past as a prevalence in patients with chances of venous thrombosis. In inflammatory processes, we also have increased values of this parameter, which suggests the existence of some inflammatory change in the body or infection(Ribera et al., 2011, Gris et al., 2011, Schwameis et al. 2015). Many studies do not prove the difference in laboratory values of d dimers in COVID 19 positive and negative orthopedic patients, so daily testing of D-dimers is irrational. Our research is among the first to compare D-dimer values in recent fractures in orthopedics and thromboembolic complications. In our research, we showed that there is no significant correlation between elevated D-dimer values in hospitalizations of fresh fractures with clinical signs and a diagnosis of vascular thrombosis. With this study, we proved that elevated D-dimer is a consequence of trauma and disruption of the continuity and integrity of bone blood vessels, both endosteal and periosteal, which results in thrombosis of small blood vessels. The healing process itself, when going through its physiological phases, monitors the high value of D dimers in fresh fractures. In addition to the fact that elevated D-dimers were used to diagnose venous thrombosis, they have been shown to be illegitimate in many studies (Chen et al., 2008). Rahhe et al. didn't prove differences in laboratory parameters of D-dimers in operated patients with and without vascular thrombosis (Rafee et al., 2008). Likewise Niimi et al. recommend a two-stage examination for thrombosis, including vascular Doppler (Niimi et al., 2009). Therefore, in medicine, we should not use value of D dimers as the only parameter for thrombosis.

CONCLUSION

Our research shows that high values of D-dimer (>250ng/mL) don't have to indicate thrombosis of blood vessels in fresh fractures in orthopedics. Diagnosis should be made by a combination of laboratory D-dimer values, clinical examination, consultation and examination by a vascular surgeon, as well as the use of radiological procedures. We had the largest number of patients with hip fractures, we conclude that increased D-dimer is not a contraindication for surgical treatment of hip fractures, any method according to the AO classification and fractures and the choice of surgical treatment.

In our study there is no conflict of interest by the author

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THE VALUES AND THE DIFFERENCES OF THE SEROTONIN LEVELS IN SERUM AND BRAIN TISSUE IN AN INDUCED DIABETIC NEPHROPATHY WHITE LABORATORY RAT UNDER THE IMPACT OF PERINDOPRIL AND CANDESARTAN

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Abstract: Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system (RAAS) and plays a role in the pathophysiology of hypertension, heart failure, renal failure and other cardiovascular disorders. RAAS is activated in diabetic nephropathy (DN) and leads to more renal damage. Angiotensin converting enzyme inhibitors (ACEis) and angiotensin receptor blockers suppress this (ARBs). A large body of evidence demonstrates that, in addition to its typical activity as a hormone, Ang II is a neuropeptide produced by the central nervous system (CNS) that acts as a regulator of neurotransmission and nerve cell excitability. Peripheral serotonin is an endocrine component that promotes energy storage efficiency. Serotonin also enters the bloodstream and interacts with multiple organs, priming the body for energy storage by promoting insulin secretion and de novo lipogenesis in the liver and white adipose tissue. However, the actions of serotonin extend beyond neuronal communication in the CNS and enteric nervous system (ENS) to peripheral tissues. Serotonin mediates numerous nonneuronal processes such as bladder function, respiratory drive, hemostasis, vascular tone, immune function, and intestinal inflammation . The goal of this study is to see how the ACE inhibitor perindopril and the ARB AT1 candesartan, taken singly and in combination (double blockade), affect serotonin levels in the serum and brain tissue of Wistar rats with DN caused by streptozotocin (STZ). The levels of serotonin in the serum and brain of four experimental groups of animals were measured using an enzyme-linked immunosorbent assay (ELISA): a control group with DN, a group with DN treated with perindopril, a group with DN treated with candesartan, and a DN group treated with a combination of perindopril and candesartan. Perindopril (6 mg/Kg/day), candesartan (5 mg/Kg/day), and dual therapy with perindopril (3 mg/Kg/day) and candesartan (2,5 mg/Kg/day) were given orally every day for eight weeks, beginning four weeks after STZ was given, whereas the control group received just water. The rats were slaughtered at the end of the therapy so that the serum and brain tissue could be used to test serotonin levels. The results showed that blocking the renin-angiotensin system (RAS) with perindopril, candesartan, or their combination considerably decreased serotonin levels in the serum but dramatically elevated serotonin levels in the brain tissue in all groups.

Keywords: serotonin, serum, brain tissue, perindopril, candesartan.

INTRODUCTION

Serotonin (5-hydroxytryptamine; 5-HT) is a biogenic amine that has a variety of physiological functions, including basic mechanisms such as homeostasis, nutrition, immunity, glucose regulation, cardiovascular function, behavior, intestinal motility, and reproduction. About 90% of the total serotonin in the human body is found in the enterochromaffin cells of the intestine, where it participates in intestinal peristaltics. The rest is synthesized in serotonergic neurons in the central nervous system (CNS). It is a derivative of tryptophan (Hernandez, L.L.,2018). Tryptophan has 2 isoforms: TPH1 is responsible for the production of 5-hydroxytryptamin (5-HT) in peripheral tissues and TPH2 leads to the synthesis of 5-HT in the central nervous system. Platelets are probably the biological repository of circulating 5-HT. Plasma 5-HT levels are elevated in a variety of conditions, including hypertension and thrombosis (Fraer, M., & Kilic, F., 2015). 5-HT, a monoamine neurotransmitter, first recognised in 1948, has a wide range of functions in the CNS, including modulation of attention, cognition, behaviour, memory, and thermoregulation, as well as in the peripheral nervous system (PNS), where it regulates, for example, gastrointestinal (GI) motility, uterine contraction, vasoconstriction, and bronchoconstriction (Scotton, W. J., et al.,2019). It is usually called the happy hormone because it contributes to wellbeing and happiness. A decrease in its level has been seen in various mental illnesses like depression and anxiety (Bruta, K., et al., 2021). Chronic

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renal failure (CRF) is a syndrome that develops as a result of a gradual, cumulative, and irreversible decrease in glomerular filtration rate (GFR) leading to uraemia. Diabetes mellitus (DM) is one of the most prominent risk factors for the development of HBI; diabetic patients account for 30 percent to 50 percent of all patients with "end-stage renal disease" (ESRD) globally (Ruiz-Ortega, M., et al., 2020). Diabetic nephropathy (DN) is becoming a leading cause of CRF and the need for hemodialysis in developed countries. The natural history of CFR or DN is weakened by the appearance of agents that block the renin-angiotensin-aldosterone system (RAAS). Renin-angiotensin-system (RAS) plays an important role in the pathogenesis and development of hypertension. Angiotensin converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) are commonly used in hypertensive patients as two targeted RAS system inhibitors (Ma, J., et al., 2021). DN is known to be one of the most common and serious complications of diabetes, for which there is still no adequate drug therapy. Given the importance of RAS in the pathophysiology of DN, it is thought that impaired renal function and impaired renal structure (which are associated with the progression of diabetes) may be ameliorated by blockade of RAS by ACEi or ARBs. ACEi and ARBs are the first-line medication therapies for diabetic patients with proteinuria. Our findings support that ACEi are relatively renoprotective and safe treatments as compared with ARBs in diabetic patients with proteinuria (Hsu, F.Y., и сор., 2017). Perindopril belongs to the ACEi class of medicines. It is used to treat essential hypertension (high blood pressure), heart failure, and stable coronary artery disease. The angiotensin-converting enzyme is inhibited (Hodzic, E., et al., 2020). Ang II receptor blockers, also known as angiotensin receptor antagonists, or sartans, are a group of drugs that work by modulating RAAS, blocking the action of the powerful vasoconstrictor Ang II (Scheinman, S.B., et al., 2021). Streptozotocin (STZ) is an antibiotic that destroys pancreatic islet cells and is commonly used in research to create a type 1 diabetes model (T1DM). STZ is a highly selective pancreatic islet-cell cytotoxic drug that, when given in a single large dose, causes full -cell necrosis and diabetes within 48 hours. The T1DM animals can develop diabetic complications, e.g., diabetic neuropathy, diabetic nephropathy and diabetic atherosclerosis (Furman, B. L.,2021).

The goal of our research was to see if the effects of perindopril and candesartan on serotonin levels in serum and brain tissue in a white laboratory rat with induced DN, both alone and in combination.

MATERIAL AND METHODS

1. Experimental animal

To carry out the experiments provided in this study, 125 male and female normal blood pressure white Wistar varieties of experimental rats were selected. To minimize the effects of individual differences, all animals were 9-11 weeks old and weighed about the same as 200-300 grams. The effects of external factors on renal function were minimized by the same volume of injection as standardized animal care. Of the administration solution. Rats were housed in 5 cages and were given standard laboratory rat feed and water freely.

2. Experimental model

In experimental scientific studies, rat-induced diabetes, and therefore the most used model of DN, is the induction of diabetes with a single dose of STZ.

3. How to measure serum serotonin in white laboratory rats

The enzyme-linked immunosorbent assay (ELISA) method was used to measure serotonin in the serum and brain tissue of white laboratory rats.

4. Test protocol

To respond to selected rats, they were divided into 5 groups, each consisting of 25 animals.

- Experimental animal

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• Protocol No. 2 (experimental)

This group of animals was a positive (diabetes) control group. In order to examine the symptoms and signs of DN in this group of rats, they were given saline in the same amount as the animals given the therapeutic active medication for the next 8 weeks after receiving STZ.

• No. 3 experimental protocol

Perindopril was given orally with an intragastric tube, dissolved in 5% glucose, at a dose of 6 mg / Kg / TT / day for 8 weeks to assess the therapeutic impact of ACEi perindopril monotherapy in the treatment of experimentally produced DN in this group of rats following 4 weeks of STZ administration.

• 4. Test protocol

After 4 weeks of STZ administration, oral administration of candesartan was started with an intragastric tube, dissolved in 5% glucose dose of 5mg / Kg / TT / day for 8 weeks in this group of rats to evaluate the therapeutic effect of monotherapy with AT1 - candesartan blocker in the treatment of experimentally induced DN.

• No. 5 experimental protocol

To assess the therapeutic effect and tolerability of RAS with ACE inhibitor and AT1-blocker, ie double blockade with perindopril and candesartan in the treatment of induced DN, this group of rats received perindopril and candesartan orally via an intragastric tube after 4 weeks of STZ administration. These medications were dissolved in 5% glucose and administered in substantially lesser amounts. For 8 weeks, patients were given perindopril at a dose of 3mg / Kg / TT / day and candesartan at a dose of 2.5 mg / Kg / day. The two medications were dosed separately, with perindopril being given first and candesartan being given 30 minutes later.

RESULTS

a) Results of serotonin level in serum

In the experiment, the effects of both drugs (peridopril and candesartan, given individually and in combination) on serum serotonin levels were examined. In order to take into account the possibility of interaction (positive or negative) between the two drugs, four experimental groups were formed in a 2x2 design scheme and the results were processed using the Two-Way Factorial ANOVA for Independent Samples. The statistical package SPSS 11 was used.

Scheme of design of experimental groups:

Scheme No. 1: Design of experimental groups

		Perindopril	
	Dose: 0 = without drug 1 = animals treated with drug	0	1
Candesartan	0	Control group	Treated with Perindopril
	1	Treated with Candesartan	Treated with Perindopril and Candesartan

The graph below (Figure 1) shows the mean values for the serum serotonin concentration in the four experimental groups.

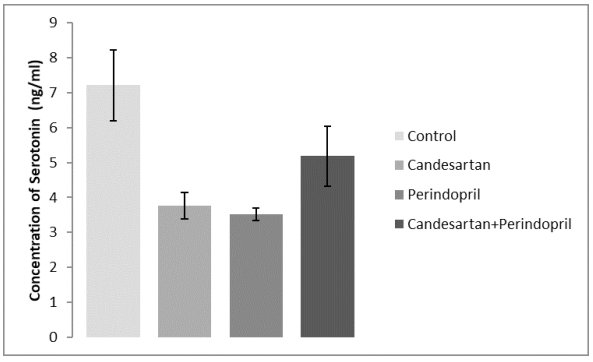

Figure 1. Serum serotonin concentration (mean ± standard error). The legend is shown on the graph itself.

