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CURRENT TRENDS IN PRESCRIBING PATTERN OF ANTI-MIGRAINE DRUGS IN PATIENTS OF MIGRAINE AT A TERTIARY CARE TEACHING HOSPITAL

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Background. *An inappropriate prescribing pattern of antimigraine drugs by doctors may often encourage inappropriate self-medication by patients because of the asymmetry of medical information.*

Objective. *The study is aimed to assess the current trends in prescribing patterns of anti-migraine drugs, rationality of prescription, and pattern of migraine severity in patients of migraine.*

Methods. *A cross sectional study was conducted at a tertiary care teaching hospital. All the prescribing details including patient's demographic details, diagnosis, details of drug therapy (drug name, dose, duration, and frequency) were recorded. Rationality of prescription was assessed using the WHO core drug prescribing indicators and the pattern of severity of migraine was assessed using MIDAS scoring system.*

Results. *Out of 85 patients, 71 were female (83.5%), mostly around 21-30 years of age, and 27 (31.7%) patients had other comorbidities. Naproxen was the most commonly used NSAID for termination of acute migraine attack (15.3 %). The most common drugs prescribed for prophylaxis included beta adrenergic blockers (Propranolol, 14.66%), antidepressants (Amitriptyline, 9.33% and Fluoxetine 3.33%), and antipsychotics (Prochlorperazine, 4.66%). Domperidone (17.30%) was the most commonly prescribed antiemetic. Prescription of triptans was low (2.66%) with Rizatriptan as the most commonly prescribed triptan.*

Conclusions. *The current study revealed that further improvements are required in prescribing practices especially in average number of drugs per prescription, prescription of drugs with generic names, and prescription of drugs of the essential drugs list.*

KEYWORDS: DALY; MIDAS Score System; migraine; WHO Prescribing Indicators.

Introduction

Migraine is a primary, heterogeneous headache disorder characterized by recurrent, very painful and long duration headache that is moderate to severe as compared to other types of headache [1]. Typically, migraine is unilateral, pulsatile, and lasts for a few hours to 3 days. Associated symptoms may include nausea, vomiting, and increased sensitivity to light, sound or smell. The pain is generally worsened by physical activity. Up to one-third of the affected people experience the aura, which is a short period of visual disturbance, signals that headache will occur soon. Occasionally, it occurs with little or no headache following it [2].

Though tension headache is the most common type of headache, migraine is the commonest headache complaint that is presented in clinical practice and is the leading cause of headache related disability in the world. It affects approximately 13% of adults in the US and its prevalence ranges between 12% and 20% in various countries around the world [3]. Being more common in females than males, 19% and 7% prevalence, respectively [4], it's Disability Adjusted Life Year (DALY) showed the maximum burden among women in the age of 30-34 years [5]. Over 70% of migraine sufferers have a positive family history, and approximately 75% of the precipitating factors include environmental exposure, travel, education, or use of contraceptives [6].

While managing any case of headache, specific type must be ascertained using the International Classification of Headache Disorders (ICHD) criteria before assessing the response or refractoriness to any specific treatment [7]. For termination of acute attack of migraine, the commonly used pharmacotherapeutic options are nonsteroidal anti-inflammatory drugs (NSAIDs), 5HT 1B/1D receptor agonists, and dopamine receptor antagonists. For prophylaxis, beta blockers, antidepressants, anticonvulsant, and flunarizine are used. In addition to these

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there are the new drugs approved by the FDA in 2018 including monoclonal antibodies that target the CGRP pathway like Erenumab, Fremanezumab, and Galcanezumab; and Ubrogepant which is a calcitonin gene- related peptide receptor antagonist. Ubrogepant is used for immediate treatment of migraine with or without aura.

Because of a boost in marketing of new drugs and variations in pattern of prescribing and consumption of drugs there is an increasing concern about delayed adverse effects, cost-effectiveness of drugs, and volume of prescription [8]. Therefore, prescription patterns for treatment of migraine needs to be monitored. Further, inappropriate drug use has occurred for as long as medicines have been available. Several choices of therapy are available in treating patients with modern medicines which might be one reason to increase the number of irrational medicine treatment encounters and ultimately, poor patient outcomes. Common drug use problems include: choosing incorrect medicines, polypharmacy, prescribing the incorrect dose, prescribing medicines that cause adverse drug reactions (ADRs) or drug interactions, and prescribing drugs by brand names which increases the cost of treatment [9]. An inappropriate prescribing pattern by doctors often encourages inappropriate self-medication by patients because of the asymmetry of medical information [10]. The attitude today is the root on which the future grows. Hence, it is generally agreed that the teaching hospitals have a special responsibility to society to promote rational prescribing by their staff and, through them – the future generations of doctors [11]. Further, to increase prescription quality and improve the rationality of drug use, we need to investigate the subjective and objective factors that affect doctors' prescription patterns [12]

Therefore, the present study was planned to assess the current trends in the prescribing pattern of anti-migraine drugs and to evaluate the distribution of severity of migraine among patients of migraine attending the outpatient Neurology Department at a tertiary care private hospital in Jaipur, Rajasthan.

Methods

A cross sectional study was conducted in the Department of Pharmacology in collaboration with the Department of Neurology in Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan in June 2020 – March 2021. The study was undertaken after approval from the Institutional Ethics Committee and an informed consent was obtained from the participants before enrolling them into the study. All patients of any gender and age >18 years attending the Neurology OPD and diagnosed with migraine according to the International Headache Society Classification characterized by presence of any two of the following criteria: at least unilateral pain, throbbing pain aggravated by movement, moderate or severe intensity, or accompanied by either nausea/vomiting or photophobia/phonophobia, were included in the study. Patients with recent history of CNS infection or any major medical illness such as malignancy, autoimmune disorder or co-existent neurological disorder, or a case where an attending physician believes any other non-migraine diagnosis to be more likely, or a patient not willing to give an informed written consent were excluded.

Data collection

All the prescribing details from each prescription were recorded in the case history form. The information included patient's demographic details (name, age, sex), diagnosis, details of drug therapy (drug name, dose, duration, and frequency).

Study tools

1) Rationality of prescription was done by using the WHO prescribing indicators. The prescribing indicators include average number of drugs per encounter, percentage of drugs prescribed by generic name, percentage of encounters with antibiotics prescribed, percentage of encounters with an injection prescribed, percentage of drugs prescribed from essential drug list or formulary.

2) The Migraine Disability Assessment test (MIDAS): The MIDAS questionnaire was put together to assess the impact headaches have on one's life. Table 1 details the MIDAS scoring.

Data was collected and tabulated using MS Excel 2007 and was checked for normalcy before analyzing. Qualitative data was presented as percentages and proportions.

Table 1. MIDAS grade, definition, and MIDAS score

MIDAS Grade	Definition	MIDAS Score
I	Little or no disability	0-5
II	Mild disability	6-10
III	Moderate disability	11-20
IV	Severe disability	21+

Results

In the present study, 85 patients with a diagnosis of migraine were recruited. Most of the patients were female (83.5%), around 21-30 years of age (31.7%), and 29.4% had a co-morbidity. The description of the study participants is presented in Table 2.

The severity of migraine was assessed using MIDAS scoring system (Migraine Disability Assessment) in which 45 (52.94%) were found to have moderate degree of migraine and 18 (21.17%) had aura. Description of severity of migraine among the study population is presented in Fig. 1a and 1b regarding the presence or absence of aura among the study population. Out of 85 patients, little disability was observed in 8.23% patients, mild in 21.12%, moderate in 52.94%, and severe in 17.71% patients.

Table 2. Description of the study participants (n=85)

Variables	Frequency (n)	Percent (%)
Gender		
Male	14	16.4%
Female	71	83.5%
Age (in years)		
10-20	7	8.2%
21-30	27	31.7%
31-40	24	28.2%
41-50	20	23.5%
51-60	5	5.8%
61-70	2	2.35%
>70	0	0%
Comorbidity		
Yes	25	29.4%
No	60	70.5%
Pattern of co-morbidities		
Benign Paroxysmal Positional Vertigo [BPPV]	1	4%
Agitated Depression	4	16%
Allodynia	3	12%
Depression	6	24%
Diabetes Mellitus	2	8%
Head Injury	4	16%
Hypertension	3	12%
Hyperprolectenimia	1	4%
Lumbar Prolapsed Intervertebral Disc [PIVD]	1	4%

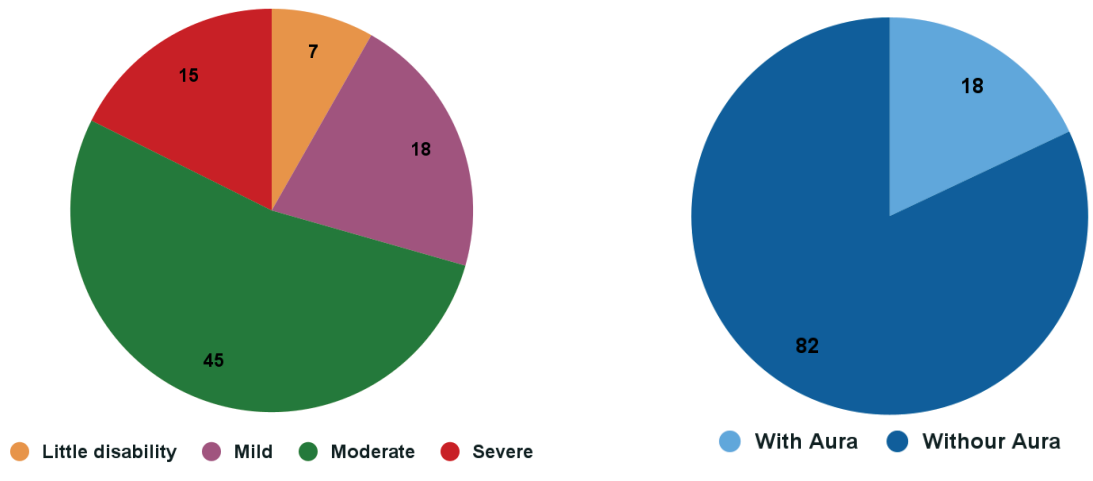

Fig. 1. *a) Severity of migraine and b) Presence of aura among the study participants (n=85).*

Out of 85 patients, 29.4% patients had comorbidities which included depression in 24%, head injury in 16%, agitated depression in 16%. alodynia (12%), hypertension (12%), diabetes mellitus, benign paroxymal positional vertigo [BPPV], hyperprolectenimia, and lumbar prolapsed intervertebral disc [PIVD]. The distribution of co-morbidities among the study participants is presented in Fig. 2.

Table 3 and Fig. 3 describes the pattern of prescription of drugs for managing migraine among the study participants. The main drug class prescribed for controlling acute attack was NSAIDs (17%), while Propranolol (14.66%) was the mainstay of migraine prophylaxis. The most common NSAID used was Naproxem followed by Etoricoxib. Antiemetics were prescribed to 17.3% patients and included D2 receptor antagonist, Domepridone in all cases. In 8% patients, antipsychotics were prescribed; Prochlorperazin in 4.66% and Olanzapine in 3.33% patients. Antidepressants were prescribed in 12.66% patients (Amitryptyline in 9.33%, and Fluoxetine in 3.33%), antiepileptics in 5.33% (Pregabalin in 4%, Topiramate in 0.60%), proton pump inhibitors (Omeprazole) in 2% patients, calcium channel blockers (Flunarazine) in 7.33 %, and anxiolytics (Clonazepam) in 2% of patients. Other miscellaneous drugs prescribed to the study patients included Calcium citrate+vitamin D3 (8%), Cyproheptadine+sorbitol+tricholine citrate (0.60%), Thiocolchicoside (2%), and Magnisium+Riboflavin (0.60%).

The observed values of the core drug prescribing indicators as compared with the WHO standard values are presented in Fig. 4. The observed average number of drugs per encounter were 3.67; the percentage of drugs prescribed by generic name and percentage of encounters with antibiotics prescribed were 0% each; 50.6% of the prescribed drugs were from the essential list, and 0.003% of the encounters were with an injection prescribed.

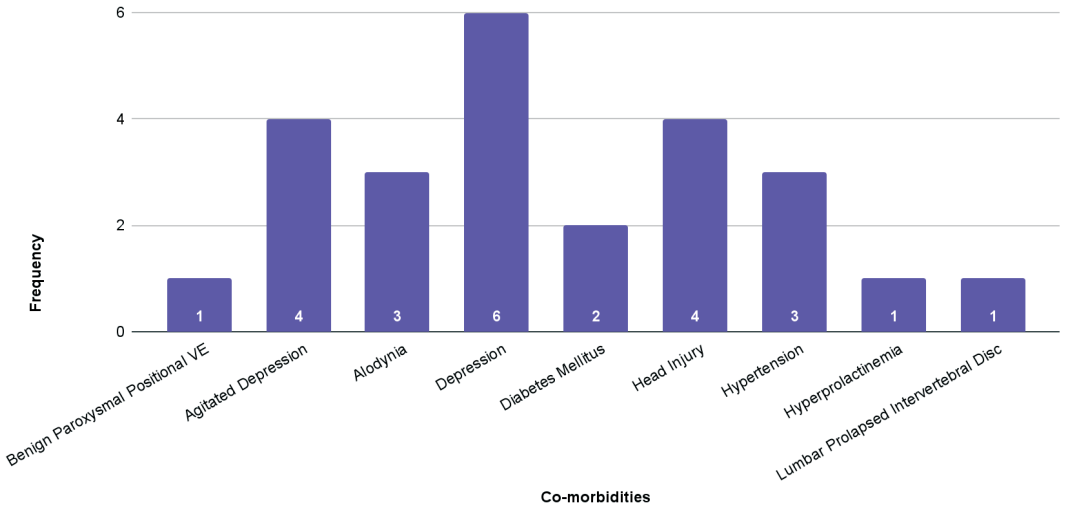

Fig. 2. *Description of co-morbidities among the study participants (n=25).*

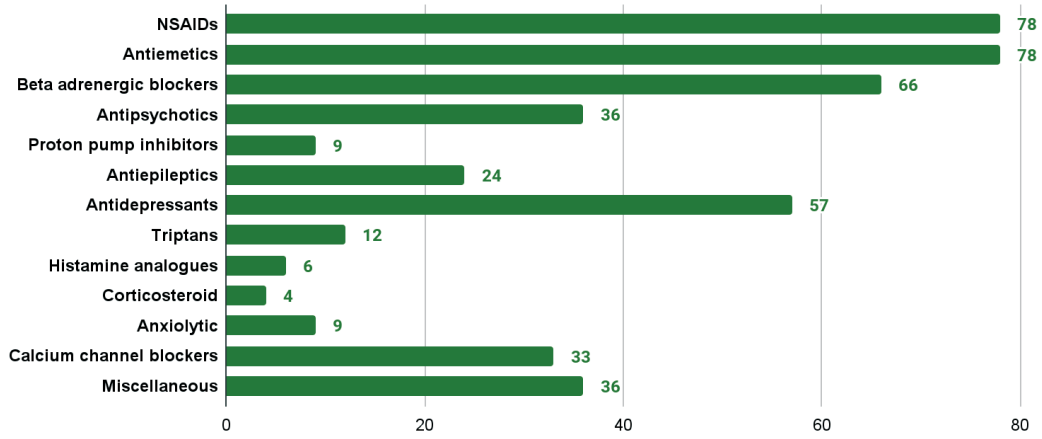

Fig. 3. *Prescription pattern of drugs for migraine among the study participants.*

Table 3. Prescription pattern of drugs for migraine among the study participants

S. No.	Drug class	Drugs	Number	Individual %	Total	Total %
1	NSAIDs	Naproxen	69	15.30%	78	17.30
		Etoricoxib	9	2%		
2	Antiemetics: D2 receptor antagonist	Domperidone	78	17.30%	78	17.30
3	β-adrenergic blocker	Propranolol	66	14.66%	66	14.66
4	Antipsychotics	Prochlorperazine	21	4.66%	36	8
		Olanzapine	15	3.33%		
5	Proton pump inhibitors	Omeprazole	9	2%	9	2
6	Antiepileptics	Pregabalin	18	4%	24	5.33
		Topiramate	3	0.60%		
		Divalproex sodium	3	0.60%		
7	Antidepressant	Amitriptyline	42	9.33%	57	12.66
		Fluoxetine	15	3.33%		
8	Triptans	Rizatriptan	12	2.66%	12	2.66
9	Histamine analogue	Betahistine	6	1.33%	6	1.33
10	Corticosteroid	Methylprednisolone	1	0.22%	4	0.82
		Prednisolone	3	0.60%		
11	Anxiolytic	Clonazepam	9	2%	9	2
12	Calcium channel blocker	Flunarizine	33	7.33%	33	7.33
13	Miscellaneous	Calcium citrate + vitamin D3	21	4.66%	36	8
		Cyproheptadine + sorbitol + tricholine citrate	3	0.60%		
		Thiocolchicoside	9	2%		
		Magnesium + Riboflavin	3	0.60%		

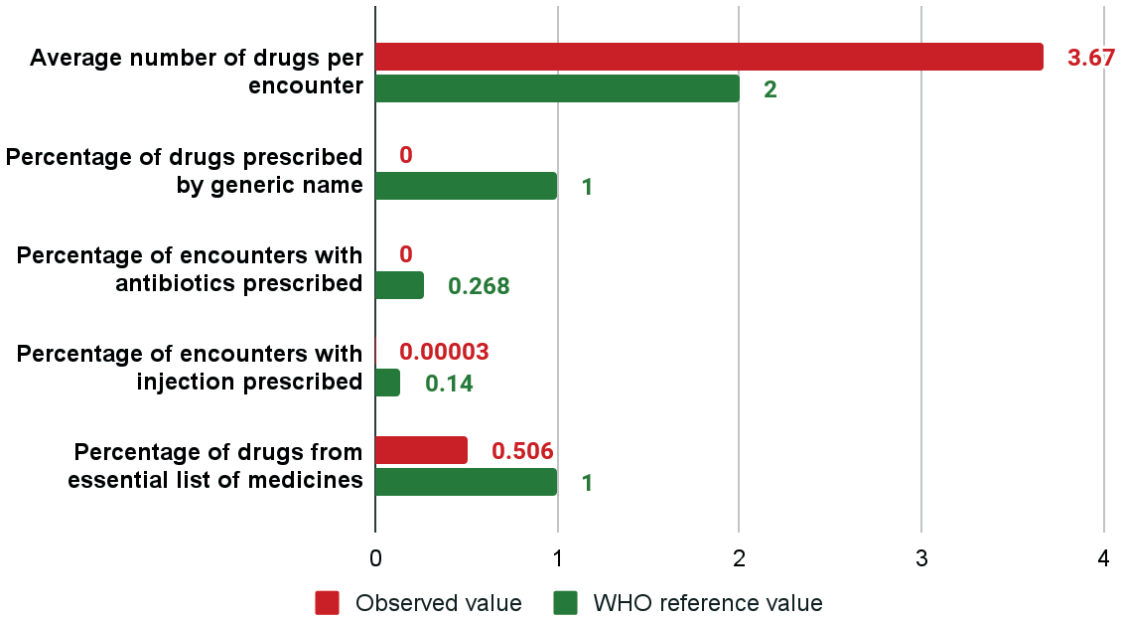

Fig. 4. *WHO Prescribing Indicators.*

Discussion

Migraine is a headache disorder characterized by throbbing pain or a pulsating sensation, usually on one side of the head. It is often accompanied by nausea, vomiting, and extreme sensitivity to light and sound. Migraine attacks can last for hours to days, and the pain can be so severe that it interferes with daily activities. The prevalence of migraine is commonly high in females of age group 21-30 years. The study was aimed to assess the current trends in the prescribing pattern of anti-migraine drugs and distribution of severity of migraine among the patients of migraine attending the outpatient Neurology Department at a tertiary care private hospital in Jaipur, Rajasthan.

It was established that the majority of the patients were females. Women reported episodic pain for a longer time and more frequent chronic pain than men. This may often result due to changes in estrogen levels. Since estrogen controls chemicals in the brain that affect the pain sensation, therefore a drop in its level can trigger a headache. Hormone levels change for a variety of reasons including menstrual cycle, pregnancy, menopause, use of oral contraceptive pills, and hormone replacement therapies.

In the study, the most common comorbidity among the study patients was depression or agitated depression. Migraine without an aura was present in two-third patients of this study. Migraine without aura is the commonest presentation in both Indian and western studies. However, in a study conducted by Mukhopadhyay et al [2] the prevalence of migraine with and without aura was reported to be 68% and 30%, respectively.

The mean MIDAS score in the study suggested that the majority of the study participants were suffering from mild to moderate migraine (grade 2 and grade 3). This is contrary to a study by Jawed et al [13], which reported that the majority of migraine patients had severe disability. Many studies have proved that the MIDAS score often correlates with a physician's assessment of migraine and is a useful tool for establishing the level of care and treatment required. Its use may improve physician-patient communication about headache-related disability and may favorably influence healthcare delivery for migraine patients. The MIDAS score indicated that in the present study, moderate disability was present in the majority of the study patients. Genetic, hormonal, psychological and other lifestyle factors might underlie these differences in MIDAS score between different families and individuals in the same family [14]. Epidemiological factors are also known to play a significant role and MIDAS scores variations have been observed across different educational levels and socio_ economic status. An increased awareness may result in avoiding the precipitating triggers and seeking appropriate and timely treatment in the educated people. Also, low socioeconomic status is likely to cause more stress and a difficult living and working environment, thus triggering an acute episode of migraine. Psychological factors were also significant in migraine disability as observed in a study showing MIDAS scores to be worse in depressed patients [2].

NASIDs were the most common class of drugs to terminate acute attack in the study and Naproxen was the most commonly prescribed analgesic among NSAIDs. These findings are similar to Khan et all [15]. Similarly, a study by Sumelathi et al [1] also states that NSAIDs are predominantly effective in both acute and chronic attack of migraine. NASIDs are the most commonly used due to their wide availability as over the counter drugs and their pharmaco-economic advantages. Kefee et al [16] reported in their study that Paracetamol was primarily used in Karachi because they provide an early symptomatic effect, thus improving the treatment acceptability by patients. However, NSAIDs may cause some serious adverse effects, most common gastrointestinal like gas, feeling bloated, heartburn, stomach pain, nausea, vomiting, diarrhea and/or constipation. These gastrointestinal symptoms can generally be prevented by taking the drug with food, milk, or antacids. NSAIDs also can induce different forms of renal injury and hepatic side effects. Long term use and an inappropriate high dose may cause high risk to all these adverse drug reactions.

However, triptans are most commonly used in developed countries for termination of acute and chronic attack of migraine (Germany, USA, Australia) [1].

Triptans are considered as first-line therapy for moderate to severe migraine and also mild to moderate migraine in selective cases [4]. It was established that the most commonly prescribed triptan was Rizatriptan. However, only 2.66% triptans were prescribed in this study. According to US National Surveillance Studies (2009), triptans are the primary pre-

scribed drugs and Rizatriptan showed the major share among all triptans. The findings of the present study are also similar to these observations except for low rates of triptan use. Shao et al [8]. suggested that reduced effectiveness in patients with late attacks may have played a role in lower frequency of triptans use. Additionally, given that Sumatriptan is contraindicated in common conditions including cardiovascular disease and pregnancy, the appropriateness of its use may be narrower than was expected previously. Shao et al [8] also believed that frequent occurrences of adverse effects in more than half of the patients after triptan administration may have led the physicians to avoid their use. Individual factors such as previously reported poor response to triptans by patients, physician's unfamiliarity with medication and their high cost may also contribute to low use. The characterization of such details in future studies will further elucidate the extent to which triptan prescription practices are deviated from guidelines, potentially allowing a more targeted solution to this problem. Further observations on whether opiates are being prescribed as first line treatment or rescue therapy and noting the eligibility of patient populations when commenting on levels of triptan therapy may also be helpful.

Beta adrenergic blockers, antipsychotics, and tricyclic antidepressants were the frequently prescribed medicines after NSAIDs. Depression is commonly present as one of the commonly associated factors of migraine. Hence, these medications are considered as better choices after NSAIDs. These findings are consistent with the guidelines that recommend beta-blockers to be prescribed to patients with both migraine and hypertension, and antidepressants – to patients with both migraine and depression [7].

In this study, antiemetics have also been prescribed along with NSAIDs. The literature indicates that patients of migraine are hypersensitive to dopamine that is important in causing some of the premonitory symptoms of migraine such as nausea and vomiting. It is established that dopamine receptor over sensitivity also is significant in pathogenesis of migraine. This may explain the use of dopamine receptor blockers like domperidone in the present study. Domperidone is a peripherally acting dopamine antagonist used for gastric motility disorder and nausea. It is less expensive, easily tolerated and is safe and efficacious in migraine treatment. Other drugs like Metoclopramide and Prochlorperazine can also be used as monotherapy for acute migraine headaches as these are also dopamine receptor antagonists and have antiemetics action.

In this study, an average of 3.6 medicines were prescribed per prescription. This finding is greater than the standard value recommended by the WHO, which is less than 2 medicines per prescription. Similar findings were reported in a study by Aravamuthan et. al [17]. This observation may be due to the fact that most of the developing countries, including India are experiencing an epidemiological shift in the disease burden of both communicable and chronic diseases. Consequently, poly-pharmacy has become more prevalent since healthcare professionals have to treat several diseases concurrently in a patient. However, this shift towards polypharmacy may result in an increased risk of drug interaction, low adherence to treatment, dispensing errors, and increase therapy cost. A relationship has been established between polypharmacy and chronic polypharmacy that is prescription of multiple medicines is a predisposing factor to adding further drugs.