From the graph shown, we can get a general impression that drug treatment leads to a decrease in serum serotonin levels. In order to make statistical processing of the data, the averages of the groups were organized in a 2x2 scheme (according to the general design given above):

Scheme No. 2: Averages of drug groups in serum

		Perindopril		
	Dose: 0 = without drug 1 = animals treated with drug	0	1	Row average:
Candesartan	0	7,209 ± 1,03	3,513 ± 0,178	5,625 ± 0,93
	1	3,766 ± 0,39	3,881 ± 0,26	3,823 ± 0,22
	Average column:	5,489 ± 0,83	3,723 ± 0,16	

The following graphs for the averages of the experimental groups were created for a clearer understanding (Figure 2):

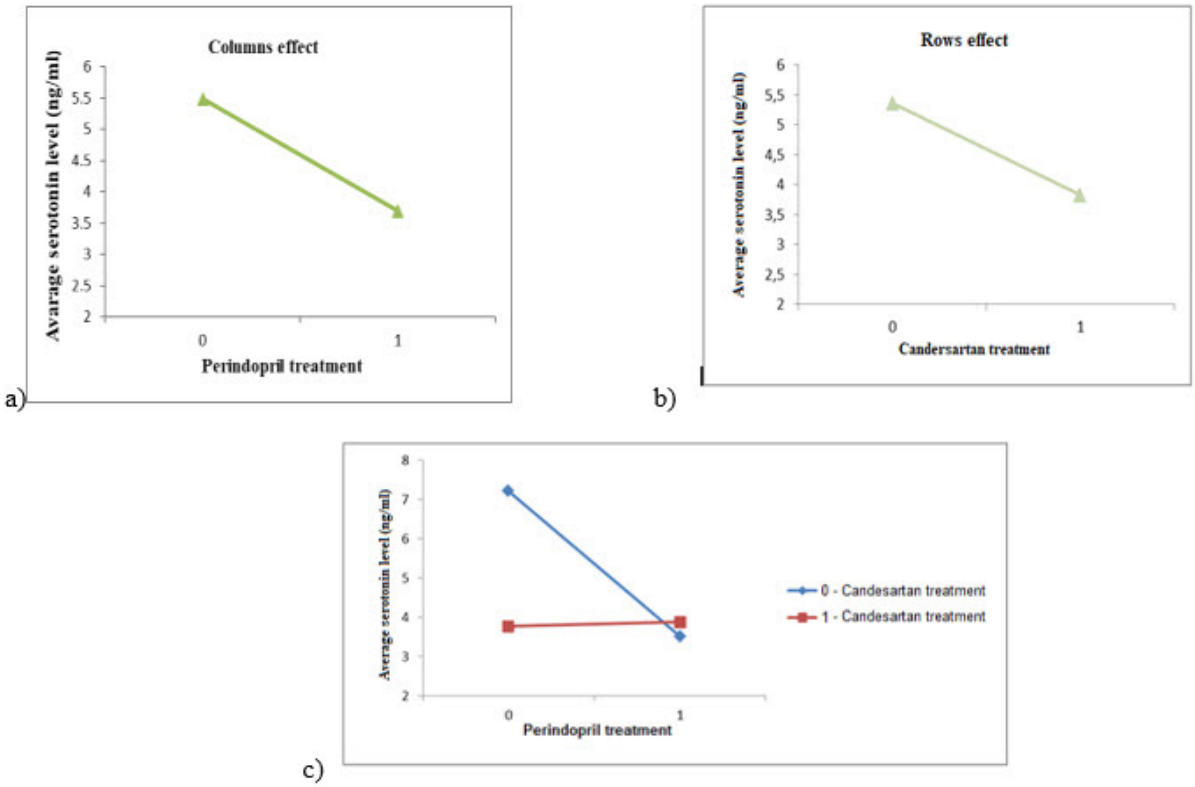

Figure 2. a) The effect of perindopril treatment (0 = control animals; 1 = treated animals). b) The effect of candesartan medication (0 = control animals; 1 = treated animals). c). Comparative graph (interaction effect) of the averages of the four experimental groups.

The intersection of the two lines (one for each of the drugs), which connect the averages when no treatment was given (0) and when the animals were treated (1), indicates the existence of a degree of interaction between the two drugs. This is confirmed by the results of the ANOVA analysis, given in the following table:

Table No. 1. Results from Two-Way Anova analysis of serum serotonin concentration data

ANOVA Summary					
Source	**SS**	**df**	**MS**	**F**	**P**
Rows	12.12	1	12.12	8.64	0.0135
Columns	11.62	1	11.62	8.28	0.015
r x c	11.83	1	11.83	8.43	0.0144
Error	15.43	11	1.4		
Total	51	14			

The influence on the columns statistics (p) truly represent the effect of perindopril medication on the level of the parameter being studied. It may be inferred that perindopril medication causes a substantial decrease in serum serotonin levels (p0.05).

The influence of candesartan medication on the level of the examined parameter is represented by the statistics (p) obtained for the effect in the rows. It may be inferred that candesartan medication causes a substantial decrease in serum serotonin levels (p0.05).

The results of the Two-Way ANOVA analysis show a significant effect of interaction between the two drugs (p <0.05). Analyzing the picture in Figure 2, it is clear that the effects of both drugs on serum serotonin levels are not simply additive. Treatment with a combination of perindopril and candesartan reduces serotonin levels to an average of 3.881 ng / ml. Animals receiving candesartan alone or perindopril alone showed even lower serum serotonin concentrations (3,766 and 3,513 ng / ml, respectively). This does not lead to the conclusion that there is a degree of negative interaction between the two drugs in terms of their effect on serum serotonin levels.

b) Results of serotonin level from brain tissue

The graph below shows the mean values for serotonin concentration in brain tissue in the four experimental groups.

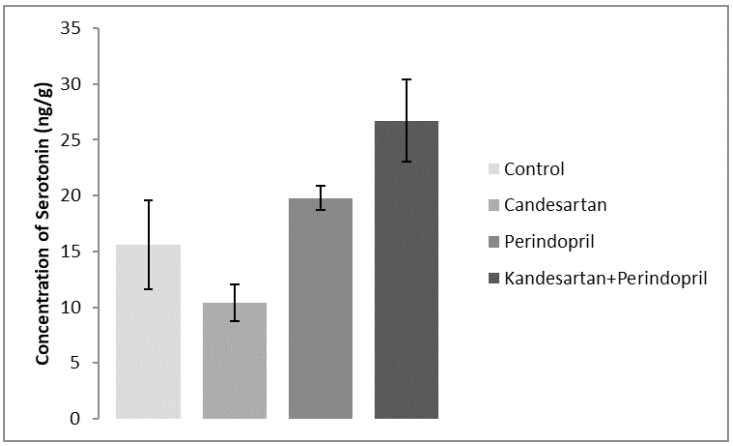

Figure 3. Serotonin concentration in the brain (mean ± standard error). The legend is shown on the graph itself.

In general, drug treatment (especially the combination of both drugs) leads to an increase in serotonin levels in the brain tissue. In order to make statistical data processing, the averages of the groups were organized in a 2x2 scheme (according to the general design given above): .

Scheme No. 3. Averages of drug groups in brain tissue

		Perindopril		
	Dose: 0 = without drug 1 = animals treated with drug	0	1	Row average:
Candesartan	0	15,595 ± 2,78	20,466 ± 0,81	17,757 ± 1,73
	1	23,178 ± 2,06	26,722 ± 3,69	24,753 ± 1,96
	Average column:	19,384 ± 2,06	23,594 ± 2,11	

For a clearer view, the following graphs for the averages of the experimental groups are constructed:

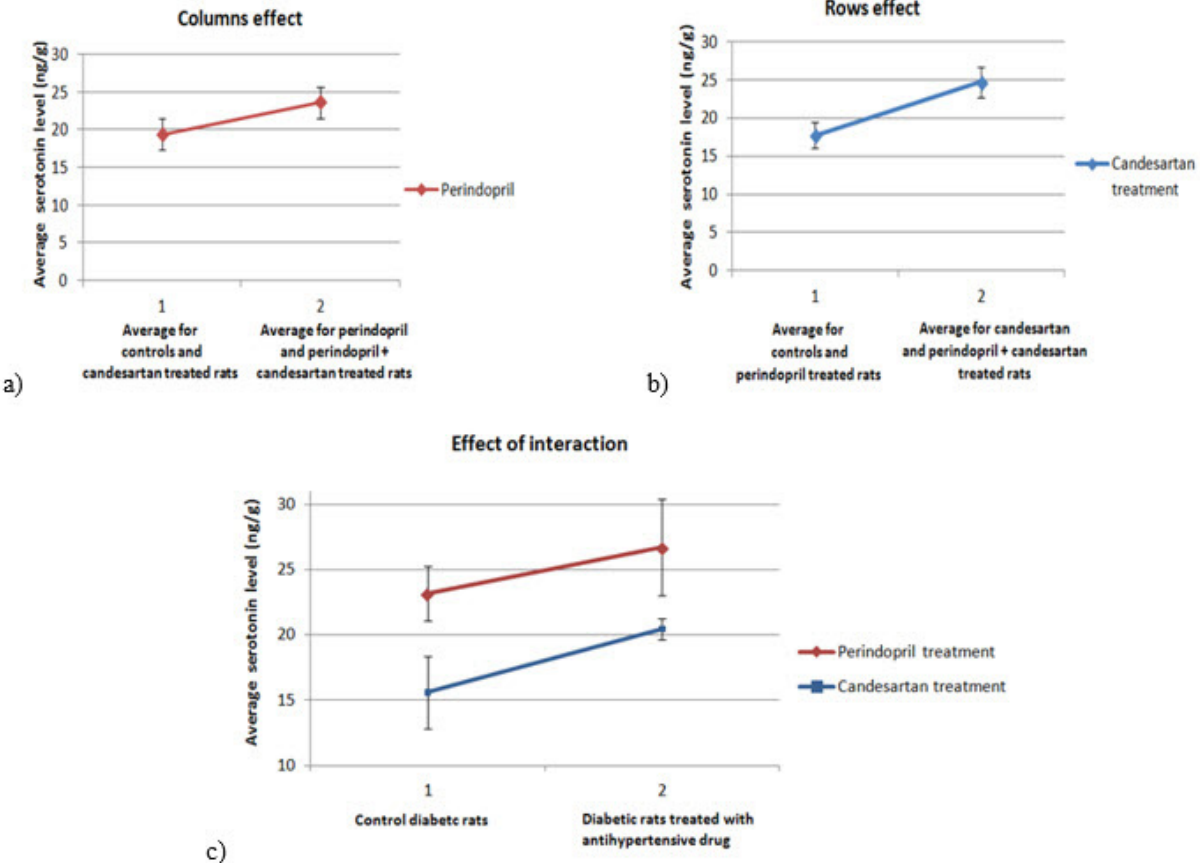

Figure 4. a) Effect of perindopril treatment (0 = level in control animals; 1 = level in treated animals). b) Effect of candesartan treatment (0 = level in control animals; 1 = level in treated animals). c) Comparative graphic (interaction effect) of the averages of the four experimental groups.

The two lines in the graph above (one for each drug), which link the averages when no treatment was given (0) and when the animals were treated (1), are almost parallel. This leads to the conclusion that there is no interaction between the two drugs. This is confirmed by the results of the ANOVA analysis, given in the following table:

Table 2. Results from Two-Way Anova analysis of data on serotonin concentration in brain tissue.

ANOVA Summary					
Source	**SS**	**df**	**MS**	**F**	**P**
Rows	220.26	1	220.26	7.51	0.0159
Columns	78.77	1	78.77	2.69	0.1232
r x c	1.97	1	1.97	0.07	0.7952
Error	410.6	14	29.33		
Total	711.6	17			

The statistics (p) for the effect in the columns represent the influence of perindopril medication on the level of the parameter under investigation. Although perindopril administration causes an increase in serotonin control levels (15,595 ng/g) in drug-treated mice, the difference in means is not statistically significant (p = 0.1232).