The prescription of drugs in generic names ensures rational use of drugs and reduces the cost of treatment. In this study, no drug was prescribed with generic names. This is very low as compared to other studies and is even lower than Ghana, Lebanon, Nepal and Pakistan (2.9% to 65.0%) and much higher indicators (75-99.8%) of generic prescription have been reported from Bangladesh, Cambodia, Ethiopia, and Tanzania [18]. Prescription of drugs in generic name may help in controlling drug costs in the healthcare service and decrease the influence of medical marketing on prescription.

The findings from this study show that no antibiotics were prescribed as compared to the WHO standard that ranged 20-26.8%. There is huge variation in this finding among other studies in India by Hazra et al. (72.8%) [18].

Percentage of encounters prescribed with injection were 0.003%. This is less than the standard WHO range (13.4-24.1%). Since the present study was done for out patients who were otherwise in optimal state health and most of the patients had mild-moderate migraine, this may be the reason for low rate of injection usage. These findings are comparable to that of Hazra et al. (8%) [18] but are very low as compared to other regions, South Ethiopia (38.1%) and Uganda (48%) [19]. The lower rate of injections use would reduce the incidence of blood borne pathogenic infection,

reduce the transmission of HIV infection, and reduce the cost of treatment, which in turn decreases the economic burden on the patient and eventually improves compliance of the patient to the treatment.

Thus, the study reported that the median value of the percentage of medicines prescribed from the essential medicine list was 50.6% that was half of the standard value suggested by the WHO. These values are also lower as compared to the other countries such as Ethiopia (99%), South Ethiopia (99.6%), and Nepal. This indicator helps in measuring the degree to which practices conform to the current National List of Essential Medicine (NLEM) of 2019. Following the essential drug list guarantees treatment of the principal diseases of the population besides controlling overall cost of medications.

Conclusions

The current trends in prescription pattern of anti-migraine drugs observed were: Naproxen was the most commonly used NSAID for termination of an acute migraine attack and for prophylaxis; beta adrenergic blockers (Propranolol), antidepressants (Amitriptyline), and antipsychotics (Prochlorperazine) were prescribed the most. Domperidone was the most commonly prescribed antiemetic. Prescription of triptans was low (2.66%) with Rizatriptan as the most commonly prescribed triptan. This study revealed that further improvements are required in prescribing practices especially in average number of drugs per prescription, prescription of drugs with generic names, and prescription of drugs of the essential drugs list.

Recommendations: Continuous education and training of physicians regarding rational use of drugs should be implemented and monitored so that the required changes in prescribing become sustainable. Further prospective analytical studies should be conducted on a large population with strict observation and follow up focusing largely on quality of life, adverse effect profiles of the drugs, compliance, and cost of treatment.

Limitations

Since the study was conducted during COVID pandemic, the number of cases attending the OPD was less than expected and only a cross-sectional study was carried out. Therefore, follow-up data, comparative analysis and tests of significance could not have been applied. We enrolled only adult patients from Neurology OPD; further research may include patients of all ages and from other departments as well.

Author's Contributions

Gopesh Soni, Anusha Vohra, Priyanka Rathi – conceptualization; *Gopesh Soni, Anusha Vohra, Prerana Shiv Goswami, Priyanka Rathi* – methodology; *Gopesh Soni, Anusha Vohra, Prerana Shiv Goswami, Shipra Jain, Priyanka Rathi* investigation, formal analysis, data curation, writing – original draft, writing – reviewing and editing.

СУЧАСНІ ТЕНДЕНЦІЇ ПРИЗНАЧЕННЯ ПРОТИМІГРЕНОЗНИХ ПРЕПАРАТІВ ПАЦІЄНТАМ З МІГРЕННЮ В УНІВЕРСИТЕТСЬКІЙ ЛІКАРНІ ТРЕТИННОГО РІВНЯ

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Вступ. *Невідповідна схема призначення протимігренозних препаратів лікарем часто може спонукати пацієнтів до самолікування через асиметричність доступної медичної інформації.*

Мета *дослідження – оцінити сучасні тенденції в призначенні протимігренозних препаратів, раціональність їх призначення та тяжкість перебігу мігрені у пацієнтів.*

Методи. *Перехресне дослідження було проведено в університетській лікарні третинного рівня. Вивчалися всі відомості про призначення, включаючи демографічні дані пацієнта, діагноз, деталі медикаментозної терапії (назва препарату, доза, тривалість та частота прийому). Раціональність призначення ліків оцінювалася з використанням основних індикаторів призначення ліків ВООЗ, а характер тяжкості мігрені – за допомогою системи оцінки MIDAS.*

Результати. *З 85 пацієнтів 71 були жінки (83,5%), переважно у віці 21-30 років, а 27 (31,7%) пацієнтів мали інші супутні захворювання. Напроксен був найбільш часто використовуваним НПЗП для припинення гострого нападу мігрені (15,3 %). Найпоширенішими препаратами, які призначали для профілактики, були бета-адреноблокатори (пропранолол, 14,66%), антидепресанти (амітриптилін, 9,33% і флуоксетин 3,33%) та нейролептики (прохлорперазин, 4,66%). Домперидон (17,30%) був найбільш поширеним протиблювотним засобом. Призначення триптанів було низьким (2,66%), при цьому найчастіше призначали різатриптан.*

Висновки. *Дане дослідження показало, що необхідні подальші вдосконалення практики виписування рецептів, особливо щодо середньої кількості ліків за рецептом, призначення ліків із загальними назвами та призначення ліків із переліку основних лікарських засобів.*

КЛЮЧОВІ СЛОВА: DALY; система оцінювання MIDAS; мігрень; індикатори призначення ВООЗ.

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RETROSPECTIVE ANALYSIS OF GENDER-AGE STRUCTURE AND COMORBID PATHOLOGY OF PATIENTS WITH VIRAL AND BACTERIAL PNEUMONIA ASSOCIATED WITH COVID-19

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Background. *In December 2019 first case of COVID-19 was first registered in Wuhan, Hubei province, China. This infectious disease primarily causes respiratory tract infection, but can also affect the other organs and systems.*

Objective. *In this study, the features of the gender-age structure and comorbid pathology of the patients with viral and bacterial pneumonia who were treated in inpatient department in the period from September to December 2020 are summarized.*

Methods. *The research was conducted in Ternopil Municipal Hospital No. 3, Ternopil, Ukraine. Clinical cases of 262 patients with viral and bacterial pneumonia associated with COVID-19 were studied retrospectively.*

Results. *Both men and women has been affected by this pathology in Ternopil region with the same frequency in contrast with the established fact that men are less resistant to infections that women. Most of the patients ranged in age from 51 to 70 years, however, a fair number of patients were over the age of 70 years. Concomitant pathology was diagnosed in 65.5% of the patients with coronavirus infection. Coronary heart disease (34.5%) is leading in the structure of comorbid conditions.*

Conclusions. *During the COVID-19 pandemic, timely diagnosis and medical care of the patients over 50 years of age is of great importance. The analysis of concomitant pathology proves that the people with cardiovascular pathology are in the increased risk group.*

KEYWORDS: viral and bacterial pneumonia; COVID-19; age; comorbidity; cardiovascular system.

Introduction

More than 238 million people have been infected and nearly 5 million have died worldwide since the beginning of the coronavirus pandemic [1]. This infectious pathology has become not only a medical but also an economic and social problem for many countries including Ukraine [2, 3]. Nowadays, Ukraine, like the rest of the world, continues to fight COVID-19. Every day the officials of the Ministry of Health report the number of new cases of infection, the number of fatalities, of those who recovered, and of vaccinated people. Although, coronavirus infection, which has spread to the whole world, has not ruled out the possibility of contracting the other respiratory viral infections the attention to latter has decreased somewhat. Over the last decades, seasonal rises in the incidence of influenza and acute viral respiratory infections have been regularly registered in our country, the etiological structure of which included certain strains of coronaviruses along with parainfluenza viruses, rhinoviruses, RS viruses [4, 5].

Back in 2017, domestic and world researchers noted that coronaviruses cause epidemic outbreaks of varying intensity, the peak of which occurs during the period of maximum circulation of the influenza virus (December-January, March-April, sometimes October-November). The number of infected people among the susceptible individuals during the outbreaks can be quite significant which indicates high contagiousness of this pathogen. The duration of outbreaks varies on average from 1 to 3 months depending on the coronavirus strain, the number of susceptible individuals and their age. However, this relates to the best studied strains of human coronavirus: HCoV-229E, HCoVOC43, HECoV, and SARS-CoV [6].

The epidemiological analysis of the 2019–2020 season confirmed the validity of these statements regarding the current coronavirus COVID-19. However, the emergence of the

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second wave of the coronavirus pandemic, which began in August–September 2020, somewhat changed the epidemic stereotype. Nevertheless, the increase in the number of inpatients and severe cases of coronavirus infection in the period from February to March 2021 fits into the general peculiarities of the epidemiology of coronavirus infection. According to many researchers, the increased detection of patients with coronavirus infection in the summer months may be due to greater availability and number of tests [4, 6].

Methods

The research was conducted in Ternopil Municipal Hospital No.3, Ternopil, Ukraine. The clinical cases of 262 patients with viral and bacterial pneumonia associated with COVID-19 were retrospectively studied. These patients were treated in a specialized department from September to December 2020. This period had been chosen due to the epidemic data within Ukraine regarding the spread of COVID-19 infection during the epidemic season 2019–2020, which demonstrated the high contagiousness of the pathogen and the epidemic rise of the morbidity rate in the fall to spring seasons. Data related to age, sex, and concomitant pathology were processed. Data was collected and tabulated using MS Excel 2013, qualitative data was presented as percentages and proportions. The diagnosis of COVID-19 has been made by SARS clinical signs detectable by computer tomography for pneumonia and confirmed by polymerase chain reaction (PCR) tests [6,10]. The collection of the samples for PCR was performed at home or in a clinic.

Results

A total of 262 clinical cases of the patients with COVID-19 were retrospectively studied. Among patients of Ternopil Municipal Hospital No. 3, men and women were almost equally affected (50.4% and 49.6%, respectively). In terms of age, all patients were divided into 4 age groups: patients under 30 years, only 0.4%; inpatients aged from 31 to 50 years – 9.9%; patients aged from 51 to 70 years – 60.3%; and the elderly over the age of 70 – 29.4%. Their demographic details are presented in Table 1.

According to the results of processing of patients' medical records in Ternopil Municipal Hospital No. 3 concomitant pathology was diagnosed in 65.6 % of inpatients (172) with coronavirus infection. Ischemic heart disease in various manifestations (cardiosclerosis, angina pectoris, etc.) (34.9%) was leading in the structure of comorbid conditions. Hypertension of various severity (30.8%) was the second by frequency. Overall, cardiovascular pathology accounted for 44.6% of patients with COVID-19 associated viral and bacterial pneumonia. This pathology comorbid with type II DM occurred in 29.1% of patients.

As presented in Figure 1, the other comorbid conditions were much less common: chronic obstructive pulmonary disease – 3.5%, others – 2.3%.

Discussion

COVID-19 is characterized not only by seasonal differences, but also pronounced age differences [7, 8]. According to the Center for Public Health in Ukraine, the majority of patients with coronavirus infection were the elderly: the majority of patients were Ukrainians aged 30-59; 22% – people from 50 to 59 years; 21% – people from 30 to 39 years; 20% – people from 40 to 49 years.

Numerous studies of the characteristics of coronavirus infection indicate that it affects men more often than women [9]. This is due to a number of social, behavioral, physiological and genetic factors. According to the statistics, for example in China, where the new coronavirus began to spread around the world, mortality among men is more than twice as high as among women from this disease [10]. In the US two-thirds of the patients were male and this sex was associated with a higher risk of death [11]. Among patients of Ternopil Municipal Hospital No.3, men and women were affected

Table 1. Demographics of participants

Demographic details		N	%
Gender	Males	132	50.4
	Females	130	49.6
Age	Under 30 years	1	0.4
	31-50 years	26	9.9
	51-70 years	158	60.3
	Over 70 years	77	29.4

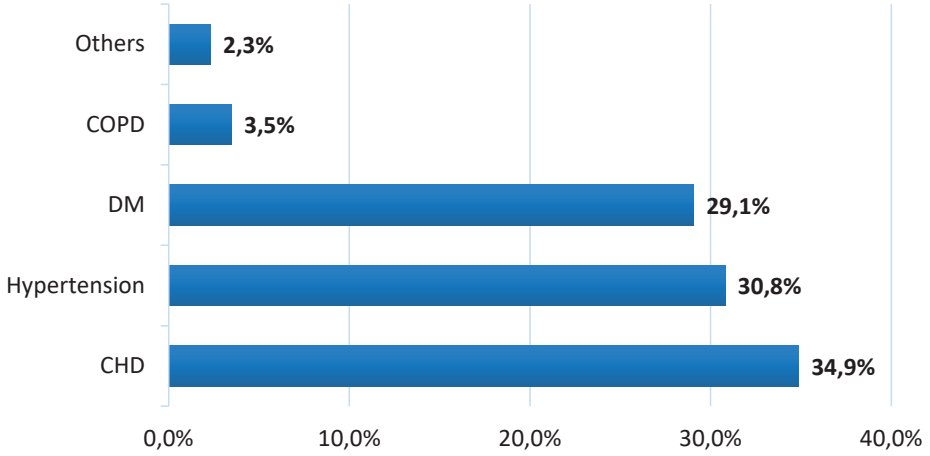

Fig. 1. *Frequency of comorbid conditions in patients with COVID-19 treated in Ternopil Municipal Hospital No.3, Ternopil, Ukraine.*

almost equally (50.4% and 49.6%, respectively), which does not align with the statistics of other countries [9, 10, 11].

According to Ternopil Regional State Administration, the age structure of the population at the end of 2019 was as follows: children under the age of 17 – 6.5%, young people under the age of 30 – 12.4%, people aged from 30 to 50 years – 32.9%, residents of the region aged 51-70 years – 33.5%, over 70 – 14.7%. Comparing the age structure of inpatients with viral and bacterial pneumonia associated with COVID-19 with the age structure of the population of the region as a whole it was established that the number of young people under the age of 30 was the lowest although this age group in Ternopil region is quite significant. This may be due to the features of the current COVID-19 pandemic that indicates mild severity in young people and a correspondingly low rate of hospitalization. On the other hand, the maximum percentage of patients was observed in the age group of 51-70 years old while in the age structure of the region's inhabitants such patients were about a third.

Analysis of clinical symptoms and severity of the disease proves a higher risk of disease in the elderly. In particular, people of age more than 50 years, especially with somatic chronic pathology, which usually complicates the course of coronavirus infection, have worse prognosis for recovery.

For comparison, we used data from the analysis of medical records of 578 French patients with coronary heart disease (CHD) [12]. According to the analysis of patients' medical records, concomitant pathology was diagnosed in 34.6% of French and 65.5% of Ukrainian patients. Among the Ukrainian patients, cardiovascular pathology dominated that corresponds with the data of French clinics. However, the frequency of these diseases in Ternopil region was much higher. The incidence of DM in both countries is similar. Chronic obstructive pulmonary disease (COPD) was more common in France and in the structure of comorbid conditions of patients in Ternopil region its incidence was almost the same.

Conclusions

According to the results of the gender-age analysis of the morbidity rate of viral and bacterial pneumonia associated with COVID-19, the following conclusions have been drawn: this pathology in Ternopil region affects both men and women with the same frequency which does not align with the statistics of other countries; which claims that coronavirus infection affects men more often. By age, the maximum number of inpatients was between 51 and 70 years old. However, a fair amount of the patients, compare to the age structure of the region, was over 70 years old. This indicates a more severe course of COVID-19 in these age groups. Cardiovascular pathology: coronary heart disease and hypertension, dominated among the comorbid pathology in patients with pneumonia. DM was the second in frequency of comorbid pathologies. Thus, the risk group for development of complicated pneumonia with underlying COVID-19 comprise people over 50 years of age, equally men and women with chronic cardiovascular disease and DM.

Conflict of Interests

Authors declare no conflict of interest.

Author's Contributions

Romanyuk Lidiya B., Volch Iryna R. – conceptualization, methodology, formal analysis, writing – original draft, writing – reviewing and editing; *Romanyuk Lidiya B., Volch Iryna R., Kravets Nataliia Y., Pyatkovskyy Taras I., Zahrychuk Oksana M.* – data curation, writing – reviewing and editing; *Romanyuk Lidiya B., Zahrychuk Oksana M.* – investigation, formal analysis.

РЕТРОСПЕКТИВНИЙ АНАЛІЗ ГЕНДЕРНО-ВІКОВОЇ СТРУКТУРИ ТА КОМОРБІДНОЇ ПАТОЛОГІЇ У СТАЦІОНАРНИХ ПАЦІЄНТІВ, ХВОРИХ НА ВІРУСНО-БАКТЕРІАЛЬНУ ПНЕВМОНІЮ, АСОЦІЙОВАНУ ІЗ COVID-19

Л.Б. Романюк, І.Р. Волч, Н.Я. Кравець, Т.І. П'ятковський, О.М. Загричук

ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ, ТЕРНОПІЛЬ, УКРАЇНА

Вступ. *У грудні 2019 року перший випадок COVID-19 був вперше зареєстрований в Ухані, провінція Хубей, Китай. Це інфекційне захворювання в першу чергу викликає інфекцію дихальних шляхів, але може вражати й інші органи та системи.*

Мета. *У даному дослідженні узагальнено особливості гендерно-вікової структури пацієнтів та коморбідної патології з вірусною та бактеріальною пневмонією у стаціонарних хворих терапевтичного відділення, котрі перебували на лікуванні у період з вересня по грудень 2020 року.*

Методи. *Дослідження проводили в міській комунальній лікарні № 3 м. Тернополя. Ретроспективно досліджено історії хвороби 262 хворих на вірусно-бактеріальну пневмонію, асоційовану з COVID-19.*

Результати. *На Тернопіллі ця патологія з однаковою частотою уражає як чоловіків, так і жінок, на відміну від відомого факту, що чоловіки менш стійкі до інфекцій, ніж жінки. Більшість пацієнтів були у віці від 51 до 70 років, проте значна кількість пацієнтів була старше 70 років. У 65,6% хворих на коронавірусну інфекцію діагностовано супутню патологію. Провідне місце в структурі коморбідних станів займала ішемічна хвороба серця (34,9%).*

Висновки. *У період пандемії COVID-19 велике значення має своєчасна діагностика та надання кваліфікованої медичної допомоги пацієнтам у віці понад 50 років. Аналіз супутньої патології, дозволяє стверджувати, що групою підвищеного ризику є особи із патологією серцево-судинної системи.*

КЛЮЧОВІ СЛОВА: вірусна та бактеріальна пневмонія; COVID-19; вік; супутні захворювання; серцево-судинна система.

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EPIDEMIOLOGY AND SEASONAL VARIATION OF APPENDICITIS – A SINGLE CENTER RETROSPECTIVE STUDY FROM NORTH-EAST INDIA

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Background. *Acute appendicitis is the most common surgical emergency presenting in emergency department, and appendectomy is one of the most common surgeries. There is a wide variation in the incidence of acute appendicitis reported for different countries, different regions, race, sex, age and also seasons.*

Objective. *The aim of this study was to understand the epidemiological trend and the seasonal variation of appendicitis in the northeast region of India.*

Methods. *It was a retrospective hospital-based study conducted in Jan 2016 – Dec 2020 at a Tertiary Care Teaching Hospital in the northeast region of India. The patient data were obtained from the Medical Record Department of the hospital and the data regarding the weather was obtained from the Indian Meteorological Department (IMD) and the website www.worldweather.com. The statistical analysis was done using SPSS software version 24.0, and the seasonal variation was studied using Kruskal Wallis test.*

Results. *Acute appendicitis affected both the sexes equally with a marginal higher incidence in males. It also had higher peak during the second and third decade of life in both the sexes. The incidence of acute appendicitis was high in the pre-monsoon and monsoon season with peak in the monsoon season.*

Conclusions. *Acute appendicitis is more common during the pre-monsoon and monsoon season, a period known for humidity, high incidence of bacterial and viral infections.*

KEYWORDS: acute appendicitis (AA), pre-monsoon season, monsoon season, Indian Meteorological Department (IMD).

Introduction

Acute appendicitis (AA) is the most common surgical emergency presenting in emergency department, and appendectomy is one of the most common surgeries [1]. AA has an increased incidence among the males as compared to the females. The lifetime risk of developing appendicitis is 8.6% for males and 6.7% for females [2, 3]. The aetiology of appendicitis is still unclear, hence various possible causes for AA are elucidated that include mechanical obstruction, inadequate dietary fiber, smoking, air pollution and familial susceptibility [3, 4, 5, 6, 7, 8, 9]. AA presents throughout the year but incidence is increased in some particular months [10, 11, 12, 13, 14, 25, 26]. Various studies were performed to determine the seasonal variation of acute appendicitis but with variable results. Some of them have concluded increased incidence in a particular month with no clear rationale behind it.

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Although numerous epidemiological studies on appendicitis, most focused on Western populations and relatively few epidemiological studies on the Asian populations. These studies were mainly concerned with the monthly variation in the incidence of acute appendicitis and the volume-outcome relationship of acute appendicitis. There is very sparse research regarding seasonal variation of acute appendicitis in Indian sub-continent and more so from the north-east region. The rationale of our study was to understand the epidemiological trend and the seasonal variation of AA in the northeast region of India.

Methods

Study Design

A retrospective hospital-based study was conducted to assess the demographic profile, incidence and seasonal variation in all patients admitted with diagnosis of acute appendicitis, who underwent operative management, in Jan 2016 – Dec 2020, at a Tertiary Care Teaching Hospital in the northeast region of India. The

pathologically proven negative appendectomy patients were excluded from this study.

Data Source and Statistical Analysis

Patient data including demographic details, operative notes and final histopathology were obtained at the Medical Record Department of the hospital. The data by Indian Meteorological Department (IMD) and the website www.worldweather.com was used to obtain information regarding the weather of the place where our study was conducted. According to the IMD there are four seasons in north-eastern region of India, i.e. winter (Jan–Feb), pre-monsoon (Mar–May), monsoon/rainy season (Jun–Sep) and post-monsoon (Oct–Dec). The raw data was entered into Microsoft Excel worksheet and analysis was performed using SPSS 24.0 software. The seasonal variation was studied regarding males and females, and inter-seasonal variation was assessed using Kruskal Wallis test. P-value less than 0.05 was taken as significant seasonal variation.

Results

During the study period a total of 405 patients underwent emergency appendectomy; all the cases were confirmed histologically as AA. There were 240 males (59.26%) and 165 females (40.74%) with male to female ratio of 1.45:1 (Table 1).

The age-specific incidence of AA followed a similar pattern for both the sexes, but males had a higher rate at virtually all ages with the highest male to female ratio in the third decade; gradually this ratio declined and was equal by the 7th decade (Fig 1). The incidence of acute appendicitis was the highest in both the sexes in the third decade (Fig 1).

The overall mean age was 25.05 years (Males – 24.68 years and females – 25.42 years). Only 6% of the cases were recorded in the first decade of life, while 65.9% occurred in the age group of 11-30 years old (Table 1).

The combined incidences of the disease were higher in the pre-monsoon and monsoon season (67.9 %, $p<0.0078$ as per Kruskal Wallis test, H statistics was 16.8029), with peaks in June, July, and August (monsoon season) corroborating with the maximum rainfall and the maximum temperature of the year (Fig. 2, 3) The incidence of the disease started declining from October (post monsoon period), with the lowest in December, followed by gradual minimal increment from January (winter season).

Table 1. Demographic trend of Acute Appendicitis

Age group (Years)	Number of cases	Percentage of the total cases	Male cases (M)	Female cases (F)	M:F Ratio
0-10	19	4.69	11	8	1.38
11-20	114	28.15	69	45	1.53
21-30	138	34.07	84	54	1.55
31-40	101	24.94	58	43	1.35
41-50	16	3.95	9	7	1.29
51-60	9	2.22	5	4	1.25
>60	8	1.98	4	4	1.00

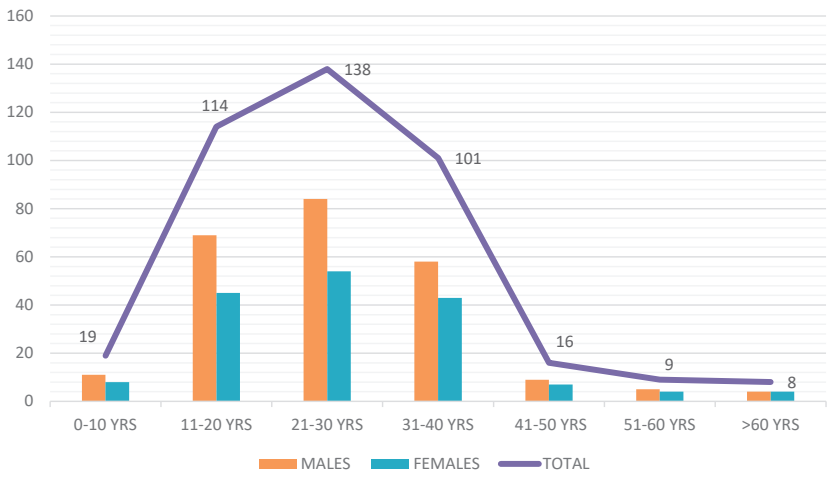

Fig. 1. *Age related distribution of acute appendicitis.*

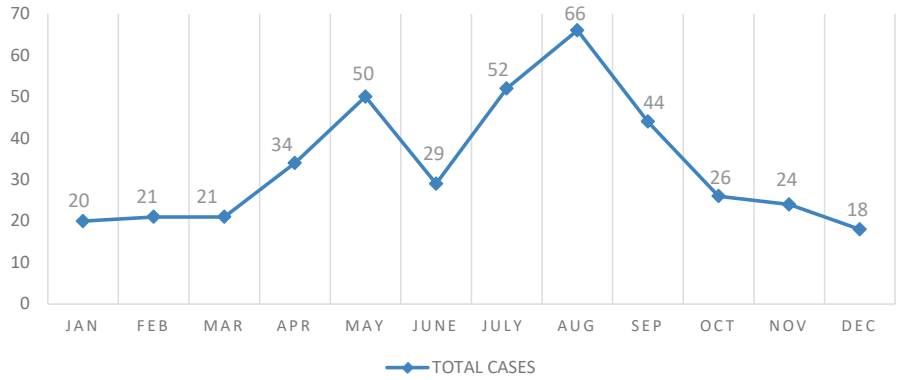

Fig. 2. *Monthly incidence of acute appendicitis in Jan 2016 – Dec 2020.*

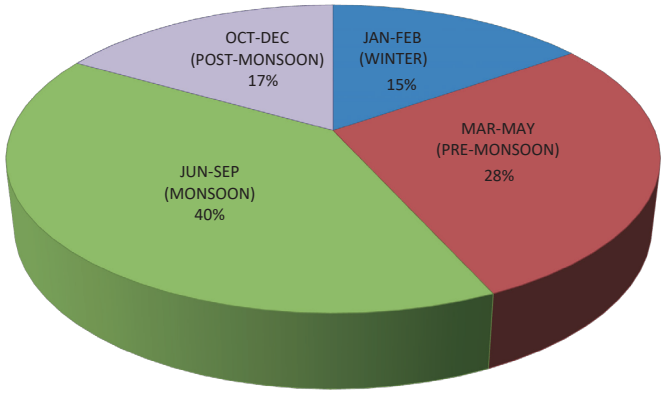

Fig. 3. *Seasonal variation of the incidence of acute appendicitis.*

Discussion

AA is a common clinical condition and appendectomy counts for about 1% of all the surgical operations [1]. It is estimated that in about 6-7% of the general population appendicitis will develop during their lifetime [15]. The incidence of appendicitis varies substantially by country, geographical region, race, sex, age, and seasons. The predisposing factors for appendicitis are multifactorial and include inadequate dietary, smoking, air pollution, infections, stress, vascular disorders and inadequate childhood breast feeding [6, 8, 9, 14, 17, 18, 19, 27].