The influence of candesartan medication on the level of the examined parameter is represented by the statistics (p) obtained for the effect in the rows. It can be inferred that candesartan medication increases serotonin levels in brain tissue significantly (p0.05).

The results of the Two-Way ANOVA analysis show the absence of a significant interaction effect between the two drugs (p = 0.7952). Analyzing the picture in Figure 4, it is clear that the effects of both drugs on serotonin levels in brain tissue are simply additive.

Based on the absorbents obtained by measuring the prepared samples, a series of data was obtained which were statistically processed and presented graphically accordingly. In all statistical tests the level of significance is defined by p = 0.5.

DISCUSION

The goal of our study was to see if the effects of perindopril and candesartan, both separately and together, would cause substantial changes in serotonin levels in the serum of white laboratory rats with induced DN. Blood pressure and renal function are both controlled by RAAS.ARBs and ACEis have been shown to be effective in reducing hypertension, slowing the progression of diabetic and non-diabetic renal disease, reducing the risk of proteinuria, and reducing proteinuria (Burnier, at al., 2019). RAS plays an important role in the pathogenesis and development of hypertension. ACEis and ARBs are commonly used in hypertensive patients as two targeted RAS system inhibitors (Ma, J., et al., 2021). Clinical trials have shown a clinically substantial effect in reducing the course of nephropathy, especially when albuminuria is present, and worldwide guidelines suggest their usage (Leoncini, et al., 2020). Serotonin is an ancient biogenic amine that has played an important role in energy balance for billions of years, according to phylogenetic analysis. By boosting the sympathetic demand for adipose tissue, serotonin in the CNS regulates behavior, suppresses hunger, and boosts energy expenditure in mammals. In addition to these central effects, new evidence points to an important role for peripheral serotonin as a factor that improves nutrient absorption and storage. As a neurotransmitter in the CNS, it is required for several brain functions and has been linked to anxiety and behavior. Furthermore, central serotonin contributes to neuronal control of peristalsis and intestinal fluid secretion. Serotonin mediates a number of neuronal processes such as bladder function, respiratory rate, haemostasis, vascular tone, immune function, and intestinal inflammation (Yabut, J. M., et al., 2019). There is partial and/or very little confirmed information in the literature on changes in serotonin levels in a white laboratory rat with induced DN under the influence of perindopril and candesartan.

Our results showed that the blockade of Ang II AT1 receptors by candesartan significantly reduced the serum serotonin concentration, ie that the reduced effect of Ang II was associated with a decrease in serotonin. Perindopril also has a significant effect on lowering serum serotonin levels. Also, significant changes, a decrease in serum serotonin levels showed the group of animals that were treated in combination with both drugs, ie with a slight increase compared to groups of animals that were treated with drug monotherapy. These results demonstrate that dual blockade of RAS by ACEi and Ang II AT1 receptor antagonists has less effect on lowering serum serotonin levels compared to monotherapy. This does not lead to the conclusion that there is a degree of negative interaction between the two drugs in terms of their effect on serum serotonin levels. In addition, the aim of this study was to determine the potential therapeutic effect of perindopril monotherapy, candesartan monotherapy, and tolerability of combination therapy with ACEi and Ang II AT1 serotonin reuptake in the treatment of STZ-induced DN. Our results show that candesartan monotherapy causes an increase in the concentration of serotonin in the brain. In contrary, treatment with perindopril did not cause a significant change in serotonin levels in the brain. The greatest substantial impact was noticed when both medications were used at the same time, implying that, in addition to their usual antihypertensive effects, these two pharmaceuticals work as antidepressants and possible anxiolytics when used together. Our findings revealed that rat brains with a drastically diminished effect of Ang II due to double RAS blockage dramatically boosted serotonin levels, implying that lower Ang II in the brain was associated with higher serotonin levels.

CONCLUSION

During this experimental work we obtained the following conclusions:

• The results reveal that blocking the RAS with perindopril, candesartan, or their combination significantly lowered serum serotonin levels in all three groups.

• The data reveal that blocking the RAS with perindopril, candesartan, or a combination of the two dramatically boosted serotonin levels in the brain in all three groups.

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EFFECTS OF THE COVID-19 PANDEMIC ON THE VISITS FREQUENCIES IN EMERGENCY SERVICE SKOPJE

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Abstract: The pandemic caused by the COVID -19 virus has affected human health, consequently the health system and health services, both worldwide and in the Republic of North Macedonia. The idea for this research was therefore to examine the impact of the conditions imposed by the pandemic on the visits of the Emergency medical service in Skopje.

For this purpose, the frequencies of visits with transport to hospital and just visits, as well as the frequencies of emergency calls and calls only for transport in the periods: before the pandemic (March 2019-February 2020) and during the pandemic (March 2020 to February 2021) were analyzed. The overall number of visits was further analyzed by categories: age and gender.

In the period from March 2019 to March 2021, a total of 49,930 visits were performed, of which 24,115 were performed during the pandemic and 25,815 before. In the same period, a total of 13,835 emergency calls were answered, of which 6,434 were during the pandemic and 7,401 before; a total of 9780 calls for transport of patients were carried out, during the pandemic 5602 and 4178 before the pandemic. The analysis showed that the number of transports was increased and the number of emergency calls decreased during the pandemic compared to the pre-pandemic period, while the number of visits during and before the pandemic did not differ significantly. Concerning age and gender, the analysis showed that the number of visits to children, men aged 20 to 40 and women over 60 years was significantly reduced compared to pre-pandemic visits, while there was no difference in other age groups. The contributions of visits related to certain diagnostic and a particular age group are discussed in this paper.

We found that the pandemic has not influenced the pace of work, apart from the conditions, only the association between the kind of calls and the diagnoses for which the visits were made has practically changed. During the pandemic, most visits for males and females over 40 were related to COVID diagnosis, while for children, men and women under 40, accidents were the most common cause.

Keywords: COVID-19, Emergency Service, Medical emergency calls, visits
Field: Medical Sciences and Health

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is defined as a disease caused by a coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first identified in the city Wuhan, Hubei Province, China. It was originally reported to the World Health Organization (WHO) on December 31, 2019. On January 30, 2020, the WHO declared a public health emergency of international concern over the global outbreak of novel coronavirus, while on March 11, 2020, a global COVID -19 pandemic (WHO, 2020).

The first positive case in the Republic of North Macedonia was registered on February 26, 2020 and by March 18, 2020, the number of confirmed cases was 35. The Government of the Republic of North Macedonia, on its 15th regular session held on March 10, reviewed the information of the Steering Committee for the Coordination and Crisis Management System to take additional and intensified measures and activities to prevent the spread of the coronavirus upon the suggestion of the Infectious Diseases Commission of the Ministry of Health (GRNM, 2020).

Subject of numerous scientific studies in recent times at a global level was examining the effects of the pandemic and thus the quarantine on health care in the health systems of many countries. Among other things, the effects of the pandemic on emergency interventions are being researched. Only some of them are cited in this work: Andrew et al., 2021, Ikenberg et al., 2020, Jesus et al., 2021, Lavine & Hardy, 2022, Saini et al., 2022, Wartelle et al., 2021, Wongtanasarasin et al., 2020.

In order to analyze the impact of the pandemic on the work of the emergency services in Skopje, a

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study was conducted, the results of which are the subject of this work. For this purpose, an analysis of the differences in visits and calls was carried out in two periods: before and during the pandemic. The study also included an analysis of visits related by age group, gender, and patient diagnosis.

MATERIALS AND METHODS

The study is a retrospective analysis of the visits and calls to the Emergency Medical Service, Public Health Institution Health Center Skopje in Skopje, Republic of North Macedonia, for the period from March 2019 to March 2021.

For the purposes of the study, the visits and calls data are grouped by months into two periods and each lasted for a year, the period during the pandemic (March 2020 - February 2021) and the period before the pandemic (March 2019 - February 2020). The visits are categorized into two groups, visits and visits with transport of a patient to the hospital in the presence of a doctor. Other data categories are emergency calls and transport calls in which the transport of patients is done without the presence of a doctor.

The analysis of the total number of visits per month, age groups and diagnoses was also the subject of this study.

Differences between the data sets were tested with the non-parametric Kruskal-Walis test using the XLstat statistical software.

RESULTS

Table 1 shows the frequency of visits, with and without transport to the hospital during and before the pandemic. The same table also lists the frequencies of emergency calls and calls for transport, which relate only to transporting a patient to a hospital without a doctor present. In the period from March 2019 to March 2021, a total of 49,930 visits were made by the Emergency medical service in Skopje. Of the total number of visits, 48.3% (24,115) were conducted during the pandemic period and 51.7% (25,815) were done before the pandemic. For the same period, 13,835 emergency calls and 9780 transport calls were answered. According to the data in Table 1, the number of emergency calls before the pandemic was higher than the number of calls during it. For transport calls, the situation is reversed, the number of calls during the pandemic is higher than the number of calls in the pre-pandemic period.

The frequency of the total numbers of visits, emergency calls and calls for transports per mount in both periods are shown in Figure 1, Figure 2, and Figure 3, respectively. In addition, Table 2 provides the total number of visits for children, male (M) and female (F) classified by age group, during and before the pandemic, and in both periods.

Table 1. Frequency of visits and calls during and before the pandemic

	During the pandemic		Before the pandemic	
	n	%	*n*	%
Visits	15047	47.4	16671	52.6
Visits with transport	9068	49.8	9144	50.2
Emergency calls	6434	46.5	7401	53.5
Calls for transport	5602	57.3	4178	42.71

Figure 1. Total numbers of visits per mounts in both periods

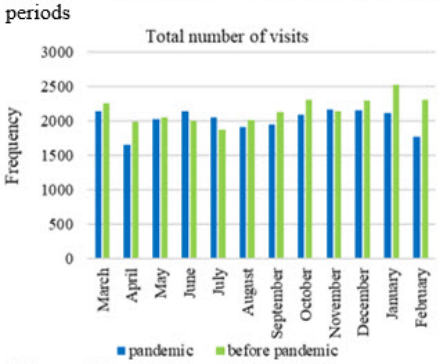

Figure 2. Frequency of emergency calls per mounts in both periods

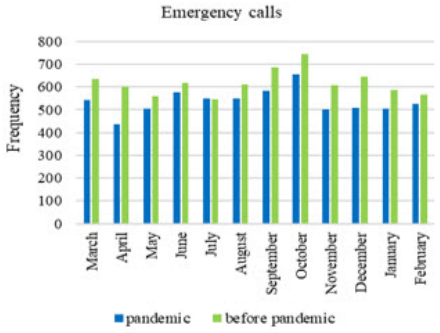

Figure 3. Frequency of calls for transport per mounts in both periods

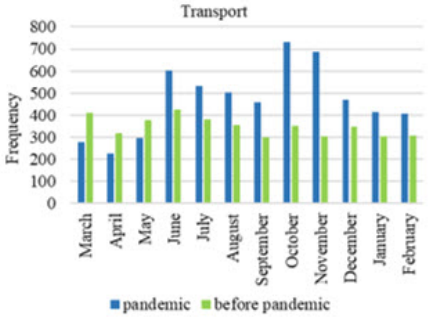

Table 2. Total numbers of visits for children, male (M) and female (F) classified by age group during and before the pandemic together, as well as in the both periods

	During the pandemic		Before the pandemic		Total	
Age group	*n*	%	*n*	%	*n*	%
Children	715	3.0	1070	4.14	1785	3.6
M (20-40y)	2112	8.8	2516	9.75	4628	9.3
F(20-40y)	1263	5.2	1279	4.95	2542	5.1
M (40-60y)	3693	15.3	3606	13.97	7299	14.6
F (40-60y)	2517	10.4	2420	9.37	4937	9.9
M (>60y)	6823	28.3	7006	27.14	13829	27.7
F (>60y)	6992	29.0	7918	30.67	14910	29.9

M-male, F-female

DISCUSSIONS

In the period from March 2019 to March 2021, a total of 49,930 visits were made by the Emergency medical service in Skopje. Of the total number of visits, 48.3% (24,115) were conducted during the pandemic period and 51.7% (25,815) were done before the pandemic (Table 1).