The obstruction of the lumen due fecalith or hypertrophy of lymphoid tissue or tumorigenesis is proposed as the main etiologic factor in acute appendicitis [3, 4, 5, 6, 11, 17, 19]. The obstructive pathology in age group <40 years is due to regional lymph node enlargement secondary to infections while in patients >40 years luminal obstruction is more likely to be caused by fecalith or neoplasia because lymphoid tissue atrophies with age [4, 5, 11]. Acute appendicitis is relatively rare in infants and becomes increasingly common in childhood and early adult life [20]. The highest incidence of appendicitis is found in the second and third decades of life [2, 3]. After 30 years of age, the incidence declines, but appendicitis can occur in individuals of any age [21]. Thus, it was established that the maximum incidence of the disease is in the third decade of life.

Acute appendicitis has an increased incidence among the males compare to the females. The lifetime risk of appendicitis is 8.6% for males and 6.7% for females [2, 3]. Among the teenagers and young adults, the male to female ratio is about 3:2. After 25 years old, the ratio gradually declines until the sex ratio is equal by the mid-30s [21]. Similar findings were noted in our study cohort. There is no definite explanation for high incidence of appendicitis in males but, genetically determined differences in the immune function as well as the variation in the concentration of sex hormones can account for this difference [22]. Hormonal differences, however, do not explain the gender differences of the incidence of the disease in preadolescents and among the elderly [22].

The seasonal variation in the incidence of acute appendicitis has been discussed in many studies but there is no definite explanation for it. The heterogeneous extrinsic factors like humidity, sun radiation, bacterial and viral infections are important in the etiogenesis of appendicitis. Appendicitis is more common during the rainy reason, a period of high humidity which is the peak period of bacterial intestinal infestations and parasitic infestation. These intestinal infestations cause intestinal lymphoid hyperplasia that leads to obstruction of the appendix lumen. The reduction of sun radiation and vast fluctuations in air temperature has also been postulated in the incidence of appendicitis [3, 12, 23, 25, 26]. Air pollution has also been found to have a significant effect on the incidence of appendicitis in the summer months [9, 11]. The high ambient temperature has been found to contribute to air pollution and hence short-term exposure to air pollution may trigger appendicitis [9, 11]. The allergic reaction to pollen from flowers, palm and maize may also account for some cases of appendicitis, as the pollens trigger immunological response in the form of lymphoid hyperplasia [24]. We have found higher incidence of AA in the monsoon and pre-monsoon season in the north-east region of India, the seasons of maximum rainfall and temperatures (Fig 4).

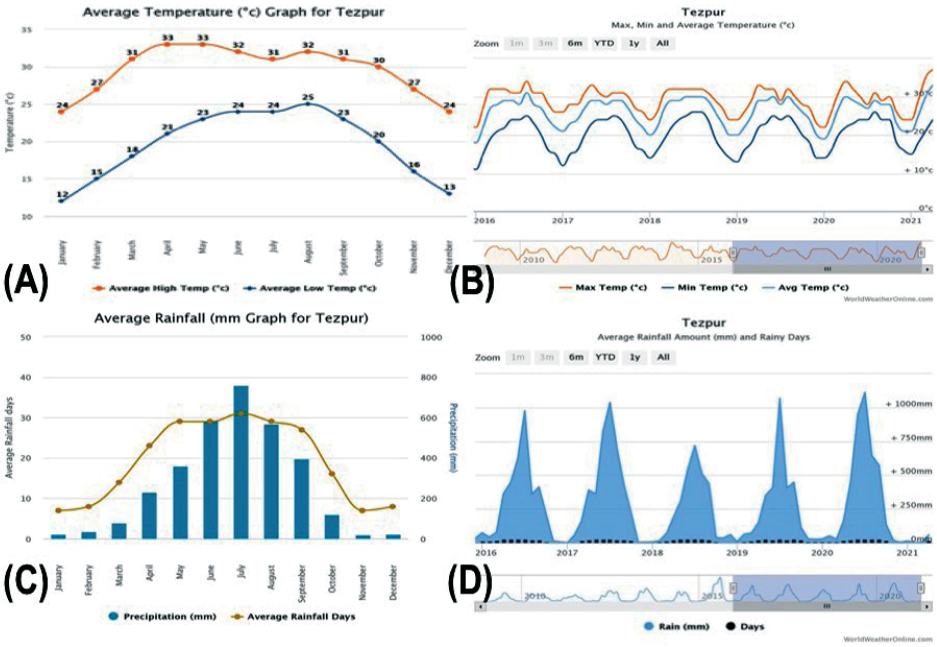

Fig. 4. *www.worldweather.com data showing weather of Tezpur, Assam, during the study period.*
(A) Average temperature graph, (B) Maximum, minimum and average temperature, (C) Average rainfall graph, (D) Average rainfall amount.

Conclusions

Acute appendicitis is still one of the most common abdominal emergencies treated by general surgeons. It affects both the sexes equally with a marginal higher incidence in the males. The disease has a higher peak during the second and third decade, the period of highly responsive lymphoreticular system. Appendicitis is more common during the pre-monsoon and monsoon season, a period known for humidity, high incidence of bacterial and viral infections.

Limitation of the study

The study population was not a true representation of the society as most of the patients were military background and the study was conducted in the north-east region of India. A larger prospective study needs to be undertaken across different geographical locations in India in order to confirm our findings of seasonal variation of AA in this sub-continent.

Conflict of Interests

Authors declare no conflict of interests.

Author's Contributions

Ranjan Kumar, Biswajit Singh Thokchom – conceptualization, methodology, formal analysis, writing – original draft, writing – reviewing and editing; *Rahul Pandey* – data curation, writing – reviewing and editing; *Sandeep Bhalla*, *Onkar Singh* – investigation, formal analysis.

ЕПЕДЕМІОЛОГІЯ ТА СЕЗОННІСТЬ АПЕНДИЦИТУ – РЕТРОСПЕКТИВНЕ ДОСЛІДЖЕННЯ З ПІВНІЧНО-СХІДНОЇ ІНДІЇ

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Вступ. *Гострий апендицит є найбільш частим хірургічним невідкладним станом у відділенні невідкладної допомоги, а апендектомія є однією з найпоширеніших операцій. Захворюваність на гострий апендицит, зареєстрована в різних країнах та різних регіонах, у людей різної раси, статі, віку, а також у різних сезонах, значно відрізняється.*

Мета. *Метою цього дослідження була оцінка епідеміологічних тенденцій та сезонних змін захворюваності на апендицит в північно-східному регіоні Індії.*

Методи. *У статті описується ретроспективне лікарняне дослідження, яке проводилося з січня 2016 року по грудень 2020 року в університетській лікарні третинного рівня медичної допомоги в північно-східному регіоні Індії. Дані про пацієнтів були отримані з медичного архіву лікарні, а дані про погоду – з Індійського метеорологічного відділу (IMD) та веб-сайту www.worldweather.com. Статистичний аналіз проводили за допомогою програмного забезпечення SPSS версії 24.0, а сезонні зміни досліджували за допомогою тесту Краскела-Уолліса.*

Результати. *Гострим апендицитом хворіли в однаковій мірі обидві статі з незначно вищою захворюваністю у чоловіків. Він також мав більш високий пік переважно на другому-третьому десятку років у обох статей. Захворюваність на гострий апендицит була високою в передмусонний сезон і сезон мусонів з піком у сезон мусонів.*

Висновки. *Гострий апендицит частіше зустрічається під час передмусонного сезону та сезону мусонів, у період з характерною високою вологістю та високим рівнем захворюваності бактеріальними та вірусними інфекціями.*

КЛЮЧОВІ СЛОВА: Гострий апендицит (АА); сезон перед мусонами; сезон мусонів; Індійський метеорологічний відділ (IMD).

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VITAMIN D3 IN TREATMENT OF OSTEOPENIC SYNDROME IN CHILDREN WITH GROWTH DISORDERS

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Background. *The efficacy of vitamin D3 agents for impaired growth of children of different cause was studied in the research. A positive effect on bone mineralization and calcium-phosphorus metabolism was evidenced. The treatment and prophylaxis charts using this drug for osteopenic syndrome are developed for children with hypothalamic-pituitary dwarfism, subdwarfism and dwarfism of constitutional genesis.*

Objective. *The aim of the research is to study the effect of calcimine and vitamin D3 in cases of impaired bone mineral density in children aged 6-18 years old with growth retardation of the hypothalamic-pituitary genesis, subdwarfism and dwarfism of constitutional origin.*

Methods. *The study involved 25 children, aged 6-18 years old with growth retardation: hypothalamic-pituitary (10 children), subdwarfism (5 children) and dwarfism of constitutional origin (10 children). The control group consisted of 20 children. The structural and functional state of bone tissue was studied using a two-photon X-ray densitometer "Lunar". In the study of calcium-phosphorus homeostasis, the level of calcium and the level of phosphorus in the blood serum were determined. Serum alkaline phosphatase levels were also studied as a marker for bone formation.*

Results. *In the examined children, there was a significant calcium deficiency at the level of the vertebrae L1–L4. The calcium content in L1 was 72.8%, L2 – 75.7%, L3 – 81.2%, L4 – 80.1%, which significantly differed from bone density in healthy children of a similar age and body weight. It was also revealed that in children diagnosed with growth retardation of the pituitary genesis, bone rarefaction was diagnosed in 100% of cases, while with subdwarfism and dwarfism of constitutional genesis these indicators were 43% and 24%, respectively.*

Conclusions. *A differentiated choice of vitamin D3 treatment, depending on the degree of osteopenia in children, allows adjusting the calcium metabolism and preventing osteoporosis in children with stunted growth. Vitamin D3 in the complex treatment of osteoporosis in children with growth impairment of different genesis normalizes calcium-phosphorus homeostasis, which increases bone mineral density and, therefore, reduces osteoporotic changes by stopping leaching of calcium from bones.*

KEYWORDS: bone mineralization; calcium-phosphorus metabolism; dwarfism; vitamin D3.

Introduction

Violation of the density and structure of bone tissue in childhood is caused by damage to the hypothalamic-pituitary system. Normally, restructuring of bone tissue is characterized by the advantage of bone formation over resorption until reaching the "peak of bone mass". Then insufficient somatotropic function of the pituitary gland causes delayed bone development: ossification nuclei develop with a significant delay and growth zones are open for a long time or close only in adulthood [1, 2]. This causes changes in bone density and impaired mineral metabolism in children with growth retardation. The situation is aggravated by the fact that the average alimentary daily vitamin D3 supply for children is more than 1.5 times less than required. To a large extent, this is due to the insufficient amount of foods containing calcium in the diet of children, socio-economic factors, as well as diverse information about the norms of daily calcium intake. However, endocrinological disorders accompanying growth retardation and a decrease in bone density with impaired mineral metabolism are crucial in this metabolic imbalance. The non-controllable intake of medications also affects, above all the complexes of microelements in the multivitamin compounds or individual preparations, i.e. magnesium, as its increase in the blood causes decreased calcium absorption. Environmental factors are also important, for example, strontium in the ter-

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ritories contaminated with radionuclides, entering the child's body acts as a calcium antagonist. Iodine deficiency territories also have negative impact not only in the formation of calcium-phosphorus homeostasis, but also in the disharmony of physical development, in particular, delayed sexual development, which due to hormonal imbalance affects the level of calcium absorption and osteogenesis. The aim of the study was to study the effect of vitamin D3 on changes in bone mineral density in children with growth retardation of hypothalamic-pituitary genesis, subdwarfism and dwarfism of constitutional genesis.

Methods

25 children aged 6-18 years old with growth retardation of hypothalamic-pituitary genesis (10 children), subdwarfism (5) and dwarfism of constitutional genesis (10) were exemined. The control group consisted of 20 children. When collecting a history of children with osteoporosis it was established that glucocorticosteroids, anticonvulsants, chemotherapeutic substances, antibiotics (tetracyclines, cyclosporins), antacids were administered. There were also: prematurity, fetal hypoxia, malnutrition, placental pathology, multiple pregnancy, short time between births, chronic diseases of women, drugs and alcohol, smoking during childbirth. The study of the structural and functional state of the bone tissue was carried out using a two-photon X-ray densitometer "Lunar". The following parameters were used for the study: Age Matched, % – the percentage deviation of bone mineral density (BMD) in the patient, the average population indicator of the identical race, sex and age at the level of the lumbar vertebrae L1–L4; Age Matched, Z-criterion – standardized deviation from the same indicator. When analyzing the results obtained, we used reference data on the indicators of the structural and functional state of the skeletal system in children and adolescents according to V.V. Povoroznyuka et al. Statistical analysis was performed using the Microsoft Excel and Statistica 5.0 software packages. In the study of calcium-phosphorus homeostasis, the level of calcium in the blood serum was determined using titrometric and photometric methods; the level of phosphorus in the blood serum was determined using a unified method for the reduction of phosphorus. The level of alkaline phosphatase in blood serum as a marker of bone formation was also studied by a biochemical method.

Results

In the examined children, there was a significant calcium deficiency at the level of the L1–L4 vertebrae. The calcium content in L1 was 72.8%, L2 – 75.7%, L3 – 81.2%, L4 – 80.1%, which significantly differed from bone density in healthy children of a similar age and body weight. It was also revealed that in children diagnosed with growth retardation of pituitary genesis bone loss was diagnosed in 100% of cases, while with subdwarfism and dwarfism of constitutional genesis these indicators were 43% and 24%, respectively, according to the deviation (standardized deviation of the bone tissue strength index of the average population index of the Z-criterion) and the classification of osteopenia and osteoporosis in children and adolescents by A.P. Krys-Pugach [3]. Three degrees of osteopenia were identified at the L1–L4 vertebrae. It was at the first step 1.0-1.5; the second and third, respectively, 1.6-2.0; 2.1-2.5. These children had a tendency to hypocalcemia and to increase in alkaline phosphatase levels. Thus, the content of the trace element calcium in the blood was reduced and fluctuated within 1.76-2.09 mmol/L. The analysis of the level of alkaline phosphatase in the blood as a marker of bone formation showed that its content was 1.54±0.09 μmol/g/L that also indicated bone loss. When comparing the activity of alkaline phosphatase and the concentration of calcium in the blood serum, it was assumed that hypocalcemia under such conditions contribute to further leaching of calcium from the bone tissue. Therefore, creating a vicious circle, in the treatment of such children in addition to etiotropic hormonal treatment, drugs should be used for prevention of leaching of the calcium from the bones before balancing the composition of the diet, which is consistent with age-related requirements for phosphorus and calcium. Vitamin D3 in the form of the drug of Cholecalciferol increases the absorption of calcium in the intestine [4] and improves the reabsorption of phosphorus in the renal tubules, helps to maintain the proper level of calcium and phosphorus in the blood, helps to optimize calcium-phosphorus homeostasis and contributes to the normal formation and growth of bone tissue that is especially important for stunted growth in children. For grade 1 osteopenia, Cholecalciferol was prescribed in courses of 2000 IU per day for 30 days, 2 times a year with an interval of 5 months between courses. In case of degree 2 osteopenia, Cholecalciferol was prescribed in courses of

4000 IU per day for 40 days, 3 times a year with a break of 3 months between courses. In case of degree 3 osteopenia, Cholecalciferol was prescribed in courses of 5000 IU per day for 45 days, 3 times a year with a break of 3 months between courses. The effectiveness of treatment was assessed by repeated densitometric examination of the lumbar spine, 3 months after the first course of treatment, analyzing the Z-criterion. There was a tendency to an increase in the density of mineral tissue according to the Z-score by 4.34-20% in each of the lumbar vertebrae. The effectiveness of the treatment was assessed by the parameters of the content of calcium and phosphorus in the blood serum, the level of alkaline phosphatase during the second examination one month after the first course of treatment. Thus, normalization of the level of calcium and phosphorus, as well as a decrease in the level of alkaline phosphatase to the upper limit of the norm was evidenced (Table 1).

Table 1. Dynamics of blood biochemical parameters in a group of 25 children (M±m) after the introduction of Cholecalciferol into treatment

Index	Before treatment n=25	After treatment n=25	P
Serum calcium (mmol/L)	1.98±0.11	2.37±0.13	<0.05
Serum phosphorus (mmol/L)	0.93±0.05	1.1±0.06	<0.05

Discussion

The results of the study proved a positive effect of vitamin D3 in the children with decrease of growth of different genesis. According to the literature, growth hormone is one of the most important components of the hormonal system for regulating bone tissue metabolism and phosphorus-calcium metabolism. In norm the restructuring of bone tissue is characterized by the advantage of bone formation over resorption until reaching the "peak of bone mass". With insufficient somatotropic function of the pituitary gland bone development is delayed: ossification nuclei appear with a significant delay, and growth zones remain open for a long time or close only in adulthood. This causes changes in bone density and impaired mineral metabolism in children with growth retardation [1,2]. Cholecalciferol normalized the level of calcium and phosphorus as well as decreased the level of alkaline phosphatase to the upper limit of the norm that prevents osteoporosis and complies the results of studies by other authors [5, 6].

Conclusions

The differentiated approach in prescribing Cholecalciferol depending on the degree of osteopenia in children allows correcting calcium metabolism and thereby ensures prevention of osteoporosis in children with stunted growth. This is caused by the pharmacological action of cholecalciferol, i.e. regulation of calcium-phosphorus metabolism, normal formation of the bone skeleton and teeth in children and preservation of the structure of bones.

Conflicts of Interest

Author declare no conflict of interest

ЗАСТОСУВАННЯ ВІТАМІНУ D В ЛІКУВАННІ ОСТЕОПОРОЗУ У ДІТЕЙ З ЗАТРИМКОЮ РОСТУ РІЗНОГО ГЕНЕЗУ

Н.Ю. Щербатюк

ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ, ТЕРНОПІЛЬ, УКРАЇНА

Вступ. *У статті наводяться результати застосування препаратів вітаміну D у дітей із затримкою росту різного ґенезу. Продемонстровано їх позитивний вплив на мінеральну щільність кісткової тканини та кальцій-фосфорний гомеостаз. Наводяться схеми лікування та профілактики остеопенічного синдрому у дітей з гіпоталамо-гіпофізарним нанізмом, субнанізмом та нанізмом аліментарно-конституційного ґенезу. Доведено ефективність їх використання.*

Мета – *дослідження впливу використання вітаміну D при змінах мінеральної щільності кісткової тканини у дітей 6-18 років із затримкою росту гіпоталамо-гіпофізарного генезу, субнанізмом та нанізмом конституційного ґенезу.*

Методи. *Обстежено 25 дітей 6-18 років із затримкою росту гіпоталамо-гіпофізарного ґенезу (10 дітей), субнанізмом (5) та нанізмом конституційного ґенезу (10). Контрольну групу становили 20 дітей. Дослідження структурно-функціонального стану кісткової тканини проводили за допомогою рентгенівського двофотонного денситометра "Lunar". При дослідженні кальцій-фосфорного гомеостазу визначали рівень кальцію та рівень фосфору у сироватці крові. Також вивчали рівень лужної фосфатази у сироватці крові як маркера формування кістки.*

Результати. *У обстежених дітей мав місце суттєвий дефіцит кальцію на рівні хребців L1–L4. Вміст кальцію в L1 становив – 72,8%, L2 – 75,7%, L3 – 81,2%, L4 – 80,1%, що суттєво відрізняється від кісткової щільності у здорових дітей аналогічного віку та маси тіла. Також було виявлено, що у дітей, яким було виставлено діагноз затримки зростання гіпофізарного ґенезу у 100% випадків діагностовано розрідження кісткової тканини, тоді як при субнанізмі та нанізмі конституційного ґенезу ці показники становили відповідно 43% та 24%.*

Висновки. *Диференційований підхід у призначенні вітаміну D залежно від ступеня остеопенії у дітей дозволяє скоригувати кальцієвий обмін та забезпечити тим самим профілактику остеопорозу у дітей із затримкою росту. Включення вітаміну D у комплексне лікування остеопорозу у дітей із затримкою росту різного генезу нормалізує кальцій-фосфорний гомеостаз, що сприяє посиленню мінеральної щільності кісткової тканини, а отже, зменшує остеопорозні зміни за рахунок припинення вимивання кальцію з кісток.*

КЛЮЧОВІ СЛОВА: мінеральна щільність кісткової тканини; кальцій-фосфорний гомеостаз; затримка росту; вітамін D3.

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DRUG THERAPY FOR PROTEIN COMPOSITION CHANGES OF BLOOD IN HYPERTENSION AND IN CASES OF COMORBIDITY

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Background. *The binding function of serum albumin (BFSA) and its changes in various diseases in recent years are of interest to researchers. Hypertension (HT) in combination with comorbidities, including non-alcoholic steatohepatitis (NASH) and type 2 diabetes mellitus (DM) can contribute to BFSA.*

Objective. *The aim of this study is to evaluate the relationship between quantitative changes in BFSA, protein fractions and indicators of endogenous intoxication (EI) in HT in combination with NASH and type 2 diabetes and to suggest drug therapy of the disorders revealed.*

Methods. *123 patients with stage 2 HT and degree 2-3 arterial hypertension were examined; they were divided into three groups: group 1 included 28 patients without concomitant diseases, 2 – 48 patients with concomitant NASH, 3 – 47 patients with NASH and type 2 diabetes. Groups 3 and 4 were divided into two subgroups (A and B): patients of the subgroup A received basic HT therapy and additionally Antral® 200 mg 3 times a day for 60 days, B – only basic HT therapy. All patients underwent a standard clinical examination, as well as for BFSA, total protein, albumin, globulins and albumin-globulin ratio, medium mass molecules (MMM) at 280 and 254 nm and erythrocyte intoxication index (EII). The comparison group consisted of 25 healthy individuals.*

Results. *It was found out that Antral® in patients with HT in combination with NASH and with NASH and type 2 diabetes with a statistically significant decrease in BFSA, total protein and albumin, as well as with increased indicators of EI (MSM_{254}, MSM_{280} and EII) caused significant improvement in BFSA, increase of total protein, serum albumin, reduce of MSM_{254}, MSM_{280}, EII and strengthening of all correlations.*

Conclusions. *Antral® therapy in patients with HT in combination with NASH as well as NASH and type 2 diabetes causes significant increase in BFSA, serum protein fractions and decreases EI.*

KEYWORDS: hypertension; non-alcoholic steatohepatitis; type 2 diabetes mellitus; binding function of serum albumin; Antral®.

Introduction

One of the important factors in the normal functioning of all organs and systems of the human body is the stability of protein content and their role in biological fluids. Albumin as the most common protein in the body is of particular interest of all the protein fractions. Normally, its content is about 55% of all proteins, so the importance of changing its content and function is not overestimated [1, 2]. The structure of the albumin molecule determines a number of its properties; the binding function of serum albumin (BFSA) is among them; BFSA is the ability to bind and transport a significant amount of biological substances of endogenous and exogenous nature: fatty acids, nitric oxide, chlorine and calcium ions, toxins, synthetic drugs and others. Violation of BFSA can have a negative impact on the body directly and reduce the effectiveness of drug treatment in various pathological conditions [3].

Endogenous intoxication (EI) is an important indicator of homeostasis. Development of EI indicates the presence of a pathological process in the body. Dysfunction of serum albumin, BFSA in particular, may directly affect the increase of EI. In diseases that are accompanied by endotoxicosis, a significant number of metabolites accumulate in the blood; most of them belong to the medium mass molecules (MMM) [4]. The accumulation of MMM as a marker of endotoxemia is a sign of intensification of the pathological process. In addition to MMM, another important indicator of EI is the erythrocyte intoxication index (EII), which evidences the permeability of erythrocyte membranes and may indicate signs of endotoxic damage to organs and tissues [5].