In the period of pandemic, the average monthly number of visits with transport to the hospital was 756, while for the period before that was 762 (Table 1). The maximum number of visits during the pandemic was done in December and the maximum number of visits in the period before refers to October. The results of the statistical test revealed that there were no significant differences between the frequencies of visits with transport in the periods during and before the pandemic (KW, p=0.2260). Furthermore, the average monthly number of visits (without transport) was only 1254 in the pandemic, while for the period before was 1389. The maximum number of visits was done in March during the pandemic and the maximum number of visits was in January in the period before. The difference in visits without transport during and before the pandemic period proved to be statistically insignificant (KW, p=0.4877) at a 95% confidence level. The analysis showed that the differences in the frequencies of the total number of visits (with and without transport) in the period during and the period before the pandemic did not differ significantly (KW p=0.2167) at a 95% confidence level (Figure 1).

In the period from March 2019 to March 2021, a total of 13,835 emergency calls were answered by the Emergency Medical Service, of which 46.5% (6,434) were answered during the pandemic and 53.5% (7401) before. Statistically significant is the difference between the period before the pandemic, which corresponds to a higher number of emergency calls, compared with the period during the pandemic (KW, p=0.0018). During the pandemic, the maximum number of frequencies corresponds to the second wave of the pandemic in October (Figure 2). While the pre-pandemic maximum number was also shown for that month.

In the period from March 2019 to February 2021, a total of 9,780 patient transports to healthcare facilities were carried out by the Emergency service. The number of transports during the pandemic is higher than in the period before (KW, p=0.0567 – the test result is significant at the 90% confidence level). During the pandemic, the frequencies of transported patients follow the trend of the first and second pandemic waves, while the trend of the transport frequencies in the period before the pandemic deviates from this and corresponds to statistical variations (Figure 3).

Further evaluation included investigation of visits regarding age group and gender. As expected, the lowest number of visits during and before the pandemic was for children, while the largest number was for the over-60s age group. A total of 715 visits were made to children during the pandemic, with an average of 60 visits per month. In the pre-pandemic period, the total number of visits was 1070 with an average of 89 visits per month. The differences between visits to children during and before the pandemic are statistically significant (KW, p=0.0007). The maximum number of visits to children was done in March during and before the pandemic. During the pandemic, the number of visits to children is lower than in the pre-pandemic period in all the months except July. During the pandemic, most visits to children are related to the: traffic accidents (20.8%) and epilepsy (17.2%). COVID -19-related visits to children were 4.5% of the total number of visits during the pandemic. In the period before the pandemic, the maximum contribution of the total number of visits refers to: trauma injuries (20.3%), traffic accidents (17.7%) and epilepsy (15.9%).

During the pandemic, a total of 2112 visits were conducted among males in the 20-40 y age group with an average of 176 visits per month, while there is a statistically significant difference (KW, p=0.0079) compared with the period before the pandemic, when 2516 visits were done, with an average of 210 visits per month. The maximum number of visits for men in this age group was done in March during and before the pandemic. In both periods, most visits among males aged 20 to 40 were related to: traffic accidents (22.2%) and trauma injuries (13.6%) in period of pandemic, and trauma injures (14.7%) and traffic accidents (19.2%) in the pre-pandemic period. Visits to men aged 20-40 y associated with COVID-19 account for 6.1% of the total visits during the pandemic.

For the period during the pandemic, a total of 1263 visits were made among women in the 20 to 40 y age group with an average value of 105 visits per month, similar to the period before (KW, p=0.9309) when the total number of visits was 1279 with an average value of 109 visits per month. The maximum number of visits to women in this age group was done in September during the pandemic and in February before the pandemic. For females aged 20-40y, during the pandemic, most visits were related to: traffic accidents (13.9%) and neurosis, stress (9.4%). The same cause was the largest contributor to the total number of visits occurred before the pandemic: traffic accidents (13.7%) and neurosis, stress (9.5%). Visits to women aged 20 to 40 y associated with COVID-19 were 7.4% of the total number of visits during the pandemic.

At the period of the pandemic, a total of 3693 visits were made to males in the 40-60 age group, with an average frequency of 308 visits per month. With a similar frequency in the period before the pandemic, the total number of visits was 3606, with an average of 301 visits per month (KW, p=0.4525). The maximum number of visits for men in this age group was done in November during the pandemic, and in March before the pandemic. During the pandemic, the highest number of visits among men aged 40 to 60 refers to visits related to COVID-19 (13.4%) and traffic accidents (7.2%) of the total number of visits during the pandemic. In the period before the pandemic, the largest contributors to the total number of visits were caused by: trauma (8.1%) and traffic accidents (7.4%).

A total number of 2,517 visits were made to women in the 40-60 age group during the pandemic, with an average of 210 visits per month. The difference in frequency of visits before the pandemic was statistically insignificant (KW, p=0.4185) and it was 2420, with an average value of 202 visits per month. The maximum number of visits to women in this age group was done in January during the pandemic, and in March before the pandemic. During the pandemic, the highest number of visits to women aged 40 to 60 refers to: COVID-19 (14.1%) and ca (12.6%). In the period before the pandemic, the largest contributions to the total number of visits refers to: (14.9%) neuroses, stress (9.0%) and diseases of the nervous system (9.0%).

During the pandemic a total of 6823 visits were made to men aged over 60, with an average of 569 visits per month. In the period before the pandemic, the total number of visits was 7006, with an average of 584 visits per month. The differences between visits in both periods were statistically insignificant (KW, p=0.7728). The maximum number of visits for men in this age group was done in November during the pandemic and in January before the pandemic. During the pandemic, the highest number of visits among men over the age of 60 refers to visits related to: ca (12.6%) and COVID-19 (14.1%). In the period before the pandemic, the largest contributions to the total number of visits were related to the diagnosis: ca (11.6%) and cvi (9%).

During the pandemic a total of 6,992 visits were made to women aged over 60, with an average of 583 visits per month. In the period before the pandemic, the frequencies of visits were significantly higher (KW, p=0.0433) with a total visit number of 7918, and an average of 660 visits per month. The maximum number of visits to women of this age group was done during the pandemic in January and in the same month in the period before the pandemic. During the pandemic, the highest number of visits among women aged 40-60 refers to: COVID-19 (10.8%) and ca (10.2%). In the period before the pandemic, the largest contributors to the total number of visits were diagnoses: ca (15.1%) and hypertension (11.4%).

It also assumed whether there was a difference between the number of visits by gender in a given age group during and before the pandemic. There is a statistically significant difference in the total number of visits for men in the age groups 20 to 40 years and 40 to 60 years during and before the pandemic, and it is higher compared with the number for women (KW, p<0.0001). During the pandemic, the total number of visits to men and women over the age of 60 does not differ. On the other hand, in the period before the pandemic, the number of visits among women over 60 is higher than the number among men.

CONCLUSIONS

In the period from March 2019 to March 2021, the Emergency service, Skopje answered a total of 49930 calls, of which 48.3% (24115) during the pandemic and 51.7% (25815) in the period before the pandemic. The total of 13,835 were emergency calls, 46.5% (6,434) were during the pandemic and 53.5% (7,401) before the pandemic. In addition, a total of 9780 transport (without a doctor) were carried out during the observation period, of which 57.3% (5602) during the pandemic and 42.71% (4178) in the period before.

Analysis of the results showed that the number of calls did not differ during the pandemic and before. On the other hand, the pandemic contributed to the number of emergency calls to decrease and the number of calls only for transport to increase. Despite statistically insignificant fluctuations in calls per month, the number of calls follows the increasing trend during the first, second and third waves of the pandemic.

A further analysis of the frequency of visits in relation to age group, gender and diagnosis only proved to be meaningful in certain groups (Table 2). In general, the lowest number of visits during and before the pandemic was for children, while the largest number was for the over the age of 60 group. For the age groups 20 to 40 years and 40 to 60 years, the frequency of visits for men was significantly higher than for women during and before the pandemic. During the pandemic, the total number of visits by men and women over the age of 60 does not differ. On the other hand, in the period before the pandemic, the number of visits among women over 60 is higher than among men.

For children, the number of visits has been reduced during the pandemic compared to the period before. Traffic accidents and epilepsy caused the largest share of visit frequency in the two studied periods, while visits related to COVID-19 are the reason for 4.5% of all diagnoses.

Males in the 20–40 age group were mainly visited for traffic accidents and trauma injures in both periods, while females in this age group had traffic accidents and neurosis. COVID -19 -related visits are the reason for 6.1% for men and 7.4% for women. The dominant contributor to the number of visits during the pandemic was the COVID -19 for the age groups 40 to 60 years: men (13.4%) and women (14.1%) and over 60 years: men (14.1%) and women (10.8). In addition to COVID -19, during the pandemic most visits for men aged 40-60 and over 60 were related to accidents or ca, respectively, while for women of the same age group were related to ca diagnosis.

Finally, as a general conclusion, it can be stated that the pandemic, except for the conditions, did not affect the pace of work, only the relationship between the types of calls and the diagnoses for which the visits were made was practically changed. During the pandemic, most of the visits to both men and women over the age of 40 were related to COVID-19 diagnosis, while in children, men and women under the age of 40 the most common cause was accidents.

Finally, as a general conclusion, the pandemic has not affected the pace of work, except for the conditions, only the relationship between the type of calls and the diagnoses for which the visits were made has practically changed. During the pandemic, most visits to men and women over 40 were related to COVID-19 diagnosis, while to children, men and women under 40, accidents were the most common cause.

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EVALUATION OF THE EFFICIENCY OF SINUS LIFTING TECHNIQUES

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Abstract: Right after teeth extraction in posterior regions, there is a following process that consists of physiological resorption and nonfunctional atrophy of the remained alveolar bone ridge. That also impacts the quality on the quality and quantity of the remained bone tissue, what later makes the implant incorporation and the prosthetic restoration much harder and complicated than usual it is. In the posterior region of the upper jaw additional complication of the prosthetic restoration process causes the existing of paranasal sinus that is located right in the body of the upper jaw maxilla. It's post extraction pneumatization reduces the height of bone tissue what causes difficulties in dental implants placement.

The aim of this survey is to evaluate the clinical outcome and the efficiency of the most often used sinus lifting techniques.

Were analyzed totally 78 published studies that were done in the last 12 years. The study is made on narrative review of published articles that were investigating the related subject. Research was done by using the most common data bases: NCBI (US National Library of Medicine), Emedicine, PubMEd, Webmd.

By using the open method for sinus lifting there needs to be formed lateral window in the bone tissue first by elevating the mucoperiosteal flap on the vestibular surface of the maxillary alveolar ridge and after that creating iatrogenic fenestration on the cortical lamina without perforating the sinus membrane. After the sinus membrane is being separated, the following step is augmentation. For this step are used four different types of bone substituent: autogenous, allogeneic, xenogeneic bone graft and synthetic alloplastic materials.

The closed method for sinus lifting is performed after previous created place for the future implant in the residual alveolar bone ridge in the maxilla, after that with special instruments a perforation is being made in the bone floor of the maxillary sinus and carefully elevating the sinus membrane up for a few millimeters. In the created space a bone graft material is being placed and at the same time a dental implant is being applied.

From the gathered results, both of the techniques are considered to be effective, in all of the followed cases the implant placements were successful with high rate of postoperative osseointegration, the healing period was without complications and also successful. There was no prosthetic failure in any case.

From this survey the final conclusion is that both of the techniques are successful when it comes to sinus lifting. Very important is to have a qualitative imaging like computed tomography or roentgen before placing the implants to be able to estimate the bone volume and height. If the residual bone height is less than 5 mm the survival rate of the future implants is not guaranteed.

Keywords: Sinus lift techniques, implant placement, bone augmentation, alveolar bone resorption.

INTRODUCTION

Implants treatment in posterior regions of upper and lower jaw can be big challenge for oral surgeons. Right after teeth extraction in posterior regions, there is a following process that consists of physiological resorption and nonfunctional atrophy of the remained alveolar bone ridge. That also impacts the quality on the quality and quantity of the remained bone tissue, what later makes the implant incorporation and the prosthetic restoration much harder and complicated than usual it is [1,2].

In the posterior region of the upper jaw additional complication of the prosthetic restoration process causes the existing of paranasal sinus that is located right in the body of the upper jaw maxilla. It's post extraction pneumatization reduces the height of bone tissue what causes difficulties in dental implants placement with required length that is necessary for correct osseointegration. If the alveolar bone in the posterior regions on the both jaws is left without physiological stimulation for a long time, the changes in the bone structure become more serious. In the lower jaw by passing the years, the upper surface of the alveolar ridge is getting closer to the canalis mandibularis and the anatomic structures inside [3,4].

Because of these changes, there is a good need for additional surgical procedures that will ensure the needed conditions for dental implants placement[5].

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Aim

The main goal of this survey is to evaluate the clinical outcome and the efficiency of the most often used sinus lifting techniques.

MATERIAL AND METHODS

Research strategy

To create this study were analyzed totally 78 published studies that were done in the last 12 years. The study is made on narrative review of published articles that were investigating the related subject, evaluation of the efficiency of the most often used techniques of sinus lifting, written in English.

Research was done by using the most common data bases: NCBI (US National Library of Medicine), Emedicine, PubMEd, Webmd and Google scholar. The key words that were used for this research were the following: sinus lift techniques, implant placement, bone augmentation, alveolar bone resorption, implant placement preparation. The search included: systematic reviews, qualitative studies and clinical studies. The research was made online by selecting the articles that contained the research key words, then the articles that met the needed criteria were selected and analyzed in details. So from the total number of 78 studies that were initially found with the research, 32 were selected for detailed analysis about the researched topic, evaluation of the efficiency of sinus lifting techniques used in patients preparing for implants placement.

Inclusion criteria for the articles analyzed for this study were: studies made in vivo; articles published in the last 15 years; articles that are written in English; studies on patients with sinus lift treatment; studies evaluating the sinus lift techniques; studies on patients preparing for implant treatment.

The exclusion criteria were: studies done in vitro; articles older than 15 years; case report articles; articles about patient with other additional sinus surgical procedures.

The collected data was gathered in a database in order of these parameters: first author's name; the year when the article is published; number of analyzed cases; treatment technique; and the clinical outcome after the intervention.

EVALUATION AND RESULTS

The sinus lifting procedure is augmentative technique that is used in cases with huge pneumatisation of the maxillary sinus. The main aim of this procedure is to offer enough height of the residual alveolar bone ridge in the posterior regions of the maxilla [6]. There are many methods that can be used for this cause, most often used are: open method for sinus lift also known as Lateral window technique; and closed method for sinus lifting known like Transcrestal approach[7,8,9].

By using the open method for sinus lifting there needs to be formed lateral window in the bone tissue first by elevating the mucoperiosteal flap on the vestibular surface of the maxillary alveolar ridge and after that creating iatrogenic fenestration on the cortical lamina without perforating the sinus membrane [10,11,12].

In the next phase the sinus membrane is being carefully separated from the bone tissue of the maxillary sinus and in that space bone graft material is being placed to fill the void. That is also known as augmentation of the maxillary sinus foundation [13]. For performing this technique, there need to be conducted clinical examination and paraclinical roentgen imaging, after that a certain plan for each case individually is being created[15]. The surgical procedure starts with applying local anesthetics on the needed region, after that horizontal crestal incision is being done in the middle of the residual alveolar bone ridge, and two vertical relaxation incisions that will allow the mucoperiostal flap to be elevated in its full thickness. The vertical incisions need to be placed on healthy bone base and not on the place where the future bone fenestration will be done. The vertical incisions are supposed to be enough long to offer a good visibility during the surgical procedure[16,17,18].

After the lateral bone wall of the sinus is being exposed, the bone fenestration is being created. It can be in a shape of a rectangle or in oval shape. For that purpose are used instruments like surgical drills that are specifically created for this purpose [19]. The fenestration placement is being planned in order of the planned future implants position, their number and their length. The inferior horizontal edge of the bone window is placed 2 mm above the bone floor of the maxillary sinus that is previously located by using a roentgen image. The superior edge of the window is planned in relation with the future implants length[20,21].

The process of fenestration needs to be done carefully in order to avoid perforation of the sinus

membrane. After marking the bone window we create bone island that can be used like a base for elevation of the sinus membrane. The surgical procedure goes on with careful separating the sinus membrane from the bone walls of the maxillary sinus, that is performed by using specific instruments for that cause knows as sinus elevators. After the membrane is separated and it can be easily moved around, the separation continues until the sinus elevator reaches the medial wall of the sinus. The membrane is supposed to be mobile totally in full length of the created bone window[22,23].

This step of the operative procedure is very important and it has a crucial meaning for the whole treatment. Unfortunately the most common complication is perforation of the sinus membrane that happens if the attention to this step is not full, and if this mistake is not recognized during the surgical treatment, it can lead to more serious complications after the operation and even to result with inflammation of the maxillary sinus[24,25].

After the sinus membrane is being separated, the following step is augmentation. For this step are used four different types of bone substituent: autogenous, allogeneic, xenogeneic bone graft and synthetic alloplastic materials. In some cases there can be also used bioresorptive collagen membrane in combination with the bone graft, to prevent sinus membrane perforation with the grafting material and to offer more stability of the tissue[26,27].

The bone substituent that is used for augmentation also can be mixed with platelet enhanced plasma that will accelerate the process of the revascularization of the bone graft and will offer growth factors in the local area. In the final step of the operative procedure the mucoperiosteal flap is being repositioned on the previous place and sutures are placed to fixate it [28].

The closed method for sinus lifting is performed after previous created place for the future implant in the residual alveolar bone ridge in the maxilla, after that with special instruments a perforation is being made in the bone floor of the maxillary sinus and carefully elevating the sinus membrane up for a few millimeters. In the created space a bone graft material is being placed and at the same time a dental implant is being applied. This method is used in cases where the residual alveolar bone ridge is at least 5 mm and with that a primary stability of the future implants can be ensured. The sinus bottom can be elevated for 5mm with this approach. Which compared to the open technique, with this technique of augmentation the bone tissue is smaller [29].

The closed technique starts with local anesthetic placement, after what crestal incision follows on the middle of the alveolar ridge, and if needed there can be also created two vertical incisions. After that the mucoperiostal flap is elevated and a preparation of the future implant bunk is created with drilling in the bone tissue. The procedure continues with special instruments osteotoms that can be with different diameter. With that the bone bottom is carefully being reduced at the same time with attention on the sinus membrane to not get punctuated. Before the augmentation it is recommended to do some test to try if the sinus membrane is being perforated or is it intact. After that the next step is bone augmentation and elevating of the sinus membrane for 3 to 5 mm. Next thing to do is to place the implant and the bone integration time is 4 to 9 months depends on the graft used. At the end the flap is being repositioned and sutured on the previous place [30,31].

From the gathered results, both of the techniques are considered to be effective, in all of the followed cases the implant placements were successful with high rate of postoperative osseointegration, the healing period was without complications and also successful. There was no prosthetic failure in any case [32].

CONCLUSION

From this survey the final conclusion is that both of the techniques are successful when it comes to sinus lifting. Very important is to have a qualitative imaging like computed tomography or roentgen before placing the implants to be able to estimate the bone volume and height. If the residual bone height is less than 5 mm the survival rate of the future implants is not guaranteed. The open approach of sinus lifting can increase the height of the residual bone up to 9 mm, and the other closed approach can offer bone enlargement for 3 to 9 mm. With that it can be concluded that the residual bone height is one of the most important factors that needs to be taken seriously when implants are planned to be placed.

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CONFLICT OF INTEREST

None

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HIDRADENITIS SUPPURATIVA

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Abstract: Hidradenitis suppurativa (HS), or still known under the name Acne Inversa is a multifactor disease that has a chronic flow and starts with the capture of follicles of fibers located in intertriginous regions or anogenital regions. It is followed by recurrent, deep, sub connected and painful nodes, connected intertriginous sinus tracts and hypertrophic scars. Women are more versatile from men, according to 3:1 and more likely to develop axillary and genitofemoral lesions than a male population that develops changes that are localized in the perineal region. The disease itself is unpredictable flow and cannot be certain whether the period of menstruation, pregnancy or menopause may affect the deterioration of the patient's condition. Usually, the bacterial infection that builds on the state itself is like a secondary phenomenon and most often isolate beta hemolytic streptococcus or staphylococcus. The pathogenesis of the disease is still unclear, but it is thought that the primary event that occurs is follicular occlusion occurring as a result of infundibular keratosis and epithelial hyperplasia. Features show that patients say that the same changes occur in other members of the family. Some genes from Secretase G family are thought to be responsible for the disease itself. On the other hand, there are autoimmune reasons for the very disease, both of the innate and the acquired immunity. However, this disease is classified as neutrophilic restriction. The simplest and most widely used instrument for HS classification in routine clinical practice. It classifies HS into three stages: Stage I: isolated, single or more painful abscesses, no scars and occurrence of cicatrix. Stage II: recurrent pain abscesses with scars, single or multiple but not so extensive. Stage III: diffuse, similar to plates, inflammatory, sick infiltrates or more mutual abscesses. Contracts of joints as a result of limited mobility associated with pain. Because the disease has more stages and treatment itself will be correlated with the stage of the disease. We should emphasize that the disease can also be worsened by some accompanying diseases from which the type 2 diabetes or some other endocrine and metabolic diseases should be distinguished in the first place. Always put the lifestyle and change in everyday habits as it is in the first place to reduce weight if it is increased as well as the cancellation of cigarette smoking. Primary in treatment is maintaining good personal hygiene with soaps that are antibacterial and pastures with mild disinfection. At the beginning of the disease, antibiotics are usually attached as local and systemic administration, most often from the group of tetracyclines. Anti-inflammatory preparations are given in order to reduce inflammation and drug reduction drugs. As antiseptics use salicylic solution, alcohol pine, camphor, ethyl alcohol or iodine. More recently, it goes to make drinks from iodine and potassium hypermangan. If it is not contraindicated, corticosteroid creams and gels as well as a local anesthetic can be reduced. Surgical intervention can be applied to make an incision of a nodule or an apex to be easier drainage and thus reduced the pain of the region concerned. It should be noted that this disease affects the whole family. In the first place, it is necessary to accept the patient's patient in order not to isolate it from the rest and to participate in social life as before the disease itself. A conversation is necessary by a psychologist with the whole family in order to facilitate life and improve the quality of it.

Keywords: hidradenitis suppurativa, pathology, stage, treatment.
Field: Medical sciences and Health

INTRODUCTION

Hidradenitis suppurativa (HS), or still known under the name Acne Inversa is a multifactor disease that has a chronic flow and starts with the capture of follicles of fibers located in intertriginous regions or anogenital regions. It is followed by recurrent, deep, sub connected and painful nodes, connected sine tracts and hypertrophic scars. The situation itself is followed by continuous pain that can vary from easy to unbearable and to a large extent difficult life and everyday activities of the patient. Women are more versatile from men, according to 3:1 and more likely to develop axillary and genitofemoral lesions than a male population that develops changes that are localized in the perineal region. The disease itself is unpredictable flow and cannot be certain whether the period of menstruation, pregnancy or menopause may affect the deterioration of the patient's condition. Usually, the bacterial infection that builds on the state itself is like a secondary phenomenon and most often isolate beta hemolytic streptococcus or staphylococcus.