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Disorders of protein metabolism with the development of EI can be caused by many diseases. However, little is known about the possibility of such changes in cases of hypertension (HT) and related comorbid conditions, in particular when combined with non-alcoholic steatohepatitis (NASH) and type 2 diabetes mellitus (DM) – a very common disease that causes systemic adverse effects on the whole body [6, 7]. In addition, they are associated with long-term use of various drugs that are mainly metabolized in the liver and can cause damage to this organ, which is the main source of protein synthesis and in particular albumin [8, 9].

Methods

The study included 123 patients with stage 2 HT and degree 2-3 hypertension in combination with diastolic heart failure FC 1–3 according to the NYHA. They were divided into three groups. Group 1 – 28 patients with HT without concomitant pathology (12 men and 16 women) aged 45-76, mean age (60.71±1.95) years. Group 2 involved 48 patients (21 men and 27 women) diagnosed with HT and concomitant NASH, aged 46-78, mean age (64.68±1.07) years. It was divided into two subgroups: 2A (27 patients) – undergoing basic HT therapy and additionally Antral® 200 mg 3 times a day for 60 days, 2B (21 patients) – only basic HT therapy.

Group 3 included 47 patients (21 men and 26 women) with HT combined with concomitant NASH and type 2 diabetes in the stage of subcompensation, aged 58-82, the average age was (68.72±0.86) years. It was also divided into two subgroups: 3A (27 patients) – in addition to basic treatment of HT and type 2 diabetes taking Antral® 200 mg 3 times a day for 60 days, 3B (20 patients) – only basic HT therapy. The comparison group consisted of 25 healthy individuals, comparable in age and sex (control group).

The duration of HT in patients ranged from 6 to 25 years. The study did not include patients with symptomatic hypertension, people who drink alcohol (more than 40 ml of ethanol per week for men and 20 ml for women), as well as those who had at the time of examination or history of acute coronary syndrome, acute disorders of cerebral circulation, cancer, viral, drug and autoimmune hepatitis, mental disorders.

The diagnosis of NASH was established according to the recommendations of the unified clinical protocol of primary, secondary (specialized) medical care "Non-alcoholic steatohepatitis" (Order of the Ministry of Health of Ukraine No. 826, dated November 6, 2014) and the recommendations of the European Association for the Study of the Liver (EASL). The functional state of the liver was examined by sonoelastography on the Ultima SM-30 device by the SWEI method to determine the stiffness of the liver parenchyma, which averaged 8.42 kPA in the patients with NASH.

All patients were determined BFSA by the method of S. I. Chager, the content of MMM at wavelengths of 280 and 254 nm and EII by the method of N. I. Gabrielyan [10]. The content of total protein, albumin, globulins in the blood serum was studied by bochemical methods and the albumin-globulin coefficient was calculated.

All patients were treated according to the criteria of the unified protocol of medical care for patients with hypertension (Order of the Ministry of Health of Ukraine No. 384, dated May 24, 2012) and the recommendations of the European Society of Cardiologists (ESC).

Patients with type 2 diabetes were treated according to the unified clinical protocol of primary, secondary (specialized) medical care "Diabetes mellitus, type 2" (Order of the Ministry of Health of Ukraine No. 1118, dated December 21, 2012).

Analysis of the obtained digital data was performed by the method of parametric Pearson correlation. The correlation dependence was considered strong at r=0.7-0.99, medium at r=0.3-0.69, and weak at r=0.01-0.29. Statistica 10 and Microsoft Excel software were used.

Results

In the control group (almost healthy individuals) indicators of BFSA, protein fractions and EI were within norm. The analysis of the correlation of BFSA with serum proteins showed a positive relationship of medium strength with the level of albumin ($r=0.68$, $p<0.05$), total protein ($r=0.52$, $p<0.05$) and albumin-globulin ratio ($r=0.69$, $p<0.05$), as well as a negative relationship of medium strength with the content of globulins ($r=-0.68$, $p<0.05$). No significant correlations were observed between BFSA and endotoxicosis indicators ($p>0.05$) (Table 1).

In patients with HT without concomitant pathology (group 1), the values of BFSA and protein fractions were close to those in almost healthy individuals. At the same time, there was a significant increase in EII and MMM_{280} concentrations ($p<0.05$). The analysis showed a positive relationship between the average

strength of BFSA with the level of albumin (r=0.45, p<0.05), total protein (r=0.38, p<0.05) and albumin-globulin coefficient (r=0,49, p<0,05) and a negative relationship of medium strength with the content of globulins (r=-0,45, p<0,05). No significant correlations of EI indicators with the content of BFSA were observed.

In patients with HT in combination with NASH (subgroup 2A) before drug therapy, a significant decrease in BFSA, total protein and serum albumin was found. In addition, there was an increase in all studied indicators of EI (p<0.05). The presence of positive relationships of medium strength of BFSA with the content of total protein (r=0.69, p<0.05), albumin (r=0.63, p<0.05) and with albumin-globulin ratio (r=0.62, p<0.05), as well as a negative relationship of medium strength with the level of globulins (r=-0.6, p<0.05). At the same time, there were significant negative correlations between the mean strength of BFSA and EII (r=-0.46, p<0.05), the concentration of MMM_{254} (r=-0.48, p<0.05) and MMM_{280} (r=-0.41, p<0.05).

Similar changes were observed in the subgroup 2B, but the strength of the relationship between BFSA and albumin, globulins and albumin-globulin ratio were slightly higher than in the previous subgroup. Regarding the level of total protein, the correlation was almost the same. EI relationships in this subgroup were also similar, but the strength of the correlation of BFSA with MMM_{254} was slightly higher, and with EII, on the contrary, lower.

In patients with HT combined with NASH and type 2 diabetes (subgroup 3A) before correction there was even more pronounced decrease in BFSA, total protein, albumin, and albumin-globulin ratio. At the same time, there was a significant increase in all studied indicators of EI (p<0.05). The presence of a positive correlation between the average strength of BFSA and the level of total protein (r=0.63, p<0.05), albumin (r=0.54, p<0.05) and albumin-globulin coefficient (r=0.56, p<0.05), as well as a negative relationship of medium strength with the level of globulins (r=-0.56, p<0.05). There was also a negative correlation of the average strength of BFSA with EII (r=-0.63, p<0.05) and MMM_{254} (r=-0.60, p<0.05) and strong with MMM_{280} (r=-0,70, p<0.05). Similar changes were observed in the subgroup 3B, but there was an increase in the negative correlation with MMM_{254} compare to the previous subgroup.

Normalization of BFSA, total protein, albumin and albumin-globulin ratio was proved to be associated with Antral® in patients of the subgroup 2A. Also, a normalization of the concentrations of MMM_{254} and MMM_{280} and a significant decrease in the level of EII compare to subgroup 2B (p<0.05) were evidenced. A strong positive relationship of BFSA with the level of total protein (r=0.84, p<0.05) was noted

Table 1. Correlation coefficients between BFSA and indicators of protein composition of blood and EI in patients with HT combined with NASH and their correction by Antral®

Indicator	Control group (n=25)	Group I (n=28)	Group II (n=48)			
			Subgroup 2A (n=27)		Subgroup 2B (n=21)	
			Before treatment	After treatment	Before treatment	After treatment
Total protein	0.52 p<0.05	0.38 p<0.05	0.69 p<0.05	0.84 p<0.05	0.72 p<0.05	0.68 p<0.05
Albumin concentration	0.68 p<0.05	0.45 p<0.05	0.63 p<0.05	0.70 p<0.05	0.73 p<0.05	0.70 p<0.05
Concentration of globulins	-0.68 p<0.05	-0.44 p<0.05	-0.60 p<0.05	-0.66 p<0.05	-0.73 p<0.05	-0.74 p<0.05
Albumin-globulin ratio	0.69 p<0.05	0.49 p<0.05	0.62 p<0.05	0.67 p<0.05	0,71 p<0,05	0.72 p<0.05
EII	-0.07 p>0.05	-0.33 p>0.05	-0.46 p<0.05	-0.62 p<0.05	-0,31 p>0,05	-0.19 p>0.05
MMM254	-0.14 p>0.05	0.01 p>0.05	-0.48 p<0.05	-0.76 p<0.05	-0,62 p<0,05	-0.65 p<0.05
MMM280	-0.29 p>0.05	-0.07 p>0.05	-0.41 p<0.05	-0.64 p<0.05	-0,38 p>0,05	-0.25 p>0.05

Note. p – statistical significance of the correlation coefficient (p<0.05).

in association with Antral®, as well as a positive relationship of medium strength with albumin content (r=0.70, p<0.05) and negative medium strength with globulin content (r=-0.66, p<0.05). Compare to the subgroup without Antral® correction, the correlation of BFSA with the level of total protein was stronger, and with the level of globulins, on the contrary, slightly lower. In addition, negative correlations were found with EII (r=-0.62, p<0.05) and MMM_{280} (r=-0.64, p<0.05); compare to the patients undergoing no treatment it changed from negative weak to medium strength, as well as a negative relationship with the content of MMM_{254} (r=-0.76, p<0.05), which changed from medium strength to strong. In subgroup 2B, all indicators did not change significantly.

The patients in subgroup 3A had a statistically significant increase in BFSA, total protein and serum albumin during Antral® treatment. There was also a significant reduction in all indicators of endotoxicosis. An analysis of BFSA correlations revealed that statistically significant strong correlations with all protein fractions occurred in cases of Antral® treatment. Thus, there was a positive relationship with the level of total protein (r=0.76, p<0.05), albumin content (r=0.81, p<0.05) and albumin-globulin ratio (r=0.78, p<0.05), as well as negative – with the content of globulins (r=-0.81, p<0.05). Analysis of the relationship of BFSA with EI showed a strong negative correlation with the level of EII (r=-0.74, p<0.05), which was stronger than in the subgroup without correction, where it was moderate. In addition, medium-strength negative correlations with the content of MMM_{254} (r=-0.69, p<0.05) and MMM_{280} (r=-0.69, p<0.05) were revealed, which compare to the subgroup without treatment were also stronger, but not significantly. The correlations in the subgroup 3B did not change significantly.

Discussion

Therefore, in patients with HT and NASH and with HT combined with NASH and type 2 diabetes, there is a statistically significant correlation of BFSA with EII, MMM254 and MMM280, which may indicate development of endotoxicosis, not excluded due to liver cell damage and systemic pathological effects of comorbid diseases [12, 13].

Since the liver is the main organ that metabolizes many toxemia products, most of which belong to medium molecular weight peptides, damage to this organ leads to an increase in MMM. In addition, in cases of development of liver disease the accumulation of free radical forms of oxygen, which in addition to promoting the increase of EI products, cause damage to cell membranes that is manifested by an increase in EII. As we can see, the changes in protein composition and endotoxicosis and

Table 2. Correlation coefficients between BFSA and indicators of protein composition of blood and EI in the patients with HT combined with NASH and type 2 diabetes and their correction by Antral®

Indicator	Control group (n=25)	Group III (n=47)			
		Subgroup 3A (n=27)		Subgroup 3B (n=20)	
		Before treatment	After treatment	Before treatment	After treatment
Total protein	0.52 p<0.05	0.63 p<0.05	0.76 p<0.05	0.69 p<0.05	0.62 p<0.05
Albumin concentration	0.68 p<0.05	0.54 p<0.05	0.81 p<0.05	0.50 p<0.05	0.55 p<0.05
Concentration of globulins	-0.68 p<0.05	-0.56 p<0.05	-0.81 p<0.05	-0.51 p<0.05	-0.54 p<0.05
Albumin-globulin ratio	0.69 p<0.05	0.56 p<0.05	0.78 p<0.05	0.53 p<0.05	0.58 p<0.05
EII	-0.07 p>0.05	-0.63 p<0.05	-0.74 p<0.05	-0.65 p<0.05	-0.65 p<0.05
MMM254	-0.14 p>0.05	-0.60 p<0.05	-0.69 p<0.05	-0.68 p<0.05	-0.63 p<0.05
MMM280	-0.29 p>0.05	-0.70 p<0.05	-0.69 p<0.05	-0.64 p<0.05	-0.60 p<0.05

Note. p – statistical significance of the correlation coefficient (p<0.05).

their relationship with BFSA are more pronounced in patients with HT combined with NASH and type 2 diabetes, which can also be explained by the processes of glycolysis of proteins, and in particular albumin, which has a direct effect on BFSA. The severity of EI syndrome in these cases may be a marker of the severity of the pathological process [14].

Antral® treatment improves BFSA and serum protein composition, as well as strengthens significant correlations with all studied indicators of protein fractions and EI. These positive changes can be explained by the anti-inflammatory and detoxifying effects of Antral® on the whole body and in particular on the function of the liver as the main protein-synthesizing organ [15, 16]. The drug has a positive effect on hepatocytes by stabilizing cell membranes and lysosomal membranes and increasing the synthesis of phospholipids. By improving the energy supply and functioning of monooxygenase systems, Antral® restores the antitoxic effect of the liver. Due to its angioprotective action by improving capillary hemoperfusion, this drug can improve microcirculation in the liver and other organs, which has a positive effect on the whole body [17].

Conclusions

In HT without concomitant diseases an increase in EII and MMM_{280} and a decrease in the strength of correlations of BFSA with the concentration of protein fractions in serum take place.

In the conditions of HT combined with NASH as well as HT with NASH and type 2 diabetes a decrease in BFSA, total protein and albumin content and increase in EI, as well as a decrease in the correlation of BFSA with albumin, globulin and albumin levels, globulin coefficient and strength increase – with the content of total protein and EI, are evidenced.

Treatment of the patients with HT with concomitant NASH with Antral® normalizes BFSA and the content of total protein and albumin, as well as MMM_{254} and MMM_{280} and significantly decreases EII. In cases of HT with NASH and type 2 diabetes a significant increase in BFSA, the content of total protein and albumin in the serum and a decrease in EI take place with the drug. All studied correlations of BFSA are enhanced under the action of the drug in both comorbid states.

Prospects for further research. In the future, it is planned to identify other effects on the changes of BFSA and development of EI in comorbid diseases associated with HT, as well as to implement the data into clinical practice.

Conflict of Interests

Authors declare no conflict of interest.

Author's Contributions

Yurii R. Dzordzo – conceptualization, methodology, formal analysis, investigation, writing – original draft, writing – reviewing and editing; *Serhiy M. Andreychyn* – data curation, writing – reviewing and editing.

МЕДИКАМЕНТОЗНА КОРЕКЦІЯ ЗМІН БІЛКОВОГО СКЛАДУ КРОВІ ПРИ ГІПЕРТОНІЧНІЙ ХВОРОБІ В УМОВАХ КОМОРБІДНОСТІ

Ю.Р. Дзьордзьо, С.М. Андрейчин

ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ, ТЕРНОПІЛЬ, УКРАЇНА

Вступ. *Зв'язувальна функція сироваткового альбуміну (ЗФСА) та її зміни при різних захворюваннях в останні роки викликають інтерес у дослідників. Гіпертонічна хвороба (ГХ) при поєднанні з супутніми захворюваннями, зокрема неалкогольним стеатогепатитом (НАСГ) і цукровим діабетом (ЦД) 2-го типу може сприяти порушенню ЗФСА.*

Мета дослідження – *дати оцінку взаємозв'язків кількісних змін ЗФСА, білкових фракцій та показників ендогенної інтоксикації (ЕІ) при ГХ у поєднанні з НАСГ і ЦД 2-го типу та запропонувати медикаментозну корекцію виявлених порушень.*

Методи дослідження. *Обстежено 123 пацієнтів з ГХ II стадії зі ступенем артеріальної гіпертензії 2-3, які були розділені на три групи. До I увійшли 28 осіб без супутніх захворювань, до II – 48 пацієнтів із супутнім НАСГ, до III – 47 осіб із НАСГ і ЦД 2-го типу. II та III групи, своєю чергою були поділені на дві підгрупи (А та Б): хворі підгруп А – отримували базову терапію ГХ та додатково препарат Антраль по 200 мг 3 рази на добу протягом 60 днів, Б – лише базову терапію ГХ. Усі хворі пройшли стандартне клінічне обстеження, а також у них досліджували ЗФСА, вміст загального білка, альбуміну, глобулінів та альбуміно-глобуліновий коефіцієнт, молекули середньої маси (МСМ) при довжині хвилі 280 та 254 нм та еритроцитарний індекс інтоксикації (ЕІІ). Групу порівняння склали 25 практично здорових осіб.*

Результати. *Встановлено, що застосування Антралю у хворих з ГХ у поєднанні з НАСГ та з НАСГ і ЦД 2-го типу на тлі статистично достовірного зниження ЗФСА, вмісту загального білка та альбуміну, а також збільшення показників ЕІ ($МСМ_{254}$, $МСМ_{280}$ та ЕІІ) супроводжується істотним покращенням ЗФСА, зростанням вмісту загального білка, альбуміну, та зниженням – $МСМ_{254}$, $МСМ_{280}$, ЕІІ й посиленням усіх кореляційних зв'язків.*

Висновки. *Лікування Антралем у хворих на ГХ в поєднанні з НАСГ та з НАСГ і ЦД 2-го типу супроводжується істотним підвищенням ЗФСА, вмісту фракцій білка сироватки крові та зниженням показників ЕІ.*

КЛЮЧОВІ СЛОВА: гіпертонічна хвороба, неалкогольний стеатогепатит, цукровий діабет 2-го типу, зв'язувальна функція сироваткового альбуміну, Антраль.

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COMPARATIVE STUDY OF CONCURRENT CHEMORADIATION USING PACLITAXEL IN TWO HISTOPATHOLOGICAL SUBTYPES (SQUAMOUS CELL CARCINOMA/ADENOCARCINOMA) OF UNRESECTABLE NON-SMALL CELL LUNG CANCER

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Background. *Lung cancer is still a global burden and with rising population and increasing life expectancy the incidence of lung cancer is still on the rise.*

Objective. *To compare the treatment response and toxicity of weekly paclitaxel in locally advanced unresectable non-small cell lung cancer (NSCLC), when administered concurrently with external beam radiation to the chest in two different histopathological types – adenocarcinoma and squamous cell carcinoma.*

Methods. *A prospective randomised control trial was conducted in 60 NSCLC patients who were divided into two arms; adenocarcinoma and squamous cell carcinoma arm. All patients were treated with chemoradiation with concurrent paclitaxel 60 mg/m^2. Data were evaluated with SPSS version 21.0 for windows with p-value <0.05.*

Results. *Haematological toxicity was the most common side effects evident from the third week of chemotherapy. At the end of 1 month of treatment, two (6.7%) patients had complete response in Arm A and one (3.3%) patient had complete response in Arm B. One (3.3%) patient had disease progression in Arm A and two patients progressed in Arm B. At 7 months post treatment three (10%) patients had complete response in both Arm A and Arm B. Four (13.3%) patients had disease progression in Arm A and ten (33.4%) patients progressed in Arm B.*

Conclusions. *Paclitaxel can be used as an alternative chemotherapeutic agent to the standard cisplatin. However, further studies with larger sample size are required to confirm the findings.*

KEYWORDS: unresectable; concurrent; adenocarcinoma; squamous cell.

Introduction

Lung cancer is one of the commonest cancers and the most common cause of cancer related mortality all over the world [1]. Lung cancer comprises two main histopathological groups - non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). The major histologic subclasses of NSCLC are adenocarcinoma (50%), squamous cell carcinoma (30-40%) and undifferentiated large cell carcinoma (10%) [2].

Approximately 80% of cases of non-small cell lung cancer (NSCLC) in men and 50% of these neoplasms in women worldwide are directly attributable to cigarette smoking. Other contributing factors includes passive smoking, genetic predisposition to this disease, occupational and environmental exposures including asbestos and silica fibres and ionizing radiation [3].

More than 70% of patients diagnosed with lung cancer present with advanced stage disease (stage III or IV) that is usually beyond surgical intervention [4]. According to the 7th edition AJCC staging classification, stage III NSCLC is often defined as locally advanced NSCLC. Stage IIIA (T1-3 N2, T3-T4 N1, T4 N0) disease involves hilar or mediastinal lymph nodes limited to the ipsilateral mediastinum and a subset of these patients are amenable to surgery. However, stage IIIB (T1-4 N3, or T4 N2) involves lymph node metastasis in the contralateral thorax or supraclavicular fossa and/ or an unresectable primary tumour, making patients with this disease not ideal candidates

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for surgical resection [5]. Concurrent chemoradiation is the mainstay of treatment in patients with locally advanced, unresectable, non-small-cell lung cancer which improved survival by reducing local tumour burden and also delaying the emergence of metastatic disease [6]. Long-term outcomes are poor, with baseline 5-year overall survival (OS) of 15%-35% for stage IIIA and 5%-10% for stage IIIB [7].

The platinum-based combination regimens are considered to be the standard treatment. But due to high incidence of platinum induced chemotoxicities and platinum resistance in many cases, a third-generation chemotherapeutic agent taxens e.g. paclitaxel were tried; they possess good activity as single agent in cases of NSCLC resulting in the arrest of cells in the G_2-M phase of the cell cycle, which is particularly responsible for much of the radiosensitizing ability of paclitaxel [8].

Even though both adenocarcinoma and squamous cell carcinoma are grouped as NSCLC, both the subtypes differ in many aspects. The monolithic treatment approach to both types of NSCLC has dramatically changed over last few years with the advent of molecular subtyping and novel histology specific targeted therapies [9].

Though, several studies have established the role of paclitaxel in NSCLC, the relative outcome response in different histopathologies (adenocarcinoma/squamous cell carcinoma) is still not clear. Hence, the present study will be aiming to compare treatment response and treatment toxicity patterns between unresectable adenocarcinoma and squamous cell carcinoma of lung treated with concurrent chemoradiation using paclitaxel.

Methods

A randomized control trial had been undertaken in the Department of Radiation Oncology, Regional Institute of Medical Sciences, Imphal, Manipur, over a period of 2 years starting from August 2017 to July 2019. The permission of the Research Ethics Board RIMS, Imphal, Manipur, was obtained to conduct the study. Initial 18 months was for patient accrual; the study and result analysis were performed after allowing minimum of 6 months follow-up for the patients.

The patients, who were histopathologically confirmed cases of unresectable non-small cell lung cancer (adenocarcinoma/squamous cell carcinoma) reporting to the Department of Radiation Oncology, RIMS, Imphal, Manipur, with Karnofsky Performance Status (KPS) ≥60%, age below 80 years, without any major comorbidity and willing to give consent, were included in the study.

The sample size is calculated using the formula:

$$N = \frac{(u+v)^2\,[\{p_1\,(100-p_1)\}] + [\{p_2\,(100-p_2)\}]}{p_1 - p_2}$$

Where N is the size per group, u=0.84 at 80% power, v=1.645 at 90% level of significance

p_1= proportion in one group =100, p_2= proportion in another group =81 [10].

Therefore, sample size of 60 (30 patients in each arm) will be considered for the study.

Patients were distributed into two separate arms – Arm A (adenocarcinoma) and Arm B (squamous cell carcinoma). Both arms received external beam radiation therapy (EBRT) by cobalt-60 teletherapy machine (Theratron 780-C. Model number: A112109-101) with a source to skin distance (SSD) of 80 cm to a total tumour dose of 60 Gy over 30 fractions five days in a week for six weeks by two opposing postero-anterior fields. Spinal cord was spared after 46Gy/23 fractions. Concurrent chemotherapy with injection paclitaxel at a dose of 60 mg/m^2 in 500 ml 0.9% normal saline over 3 hours intravenous weekly before radiotherapy for 6 weeks was administered along with all the necessary pre-medications.

During concurrent chemoradiation (CCRT), the patients were evaluated weekly for development of any skin, pulmonary or oesophageal toxicity. Acute treatment toxicity was evaluated weekly during course of treatment and late treatment toxicity was evaluated monthly till the end of the treatment in accordance with RTOG criteria [11]. The early treatment response was assessed at 1 month and it was assessed again at 7 months following completion of CCRT, in accordance with RECIST criteria [12]. After completion of CCRT, patients were followed up monthly for a minimum period of 6 months and thereafter every 2 months.

Statistical analysis: Descriptive data like age was presented in terms of mean and standard deviation. Data like sex, stage, response and toxicity profile was presented in terms of percentages and proportions. Data entry and statistical analysis was conducted using IBM SPSS statistics 21 for windows (IBM Corp, 1995, 2012). Statistical significance was analysed using the chi square and Fisher's Exact Test and p-value of <0.05 was considered statistically significant.

Results

It is established that most of the patients fall in the age range of 61-70 years with 46.7% in arm A and 50% in arm B. We can also appreciate that in younger age group 51-60 years adenocarcinoma lung are more than squamous cell carcinoma (40% vs 30%) while in older age group squamous cell carcinoma are slightly more than adenocarcinoma in this study.

Out of 30 patients in Arm A, 17 (56.7%) patients were female and 13 (43.3%) patients were male. In Arm B, 19 (59.4%) patients were male and 11 (39.3.%) were female. The sex-wise distribution shows that adenocarcinoma is more common in females whereas squamous cell carcinoma is more common in males. Majority of the patients had 80% KPS where 15 (43.3 %) patients were in Arm A and 16 (53.3%) patients in Arm B. In Arm A adenocarcinoma patients, cough was the most common presentation followed by dyspnoea, chest pain, and haemoptysis. In arm B squamous cell cancer patients, cough also was the most common presentation followed by haemoptysis, dyspnoea and chest pain.

In arm A, 46.7% disease were found in the right lung whereas 53.3% of disease were found in the left lung. In Arm B, 43.3% disease were found in the left lung whereas 56.67% of disease were found in the right lung. In stage IIIA, 8 (26.6%) patients were in Arm A and 10 (33.3%) in Arm B. While in stage IIIB, 22 (73.3%) and 20 (66.7%) were in Arm A and Arm B respectively. This distribution shows the p-value of 0.389 which is statistically insignificant (Fig. 1).

Early toxicities particularly nausea/vomiting and haematological parameters were assessed after each cycle of chemotherapy. During radiation treatment lung and oesophageal toxicity were assessed every week for 6 weeks. The most common side effects during CT were anaemia (63.33% in Arm A and 53.33% in Arm B) during the third week, neutropenia (36.66% and 33.33% in Arm A and Arm B respectively) seen mostly during the 3rd week, thrombocytopenia (16.66% and 40% in Arm A and Arm B respectively) during the 4th cycle of CT and were mostly grade 1. None of the patients in both arms experienced peripheral neuropathy. The side effects of RT were mostly seen from the 3rd week after starting of treatment in both arms and the most common toxicity experienced was grade 1 lung and esophagus toxicity (Table 1).

In 1 month of treatment the result shows a significant improvement of the symptoms in both the Arms. Arm A shows most significant improvement in dyspnoea and chest pain with the p-value of 0.487 and 0.471, respectively, which was statistically not significant. Whereas arm B shows improvement in cough with the p-value of 0.128 and haemoptysis with the p-value of 0.487, which were statistically not significant (Table 2).

The median follow-up duration of patients was estimated to be 17±2.87 months in Arm A and 17±3.73 months in Arm B (p-value 0.634). All the 60 patients (in both arms) were available for assessment at the end of the 1st month. Two complete responses and 24 partial responses were obtained in Arm A (adenocarcinoma arm). One complete response and 23 partial responses were obtained in the Arm B (squamous cell carcinoma arm). The response rates were 86.66% with Arm A and 79.99% with Arm B (all assessable patients). The differences were statistically significant (p=0.000). The disease

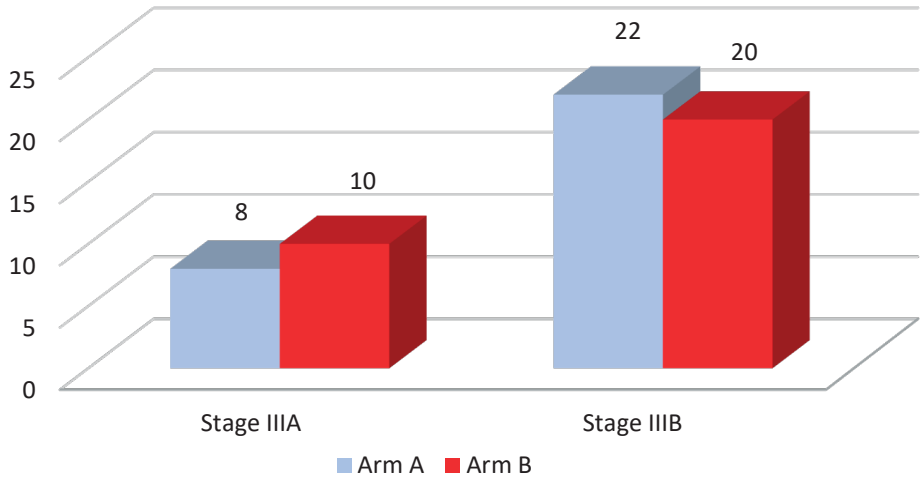

Fig. 1. *Stage distribution in both the arms.*

Table 1. Early radiation toxicity

Symptom	Week	Grade	Arm A	Arm B
Cough	Week 3	1	20 (66.67%)	21 (70%)
	Week 4	1	21 (70%)	21 (70%)
	Week 5	1	23 (76.7%)	23 (76.7%)
	Week 6	1	23 (76.7%)	23 (76.7%)
Esophagitis	Week 3	1	18 (60%)	19 (63.3%)
		2	6 (20%)	4 (13.33%)
	Week 4	1	16 (53.33%)	11 (36.66%)
		2	7 (23.33%)	4 (13.33%)
	Week 5	1	19 (63.3%)	19 (63.3%)
		2	6 (20%)	3 (10%)
		3	1 (3.33%)	0 (0%)
	Week 6	1	18 (60%)	18(60%)
		2	5 (16.7%)	3 (10%)
		3	3 (10%)	0 (%)
Nausea/vomiting	Week 3	1	3 (10%)	4 (13.33%)
	Week 4	1	6 (20%)	2 (6.66%)
	Week 5	1	2 (6.66%)	2 (6.66%)
	Week 6	1	2 (6.6%)	3 (10%)
Haemoglobin	Week 3	1	19 (63.33%)	16 (53.33%)
		2	0 (0%)	3 (10%)
	Week 4	1	14 (46.66%)	13 (43.33%)
		2	5 (16.66%)	1 (3.33%)
	Week 5	1	16 (53.33%)	11 (36.66%)
		2	3 (10%)	1 (3.33%)
	Week 6	1	16 (53.33%)	5 (16.66%)
		2	3 (10%)	0 (0%)
TLC	Week 3	1	11 (36.66%)	10 (33.33%)
		2	0 (0%)	2 (6.66%)
	Week 4	1	6 (20%)	9 (30%)
		2	5 (16.66%)	3 (10%)
	Week 5	1	6 (20%)	9 (30%)
		2	5 (16.66%)	3 (10%)
	Week 6	1	9 (30%)	9 (30%)
		2	3 (10%)	3 (10%)
Platelet	Week 3	1	9 (30%)	10 (33.33%)
		2	0 (0%)	2 (6.66%)
	Week 4	1	5 (16.66%)	12 (40%)
		2	0 (0%)	1 (3.33%)
	Week 5	1	5 (16.66%)	11 (36.66%)
		2	0 (0%)	1 (3.33%)
	Week 6	1	5 (16.66%)	6 (20%)
		2	0 (0%)	1 (3.33%)
Peripheral neuropathy			–	–

stabilized in three patients in Arm A and in four patients in the Arm B. Early progression (during therapy) occurred in 1 patient in treatment Arm A (adenocarcinoma) and 2 patients in Arm B (squamous cell carcinoma). In adenocarcinoma arm, 77.77% of the patients in stage IIIA and 90.47% of the patients in stage IIIB had a good response to the treatment, whereas about 80% of the patients in both stage IIIA and stage IIIB had a good response to the treatment in squamous cell carcinoma arm (Table 3).

The late side effects of treatment were assessed as per RTOG criteria [11]. In both Arm A and Arm B, toxicities were assessed monthly

Table 2. Symptomatic response before and after treatment

Symptoms	Grade	Pre-treatment symptoms		Symptoms after 1 month of treatment		P-value
		Arm A	Arm B	Arm A	Arm B	
Cough	1	20 (66.66%)	9 (30%)	13 (43.33%)	12 (40%)	0.128*
	2	5 (16.66%)	13 (43.33%)	5 (16.66%)	0 (0%)	
	3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Chest pain	1	10 (33.33%)	4 (13.33%)	8 (26.66%)	7 (23.33%)	0.471*
	2	5 (16.66%)	4 (13.33%)	0 (0%)	2 (6.66%)	
	3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Dyspnoea	1	19 (63.33%)	8 (26.6%)	6 (20%)	5 (16.66%)	0.487*
	2	4 (13.33%)	0 (0%)	2 (6.66%)	0 (0%)	
	3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Haemoptysis	1	6 (20%)	9 (30%)	5 (16.66%)	6 (20%)	0.487*
	2	1 (3.33%)	5 (16.66%)	0 (0%)	2 (6.66%)	
	3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	

*Note. * – Fisher's Exact test.*

Table 3. Early treatment response at the end of the 1st month, Arm A versus Arm B

Treatment response	Treatment Arm		P-value
	Arm A	Arm B	
CR	2 (6.66%)	1 (3.33%)	0.000*
PR	24 (80%)	23 (76.66%)	
SD	3 (3.33%)	4 (13.33%)	
PD	1 (3.33%)	2 (6.66%)	
Total	30	30	

*Note. * – Fisher's Exact test.*

after completion of treatment for 6 months. The most common late side effects of treatment were grade 1 lung fibrosis (50% in Arm A and 46.7% in Arm B) at the 6th month, grade 1 oesophageal toxicity (50% in Arm A and 40% in Arm B) at the 6th month and grade 1 cardiac toxicity (16.7% and 3.3% in Arm A and Arm B respectively). None of the patients in both arms experienced myelitis or nephrotoxicity (Table 4).

At the end of the 7th months in Arm A, 17 (56.6%) patients had partial response, 6 (20%) patients had stable disease, 3 (10%) – complete response and 4 (13.3%) – progression of the diseases. About 23.3% of the patients in stage IIIA and 43.3% of the patients in stage IIIB had a good response to the treatment. In Arm B, 3 (10%) patients had complete response, 12 (40%) patients – partial response, 5 (16.6%) patients – stable disease and 10 (33.4%) – progression of the disease. Late treatment responses were statistically significant (p-value 0.000) (Table 5).

Discussion

The two study groups were formed by histopathology – Arm A adenocarcinoma, Arm B squamous cell carcinoma, but all other patient characteristics in both groups were well balanced without statistically significant differences in age, stage, KPS.

In this study, adenocarcinoma lung was more than squamous cell carcinoma (40% vs 30%) in the younger age group, while in the older age group squamous cell carcinoma was slightly more than adenocarcinoma. This is in consistent with the study conducted by A.L. Rich et al [13].

The sex wise distribution was similar to the study by Price PW et al, where adenocarcinoma was more common in women than in men (41% versus 31%, p<0.0001) and squamous cell carcinoma more common in men than women (43% versus 31%, p<0.0001) [14].

Toxicity profile (acute toxicities)

In this study, during 6 weeks of treatment it was observed that toxicities were mostly seen at the 3rd week after treatment starting with grade 1 lung and esophageal toxicity being the most common in both the arms. This was similar to a study conducted by Huber RM et al,

Table 4. Side effects of treatment, assessed monthly for 6 months post treatment

Adverse effects		Arm A	Arm B	P-value
Lung fibrosis				
Month 1	Grade 1	15 (50%)	16(53.3%)	0.000*
	Grade 2	2 (6.7%)	2 (6.7%)	
	Grade 3	0 (0%)	0 (0%)	
Month 2	Grade 1	15 (50%)	19 (63.3%)	0.000*
	Grade 2	2 (6.7%)	2 (6.7%)	
	Grade 3	0 (0%)	0 (0%)	
Month 3	Grade 1	18 (60%)	17 (56.7%)	0.000*
	Grade 2	3 (10%)	3 (10%)	
	Grade 3	0 (0%)	0 (0%)	
Month 4	Grade 1	17 (56.7%)	17 (56.7%)	0.000*
	Grade 2	3 (10%)	3 (10%)	
	Grade 3	1 (3.3%)	2 (6.7%)	
Month 5	Grade 1	19 (63.3%)	17 (56.7%)	0.000*
	Grade 2	5 (16.7%)	3 (10%)	
	Grade 3	2 (6.7%)	2 (6.7%)	
Month 6	Grade 1	15 (50%)	14 (46.7%)	0.000*
	Grade 2	8 (26.7%)	7 (23.3%)	
	Grade 3	2 (6.7%)	3 (10.0%)	
Dysphagia				
Month 1	Grade 1	5 (16.7%)	4 (13.3%)	0.000*
	Grade 2	0 (0%)	0 (0%)	
	Grade 3	0 (0%)	0 (0%)	
Month 2	Grade 1	7 (23.3%)	6 (20%)	0.000*
	Grade 2	0 (0%)	0 (0%)	
	Grade 3	0 (0%)	0 (0%)	
Month 3	Grade 1	7 (23.3%)	7 (23.3%)	0.000*
	Grade 2	2 (6.7%)	1 (3%)	
	Grade 3	0 (0%)	0 (0%)	
Month 4	Grade 1	9 (30%)	10 (33.3%)	0.000*
	Grade 2	3 (10%)	2 (6.7%)	
	Grade 3	0 (0%)	0 (0%)	
Month 5	Grade 1	9 (30%)	11 (36.7%)	0.000*
	Grade 2	5 (16.7%)	3 (10%)	
	Grade 3	0 (0%)	0 (0%)	
Month 6	Grade 1	15 (50%)	12 (40%)	0.000*
	Grade 2	6 (20%)	3 (10%)	
	Grade 3	0 (0%)	0 (0%)	
Cardiac toxicity	Grade 1	5 (16.7%)	1 (3.3%)	0.000*
	Grade 2	0 (0%)	0 (0%)	
	Grade 3	0 (0%)	0 (0%)	
Myelitis		–	–	
Nephrotoxicity		–	–	

*Note. * – Fisher's Exact test.*

Table 5. Treatment Response at the end of the 7th months

	Late treatment response				P-value
	CR	PR	SD	PD	
Arm A	3 (10%)	17 (56.6%)	6 (20%)	4 (13.3%)	0.000
Arm B	3 (10%)	12 (40%)	5 (16.6%)	10 (33.4%)	

where grade 3 esophageal toxicity was seen in 13% [15], but was much lower than RTOG 94-10 trial, where grade 3 esophageal toxicity with CCRT was seen in 22% [16].

Haematological toxicities were also present and comparable in both arms. Other studies also showed that neutropenia was a common toxicity with paclitaxel [17,18]. However, in this study, in both arms none of the patients experienced peripheral neuropathy. This may be due to the low dose of injection paclitaxel (60 mg/m^2) used in the study [19].

Nausea and vomiting were not common and grade 1 nausea was present in only 10% and 13.33% in Arm A and Arm B, respectively, at week 3. This may be due to low emetogenic potential of paclitaxel that has also been proven by other studies [20,21].

Tumour response rate after treatment

The response rates in both the Arms were similar to the rates in other trials [22,23]. The findings of this study are consistent with that by Choy H et al, where 86% of overall response rate have been achieved: adenocarcinoma having 100% partial response and squamous cell carcinoma having 86% partial response. Patients with stage IIIB disease responded equally to stage IIIA disease (82% and 92%, respectively; p=0.62) [10]. In this study, since the response rates achieved in both arms are comparable, a conclusion could be drawn that response rates of weekly paclitaxel in adenocarcinoma lung and squamous cell carcinoma lung are similar.

Symptomatic response post treatment

Buccheri G et al conducted a single institute study on lung cancer clinical presentation and found that the most alarming symptoms with adenocarcinoma lung was cough (18.4%) followed by chest pain (13.7%), bloody sputum (13.4%) and dyspnoea (11.7%). The alarming symptoms of squammous cell carcinma were bloody sputum (24%) followed by cough (19%), chest pain (10.7%) and dyspnoea (10.4%) [24]. This was almost similar with our study.

Regarding assessment of symptom response, in 1 month significant improvement of all the symptoms in both the arms was evidenced that is similar to the studies by Barwal KV et al [25] and Langendijk et al [26].

Treatment response (at the end of the 7th months):

At the end of the 7th months, 4 patients in arm A and 10 patients in arm B had disease progression in this study. Bone is the most frequent site of distant metastasis followed by liver and brain. In a study conducted by Liew SM et al locoregional, contralateral relapses, and distant metastases were observed in 34 (45%), 16 (21%), and 47 (63%) patients, respectively. Among the 47 patients with late relapse, bone metastases were observed in 16 (34%) patients and were the most frequent site of distant metastases. This was followed by liver (n=13.28%), brain (n=12.26%), and adrenal (n= 4.9%) [27]. Those with adenocarcinoma showed adrenal metastases in 54% of cases followed by liver metastases (27%). Squamous cell carcinoma spread to the liver in 67% of cases as well as to adrenal glands and bones (33% each) [28].

Toxicity assessment (late toxicities)

In this study after 6 months of treatment grade 1 lung fibrosis was evidenced in 50% of the patients in Arm A and 46.7% of the patients in Arm B after radiological assessment with chest x-ray and/or CT scan thorax. This was much higher than the old RTOG data, where the average incidence of pneumonitis (grade 2 and above) and fibrosis was 14.6% and 28%, respectively, after 2DRT [29].

Grade 1 cardiac toxicity was seen in 16.7% of patients in Arm A and 3.3% of patients in Arm B. Arm A had a slightly higher percentage of cardiac toxicity. This might have been due to greater number of left sided lung tumours in Arm A (53.33%) compare to Arm B (43.33%), where portion of heart could not be avoided in the radiation.

In this study grade 1 oesophageal toxicity was another radiation toxicity with no grade 3 or higher esophageal toxicity evidenced in both arms. A study conducted by Curran JW et al found that in CCRT arm grade 3 esophageal toxicity was present in 3% patients and grade 4 esophageal toxicity – in 1% patients only [16].

Conclusions

Locally advanced non-small cell lung cancer (LA NSCLC) comprises the most heterogeneous group of patients. Over the years even with continuous evolution of treatment strategies, overall survival (OS) is still low and management of stage III LA NSCLC is still a challenge today. The results after 1 month showed significant improvement of symptoms in both the arms and the responses were comparable in both the arms. This study is one of the first ones on comparison of efficacy of paclitaxel as a radiosensitiser in CCRT in two main histopathological types of non-small cell lung cancer (adenocarcinoma and squamous cell carcinoma) of this region with limitations of small sample size

and the short study duration for which survival benefit could not be analysed. Further studies have to be done on a larger population and over a longer study period to confirm the findings of this study.

Conflict of Interests

Authors declare no conflict of interest.

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Author's Contributions

Daffilyne Lyngdoh Nongrum, Yumkhaibam Sobita Devi, Laishram Jaichand Singh – conceptualization, methodology, formal analysis, writing – original draft; *Daffilyne Lyngdoh Nongrum, Srigopal Mohanty, Kishalay Baidya* – data curation, writing – reviewing and editing; *Deiwakor Chyrmang, Hari Krishna Rai* – investigation, formal analysis.

ПОРІВНЯЛЬНЕ ДОСЛІДЖЕННЯ ОДНОЧАСНОЇ ХІМІОПРОМЕНЕВОЇ ТЕРАПІЇ З ВИКОРИСТАННЯМ ПАКЛІТАКСЕЛУ У ДВОХ ГІСТОПАТОЛОГІЧНИХ ПІДТИПАХ (ПЛОСКОКЛІТИННИЙ РАК/АДЕНОКАРЦИНОМА) НЕРЕЗЕКЦІЙНОГО НЕДРІБНОКЛІТИННОГО РАКУ ЛЕГЕНІВ

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Вступ. *Рак легень все ще є глобальною проблемою і з ростом населення та збільшенням тривалості життя захворюваність на рак легень продовжує зростати.*

Мета. *Порівняння відповіді на лікування та токсичність тижневої терапії паклітакселом при локально розповсюдженому нерезектабельному недрібноклітинному раку легенів (НДРЛ), що застосовується одночасно із зовнішнім променевим випромінюванням у грудну клітку при двох різних гістопатологічних типах аденокарциноми та плоскоклітинної карциноми.*

Методи. *Проспективне рандомізоване контрольне дослідження було проведено у 60 пацієнтів з НДРЛ, які були розділені на дві групи: А (аденокарцинома) та Б (плоскоклітинна карцинома). Всім пацієнтам проводили хіміопроменеву терапію одночасно з паклітакселом 60 мг/м^2. Дані були оцінені за допомогою статистичного пакету SPSS версії 21.0 для Windows з p-значенням <0,05.*

Результати. *Гематологічна токсичність була найпоширенішим побічним ефектом, який проявлявся на третьому тижні хіміотерапії. Наприкінці 1 місяця лікування у двох (6,7%) пацієнтів була повна відповідь у групі А, а у одного (3,3%) пацієнта була повна відповідь у групі Б. У одного (3,3%) пацієнта прогресувала хвороба у групі А, а у двох пацієнтів було прогресування у групі Б. Через 7 місяців після лікування три (10%) пацієнти мали повну відповідь як у групі А, так і в групі Б. У чотирьох (13,3%) пацієнтів прогресування захворювання в групі А було у десяти (33,4%) пацієнтів.*

Висновки. *Паклітаксел можна використовувати як альтернативний хіміотерапевтичний засіб стандартному цисплатину. Однак для підтвердження результатів необхідні подальші дослідження з більшим розміром вибірки.*

КЛЮЧОВІ СЛОВА: нерезектабельний; одночасна терапія; аденокарцинома; плоскоклітинний рак.

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REHABILITATION OF PATIENTS AFTER CARDIAC SURGERY

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Background. *Patients undergoing cardiac surgery are under a high risk of post-operative reductions in respiratory muscle strength and pulmonary function as well as lowered functional capacity. In-hospital physical inactivity and inappropriate rehabilitation increases the chances for development of these complications and affects patients' future independence in daily routine. Cardiac rehabilitation is crucial in preventing complications and assisting the early function recovery. However, despite the evidences for its benefits and strong guideline recommendations, the uptake of cardiac rehabilitation remains poor.*

Objective. *this study is aimed at promotion of cardiac rehabilitation and sharing successful experience of using it.*

Methods. *Post-surgical treatment and rehabilitation of 387 patients with cardiovascular pathology in the Department of Vascular and Cardiac Surgery of Municipal Non-Commercial Enterprise "Ternopil Regional Clinical Hospital" of Ternopil Regional Council has been analysed.*

Results. *The experience of successful post-surgical treatment and rehabilitation allowed establishing the basic approaches to perioperative management of patients with cardiovascular surgical pathology. Key principles include minimized ICU stay and artificial ventilation time, early verticalization and beginning of physical activities, early removed drainage tubes, tracheobronchial tree drainage, nutritional balance, lymphatic drainage massage, application of elastic jersey on the lower extremities, early transferring to the surgery ward and returning to the regular daily activities, circumstantial health education, complex work of a multidisciplinary team.*

Conclusions. *This set of rehabilitation measures helps prevent complications after cardiac surgery as well as provide a faster patient's daily routine.*

KEYWORDS: cardiac surgery; cardiac rehabilitation; exercise; recovery of function; health education.

Introduction

The increasing prevalence of risk factors such as age, obesity, diabetes, hypertension and dyslipidaemia in patients undergoing cardiac surgery causes a significant rise of possible complications [1]. Those patients commonly experience reductions in respiratory muscle strength and pulmonary function [2-3]. These complications lead to longer hospital stay, higher rehospitalisation risk, reduced health-related quality of life and higher costs for healthcare [4-6]. Also, makeable reduction in functional capacity can occur, which only gets worse if patients spend the majority of their time sitting or in a supine position due to the inappropriate care [7-8]. In-hospital physical inactivity causes muscle weakness and aerobic capacity decrease, which can seriously affect patients' independence in daily routine [9-10].

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Cardiac rehabilitation is crucial in prevention of these complications and assisting the early function recovery [11]. Cardiac rehabilitation is a complex intervention that includes post-operative management, exercise training, physical activity promotion, health education and psychological support [12]. Special emphasis in the latest guidelines is made on involving a multidisciplinary team to the rehabilitation complex [13]. In addition to cardiac surgeons and ICU anaesthesiologists it should include cardiologists, nursing specialists, physiotherapists, nutritionists and psychologists, trained in the core competencies of a comprehensive cardiac rehabilitation programme. However, despite the evidence for its benefits and strong guideline recommendations, the uptake of cardiac rehabilitation is poor [14]. Therefore, nowadays promotion of cardiac rehabilitation and sharing the successful experience in this field is essential, as the success of heart surgery depends not only on its type or the patient's

health before the surgery, but also on proper rehabilitation, both in the early and late post-operative period.

Methods

Post-surgical treatment and rehabilitation of 387 patients with cardiovascular pathology in the Department of Vascular and Cardiac Surgery of Municipal Non-commercial Enterprise "Ternopil Regional Clinical Hospital" of Ternopil Regional Council has been analysed in this study.

Results

The experience of successful post-surgical treatment and rehabilitation allowed establishing the basic approaches to perioperative management of patients with cardiovascular surgical pathology. We are supporters of the fast and early activation concept or "Fast Track". During the ICU stay we adhere to the following principles: time of intubation and artificial ventilation is minimized; physical activity usually begins 12-15 hours after the surgery. The patients are verticalized – helped to sit and stand under doctor's supervision. At the same time, we help patients to perform a small walk on place. This improves blood flow to the right heart chambers. Walking also helps to restore motor function of the intestine. Verticalization of the patient helps to restore vascular tone, and is also one of the mechanisms of hypertension correction. Tracheobronchial tree drainage is performed by hyperventilation of the patient, as well as by forced coughing along with vibrating chest massage. This improves oxygenation and pulmonary function.

After the first activity session the stability of haemostasis in the chest is checked and if no signs of bleeding are observed, drainage tubes are immediately removed. Delay in this can lead to the patient's prolonged ICU stay, immobilization in bed, respiratory function limitations and development of arrhythmias caused by irritation of the heart reflex zones.

One more vital thing is the nutritional balance. Thus, before the operation, the patient's diet includes high-calorie food rich in protein, vitamins and microelements that provide a good "pool" for rapid recovery of the patient in the post-operative period and high reparative potential for wound healing. In the postoperative period along with the restoration of peristalsis, the patient begins to drink, and after a short time to eat liquid, easily digestible food. This contributes to the full recovery of the gastrointestinal tract and improves the overall psycho-emotional state of the patient.

Lymphatic drainage massage, application of elastic jersey on the lower extremities has a good therapeutic effect on the swelling caused by congestive heart failure.

If no major complications take place by the middle of the first post-operation day the patient is transferred from the ICU to the surgery ward. It also helps motivate our patients for early returning to their regular daily activities. They are trained to do exercises and are informed about all the restrictions for protection of the breastbone during physical activities and sleep time. Also, we provide some health education consultations in order to inform the patients about their state and the following rehabilitation programme, which may last up to 6 months.