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ETIOLOGY AND PATHOGENESIS

The pathogenesis of the disease is still unclear, but it is thought that the primary event that occurs is follicular occlusion occurring as a result of infundibular keratosis and epithelial hyperplasia. Features show that patients say that the same changes occur in other members of the family. Some genes from Secretase G family are thought to be responsible for the disease itself. On the other hand, there are autoimmune reasons for the very disease, both of the innate and the acquired immunity. However, this disease is classified as neutrophilic restriction. Increasing the levels of IL-1, IL-10, IL-12, IL-17, IL-23, TNF, CASPASE-1, S100A8, and S100A9 in inflammatory tissue, point out the role of the adaptive immune system. According to this evidence, autoimmune disorder it's fundamental role in HS, especially in patients with syndrome phenotype.

• Bacteria: The bacteria, as the follicular occlusion, is considered to play a role in the pathogenesis of the disease itself. Often, these patients also note disburses and disruption of the bio flora of the skin.

• Androgens and estrogens: Although sometimes there are no correlation with the weight of the clinical picture, many women reported that in the premenstrual period there were deterioration in the state of the disease, while remission during pregnancy. Usually in girls with the occurrence of early men, there is a familial form of hidradenitis and a much stronger pronounced form of disease. The premenstrual falling levels of estradiol and progesterone indicates that hormonal changes during the menstrual cycle can affect the start and symptoms of HS. Today, the effects of hormone therapy, such as testosterone, have become one of the most controversial issues related to the treatment of hidradenitis.

• Lifestyle wearing tight clothing that increases friction can exacerbate the state of the disease. Some women found that the use of tampons compared to sanitation pads reduces the friction of the skin. We cannot say that the unhygienic is the cause of the painful nodules, but the use of personal hygiene objects that irritate the skin can be a trigger factor for worsening the situation.

• Mechanical stress; Many skin disorders are due to mechanical stress. Friction may occur on different parts of the body. Areas of body with the highest risk are the axilla, groin, buttocks, neck and waist

• Mental stress plays a very big role for the disease itself. Additional deterioration may occur if other inflammatory diseases are present, the skin that violate its integrity.

• Smoking; More than 70% of patients with HS are smokers. Smoking cigarettes are associated with heavier symptoms of HS and increased sweeping secretion by the eccrine sweat glands and on the other hand and reducing the immune response of the home.

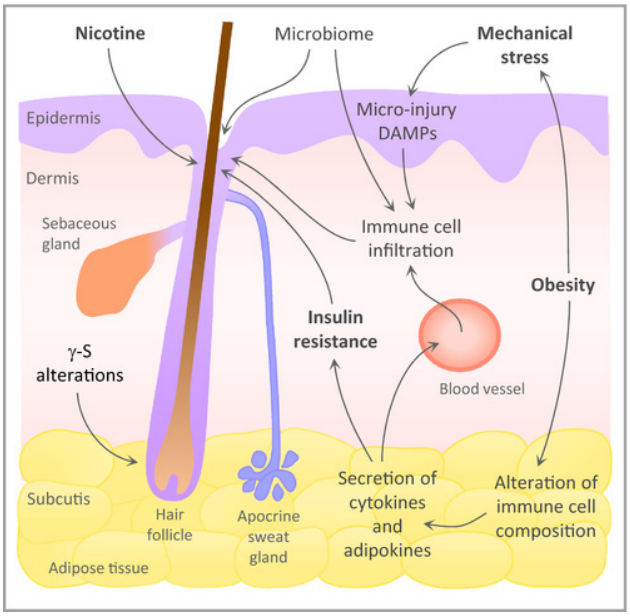

Figure 1. Pathogenesis of HS

3.CLINICAL ASPECTS

In the early stages of the disease of the affected regions, inflammatory surfaces with bright red color, painful nodes and nodules appear. These changes often merge into many sick air detections that are above the surface of the skin and in a few days (7-10 days) are opened on the surface of the skin and

expires a purulent secretion that has an unpleasant smell. Usually, the affected places are with limited mobility and the patient often saves and occupies forced position in bed in order to reduce pain. The pain usually occurs at night and patients have disturbed sleep and thus reduced quality of life. Usually, the friction itself leads to other sick nodules and the apples that further exacerbate the situation. The person concerned is usually closed within himself and is distanced from other people who result in depression and mood change.

The simplest and most widely used instrument for HS classification in routine clinical practice. It classifies HS into three stage:

- Stage I: isolated, single or more painful abscesses, no scars and occurrence of cicatrix
- Stage II: recurrent pain abscesses with scars, single or multiple but not so extensive
- Stage III: diffuse, similar to plates, inflammatory, sick infiltrates or more mutual abscesses. Contracts of joints as a result of limited mobility associated with pain.

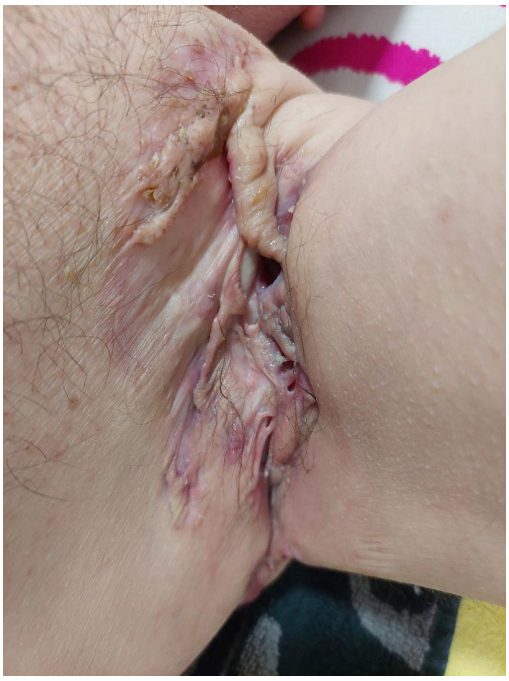

Figure 2. HS of axila

Figure 3. HS of gluteus

Figure 4. HS of perianal regia

TREATMENT OF HS

Because the disease has more stages and treatment itself will be correlated with the stage of the disease. We should emphasize that the disease can also be worsened by some accompanying diseases from which the type 2 diabetes or some other endocrine and metabolic diseases should be distinguished in the first place. Always put the lifestyle and change in everyday habits as it is in the first place to reduce weight if it is increased as well as the cancellation of cigarette smoking.

Primary in treatment is maintaining good personal hygiene with soaps that are antibacterial and pastures with mild disinfection.

At the beginning of the disease, antibiotics are usually attached as local and systemic administration, most often from the group of tetracyclines. Anti-inflammatory preparations are given in order to reduce inflammation and drug reduction drugs. As antiseptics use salicylic solution, alcohol pine, camphor, ethyl alcohol or iodine. More recently, it goes to make drinks from iodine and potassium hypermangan. If it is not contraindicated, corticosteroid creams and gels as well as a local anesthetic can be reduced. Surgical intervention can be applied to make an incision of a nodule or an apex to be easier drainage and thus reduced the pain of the region concerned.

System therapy is indicated when we already have a second or third stage of the disease. The most commonly attached drugs are as follows:

- Clindamycin-Rifampicin (300 mg + 600mg) in one or divided into two doses for a duration of 10 weeks
- Tetracycline (100 to 200 mg per day)
- Rifampicin-moxifloxacin-metronidazole (Rifampicin 10 mg / kg once a day, moxifloxacin 400 mg once a day and metronidazole 500 mg for a duration of 6 weeks)
- Ertapenem (1 gram per day intravenous for 6 weeks)
- acitretin (daily dose of 0.25-0.88 mg / kg for 3-12 months)
- Cyclosporine.
- Dapsone
- Isotretinoin.
- Biologics.

Laser hair removal, surgical treatment for affected regions, incisions, excises are additional therapeutic approaches to this disease.

LIFESTYLE MODIFICATIONS

Depending on the severity of the disease and the stadium for the same to improve the quality of the news, some certain habits must be changed. In the first place is maintaining good personal hygiene. Regular application of disinfectant and preferably removing the hair from the affected places. It is not allowed clenching, pressing the apples and their friction, but wearing comfortable and cotton clothes that would reduce friction and sweating. Running healthy life and healthy dietary habits. Decreased input of red Messi and foods containing preservatives, entering fresh food and supplements in order to strengthen immunity, stop smoking and weight loss. If there are other accompanying diseases it is obligatory to keep under control by taking appropriate therapy. Reducing the leans in the blood and regulation of diabetes mellitus.

CONCLUSION

It should be noted that this disease affects the whole family. In the first place, it is necessary to accept the patient's patient in order not to isolate it from the rest and to participate in social life as before the disease itself. A conversation is necessary by a psychologist with the whole family in order to facilitate life and improve the quality of it.

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THE INFLUENCE OF COVID-19 PANDEMIC ON THE VACCINATION OF THE POPULATION WITH THE INFLUENZA VACCINE IN THE REPUBLIC OF NORTH MACEDONIA

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Abstract: The implemented actions to minimize the spread of the COVID-19 pandemic had a powerful effect on the transmission of other respiratory viruses, particularly influenza viruses. Influenza is a disease of viral aetiology that causes epidemics and occasionally pandemics during the wintertime almost every year. Generally, it is a mild and self-limiting disease, but it can represent high morbidity and even mortality when affecting the elderly population or people with latent chronic diseases. The existing circumstances of a persistent and ongoing epidemic caused by the SARS-CoV-2 virus, increase the probability of having active coincidence with the anticipated annual epidemic of influenza. Thus, the key is a logistic strategy for clinical and viral diagnosis of the SARS-CoV-2 virus that will determine the importance of understanding the role of influenza vaccines in virus-induced COVID-19 disease. This paper aims to compare the potential impact of the COVID-19 pandemic on the vaccination coverage of the population with the influenza vaccine. The official data for seasonal influenza vaccination were used, obtained from the weekly reports on the influenza situation in the Republic of North Macedonia from the Institute of Public Health as well as the data from the national system "MojTermin" for total vaccinated individuals with influenza vaccine for the season 2020/2021 and 2021/2022 including the 5th week.

The analyzed data for the season 2021/2022 show an increase of applied doses by 8.3% compared to the season 2020/2021 and an increase of 11.5% compared to the season 2019/2020. Regarding the target groups in the season 2021/2022, including the 5th week, the coverage of influenza vaccination in children aged 6 months to 5 years has a significant decrease of 87.9% compared to the season 2020/2021. There is an increase in coverage in health professionals by 24.3% compared to last season, in the chronically ill the decrease of the applied doses is by 11.4% compared to last season, and in the elderly, over 65 it is noticeable an increase in coverage by 100% compared to the 2020/2021 season. Furthermore, there is a significant decrease of 95.7% in the vaccines administered to pregnant women compared to last season. The reduced coverage of influenza vaccination is partly due to the ambiguities arising from the influenza immunization campaign, which emphasized the importance of receiving a vaccine to minimize the spread of the influenza virus as an additional threat to the presence of COVID-19. Although the influenza vaccine does not protect against COVID-19, influenza vaccination has been part of the public health strategy to flatten the disease curve caused by respiratory viruses that attack the respiratory system, to protect and preserve the health of healthcare professionals providing care to patients with COVID-19. Influenza vaccination is still the most efficient preventive measure against influenza infections at our disposal and it is recommended by the most expert bodies including CDC, WHO, ECDC, and the National Committee for Immunization of the Republic of North Macedonia.

Keywords: vaccination, influenza, COVID-19, coronavirus, SARS-CoV-2.

NTRODUCTION

The COVID-19 pandemic challenged society around the world. It has been more than two years since the pandemic first began. Policymakers worldwide have implemented stringent mitigation efforts to reduce transmission of severe acute respiratory syndrome virus 2 [SARS-CoV-2] (Groves, HE., et al., 2021). The Government of North Macedonia has been very dedicated to taking measures for handling the situation with the pandemic, so on March 18, 2020, it declared a state of emergency to fight against the spread of Covid-19. When deemed necessary, the government did not hesitate to take strong action. Having only 35 confirmed cases, the state of emergency was declared across the country on March 18, 2020. All borders and the airport were closed. To fight corona virus almost all government actions have

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been mobilized, along with the increasing emergency response mechanisms in all sectors. There has been a positive response and consent from society as well as more confidence in the government protective measures and guidelines for social distancing. Simultaneously, through social networks, television, and other media, the Ministry of Health has launched an active risk communication campaign, having substantial support from the WHO and the other international agencies. But, such restrictions resulted in many negative effects too. Namely, people could not access medical services, although available due to economic difficulties, interruptions in transportation, and the fear of leaving home or visiting a physician as a preventive measure against exposure to SARS-CoV-2. The effect on health and early death caused by the suspension of ordinary daily obligations is not known yet. Generally, the extensive research performed during the initial pandemic phase by the World Health Organization informed a serious reduction in all routine health services, having a 70% reduction in routine immunization services. Vaccination coverage estimations in 2020 indicate that 23 million children missed their regular vaccination through the scheduled immunization services, which is about 3.7 million more compared to 2019 (World Health Organization [WHO], 2020).

Seasonal flu, a highly contagious acute disease of the respiratory tract caused by influenza viruses is a serious risk to the health of the world's population. It is estimated that half a million deaths and five million cases of critical illness occur as a result of seasonal influenza worldwide each year (Schmid, P., et al., 2017).

In the northern hemisphere, including Europe, seasonal flu mainly occurs in the form of epidemics between November and April each year, while in the southern hemisphere between June and October. Many other viruses and bacteria cause similar symptoms, so much of the flu-like illness (ILI) is not caused by the flu.

Flu pandemics appear at irregular intervals. Influenza monitoring is performed worldwide.

Due to the epidemiological characteristics of influenza as a medical entity, the occurrence of an epidemic form such as damage to human health, death rate, high morbidity, and mortality, is not only a medical but also a social, economic and financial problem for any health system as well as a significant threat to the population.

The Republic of North Macedonia (MKD) is a relatively small country with a population of 2 million people, which has a long-standing tradition of immunization. Compulsory immunization, with a strong legal basis, is present since the 1960s, while influenza vaccination is optional. Until the 2018/2019 season, the people who were vaccinated participated with their financial means, and seasonal influenza vaccine coverage was low, with an average of 25,000 to 30,000 people being vaccinated per year.

There is a multi-year influenza vaccination plan or policy in MKD. Every year MOH prepares Annual Information for influenza immunization which is approved by the Government of MKD. This information specifies the (1) quantities of vaccines to be procured, (2) necessary budget, (3) the categories that will be covered by free vaccination, and (4) the implementation of the vaccination. The recommendation for influenza vaccination is given by the National Commission for communicable diseases in coordination with National Committee for Immunization, both as advisory bodies in MOH. The information on influenza immunization, influenza program, estimation of the number of vaccines to be procured, target groups, and recommendation of the type of influenza vaccines to be used is prepared by the Institute for Public Health, accepted by the National Commission for communicable diseases in coordination and National Committee for Immunization and then proposed to the Minister of Health, who gives the final decision. The type of vaccines, their formulation, and presentation is defined by National Committee for Immunization in coordination with experts from the Macedonian Agency for Medicines and Medical Devices – MALMED and following the relevant legislation and regulations.

The free of charge influenza vaccines that are procured by MOH are for specific population groups defined as (1) Elderly people (over 65 years old), (2) People with chronic diseases, (3) Healthcare workers, (4) Pregnant women, and (5) Children aged 6 months to 5 years. There is low acceptance of maternal immunization against influenza due to general reluctance to vaccinate among pregnant women, the complexity of vaccination pathways, as well as lack of understanding of the need for vaccination. The same low acceptance is present for influenza vaccination in children.

At the start of the influenza season 2021-22, all along with the still growing COVID-19 pandemic, the potential impact on complications caused by the flu should have been taken into consideration since that could further burden an already overloaded and strained health system (Patel Murthy, B., et al., 2021).

As a reaction to the coronavirus pandemic, much attention has been paid to promoting vaccination against Covid-19. Nevertheless, the effect and the power of seasonal influenza should not be overlooked, especially during the winter influenza wave.

MATERIALS AND METHODS

The data used for the seasonal influenza vaccination are obtained from the weekly reports on the flu situation in the Republic of North Macedonia, disclosed weekly on the website of the Institute of Public Health. (www.iph.mk) as well as the data obtained from the national system "MojTermin" for the season 2020/2021 and 2021/2022. The data on the total influenza vaccination for the seasons 2019/2020, 2020/2021, and 2021/2022 up to the 5th week in 2022 have been compared.

Influenza monitoring includes levels of regular reporting, organized collection, processing, analysis, and evaluation of data as well as distribution of relevant information to the institutions that propose and adopt legal solutions that should be implemented at the national level. According to the legislation, the Centers for Public Health of RNM, weekly submit (distribute) data for individuals vaccinated with influenza vaccine to the Institute of Public Health of RN Macedonia, (IPH), additionally processed by the department of epidemiology.

RESULTS

In the season 2021/2022, a total of 49.320 people were vaccinated against influenza. There is an increase of the applied doses by 8.3% compared to the season 2020/2021 when the total number of applied influenza vaccines was 45.561 and an increase of 11.5% compared to the season 2019/2020 when the number of applied vaccines was 43.639.

The analyzed data for the season 2021/2022 show that the coverage of influenza vaccination in children aged 6 months to 5 years has a significant decrease of 87.9% compared to the season 2020/2021. Taking into consideration the health professionals and compared to last season, there is a 24.3% increase in the coverage, the reduction of the applied doses in the chronically ill is by 11.4%, while in the elderly over 65 we identified an increase in coverage by 100% compared to the season 2020/2021.Furthermore, compared to last season there is an extreme drop of 95.7% in the vaccines administered to pregnant women.

Figure 1. Total number of vaccinated people for the seasons 2019/2022

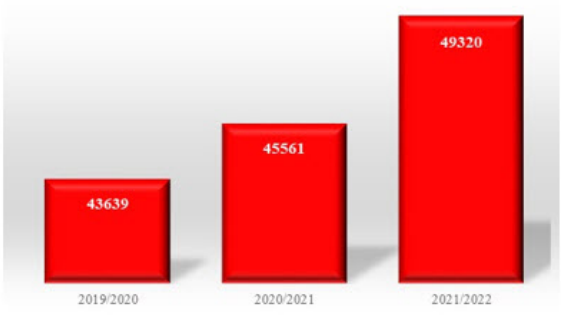
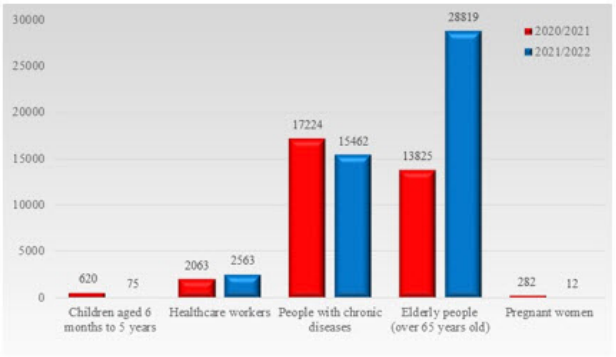


Figure 2. Vaccinated people with influence vaccine according priority groups for the period 2020/2022



DISCUSSION

The changes in influenza vaccination intention and reasons for changes were reported in recent meta-analysis and systematic review conducted on Embase, PubMed, and CNKI including twenty-seven studies with 39,193 participants, reporting rates of influenza vaccination pre-COVID-19 (19/20 season) and post-COVID-19 (20/21 season). All studies reported increased influenza vaccination intention in post-COVID-19 season (Kong, G., at al., 2022).

Our results show that the total number of applied influenza vaccines in the season 2021/2022 was higher by 8.3% compared to last season. This increase happens to be due to the 40.000 free doses of quadrivalent seasonal influenza vaccines for populations at-risk and the additional 20.000 doses of quadrivalent vaccines provided through a donation from PIVI (Partnership for Influenza Vaccine Introduction), procured by the Ministry of Health.

Although 40.000 doses of free quadrivalent influenza vaccines were procured for the season 2020/2021, the overall increase is due to the 100% increase in the applied doses of influenza vaccines in the elderly over 65 years. In contrast, the number of doses administered to children 6 months to 5 years of age, chronically ill, and pregnant women have been significantly reduced.

There is also an increase in the coverage of influenza vaccine among health professionals since the priority groups for influenza vaccination and of course a challenge given by the small coverage are healthcare workers. Their influenza vaccination is recommended, and they participate in it from their funds. Similar to these results, findings from one observational study conducted in an Italian teaching hospital located in Rome, Italy, showed an encouraging vaccination coverage rate among healthcare workers, where physicians reached the highest coverage followed by others healthcare workers and nurses (Ambrosio, FD., et al., 2021). In addition, results from survey conducted on flu and COVID-19 vaccines attitudes, distributed to employees and residents in Pisa university hospital, showed that 70.97% of healthcare workers agreed that being vaccinated against influenza would be more important than the previous years because of COVID-19 emergency (Scardina, G., 2021).

In 2019, a survey was conducted on knowledge, attitudes, and practices (KAP) related to influenza vaccination among health professionals in the Republic of North Macedonia. The results of this study were unfortunately negative, which is why an even greater challenge to increase the coverage in this target group. Through this research, it was concluded that for some health professionals the price of the vaccine is the reason why they are not vaccinated, as well as more difficult logistics because the vaccines are applied only in one Center on the territory of the city of Skopje. Therefore, the MOH made some changes to increase the availability of vaccines. In the season 2019/2020, it included the health workers in free of charge vaccination and included 3 additional vaccination points in Skopje (part of the Health Home Skopje). With these changes, in season 2019/2020, 1.252 health workers were vaccinated with free vaccines, which is an increase of 58% compared to the previous season. Also, the low consumption of vaccines in this target group is affected by the legislation. Unfortunately, it does not allow healthcare professionals (secondary and tertiary level) to be vaccinated in their health facilities by a team from the facility itself. Therefore, the possibility of finding an administrative solution to vaccinate health workers in their home institutions is being considered. Another option is for the Centers to carry out field vaccination, but this method is more difficult due to the staff capacity of the Centers.

The reduction in influenza vaccination coverage is partly due to ambiguities stemming from the influenza immunization campaign, which highlighted the importance of taking a vaccine to reduce the spread of the influenza virus as an additional threat to the presence of COVID-19. Although the influenza vaccine does not protect against COVID-19, influenza vaccination has been part of the public health strategy to mitigate the incidence of diseases caused by respiratory viruses that invade the respiratory system, to protect and preserve the health of healthcare professionals providing care to patients with COVID-19 (Patel Murthy, B., et al. 2021).

The coverage of seasonal influenza vaccination world wide and also in RNM for the season 2020/2021 was unusually low. Preventive public health measures to restrain the spread of the SARS-CoV-2 virus, such as wearing masks, following recommendations to stay at home, closing schools, and physical distance, have helped in reducing the number of flu-like illnesses by 2020 (Fogel, B., et al., 2021).

Online classes were one of the measures in R.N. Macedonia that certainly influenced parents not to vaccinate their children since homeschooling as an alternative lowered the risk of catching the flu (Fogel, B., et al., 2021).

Although there are optimal conditions for sustained vaccination and also there is still a sufficient amount of vaccines to implement the regular immunization calendar, the regular vaccination reports show that there is a reduction in regular vaccinations of children. All of this suggests that the COVID-19 pandemic indirectly led to a reduction in vaccine coverage in the routine vaccination calendar (Santoli, JM., 2020). The effect of the restrictive measures and of course, parents' fear of a potential COVID-19 infection that actually exists, led to a decline in interest and thus a significant reduction in the vaccination coverage of children in 2020 (Patel Murthy, B., et al. 2021).

CONCLUSION

This flu season 2021/2022 also coincided with the ongoing COVID-19 pandemic, so MOH should provide necessary strategic efforts, to ensure a higher vaccination coverage of the population with influenza vaccine on all age groups. The focus should be particularly placed on children aged 6 months to 5 years since there is a serious decline in the number of administered doses of influenza vaccine, as well as those

from the scheduled vaccination calendar because children at this age are not yet eligible to the COVID-19 vaccine (Grohskopf, LA., 2021). The National Immunization Committee recommends routine annual influenza vaccination for all individuals over 6 months of age, in those who have no contraindications.