Discussion

The efficacy and safety of complex cardiac rehabilitation in patients provided with different kinds of surgical procedures was evaluated in the study. A short-term impact of different procedures on patients might differ significantly, as valvular surgery, CABG, surgery on thoracic aorta and their various combinations are provided in our clinic. Post-isolated CABG patients might therefore respond differently to the rehabilitation complex compare to those who underwent a complicated combined surgical procedure. We tried to develop a unified complex of rehabilitation measures according to the International Guidelines and our own experience. Not separating and analyzing patients as separate groups might therefore be a limitation to this study.

While current guidelines of the European Society of Cardiology [15] emphasize mainly on exercise-based cardiac rehabilitation after heart surgery, our findings coincide more with the Cochrane systematic review by Abraham et al., who recognized that rehabilitation interventions complex may also need to include breathing and coughing exercises and vocational evaluation advice in addition to the physical exercises [16].

Conclusions

Key principles include minimized ICU stay and artificial ventilation duration, early verticalization and beginning of physical activities, early removed drainage tubes, tracheobronchial tree drainage, nutritional balance, lymphatic drainage massage, application of elastic jersey

on the lower extremities, early transferring to the surgery ward and returning to the regular daily activities, circumstantial health education, complex work of a multidisciplinary team. This set of rehabilitation measures helps prevent complications after cardiac surgery as well as provide faster patient's daily routine.

Conflict of Interests

Authors declare no conflict of interests.

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Author's Contributions

Volodymyr Moroz, Taras Romaniuk – conceptualization, methodology, formal analysis, writing – original draft, writing – reviewing and editing; *Sofiia Maslii, Zoriana Vivchar* – data curation, writing – reviewing and editing, investigation, formal analysis.

ОСОБЛИВОСТІ РЕАБІЛІТАЦІЇ ПАЦІЄНТІВ ПІСЛЯ КАРДІОХІРУРГІЧНОЇ ОПЕРАЦІЇ

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ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ, ТЕРНОПІЛЬ, УКРАЇНА

Вступ. *Пацієнти, які перенесли операцію на серці, мають високий ризик післяопераційного зниження сили дихальних м'язів і функції легень, а також зниження функціональних резервів. Відсутність належної фізичної активності у ранньому післяопераційному періоді та невідповідна реабілітація збільшують ймовірність розвитку цих ускладнень і впливають на майбутні можливості пацієнтів щодо їх повсякденної діяльності. Вирішальну роль у попередженні ускладнень та сприянні ранньому відновленню функцій організму відіграє кардіологічна реабілітація. Однак, незважаючи на її доказові переваги і сильні рекомендації світових гайдлайнів, якість кардіологічної реабілітації залишається слабкою.*

Мета. *Метою цієї роботи є популяризація кардіологічної реабілітації та обмін успішним досвідом у цій сфері.*

Методи. *Проаналізовано післяопераційне лікування та реабілітацію 387 пацієнтів із кардіохірургічною патологією відділення судинної хірургії з кардіохірургією Комунального некомерційного підприємства «Тернопільська обласна клінічна лікарня» Тернопільської обласної ради.*

Результати. *Проведений аналіз успішного досвіду післяопераційного лікування та реабілітації пацієнтів із кардіохірургічною патологією дозволив нам встановити основні принципи їх періопераційного ведення. Вони включають мінімізацію часу штучної вентиляції легень та перебування у реанімаційному відділенні, ранню вертикалізацію та початок фізичних навантажень, раннє видалення дренажних трубок, дренаж трахеобронхіального дерева, збереження нутритивного балансу, лімфодренажний масаж, накладення еластичного трикотажу на нижні кінцівки, раннє переведення в палату хірургічного відділення та повернення до звичайних повсякденних справ, ретельне навчання пацієнтів, комплексна робота багатопрофільної команди.*

Висновки. *Цей комплекс реабілітаційних заходів допомагає запобігти ускладненням після кардіохірургічних операцій, а також забезпечити швидке повернення пацієнта до нормального життя*

КЛЮЧОВІ СЛОВА: кардіохірургія; кардіологічна реабілітація; фізичні вправи; відновлення функції; медична освіта.

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DENTAL ASSISTANCE TO MILITARY PERSONNEL OF THE ARMED FORCES OF UKRAINE

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Background. *At present, the formation of military units of the Armed Forces of Ukraine during mobilization takes place with underlying high dental morbidity of the population of the country.*

Objective. *The aim of this research was to study dental health of the personnel of military units and the problem of providing dental care to military personnel according to the analysis of modern scientific literature.*

Methods. *The following research methods were used to analyse dental care for military personnel, namely: bibliographic, analytical, systems approach.*

Results. *Hygiene of the oral cavity is mandatory in military units and should be routinely carried out. It was found that the main reason for seeking dental care among military personnel was treatment of major dental diseases. A low number of military personnel seeking for dental preventive examination was noted that proved a low level of primary prevention among this category of people.*

Conclusions. *Therefore, the obtained data on the state of dental health of military personnel require a purposeful approach to organization of prophylaxis and prevention of complications through professional hygiene and early prosthetics.*

KEYWORDS: military personnel; dental diseases; prevention; professional hygiene of the oral cavity.

Introduction

The current socio-political situation is characterized by a large number of local military conflicts in many countries, including Ukraine. It is true that military conflicts lead to mass disability and death of people, including military personnel performing their duty at the territories of combat operations [1].

A large number of publications in the military medical literature aimed at improving organization of dental care due to specific living conditions and combat effectiveness of military personnel of the Armed Forces of Ukraine, the peculiarities of the military profession, as well as factors influencing the course of pathological processes of the dentoalveolar apparatus, methods of their prevention and treatment [2].

At present, formation of military units of the Armed Forces of Ukraine during mobilization takes place with a high dental morbidity of the population in the country [3, 4].

After special missions, military personnel often complain of a sharp deterioration in dental health, which is associated with the inability to receive qualified assistance at the place of temporary deployment of the unit. As a rule, this is due to the lack of dentist or appropriate materials and equipment, the difficulty of transporting a serviceman to the place of timely, sometimes emergency dental care [5].

The level of dental health of organized military contingents depends on the motivation of the personnel, social and hygienic factors, which include ecological situation in the region, as well as on the development of dental services, principles of organization of medical care, and prevalence of dental diseases [4, 6].

Military service and combat missions by personnel is invariably accompanied by high emotional and psychological stress, various kinds of disorders in their health, including dental health.

Therefore, the measures for prevention of dental diseases before military missions is very important. Unfortunately, organization of dental care is insufficient.

Therefore, the objective of the research was to study the level of dental health of the personnel of military units and the problems of providing dental care to military personnel according to the analysis of modern scientific literature.

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Review

A large number of publications in the military medical literature are aimed at improving the organization of the dental care system. This is due to the specific living conditions and combat effectiveness of the military personnel of the Armed Forces of Ukraine, due to the peculiarities of the military profession, as well as factors influencing the course of pathological processes of the dentoalveolar apparatus, requiring methods of prevention and treatment. Diseases of the teeth and their complications reduce the working and combat efficiency of military personnel, so the provision of dental care to this category is a problematic issue [7].

Naumenko K.E., Belikov O.B. (2018) after examining military personnel for dental morbidity, it was found that the prevalence of caries among conscripts was 100%, and among contract soldiers – 93.41%. When assessing the indicators of the need for military personnel in various types of outpatient dental care based on the analysis of the structure of the KPU indices, the authors found that 32.83% of the conscripts needed caries treatment, 16.41% – its complications, 17.91% – tooth removal. The amount of already filled teeth was about 22.38%, and removed – 10.44%. Among the contract servicemen, 23.10% had teeth with caries, 39.29% – filled, 16.78% – removed. There is also a tendency that the need for treatment increases with age due to the number of removed teeth [8].

Authors analysed the dental morbidity rate among military personnel of various branches of the Chernivtsi garrison based on the analysis of medical reports and outpatient journals. Among the nosological units of dental morbidity in 35.20% of cases uncomplicated caries was found, in 44.89% – its complicated forms, in 13.26% – periodontal disease, 5.35% – deformities and occlusion anomalies, and only 1.27% were inflammatory diseases of the oral mucosa. 63.25% of servicemen needed therapeutic treatment, 19.77% – surgical, 15.42% – orthopaedic and 1.56% – orthodontic care [2, 8].

Among the military personnel who need therapeutic treatment, acute forms of periodontitis were the most often in 39.11%, acute and chronic medium caries – 35.08%, acute forms of pulpitis – 25.80%. Among periodontal diseases, periodontitis of the first degree prevailed – 42.30% and the second degree– 36.53%, catarrhal gingivitis – 21.15% [9, 10].

According to the researchers, the prevalence of dentoalveolar anomalies among pre-conscripts is 63.3%. At the same time, almost 2% of these young people have absolute restrictions on military service. In addition, defects in the dentition is revealed in 22.6% of people aged 18-22 years, who study in military schools in Kiev [9].

According to the results of dental examinations of conscript cadets aged 18-22, it was found that of the total number of conscripts routinely surveyed, 52.4% needed dental care, and in the western region of our country this number was 80-85%. The authors associate this first of all with the extremely low level of dental care just before the conscription of this category of the population in medical and preventive institutions of the Ministry of Health of Ukraine [9, 10].

The above materials indicate a fairly high level of dental morbidity among the military personnel of Ukraine, an extremely low level of dental care for this category of the population.

The authors also found that the increase in the need for orthopaedic treatment depended on the age of the military personnel. The category of 19-24 years old required the restoration or manufacture of artificial crowns, the category of 25-30 and 30-35 years old – crowns and bridges, and 35 years old and older – bridges and partial removable structures [9].

Lyshchyshyn M.Z. and co-authors (2020) after examining military personnel for periodontal tissue diseases, found that among conscripts, gingivitis was revealed in 23.33%, and periodontitis – in 13.33%. In soldiers of the contract form of service, on average, 32.76% of the surveyed had periodontitis and 34.76% – gingivitis. At the same time, the worst indicators were in the age groups of 19-24, 30-35 and 35 years old and older [10, 11].

Rachinsky S.V. and co-authors analysing oral hygiene among both conscripts and contract soldiers found out that the level of hygiene was "satisfactory" and "unsatisfactory", and only in some categories of servicemen 11.50% it was "good". This indicates on a lack of sanitary and educational work [12].

The main tasks of the dental service of the Armed Forces of Ukraine are to provide certain medical assistance to the military for each level, dental care to the wounded and sick (dental care) and medical rehabilitation of combatants [13].

Thanks to the signed Memorandum of Cooperation between the Military Medical Department of the Ministry of Defence and the Association of Dentists of Ukraine, dental

offices have been established at all training grounds and centres [13, 14].

Most of the military returning from the zone of hostilities in the Eastern Ukraine need medical rehabilitation, including modern dental care and dental prosthetics. Garrison dentists are important for dental assistance to the military.

Badiuk M.I. (2020), analysing the organization of dental care for soldiers of the Armed Forces of Ukraine, established an increase in the number of maxillofacial wounded in the overall sanitary losses. The authors emphasize the importance of restoring mobile dental offices to improve the level of dental care for soldiers [16, 17].

Mobile dental office (MDO) is a unit of the medical service designed to provide outpatient dental care to the personnel of units and subdivisions that do not have regular dental offices [14].

The mobile dental office is used to provide dental care in the field and outside of military garrisons - during the conduct of hostilities, conducting exercises, field training sessions, and eliminating the consequences of emergencies [18].

Mobile dental office is part of the clinics of maxillofacial surgery and dentistry of military medical clinical centres of the regions, the Central Dental Clinic of the Ministry of Defence of Ukraine and the Ukrainian Military Medical Academy (as an education unit) [14, 18].

The mobile dental office is deployed in a special modular unit based on a truck. The design and complete set of the mobile dental office gives the chance to provide out-patient dental services autonomously, in full and in comfortable conditions [14, 19].

The dental care to the personnel of the military unit is provides by a dentist of the medical centre, who is subordinate to the Head of the Medical Centre, and on special issues – to the garrison dentist and follows their instructions. The duties of a dentist of a military unit are to provide outpatient dental care to the personnel of the unit as well as first aid for injuries of the maxillofacial area and to ensure timely hospitalization and treatment of dental patients [20].

In a separate medical battalion (OMedB) the unit has a dental office, which includes a dentist (the head of the dental office OmedB) and a nurse.

In the context of reforming of the medical system, still there are a number of issues on organization of therapeutic and prophylactic dental services in the Armed Forces of Ukraine.

Belikov A. (2017) analysed the level of dental care for servicemen according to the survey data. The author claims that the main reason for seeking dental care among the respondents was the treatment of major dental diseases. A low percentage of military personnel who consulted a dentist for a preventive examination was recorded that proved a low level of primary prevention among this category of population [19].

Dentists of medical companies provide dental care to subordinate personnel only as emergency care (removal, disclosure of subperiosteal abscesses, disclosure of root canals, etc.), as complete equipment is not used. Therefore, in the field dental care is provided sporadically and as an emergency care for acute cases (acute pulpitis, exacerbation of periodontitis, and trauma). It has been established that dentists of medical brigades perform their duties, mainly in the field and outside of their permanent locations. It has been proved that the main burden of providing dental care to military personnel in the combat zone is borne by the dental offices of military mobile hospitals. Since 2014, the work of regular mobile dental offices has been resumed. At the same time, the office is constantly changing its location and provides dental care directly at the locations of various departments. Analysis of the work of this cabinet shows high efficiency of its use in various military units [21].

Dental care for maxillofacial wounded is provided within the general structure of medical and evacuation measures of the medical services of the Armed Forces of Ukraine, including by regular dentists. Specialized treatment of such wounded is carried out in specialized clinics of maxillofacial surgery, dentistry of military medical clinical centres and dental departments of hospitals.

The dental care to military personnel is carried out with a very high dental morbidity among the personnel of the units.

Therefore, the full-time dentists of the brigades face a significant burden as they often treat servicemen in difficult field conditions during hostilities. Most of this assistance is provided in the form of emergency dental care. The main burden of providing dental care is assigned to the dental service of the military mobile hospitals [20].

Mobile dental offices were introduced into these hospitals, which made it possible to

significantly improve the quality of dental care for military personnel and bring it closer to the deployment sites of military units.

Today, a new model of providing dental care to military personnel has been developed and is successfully functioning in Ukraine, represented by a network of stationary and mobile offices. Depending on the peculiarities of the functioning, provision and volume of care for the wounded and dental patients, the specified model provides for division of the involved dental offices into 3 types by "categories". In the dental departments of military hospitals and specialized clinics of military medical clinical centres, dental care for military personnel is provided in full, including orthopaedic care [14, 21].

Some scientists compared the level of dental care in the units of the Armed Forces of Ukraine and NATO countries.

The health protection measures for the military personnel of NATO countries are an integral element in the system of combat readiness of troops. Document AJP-3.14 "Allied joint doctrine for forse protection" defines health care as a very important part of their protection [22].

NATO National Military and Allied Commands emphasize the importance of ensuring an adequate level of medical, dental and mental health for troops. The experience of the alliance countries asserts that the presence of dental diseases reduces the combat readiness of troops. Routine dental examinations and standardized treatment programs ensure that personnel remain healthy during troop deployments in the war zone [15].

According to the STANAG 2466 standard "Dental Fitness Standards for Military Personnel and a Dental Fitness Classification System", which regulates monitoring of dental health of military personnel even before the deployment of medical units in the combat zone, NATO has introduced a system of comprehensive prevention of dental morbidity among military personnel [16].

The routine of planned dental examinations, preventive measures and unified standardized treatment programs minimizes the incidence of acute forms of oral diseases in military personnel within the combat zone.

Therefore, for improvement of dental care for servicemen of the Armed Forces of Ukraine, this should be taken into account and brought in line with the requirements of NATO standards.

Implementation of NATO standards facilitates improvement of the level of dental care for military personnel, which is one of the key state tasks in improvement of defence of Ukraine.

Significant attention is paid to dental care as a component of medical support for troops in the armies of the NATO countries.

That is why following the Euro-Atlantic standards by military dentistry in Ukraine is a serious tool for further improvement of dental care for military personnel.

Among all the medical standards of the Euro-Atlantic alliance, there are three that should be singled out, they directly relate to the dental care of military personnel. All standards provide for the use of forces and means in the zone of hostilities.

The first is preventive, or STANAG 2466 "Dental Fitness Standards for Military Personnel and a Dental Fitness Classification System" [23]. It has been established that the armies of the NATO countries have introduced a system of comprehensive prevention of dental morbidity among military personnel. The system of planned dental examinations, preventive measures and unified standardized treatment programs excludes the entry of military personnel with acute forms of dental diseases into the zone of hostilities. This standard contains a unified classification of the dental health of military personnel, provides 4 groups or classes [10, 23].

Analysing the situation, it should be noted that, unfortunately, in Ukraine, dental prevention programs have been curtailed both at the state level and in the Ukrainian Armed Forces.

There is a clear tendency towards an increase in dental morbidity among military personnel in a special period, which indicates the low quality of the military medical examination.

The second STANAG 2453 AMedP-35 "The Extent of Dental And Maxillofacial Treatment at Role 1-3" [24] defines the staffing, logistics and volume of medical care for servicemen with dental diseases and injuries of the maxillofacial area at three levels, deployed in the area of military action.

The third dental standard – STANAG 2464 AMedP-3.1 "Military Forensic Dental Identification" [25] provides for participation of the dentist in the forensic medical examinations and is based on modern international protocols and procedures for identifying people by examining the remains of the oral cavity.

In Ukraine, in order to meet the requirements of this standard, it is necessary to introduce

legislative changes for the possible admission of military dentists to the process of forensic medical examination in the combat zone. To create a single electronic database of orthopantomograms for all military personnel, it is necessary to provide all hospitals with modern digital dental X-ray equipment. This will ensure not only implementation of the direct use of STANAG 2464 AMedP-3.1, but also significantly increase the clinical and diagnostic capabilities of military dental units in Ukraine [10].

Conclusions

Diseases of the teeth and oral cavity negatively affect the combat effectiveness of military personnel and worsen the course of existing concomitant diseases. Therefore, professional hygiene of the oral cavity is mandatory in military units and should be routinely carried out. It is established that the professional hygiene of the oral cavity depends on the precise organization of dental care in military units. It should be noted that the domestic military dentistry requires further improvement.

The increase in the number of military personnel with requests for dental care is associated with a decrease in the number of preventive examinations, a decrease in the number of sanitized people and an increase in those who need dental hygiene. This proves insufficient medical care for this category of the population. Thus, the attained data on the state of dental health of military personnel require a purposeful approach to the organization of prophylaxis, prevention of complications through professional hygiene and early prosthetics.

Therefore, new approaches to organizing and ensuring the provision of dental care to military personnel taking into account NATO standards should be developed in Ukraine. This ensures a high level of dental care for this category of population.

Conflict of Interests

Authors declare no conflict of interest.

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Authors Contributions

Oksana Ya. Lavrin – writing – original draft, writing – reviewing and editing; *Oleksandr V. Avdeev* – writing – reviewing and editing; *Nina Ye. Romanjuk* – data collection, investigation, formal analysis; *Oleksandr A. Bedenyuk* – conceptualization, methodology, formal analysis.

ОСОБЛИВОСТІ НАДАННЯ СТОМАТОЛОГІЧНОЇ ДОПОМОГИ ВІЙСЬКОВОСЛУЖБОВЦЯМ ЗБРОЙНИХ СИЛ УКРАЇНИ

О.Я. Лаврін, О.В. Авдєєв, Н.Є. Романюк, О.А. Беденюк

ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І.Я. ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ, ТЕРНОПІЛЬ, УКРАЇНА

Вступ. *В умовах сьогодення формування бойових підрозділів Збройних Сил України під час мобілізації відбувається на тлі високої стоматологічної захворюваності населення держави.*

Мета *роботи вивчення рівня стоматологічного здоров'я особового складу військових підрозділів та проблеми надання стоматологічної допомоги військовослужбовцям згідно аналізу сучасної наукової літератури.*

Методи. *Для аналізу стану стоматологічної допомоги військовослужбовцям використано такі методи дослідження, а саме: бібліографічний, аналітичний, системний підхід.*

Результати. *Санація порожнини рота є обов'язковою у військових частинах та повинна проводитися в плановому порядку. Встановлено, що основною причиною звернень за стоматологічною допомогою серед військовослужбовців було лікування основних стоматологічних захворювань. Відмічено низький відсоток військовослужбовців, які звернулися до стоматолога з метою профілактичного огляду, що свідчить про низький рівень первинної профілактики серед вказаної категорії осіб.*

Висновок. *Отже, отримані дані щодо стану стоматологічного здоров'я військовослужбовців потребують цілеспрямованого підходу до організації профілактики, попередження ускладнень шляхом санації і раннього протезування.*

КЛЮЧОВІ СЛОВА: військовослужбовці; стоматологічні захворювання; профілактика; санація ротової порожнини.

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CURRENT DIAGNOSIS, PREVENTION AND TREATMENT OF DRY SOCKET (literature review)

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Background. *Tooth extraction is the most common surgical intervention in the outpatient practice of a dental surgeon. In most cases, bone wound healing is uncomplicated. However, in some patients the course of healing is complicated by acute inflammatory process of dry socket (alveolar osteitis), the frequency of which increases with increasing trauma of surgery. In dentally healthy patients with typical tooth extraction, dry socket occurs in 2.55%, with difficult – in 9.84%, with atypical extraction of the lower wisdom tooth – in 31.03% of cases. In the presence of diabetes, the incidence of dry socket with typical removal is much higher and according to various authors it is 9.7-13.5%.*

Objective. *The aim of the research was to study the publications and their analysis on the current diagnosis, prevention and treatment of patients with dry socket.*

Methods. *Scientific sources were the articles in world periodicals on dental surgery and therapy, microbiology as well as some electronic resources and patents.*

Results. *At present, many techniques, methods, schemes, compositions for treatment of various forms of dry socket are established. Most often, antibacterial drugs or their combinations with other drugs are used. However, antibacterial drugs do not always have a pronounced anti-inflammatory effect due to the high resistance of the oral microflora. In these cases, contemporary drugs in the form of a composition with long-term antiseptic, anti-inflammatory and analgesic action are rational.*

Conclusions. *The action of a Flupetsal composition, which contains antimicrobial and immunomodulatory drug flurenizide, was clinically proven for treatment of patients with dry socket; the properties of the available ingredients provide a high disinfectant effect, prevent development of inflammation in the tissues and its transition to purulence. A contemporary effective method of treating patients with dry socket is carried out according to the developed method.*

KEYWORDS: dry socket; treatment; compositions; medicines; Flupetsal.

Introduction

Outpatient dental care is one of the most popular types of medical care [1]. Tooth extraction is the most common surgical dental surgery performed at outpatient clinic [2].

Improving the quality of dental surgery depends on the qualifications of a dental surgeon and effective drugs for treatment after reducing complications. Improvements in dental treatment methods, recent dental equipment and the latest filling materials have significantly limited the indications for tooth extraction surgery. Indications for tooth extraction are pathological processes caused by complicated caries, which cannot be eliminated by other methods of treatment. Sometimes tooth preservation is not possible due to the large resorption of alveolar tissue caused by periodontal disease. Improperly erupted teeth are removed only when orthodontic treatments are ineffective. Removal of overcomplete teeth that erupted outside the dental arch also is possible.

A simple or atypical method of hollowing out and alveolotomy are often used. Frequently these methods are combined, an experienced doctor chooses the least traumatic. The surgery can be very simple or technically complex, long, sometimes requiring hospitalization of the patient. Surgical intervention in the removal of teeth is the rupture of periodontal tissues associated with simultaneous damage to the bone tissue of the alveolar processes of the jaws resulting in a wound of varying degrees of infection [2]. During the surgery, it is necessary to remember to treat the tissues sparingly, to avoid unnecessary injuries and ruptures of the mucous membrane. In the case of tooth extraction, the peculiarities of the structure of the dental-maxillary system, general diseases of the patient and local pathological processes

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are taken into account. In other cases, postoperative pain continues for a long time after tooth extraction due to a violation of tooth extraction techniques and improper treatment of the cavity.

Anaesthesia is a very important stage of the surgery. Anaesthetic effect and effective anaesthesia provide for surgical manipulations, allow avoiding tissue injuries [2, 3]. The wound is healed by the type of secondary tension under the cover of a blood clot. In dental practice, it is important to eliminate the negative impact of psycho-emotional state on the patient's CNS after surgery and the feeling of post-extraction pain [4]. Currently, foreign-made painkillers are used in various dosage forms, which are produced using the latest pharmaceutical technologies [5]. In recent years, dentists have used ketones (syn. Tromethamine, ketorolac) – a non-steroidal non-narcotic analgesic that relieves pain of various origins. Its positive effect on hemodynamics and oxygenation of blood is proved. Anaesthesia, proper selection of tools for removal, compliance with the rules of asepsis and antiseptics, timely treatment and prevention minimize the possible complications after tooth and root removal [6].

Review

After the tooth is removed, the hole is filled with a blood clot. The formation of a blood clot in the hole is the main condition for the healing of the postoperative wound by primary tension. The blood clot should be properly formed with a sterile tissue. The first stage of healing is the formation of a blood clot in the hole with fibrin deposition, which occurs within an hour after the tooth extraction operation. For the next 4-5 days after the tooth extraction surgery, the blood clot is replaced with granulation tissue. Then the granulation tissue is replaced by connective tissue rich in collagen fibres. At this time, the epithelium at the edges of the hole begins to proliferate and grow rapidly towards the centre of the hole to completely cover it in 24-35 days after tooth extraction. In about 1 month, a net of spongy beams appears in the area of the hole; in 2-2.5 months the bone structure of the alveoli becomes almost identical to the surrounding bone tissue; in 3-4 months the formation of bone tissue is finally completed. During this period, the alveolar edges are resorbed and rebuilt, they become lower and thinner than before tooth extraction [6].