The CDC, WHO, and ECDC recommend that all healthcare professionals should advise their patients and convince them to take the COVID-19 vaccine at the same time as the routine influenza vaccine (Grohskopf, LA.,2021) to emphasize the importance of influenza vaccination during the COVID-19 pandemic.

WHO and the CDC have increased influenza vaccines availability and conducted targeted communication contact with higher-risk populations, such as patients ≥65 years of age, young children, pregnant women, and people with specific chronic health conditions.

Influenza vaccination can reduce the spread of the virus, which will also reduce the number of potential patients with respiratory diseases in the health care system that is already overloaded with patients infected with COVID-19.

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THE ROLE AND SIGNIFICANCE OF HARMFUL HABITS AND HERITABLE FACTORS IN THE DEVELOPMENT OF CHRONIC VASCULAR DISEASES

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Abstract: Chronic Arterial Insufficiency of the Limb is a condition of chronical reduction of blood flow delivered from the arteries to a limb. It is also known as Peripheral Arterial Disease (PAD). The most commonly affected are the aorto-iliac segment and the arteries of the lower extremities. The most common causes are diabetes and / or atherosclerosis, but the bad habits and hereditarity are also important. The varicose disease is a process of superficial venous dilatation of the lower extremities. The most important reason of chronic venous disease is correlated with hereditary factors and the bad habbits. The secondary varicose is caused by malformations, traumatism and deep vein thrombosis. The lymphedema is a chronic disease, manifested by slowly progressing edema of the skin and skin. Due to the reduction of the transport function of the lymphatic system – the flow of lymph slows that leads to an increase in fluid in the intercellular space- edema. May affect any part of the body, but most often are affected one of the upper or lower limb.

Purpose: evaluation of the bad habits and the hereditary factors as a reason for chronical vascular diseases.

Methodology: for the purpose of this study a new anonymous questionnaires were created.

Results: this study includes patients with chronical vascular diseases and was made in university hospital – clinc of Vascular surgery and in heathcare medical center.

Conclusions: The bad habits and the hereditary factors are the main reason for development of chronical vascular diseases.

Keywords: venous disease; PAD; atherosclerosis; bad habits; hereditary factors.

Field: Medical sciences and Health

INTRODUCTION

Vascular diseases provoke a serious research interest aimed at revealing the relationships between the origin and course of the disease and the psychogenic elements involved in the overall disease process (Крумова-Пешева, & Пешев, 2020). According to the WHO, chronic diseases are defined as "any disorder or abnormality that has one or more of the following characteristics: permanent, causing disability, resulting from irreversible pathological changes, requiring rehabilitation treatment, or expected to require long-term supervision or care. Chronic Arterial Limb Insufficiency is a condition of chronic reduction of blood delivered from the arteries to a limb. It is also known as Peripheral Arterial Disease (PAD). The main clinical symptoms of PAD are a pain in the limb when traveling a certain distance, which progressively decreases with the development of the disease, the so-called "claudicatio intermitents", trophic skin changes, atrophy of the muscles and difficult of wounds healing. The pain seriously provokes anxiety oft ambiguity and uncertainty. This is one of the main existential threats that the patient has difficulty coping with mentally (Крумова-Пешева, & Пешев, 2017). The pain causes the patient to regress to early childhood reactions and behaviors, seeking solace and care (Крумова-Пешева, Гиров, & Пешев, 2012). Pathological mental reactions are a paradoxical way of not accepting the real facts of amputation and seriously impede the mental and physical patients' recovery (Крумова-Пешева, & Пешев, 2017).

The most common chronic venous diseases disease is varicose. About 41% of patients in Bulgaria over the age of 18 have chronic venous disease (Гиров, 2019). Almost every second adult in Europe suffers from a venous disease. Only 15% of cases are considered risky for the patient. The spectrum of venous diseases ranges from venous telangiectasias to chronic varicose veins and sometimes fatal end, such as venous thromboembolism. In vascular surgery, varicose veins are extremely important. Any varicose change leading to symptoms such as swelling or ulceration of the lower extremities is subject to surgical treatment (Agus et al, 2001). The chronical venous disease is a very common problem, and

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varicose veins affect more than 25 million adults in the United States (Barwell et all, 2004). Due to the high prevalence of varicose veins and Chronical Venous Insufficiency (CVI), a national screening program has been established in the United States. The program identified varicose veins in 32% of participants (Beebe-Dimmer et all, 2005).

Chronic lymphedema is a permanent and evolving increase in the volume of a certain part of the body caused by lymphatic stasis due to congenital or acquired changes in the lymphatic system. As a result of these anomalies or changes in the lymphatic system, lymphatic drainage failure occurs. The result of these changes is a mild edema (swelling), which increases progressively.

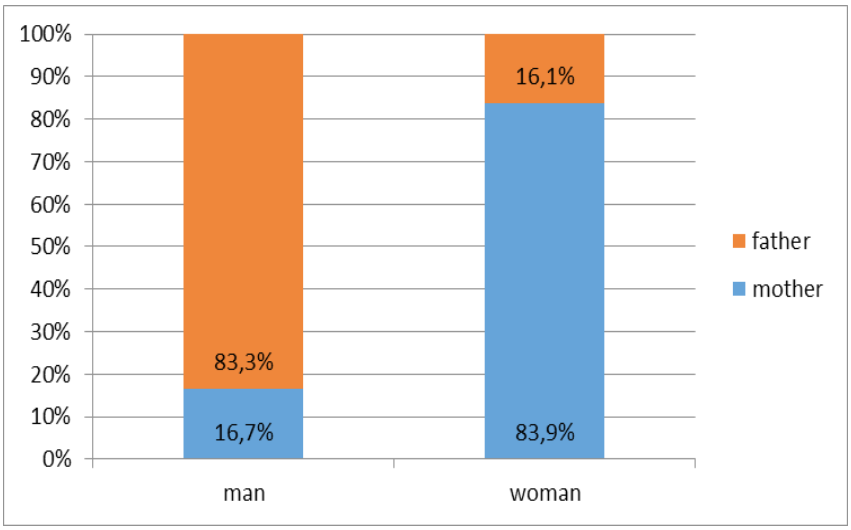
In order to minimize the harmful effects of immobilization, due to the reduced motor activity, the circumstances that can lead to the development of chronic vascular disease should be limited. Decreased motor activity in chronic vascular disease leads to bad changes in blood circulation: reduction of number of reserve capillaries, reduced blood flow, changes in the elasticity of blood vessels and edema. The increased physical activity and the reduction of harmful habits and heritable factors aims to reduce edema in chronic venous insufficiency (CVI) and chronic lymphedema, and to improved perfusion in patients with chronic arterial insufficiency.

MATERIALS AND METHODS

The current study included 80 patients from different age groups. Anonymous questionnaires were prepared for the purpose of the study. The category variables are presented as the absolute number and relative share of each of their categories, and the quantitative variable (age) - as the median and scope, as its distribution differs significantly from the Gaussian. The arithmetic mean is given for completeness and easier understanding by a wider audience. The Kolmogorov-Smirnov test was applied to verify the form of the distribution. When looking for connections between categorical variables (influence of gender, place of residence, education on patient awareness; connections between the individual questions in the survey), a hi-square analysis was applied. Non-parametric Mann-Whitney and Kruskal-Wallis tests were used to compare mean (median) age values of individual patient categories. Values of $p < 0.05$ are considered significant, and those between 0.05 and 0.1 are considered marginal significant.

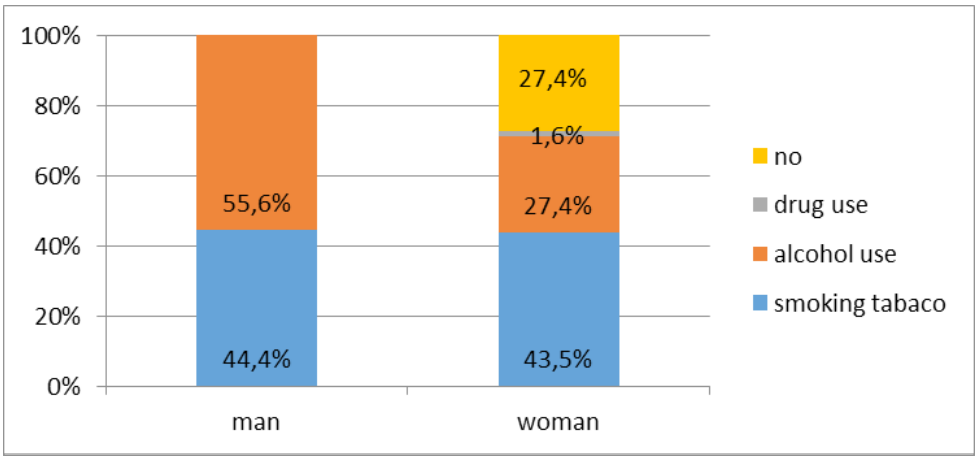
RESULTS

80 patients were interviewed. The median age was 48.5 years, with the youngest participant being 28 and the oldest 72. The arithmetic mean age was 49.8 g. Among patients, women had a large predominance, 77.5% compared to only 22.5% men. Respondents live mainly in cities - 62.5%, while in the villages are only 37.5%. Over two thirds of the respondents (68.8%) reported a family heredity on the part of the mother, and another 31.1% reported it on the part of the father. It was proved that in men the family heredity is significantly more often on the father's side, while in women - more often it is on the mother's side ($p < 0.001$) (Pic. 1).



Pic. 1. Distribution of answers to the question "Family heredity " by gender (relative share)

It is interesting to note that bad habits are significantly more common among men - in the survey there is no man who answered that none of the three listed bad habits, while in women they are 27.4%. The number of smokers between the sexes is similar (about 44%), but the difference is due to alcohol use - it is significantly more common among men (55.6%) than among women (27.4%). = 0.037. Smoking is the most commonly reported harmful habit associated with the disease (43.8%), followed by alcohol use (33.8%), and one patient (1.3%) reported drug use. In total, 78.8% of patients have one of the listed bad habits, while only 21.1% have not reported such habits (Pic. 2).



Pic. 2. Distribution of answers to the question "Harmful habits" by gender (relative share)

DISCUSSION

The treatment of chronic vascular diseases and their complications is complex and concern more than one specialty. Vascular surgeons and anghiologists mainly deal with this disease, but in the event of complications such as lipodermatosclerosis and venous ulcers, the help of dermatologists and plastic surgeons is often sought. The treatment of chronic vascular diseases as well as any other disease begins with prevention. Prevention includes appropriate exercise regime, medication and rehabilitation. The purpose of prophylactic treatment is to slow or stop the development of the relevant vascular disease. Awareness of patients to develop active behavior in chronic vascular disease will help them to have healthier lives and lower stress levels. More than two thirds of the respondents reported a family heredity on the part of the mother, and one third on the part of the father. It was proved that in men the family heredity is significantly more often on the father's side, while in women - more often it is on the mother's side ($p < 0.001$). It is interesting to note that bad habits are significantly more common among men - in the survey there is no man who answered that none of the three listed bad habits, while in women they are below 30%. The sedentary lifestyle and the reduced physical activity slow down the reduction of venostasis or lymphostasis. Smoking is one of the main reasons for the development of chronic arterial insufficiency of the limbs.

CONCLUSIONS

1. The treatment of chronic vascular diseases and their complications is a complex process.
2. The treatment of chronic vascular diseases as well as any other disease begins with prevention.
3. Prevention includes appropriate physical activity, medication and rehabilitation.
4. The purpose of the prophylactic treatment is to slow down or stop the development of the relevant vascular disease.
5. Hereditary factors are an important reason for the development of chronic vascular diseases.
6. Bad habits such as smoking are one of the main reasons for the development of chronic arterial insufficiency of the limbs.

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