One of the most common complications associated with direct tooth extraction is bleeding from the hole. Bleeding may be from vessels of the mucous membrane, the periosteum of the hole, the granulation tissue left in the hole, or from damaged branches of the interdental artery during the curettage of the hole. These types of bleeding depend on the degree of injury to the soft and bone tissues that develop during the surgery. In some cases, bleeding may occur later due to purulent melting of the clot that closes the lumen of the vessel. The cause should be established and the bleeding is stopped by stitching the soft tissues, tamponade of the hole with iodoform turund or haemostatic sponge, hemophobin [7].

If there is pain after extraction in the absence of a blood clot, it is necessary to scrape the hole with a sharp surgical spoon after anaesthesia, clean it of the softened bone and form a "fresh" full-fledged blood clot, but do not always completely scrape the hole. Inaccuracies in the treatment of periodontal and periodontal diseases in the absence of radiographs were observed in more than 75% of patients [8].

Thus, the qualification of the dentist-surgeon, preliminary X-ray examination, choice of analgesic, high quality haemostasis and management after the extraction wound is the key to the prevention of dry socket.

Dry socket (dolores post extractionem) is inflammation of the walls of the alveoli of the tooth with suppuration of the bone wound after its removal [9]. Dry socket is significant among the complications after tooth extraction surgery. According to the authors, dry socket occurs from 33.2% to 35% of the number of cases of all complications after tooth extraction [10].

In the monograph by O.O. Timofeev it is established that 33.2% of removed teeth are complicated by dry socket. Treatment of dry socket should be preceded by X-ray examination of the tooth removal site, in 92.3% of cases the radiograph reveals bone fragments, tooth root and others that are important in choosing treatment tactics.

If examination of a patient with dry socket does not reveal a blood clot in the hole, after anaesthesia it is necessary to cure the hole, clean it of the softened bone and form a "fresh" full-fledged blood clot. If a blood clot is partially preserved in the tooth cavity, the cavity should be rinsed with a warm solution of antiseptic

(furacillin, chlorhexidine, Givalex, Flupetsal, etc.) after anaesthesia the alveolar bone fragments, food debris and decay products should be removed. Then an excavator or a sharp surgical spoon is used to remove the surface layer of the blood clot and fill the hole with the drug (iodoform turunda, solcoseril gel, gelevin, oxycelodex, dermazin cream) [11].

The cause of dry socket is caused by objective and subjective factors. Objective causes of dry socket occur after removing of retained teeth, including third molars of the mandible, tooth removal surgeries, traumatic tooth extraction without a blood clot in the hole, after prolonged bleeding, repeated removal of adjacent tooth roots [12].

Anaesthesia, proper selection of tools for removal, compliance with the rules of asepsis and antiseptics, timely treatment and prevention measures minimize the possible complications after tooth and root removal [13].

Currently, the issue of haemostasis after tooth extraction is still topical, despite the sufficient number of haemostatic agents. Bleeding after tooth extraction is stopped by local haemostatic agents. Studies have shown the advantage of collagen sponge over hemophobin and oxycelodex [14]. An antiseptic sponge with kanamycin is promising for prevention of complications after tooth extraction. Antiseptic sponge with kanamycin has not only pronounced haemostatic, antimicrobial properties, but also stimulates reparative processes in the wound leading to its high therapeutic efficacy [14].

Patients with hemophilia A should have their teeth removed in the haematology department. Patients with pathology of the hepatobiliary system are allowed local targeted haemostatic agents [15]. The results of research prove that the causes of bleeding after tooth extraction might be mild and latent forms of coagulopathies and thrombocytopathies, which have certain clinical and laboratory features and require appropriate treatment [16, 17].

Clinical observations in patients with ventricular haemorrhage caused by bone trauma due to difficult tooth or atypical root removal, as well as the experience in use of gelevin, oxycelodex, traumacil and honsuride dental pins have been described [18]. Although the risk of inflammatory complications in such interventions is not significant, it is necessary to provide antimicrobial treatment of the wound with local antiseptics. The choice of a drug for local preoperative prevention of infectious complications in tooth extraction surgeries is determined by the nature of surgery, its duration, trauma, degree of wound infection, individual sensitivity to a drug, availability and other general and local factors [19, 20].

It is established that the oral cavity is under the influence of both the body and the environment. Clinical, epidemiological, microbiological studies have shown that the violation of the microbial biocenosis is one of the main factors in the emergence and development of dry socket [21-24].

the diagnosis of giardiasis in the oral cavity are described in some research. Yu.V. Lakhtin [25], studying the morphobiological features of oral protozoa, suggested the most rational methods of diagnosis and treatment of generalized periodontitis in the invasion of oral protozoa.

Thus, the literature suggests that, one of the reasons for development of dental diseases is a wide range of microorganisms. The use of microbiological technologies allows effective treatment and prevention of dental diseases [26, 27].

It is established that the main condition for rational antimicrobial therapy is the isolation of pathogens from the source of infection, their identification and determination of antibiotic susceptibility. Currently, due to the lack of bacteriological results on the day of drug administration, the choice of antibacterial drug, dosage and duration of its reception is determined mainly empirically [28]. The selected drug does not always adequately affect the microorganisms of the lesion, which does not improve the patient's condition and leads to significant disruption of microbiocenosis, reduced local and general immunological reactivity, deficiency or elimination of obligate microflora of the oral cavity. The irrational, often uncontrolled and widespread use of antibiotics at high rates of bacterial reproduction leads to acceleration of resistant strains, and, consequently, reduces the effectiveness of drugs used.

Thus, bacteriological research is urgent for the final diagnosis and treatment planning, justification of indications for antimicrobial therapy and evaluation of its effectiveness [29, 30].

It is proved that the microflora of the serous or purulent contents of the post-extraction area is quite diverse that should be taken into account in combined antimicrobial therapy

aimed at various components of microbial associations (including fungi). The variety of pathogens of nonspecific and specific inflammatory processes, their different sensitivity to antibiotics have determined a large number of antibacterial drugs that are offered in clinical practice. However, the widespread use of antibacterial therapy has led to an increase in the number of resistant strains and polyresistance. This is due to both chromosomal and non-chromosomal mechanisms (R-plasmids that provide the transfer of genetic information during recombination). R-plasmid genes control various mechanisms of resistance to antibacterial drugs, primarily the bacterial synthesis of enzymes such as β-lactamases, which destroy antibiotics.

There are different ways and methods of administration of antibacterial drugs. However, in the treatment of dry socket local administration of drugs are used in the form of solutions for short-term washing of the hole, water-soluble ointments – as part of complex drugs, antibiotics are introduced for electrophoresis etc. Administration of the main drugs may be combined with the of antibiotics in injections or tablet form.

The method of administration of the antibacterial drug into the body depends on its solubility, toxicity, irritant effect, ability to be absorbed through the gastrointestinal tract, and in some cases taking into account patient's condition. It is established that all antibacterial agents are divided into drugs for the most common use (drugs of choice), for severe cases and support. Maxillofacial infections require a similar treatment; antibacterial drugs, both for local and general treatment, can be used.

Antibacterial therapy to obtain data on the composition of the microflora and its sensitivity is chosen taking into account the literature on the highest frequency and structure of pathogens depending on the nosological form of the disease [30, 31].

According to the literature, main drugs for treatment (furacillin, lysozyme, balis-2) should be used. The sharp decrease in their antibacterial activity is caused by developed resistance to pathogens of purulent-inflammatory diseases of the maxillofacial area and neck (especially odontogenic); thus, their use is impractical.

Treatment and prevention of dry socket involves various antimicrobial drugs depending on the sensitivity of the isolated microorganisms. Since chemotherapeutic drugs are administered through the oral cavity to treat diseases of various organs and systems of the body, it is necessary to study their influence on the microbiocenosis of various human habitats, possible development of resistance of microorganisms to drugs.

The study of the physiological microbial system, microbial landscape and identification of oral microorganisms during various dental diseases provides not only objective data on the nature of the pathological process, but can significantly assist in diagnosis, choice of antibiotics, treatment plans, oral hygiene procedures, and formation of a protective physiological microbial system [31].

Nevertheless, the volume of primary medical care is large and a mass microbiological research in dental pathology is quite complex and economically unprofitable, it can be useful and justified. Various microorganisms can be detected using microbiological research methods such as bacterioscopic, bacteriological, serological, genetic and immunological.

The material for microbiological examination in dry socket is the contents of the hole, nose, throat, saliva, scrape from the tongue, especially in its posterior parts. It must be collected in the morning on an empty stomach with a sterile swab.

Therefore, the reasons for the development of dry socket are violation of microbiocenosis of the oral cavity towards the predominance of aggressive microflora, the complexity of microbiological methods, insufficient effectiveness of antibacterial drugs that necessitates the search for new methods of diagnosis and treatment.

The problem of prevention of postoperative complications, purulent-inflammatory diseases of the maxillofacial area is a topical issue for scientists and practitioners. In order to prevent postoperative complications in outpatient surgeries on the jaw, it is suggested to use drugs that contain chlorhexidine bigluconate [32-34]. Chlorhexidine bigluconate 0.05%, 0.2% aqueous solution in the form of irrigation, rinsing, applications, affects bacteroids, actinomycetes, is effective in the treatment of dry socket.

Chlorhexidine is established to have not only antimicrobial but also anti-inflammatory effect. For the favourable course of the first phase of the wound process using the film Diplendent HD for isolation of the bone wound in the first phase of healing of purulent-inflammatory diseases of the maxillofacial area new combined drugs were used: chlorhexidine +

calcium carbonate called elgidium "Pierre Fabre Medicament", chlorhexidine + metronidazole "Metrogil dent", chlorhexidine + lidocaine called lidochlor by Unique Pharmaceutical Laboratories; chlorhexidine + thyrotricin + lidocaine under the trade name "Trachisan" [35, 36].

For prevention of infectious-inflammatory complications and dry socket, restoration of microbiocenosis in surgical dentistry, phyto rinsing of the oral cavity "Naturosept" is used for patients after tooth extraction that reduces development of opportunistic microflora in the tooth cavity by 20%. [37, 38]. The drugs used for prevention: elgidium (toothpaste), elugel (gel, 0.2%), eludril (solution, 0.1%). This preparation allows heeling the wound in the oral cavity as a "clean" wound and preventing microbial infection during surgery.

Antiseptic and disinfectant "D08A" are the drugs to improve trophism, "D0ZAN" to stimulate regeneration processes. It is recommended to use doxidine, gramicidin, furagin, chloramphenicol in various combinations: in the form of solution, ointment, gel [38].

In outpatient surgical and dental practice, antibiotic prophylaxis is prescribed in two cases: high risk of postoperative infection, secondary (opportunistic) infection, which develops on the background of a burdensome history and is a direct threat to the patient's life. General requirements for the choice of antibiotic for dental surgeries, i.e.: the spectrum of action of the antibiotic should cover microflora of the patient, the drug should at least induce resistance of microflora, the antibiotic should easily penetrate into the tissues in the area of surgery and excrete antibiotic fluid, gums in tissues, wounds, should exceed the minimum inhibitory concentration for possible pathogens during surgery, the antibiotic should be characterized by minimal side effects (do not interact with anaesthetics, analgesics and other drugs). For preoperative prevention, the antibiotic is chosen according to the peculiarities of its pharmacodynamics, pharmacokinetics and spectrum [39-42].

Givalex is one of the remedies that can be used for application and irrigation with preventive and curative effects in dry socket. The antimicrobial actiion of Givalex is caused by hexitidine, which has antibacterial effect on gram-positive, gram-negative microorganisms. Givalex has antifungal and weak bactericidal action [41].

A new antiseptic drug "Gorosten" is promising in prevention of dental diseases [43-47]. The antiseptic "Natursept" of antiseptic, wound-healing and anti-inflammatory action, is quite effective [37].

In contemporary dental practice, Ukrainian-made Dimexid is most often used in combination with well-known antiseptic, disinfectant, antibacterial, anti-inflammatory, anaesthetic agents in order to expand the spectrum of action on the resistant microflora of the oral cavity, to achieve the best clinical effect. The use of Dimexid with various drugs in the complex treatment of dental patients in outpatient dental practice has proved to have positive results. The day reduction or control of pain, facial oedema, cessation of discharge, normalization of body temperature, appetite, sleep, full recovery were evidenced. The authors confirmed significant antiseptic and anti-inflammatory effect of Dimexid and the feasibility of its use in treatment of various inflammatory diseases in dental patients [48]. In addition to antimicrobial action, Dimexid has a local anesthetic, anti-inflammatory, desensitizing, antifungal, high penetrating action, activates and potentiates the effect of drugs. The largest arsenal of drugs is used in the postoperative period, especially widely represented means for processing the postoperative hole. Thus, parasept, autopack, and septopack bandages are effective for interventions on the alveolar process. Sodium mefenamate and methyluracil are administered to reduce the treatment duration.

The effectiveness of "Aloroma" and Trichopol, "Alvostaz" and "Povisep", "Alvogyl" and polybiolin-curiosone mixture for treatment of dry socket has been proven [49, 50]. Currently, according to the Law of Ukraine "On Medicinal Products", a new drug flurenizide has been widely used [51-55]. "Flupetsal", the composition based on flureniside, has antimicrobial and immunomodulatory properties and significant therapeutic effect [56-58].

Conclusions

Thus, the contemporary drug composition of "Flupetsal" according to the developed method is quite effective, affordable, low-cost for treatment of patients with dry socket.

Conflict of Interests

Authors declare no conflict of interest.

СУЧАСНІ ПІДХОДИ ЩОДО ДІАГНОСТИКИ, ПРОФІЛАКТИКИ ТА ЛІКУВАННЯ АЛЬВЕОЛІТУ (огляд літератури)

Н.С. Гутор
ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І.Я. ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ, ТЕРНОПІЛЬ, УКРАЇНА

Вступ. *Екстракція зуба є найчастішим оперативним втручанням в амбулаторній практиці хірурга-стоматолога. У більшості випадків загоєння кісткової рани проходить без ускладнень. Однак у частини пацієнтів перебіг загоєння ускладняються гострим запальним процесом – альвеолітом, частота виникнення якого зростає по мірі росту травматичності оперативного втручання. У соматично здорових пацієнтів при типовому видаленні альвеоліт виникає у 2,55%, при складному – у 9,84%, при атиповому видаленні нижнього зуба мудрості – у 31,03% випадків. При наявності діабету відсоток виникнення альвеоліту при типовому видаленні значно вищий і за даними різних авторів складає 9,7-13,5%.*

Мета. *Метою нашого огляду було дослідження опублікованої інформації та її аналіз щодо застосування сучасної діагностики, профілактики та лікування у хворих на альвеоліт.*

Методи. *Науковими джерелами були статті у зарубіжних періодичних виданнях з хірургічної та терапевтичної стоматологій, мікробіології, електронні ресурси, патенти.*

Результати. *На сьогоднішній день відомо багато методик, методів, схем, композицій для лікування різних форм альвеоліту. Найчастіше при цьому використовуються антибактеріальні препарати або їх комбінації з іншими лікарськими препаратами. Однак антибактеріальним препаратам не завжди притаманний виражений протизапальний ефект через високу резистентність мікрофлори ротової порожнини. Раціональним в цих випадках є місцеве застосування лікарських препаратів в вигляді композиції з тривалою антисептичною, протизапальною та анальгезуючою дією.*

Висновки. *Клінічно підтверджено дію композиції під назвою „Флупетсаль", яка містить протимікробний та імуномодуляційний лікарський засіб флуренізид для лікування хворих на альвеоліт, властивості наявних інгредієнтів забезпечують високий знезаражувальний ефект, запобігають розвитку процесу запалення у тканинах та його переходу в гнійно-некротичну фазу. Сучасний, ефективний метод лікування хворих на альвеоліт здійснюють згідно з розробленою методикою.*

КЛЮЧОВІ СЛОВА: альвеоліт; лікування; композиції; лікарські засоби; „Флупетсаль".

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BONE TISSUE METABOLISM AND CHANGES IN THE ORAL CAVITY IN REDUCED FUNCTIONAL ACTIVITY OF THE THYROID GLAND (literature review)

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Background. *Decreased functional activity of the thyroid gland leaves affects many organs and systems as well as bone tissue, pathological changes of which in the oral cavity are most often observed in periodontitis. However, the relationship between thyroid hypofunction and periodontitis or other inflammatory diseases of the oral cavity is still not confirmed.*

Objective. *The aim of the review was to study the published information and analyse bone metabolism and its relationships between autoimmune thyroiditis and oral diseases.*

Methods. *The articles in foreign periodicals on endocrinology, pathophysiology, dental surgery and therapy were the scientific sources for research.*

Results. *Understanding the mechanisms of bone metabolism under the action of thyroid hormones is an important aspect of treatment and diagnostic process, as local treatment of dental pathology without reducing the impact on systemic factors ultimately does not have any positive result. Decreased functional activity of the thyroid gland leads to homeostasis imbalance in the body. The thyroid hormones are important for bone metabolism, publications on periodontitis incidence in cases of autoimmune pathology of the thyroid gland are the most common. However, despite the number of studies, most authors agree that they are currently insufficient to clearly establish a causal relationship between autoimmune thyroid disease and maxillofacial disorders.*

Conclusions. *The study expands our knowledge, but there is still a need for further detailed studies that would clearly define the mechanisms of development of the disorders of the oral bone tissues and its relationships with autoimmune pathology of the thyroid gland.*

KEYWORDS: periodontitis; thyroid gland.

Introduction

Increased attention to the diseases of the thyroid gland is caused by challenging statistics on the increase in its incidence according to the Ministry of Health of Ukraine [1]. This trend is traced in the recent studies [2], their results show that the incidence of thyroid pathology has increased and is 46% of the total endocrinological morbidity. According to the author, during the last 5 years in the western region of Ukraine the incidence of hypothyroidism increased by 28.4%, the increase of thyrotoxicosis – by 8%, and the prevalence of thyroiditis – by 12.7% [2]. These indicators are higher than the national average indicators and that of the north-eastern regions.

According to official WHO data, about 1.5 billion people suffer from thyroid disease at present. However, despite the effective treatment of endocrine pathology, the tendency to its reduce in the world is not observed [3].

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Review

Hypothyroidism, as the most common pathology of the thyroid gland, surely affects the functions and morphology of all tissues and organs, the maxillofacial area as well. It is established that insufficient thyroid hormones adversely affect both tooth mineralization, bone mineral density and calcium-phosphorus metabolism that is clinically observed in the oral cavity as periodontitis, gingivitis or lesions of the tooth hard tissues [4,5]. Understanding the mechanisms of bone metabolism under the action of thyroid hormones is an important aspect of treatment and diagnostic, as local treatment of dental pathology without reducing the impact on systemic factors does not have any positive result [6,7].

It is established that bone tissue is a constantly renewing tissue where remodeling processes take, place i.e. the processes of formation and destruction of osteotissue, provided by osteoblasts, osteoclasts and osteocytes, which functional activity depends on exogenous and endogenous factors, some of which are

thyroid hormones. Although, according to Allen M.R. et al. [8] there are 2 types of remodeling. The first type – targeted remodeling, in which a specific local signal directs the osteoclast to a specific location to begin remodeling (e.g., in the areas of microdamage); the second – chaotic remodeling, a random process in which osteoclasts begin remodeling without any signaling. This type of recovery is significant in calcium homeostasis. At the cellular level, both types of remodeling are equal [8]. According to present scientists, the remodeling cycle has 5 stages (Fig. 1) [9].

In the *first* stage, the stage of activation, the stimulating signals by osteocytes and their transmission to cells of osteoclastic diferon are recognized. In response to this process, monocytic-macrophage cells are attracted to the bone surface, stimulated, proliferated and differentiated into osteoclasts. At the heart of the molecular understanding of regulation, RANKL (receptor activator of nuclear factor kappa B ligand) is a transmembrane ligand of the nuclear factor activator receptor produced by osteoblasts that activates lymphocytes and macrophages. RANKL molecules may remain attached to the surface of osteoblasts or stromal cells for some time. RANK is a transmembrane receptor of nuclear factor activator. RANKL interacts with RANK, which is accompanied by the fusion of several osteoclast progenitor cells into one large structure and mature multinucleated osteoclasts are formed. Thus, osteoblasts regulate formation of osteoclasts [11]. OPG-osteoprotegerin is a protein synthesized by osteoblasts and bone marrow stromal cells. It is proved that at the stage of osteoclast formation, the process can be blocked by the protein OPG-osteoprotegerin, which can bind to RANKL, that prevents formation of the RANKL/RANK complex and thus stops resorption processes [12].

According to recent studies [13], not only in osteoblasts but also in osteocytes, most of the recently synthesized RANKL form a protein complex with OPG and is selectively directed to lysosomes. Only a small fraction of newly synthesized RANKL, which does not form a complex with OPG, is transported to the cell surface. Subsequently, transmembrane RANKL is delivered to the surface of osteoclast precursors to stimulate RANK, and induce activation of the subsequent signaling pathway. According to the authors, the ability of osteocytes to support formation of mature osteoclasts probably depends on the number of RANKL molecules present on their cell surfaces. However, the way in which osteocytes embedded in the bone matrix deliver transmembrane RANKL to the cell surfaces of osteoclast precursors that are localized in the bone marrow cavity should be elucidated.

The *second* stage is the stage of resorption – due to production of enzymes osteoclasts destroy the bone matrix. According to some scientists, at this stage, activated osteoclasts are phagocytes for bone. Lysosomal collagenase is synthesized in large quantities that leads to disruption of the order in the structure of collagen. The products of hydrolysis enter the

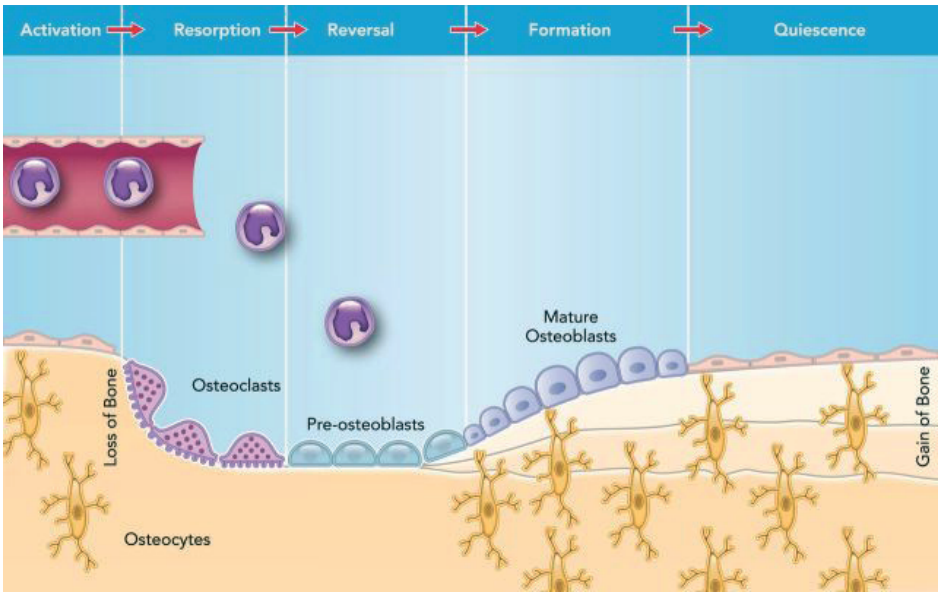

Fig. 1. *Physiological bone remodeling, J.A. Siddiqui and N.C. Partridge [10].*

osteoblast from the "corrugated bristles" by endocytosis, and are released from the basement membrane, which is in contact with the blood vessel. The acidic environment in the area of resorption promotes leaching of calcium from apatites; the so-called "resorptive bone gaps" are formed; as a result, calcium and phosphates get into the blood.

The *third* stage, the stage of reversion, osteoclasts undergo apoptosis, they are replaced by mesenchymal cells, which differentiate into osteoblasts [15]. Active osteoclasts synthesize and secrete acid phosphatase, which dephosphorylates osteopontin, a sialoprotein that attaches to cells in the resorption zone. The connection with the bone surface becomes weak, so the resorption gradually decreases. A cementing line (a layer of secretory glycoproteins) is formed on the resorbed surface, which is able to hold colonies of osteoblasts, an additional prerequisite for this is the availability of local osteoprogenitors [16].

The *fourth* stage, the stage of bone formation, osteoblasts synthesize the main organic substance of the bone matrix – collagen and substances that regulate mineralization (osteocalcin, osteonectin, etc.) [17]. The "matrix bubbles" of osteoblasts are significant in the process of mineralization. Amorphous $Ca_3(PO_4)_2$ is formed first in them, and later – hydroxyapatite: "matrix bubbles", which enter the extracellular space, contain high concentrations of calcium ions, according to Vavilova T.P., in 25-50 times more, than in osteoblasts, as well as enzymes: alkaline phosphatase, pyrophosphatase. In the intercellular matrix, membrane vesicles are destroyed with the release of calcium ions. Due to the influence of alkaline phosphatase, Ca^{2+} ions combine with PO_4^{3-}, resulting in the formation of amorphous calcium phosphate. At the same time, Ca^{2+} and PO_4^{3-} ions bind to collagen and non-collagen proteins and matrix is formed, which is accompanied by the formation of nuclei. On the formed nucleus there are spiral structures, the growth of which takes place on the principle of adding new ions. The step of such a spiral is equal to the height of one structural unit of the crystal. Crystal formation leads to the appearance of other crystals, this process is called epitaxis or epitaxic enucleation [18].

Thus, mineralization occurs through the formation of calcium phosphate compounds that enter the bloodstream and their subsequent crystallization into hydroxyapatite followed by deposition of calcium hydroxyapatite along the collagen fibers [18]; osteoblasts play the main role in collagen synthesis [10].

The *fifth* stage, the final stage, is characterized by differentiation of osteoblasts into osteocytes. After the bone formation stage is finished, the resting stage takes place, the osteoblasts are walled up in the matrix created in them, they lose activity and transform into osteocytes [19], which even recently were considered low metabolically active cells. But, as has been discovered, due to the mechanosensory properties that occur through the induced flow of fluid through the lacuno-tubular system, they regulate remodeling processes [20] and, as studied by Cappuli [21], regulation is carried out by sclerostin protein (SOST), which inhibits osteoblast differentiation.

The process of remodeling is regulated by numerous hormonal and local factors, neuroendocrine and metabolic (Fig. 2) [10]: glucocorticoids reduce synthesis of osteoblasts, which slows down formation of bone tissue; the influence of thyroid hormones (thyroxine and triiodothyronine) increases activity of osteoclasts, which contribute to catabolism of bone tissue. At the same time, sex hormones, especially estrogens, have antiresorptive properties. Somatotropic hormone stimulates proliferation of osteoblasts and growth factors. It is established that with a decrease of the concentration of Ca^{2+} ions in the blood the secretion of parathyroid hormone (PTH) increases, which is produced by cells of the parathyroid glands, and under its influence activates osteoclasts in bone tissue that increases bone resorption. As Ca^{2+} ions increase, the hormone calcitonin is secreted in the blood, which is produced by parafollicular thyroid cells and which bone mineralization increases and the number of osteoclasts reduces, i.e. resorption processes inhibits and, consequently, bone formation accelerates.

Vitamin D is important in regulation of concentration of Ca^{2+} ions in the blood, which are involved in the biosynthesis of Ca^{2+}-binding proteins required for intestinal calcium absorption, renal reabsorption and mobilization of calcium from bones. Recently, evidence has emerged that vitamin D is involved in development of many autoimmune diseases, including patients with autoimmune thyroid disease (AITD) [22].

It is established that thyroid hormones directly affect both remodeling processes, as they activate both osteoblasts and osteoclasts, and the process of calcium-phosphorus me-

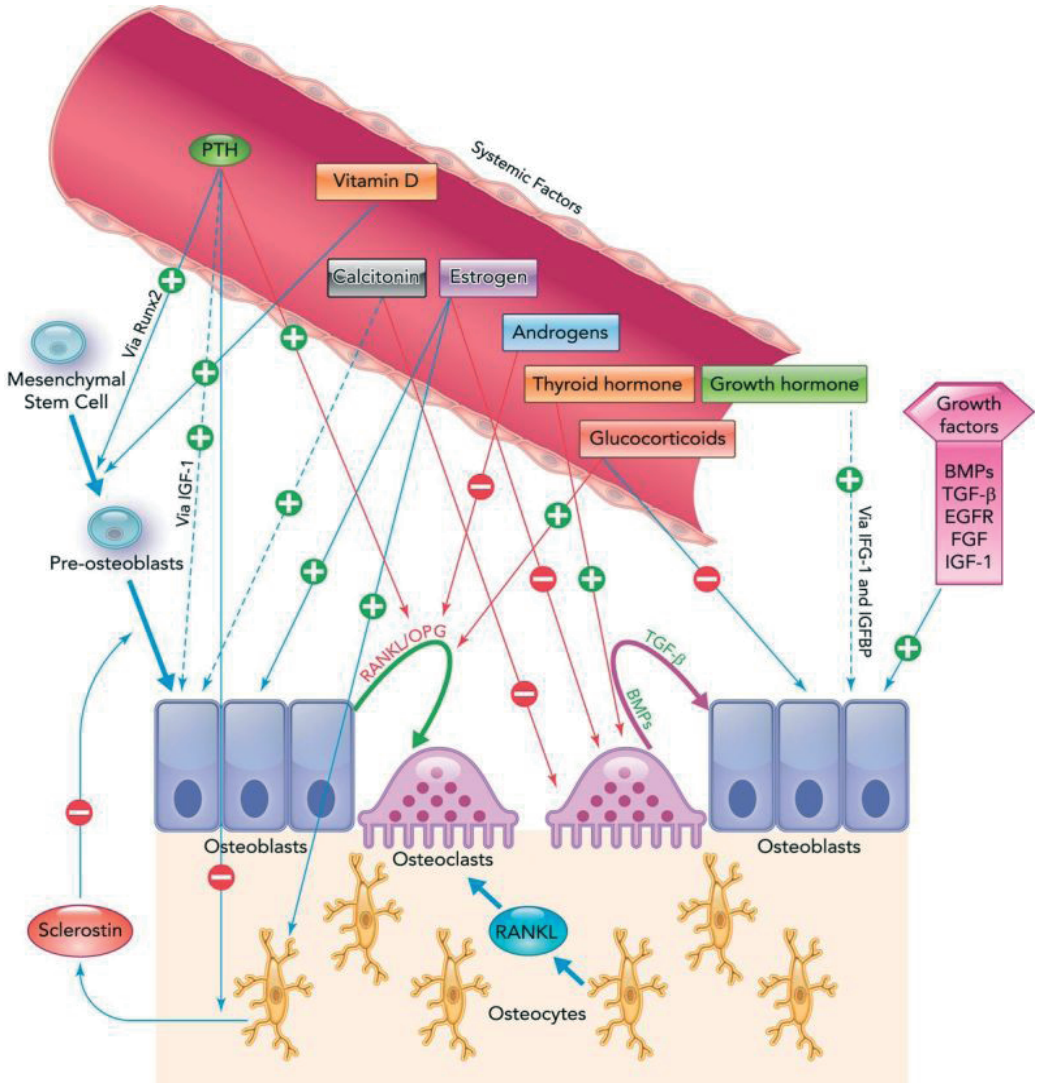

Fig. 2. *Systemic regulation and growth factor of bone remodeling, J. Siddiqui, N. Partridge [10].*

tabolism [24]. The thyroid gland secretes thyroxine (T_4), triiodothyronine (T_3) and calcitonin. The functional activity of the gland is regulated by thyroid-stimulating hormone (TSH), which is synthesized by the pituitary gland in response to the secretion of thyroliberin (TRG) by the hypothalamus. With a decrease in the concentration of thyroid hormones the secretion of TSH increases resulting in an increase in their formation in the thyroid gland, and, vice versa, with an increased concentration of thyroid hormones the formation of TSH decreases [17, 24]. Thus, this cooperation of the main endocrine gland functions on the principle of "negative feedback" that ensures a constant level of hormones. Violation of the concentration of one of the elements of the chain leads to changes in others that ultimately leads to dysfunction of both the endocrine glands and other organs and systems that depend on them.

In the context of bone tissue, according to Pankiv I.V. [4], and as seen at the scheme, thyroid hormones affect bone metabolism by increasing the activity of osteoclasts, which contribute to bone catabolism. There are studies [4, 25, 26], in which the authors indicate of osteoporosis of bone tissue with underlying hypothyroidism. According to [4], in persons with thyroid pathology, changes in bone mineral density were detected in 59 (39.9%) cases: osteopenia – in 45 (30.4%) and osteoporosis – in 14 (9.5%) cases. The incidence of osteopenia and osteoporosis was likely to increase in all groups of patients with thyroid functional disorders. The main factor that leads to decrease in bone strength in patients with thyroid disease is excessive or insufficient production

of thyroid hormones, as well as treatment with suppressive doses of levothyroxine. It is proved that the effect of thyroid hormones on the body cells is caused by the presence of receptors (TR) on their surface (Fig. 3). It is established that there are several types of thyroid receptors: TRα1, TRα2, TRβ1, TRβ2 [10]. It was established that only TRα and TRβ receptors on the surface of osteoblasts and chondrocytes were detected in bone cells [28]. Accordingly, T_3 (triiodothyronine) induces osteogenesis by direct action on osteoblasts. However, recent studies [29] have proved that expression of thyroid receptor (TR) genes α1 and β1 is confirmed in osteoclasts, but it is still indefinite whether triiodothyronine (T_3) stimulates osteoclast activity directly or whether these processes are the result of T_3 action in osteoblasts, osteocytes or other cells.

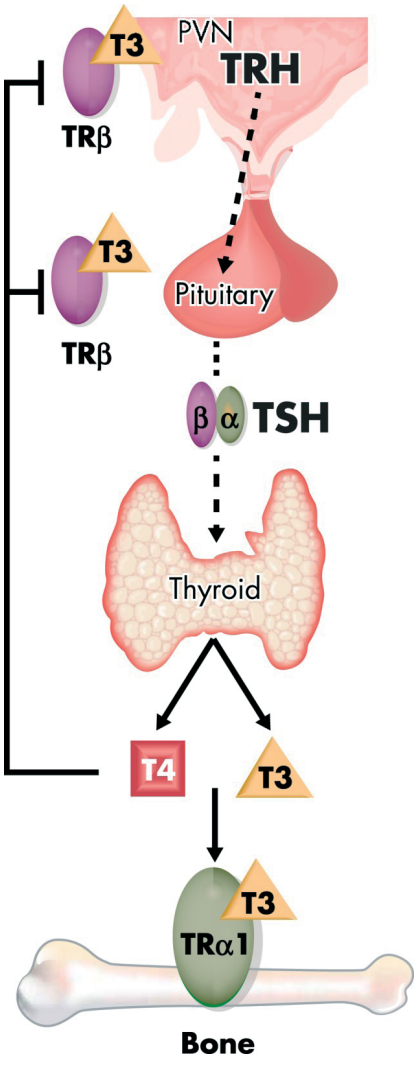

Fig. 3. *The thyroid gland secretes the prohormone T4 and the active hormone T3, and circulating concentrations are regulated by the classical endocrine cycle of negative feedback, which maintains the physiological feedback between TSH and T_4 and T_3. PVN, paraventricular nucleus (Bassett J.H, Williams G.R.) [28]*

As for the TRβ2 receptor, there is evidence that it is associated with the hypothalamus and pituitary gland, where it inhibits the secretion of TRG and TSH, so the hypothalamic-pituitary-thyroid relationship is important in regulation of bone metabolism.

To date, there are still debates on the key role in the functioning of bone tissue:by TSH or thyroid hormones [29]. The recommendations of the American Thyroid Association [30] state that serum TSH levels are one of the most informative indicators of thyroid function, and the Association recommends that all patients have serum TSH levels determined from the age of 35 and monitored every 5 years, which is an important diagnostic aspect.

However, confirmation is found in the literature: hypothyroidism causes general hypometabolism [31], a decrease in osteoblast formation and resorption of osteoclasts, and leads to low bone metabolism or slowing down the remodeling process. According to the author, the processes of osteo formation are slowed down by 50%, the processes of resorption – by 40% [31]. Calciuria decreases, serum concentrations of osteocalcin and alkaline phosphatase decrease, but the concentration of parathyroid hormone and vitamin D in the serum may increase [31].

Analysing this data and drawing parallels with clinical symptoms, scientists pathogenetically distinguish the following types of hypothyroidism:

1. Primary hypothyroidism caused by primary pathology of the thyroid gland, which is divided into hypothyroidism due to a decrease in the amount of functionally active tissue of the gland and impaired biosynthesis of thyroid hormones.

2. Secondary (pituitary) hypothyroidism caused by a decrease in TSH production.

3. Tertiary (hypothalamic) hypothyroidism due to a decrease or production of thyroliberin.

4. Peripheral (tissue) resistance to thyroid hormones [24].

Autoimmune thyroiditis (AIT) is the most common cause of primary hypothyroidism [32]. Taking into account the complex mechanism of metabolic thyroid hormones metabolism, the question is whether thyroid dysfunction affects the course of oral diseases, the development of which is accompanied by destructive processes in bone tissue.

Periodontal diseases are foremost in the structure of dental pathology due to the significant spread among the population of Ukraine [33]. This pathology is characterized by inflammatory-destructive changes of the periodontium, progressive nature of their course and leads to early tooth loss [34]. According to recent literature, the causes for this are both local and systemic factors [35], and sometimes a combination of both. Local factors include microbial film, small orifice of the mouth, pathology of the bridles and the existing strands of the mucous membrane, crowding of the teeth, impaired occlusion. Regarding the systemic factors that contribute to development of periodontal diseases, chronic cardiovascular, digestive and endocrine diseases are important. Most scientists today are inclined to the dominant role of the influence of microorganisms and tissue inflammatory response as a consequence of their activities [36]. The most common microorganisms of the dental microbial film are gram-negative anaerobic bacteria Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola, Prevotellaintermedia [37, 44]. The mechanism of action of microorganisms is explained by their penetration through the connective tissue epithelium of the gingival sulcus that disrupts the integrity of the gingival junction and affects the periodontal tissues located deeper [37]. In cases of the inflammatory process in the periodontium microcirculation is violated that is accompanied by an increase in vascular permeability with insudation of blood plasma proteins into the walls of blood vessels and perivascular tissue. It has been proved that pathology in periodontal vessels is a trigger for progression of periodontitis [38]. In a comparative study of the microcirculation of healthy patients and in the examination of persons with periodontitis of varying severity (1-3 degrees), (127 people), according to laser Doppler flowmetry, it was found that in periodontitis 1st degree severity, in hemodynamics is decreased, compare to the healthy group of people, congestion in the microcirculatory tract is present with further development of rheological disorders. In generalized periodontitis of the 2nd degree, the main indicators of tissue blood flow are reduced, compare to the previous group, and in periodontitis of the 3rd degree microcirculatory disorders worsen with the involvement of all parts of compensatory regulation [38]. Thus, violation of microcirculation in the presence of microbial mechanisms leads to slowing of blood flow, venous stasis, impaired vascular transport [40].

Due to the possible systemic effects of thyroid dysfunction, periodontal tissue microcirculation in this aspect was studied by Scardina G.A., Messina P. (2008) [41], who assessed morphological microcirculation of interdental papillae in patients with Hashimoto's thyroiditis and possible associated periodontal disease. It was emphasized that the group of healthy patients deliberately did not involve the persons with conditions that disrupt microcirculation, such as diabetes or hypertension. All patients did not smoke. Microcirculation was assessed by capillaroscopy. For each patient, visibility, course, tortuosity, average capillary loop size and number of visible capillary loops per square millimeter were investigated. In patients with Hashimoto's thyroiditis, a reduced capillary caliber, as well as a greater number and tortuosity of capillary loops were evidenced. This study showed that changes in the capillaries in patients with Hashimoto's thyroiditis occurred in cases of violation of gums microcirculation that is characteristic of periodontitis.

The opinion that periodontitis is a multifactorial disease with a microbial initiator, the manifestation and progression of which is predisposed by a wide range of factors, one of which is Hashimoto's thyroiditis, is more and more popular [42, 43]. According to Molaris A. et al. [42], after analyzing the data of 30 articles on the relationship between periodontitis and Hashimoto's thyroiditis regarding etiopathogenetic mechanisms, have established that it occurs because some of these mechanisms are accompanied by vascular endothelial dysfunction, microcirculation disorders, as well as due to the impact of hypothyroidism on alveolar protease metabolism, but a causal relationship between the two nosologies requires further research.

According to Patil B., Patil S., Gururaj, T. (2011) [7], their study was initiated due to the lack of effective local therapy of periodontitis in thyropatients. Kothiwale S. et al. [5] presented a very interesting study regarding the impact of thyroid hormone dysfunction on the progression of periodontitis, systemic health of the patient, in which local treatment of periodontal tissues as a complex with endocrine compensation was proved. It was emphasized that the etiotropic phase of dental treatment lasted 8 weeks with the prescribed 150 mg of systemic thyroxine per day. During the dynamic ob-

servation, the hygienic index of the oral cavity improved, but the bleeding did not disappear. After 12 weeks of follow-up, after stabilization of thyroid hormones, a clear decrease in gingival bleeding was evidenced. The need for frequent professional evaluation, training of patients, motivating them to frequent systematic examinations was emphasized, as the treatment of such patients and achieving long-term remission would provide a positive result only in endocrinologist-dentist tandem.

According to Brankhar R.R. et al. (2017) [43] the endocrine system works together with the immune system. Despite the fact that the bilateral effects of systemic diseases on the periodontium are proved, there are a few studies on the effects of periodontal therapy on hormone levels. In the study, the effect of non-surgical periodontal therapy (NSPT) on serum stimulating hormone (TSH) levels in patients with hypothyroidism and periodontitis was assessed. Clinical parameters and serum TSH levels were recorded at baseline in the experimental and control groups and compared with TSH data in 3 months after NSPT in the patients with hypothyroidism. The results of the study showed that NSPT was significant in improving the condition of the periodontium by reducing inflammatory markers and thus affecting thyroid hormone, a significant decrease in TSH in patients with hypothyroidism in 3 months after NSPT.

Chingiz Ragim Ogly Rakhimov, (2020) [44] presented data on the clinical efficacy of hyaluronic acid in the treatment of periodontal disease in patients with hypothyroidism. According to the evaluation of the main hygienic and periodontal indices, it was found that a decrease in the content of thyrohormones led to an increase in the frequency and inflammatory-destructive forms of periodontal disease. In such patients, high-frequency of Porphyromonasgingivalis (25% and 15% in somatically healthy patients) and increased colonization of yeast-like fungi of the genus Candida albicans were evidenced in the oral cavity. After the treatment, there was a positive clinical dynamic, but in patients with impaired gland function had worsening of the oral cavity in a month that confirmed the idea of ineffectiveness of only local dental treatment and the need for dynamic monitoring of hormonal status.

There are studies on effectiveness of intraligamentous administration of vitamin D and calcium in the treatment of chronic periodontitis associated with hypothyroidism. In 3 months, there was a significant decrease in mobility, pocket depth and bleeding in the treatment of chronic periodontitis associated with hypothyroidism. The need for clinical trials with a large sample size and long-term observations was emphasized [45]. The significance of vitamin D in the development of autoimmune thyroiditis was covered by Bizzaro G. et al. [46, 47].

There is no doubt that patients with established hypothyroidism need a replacement therapy, and the study of periodontal status when taking thyroxine is the basis of further research [48]. After analyzing the plaque index, bleeding index, pocket probing depth [PPD], level of clinical attachment [CAL] and radiological parameters, in the study group (52 patients) statistically significantly higher PPD and loss of clinical attachment compare to the control group was established. With the beginning of treatment of periodontitis and hypothyroidism improvement in oral hygiene and a decrease in bleeding gums was evidenced. Regression analysis showed that hypothyroidism and thyroxine replacement therapy were important predictors of PPD and CAL, but it still requires further study. The same opinion is traced in the study by Hajer A. Aldulaijan et al. (2020), who analyzed 847 publications and applied their inclusion and exclusion criteria; thus only 29 publications were selected, which were more critically analyzed. As a result, only four publications were used to further assess the hypothyroidism-periodontitis relationship, including one research note on association between hypothyroidism and periodontitis. Hence, further well-controlled, clinical and immunological studies are needed to confirm this relationship [6].

Conclusions

The results of the studies prove that there is a significant effect of the thyroid gland on the state of the oral cavity that can be manifested by periodontitis, which is accompanied by bone destruction and inflammatory processes in the gum tissue. Local treatment of dental pathology without correction of thyrohormonal status does not provide effective treatment, so the correct diagnosis, selection of treatment and medical cooperation of a dentist and endocrinologist is necessary. Such disorders are common, but there is still a lack of accurate and improved examinations of this problem, which will be the goal of our further research in the future.

Conflict of Interests

Authors declare no conflict of interest.

Authors' Contributions

Olha Skochylo – investigation, formal analysis, writing – original draft. *Svitlana Boitsanyuk* – formal analysis, writing – reviewing and editing, data curation. *Nataliya Tverdokhlib* – conceptualization, methodology, writing – reviewing and editing.

ОСОБЛИВОСТІ МЕТАБОЛІЧНОГО ОБМІНУ У КІСТКОВІЙ ТКАНИНІ ТА ЗМІНИ ЗІ СТОРОНИ РОТОВОЇ ПОРОЖНИНИ НА ГРУНТІ ЗНИЖЕННЯ ФУНКЦІОНАЛЬНОЇ АКТИВНОСТІ ЩИТОПОДІБНОЇ ЗАЛОЗИ (огляд літератури)

***О.В. Скочило, С.І. Бойцанюк, Н.О. Твердохліб**

ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І.Я. ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ, ТЕРНОПІЛЬ, УКРАЇНА

Вступ. *Зниження функціональної активності щитоподібної залози залишає свій слід на багатьох органах та системах. Не виключенням є і кісткова тканина, патологічні зміни якої в ротовій порожнині найчастіше спостерігаємо при пародонтитах. Проте, все ще залишається не підтвердженим взаємозв'язок між гіпофункцією тиреоїдної залози та пародонтитом чи іншими запальними захворюваннями ротової порожнини.*

Метою *нашого огляду власне, і було дослідження опублікованої інформації та її аналіз щодо метаболізму кісткової тканини та її взаємозв'язоку між автоімунним тиреоїдитом та захворюваннями ротової порожнини.*

Методи. *Науковими джерелами були статті у зарубіжних періодичних виданнях з ендокринології, патофізіології, хірургічної, терапевтичної стоматологій.*

Результати. *Розуміння механізмів кісткового метаболізму під дією гормонів щитовидної залози є важливим аспектом лікувально-діагностичного процесу, оскільки місцеве лікування стоматологічної патології без виключення впливу на системні чинники у підсумку не дає позитивного результату. Зниження функціональної активності щитоподібної залози призводить до дисбалансу в гомеостазі організму. Оскільки гормони щитоподібної залози відіграють важливу роль у обміні кісткової тканини, то найчастіше зустрічаються публікації стосовно виникнення пародонтиту на фоні автоімунної патології щитоподібної залози. Проте, незважаючи на існуючі дослідження та зафіксовані зміни, більшість авторів згідні з думкою, що таких досліджень на даний час є недостатньо, щоб чітко встановити причинно-наслідковий взаємозв'язок між автоімунним процесом щитоподібної залози та патологією щелепно-лицевої ділянки.*

Висновки. *Представлені дані розширюють існуючі знання, проте все ще існує потреба в подальших сучасних детальних дослідженнях, які б чітко дали відповідь на механізми виникнення та розвитку взаємозв'язку між автоімунною патологією щитоподібної залози та станом кісткової тканини ротової порожнини.*

КЛЮЧОВІ СЛОВА: пародонтит; щитоподібна залоза.

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EVALUATION OF IMMUNOBLOT RESULTS FOR DETERMINATION OF ANTIBODIES TO LYME DISEASE PATHOGENS IN CHILDREN OF TERNOPIL REGION

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Background. *Lyme disease (LD) is a multisystem disorder caused by Borrelia burgdorferi and other similar tick-borne Borrelia.*

Objective. *The aim of the research was to compare the results of the serological examination of children with different forms of Lyme disease.*

Methods. *We observed the group of children (n=178) aged 1 to 14 years who were bitten by ticks. The control group consisted of 30 healthy children. Ticks were identified using a stereomicroscopic SEO system which included a stereomicroscope, a colour digital camera and a photoadapter. B. burgdorferi sensu lato (sl) (B. burgdorferi sensu stricto, B. afzelii and B. garinii), B. miyamotoi, A. phagocytophilum DNA in blood were determined by real-time PCR. Baseline investigations related to clinical and immunological studies, including ELISA and Immunoblot, were performed.*

Results. *The survey covered 178 child parents bitten by ticks. Borrelia burgdorferi sensu lato (B. afzelii, B. burgdorferi sensu stricto and B. garinii), B. miyamotoi and A. phagocytophilum were identified. Serological results in children with different forms of Lyme disease were compared.*

Conclusions. *It is established that B. burgdorferi sensu lato; B. miyamotoi; and A. phagocytophilum are pathogens that cause erythema migrans in children. The presence of specific IgG (only positive results) to B. burgdorferi s.l. by immunoblot was confirmed in 83.8% of individuals who had positive and intermediate results in the ELISA test.*

KEYWORDS: Lyme disease; borreliosis; ELISA; immunoblot; tick bite.

Introduction

Lyme disease (LD) is a multisystem disorder caused by Borrelia burgdorferi and other similar tick-borne Borrelia.

This acute systemic disease often occurs in children and is characterized by the presence of erythema migrans (EM), and in some untreated patients of inflammatory arthritis, erythema migrans as well.

Lyme disease, caused by *Borrelia burgdorferi*, is the most common vector-borne disease. In Western Europe it is caused by *B. afzelii ma B. garinii*, [2] whereas in the United States – by *B.burgdorferi* [3]. The epidemics of Lyme disease is challenging in Poland and Ukraine. In western Ukraine, *B. burgdorferi s.l* were revealed in 14.2-17.2% of adult *Ixodes scapularis* ticks [4]. In 2020-2021, the disease incidence in Ukraine and Ternopil region was 10.62 and 20.05 per 100 thousand population, respectively (Public Health Center.org.ua).

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On the basis of MKH-10 allocate "Lyme disease" A69.2. Clinical manifestations of Lyme disease can be divided into three stages: the early localized stage characterized by erythema migrans at the site of the tick bite, multiple Erythema migrans**,** Borrelia lymphocytoma; early disseminated form with early symptoms confined to peripheral nervous system, carditis or arthritis, late disseminated form – late symptoms confined to peripheral nervous and central nervous system, manifestations of late arthritis, cardiac complications. The pathogenesis, ecology, and epidemiology of Lyme disease are well described; the developed and suggested antimicrobial treatment is very effective [2, 5].

The study aimed to assess the incidence of clinical suspicion of LD among children in Ternopil region (Western Ukraine) by serological examination of children bitten by ticks.

Methods

The children's blood tests were studied in the laboratory of the Centre for the Study of

Lyme Disease and Other Tick-Borne Infections of I. Horbachevsky Ternopil National Medical University. Ticks were identified using a stereomicroscopic SEO-IMAGLAB system.

Special defining tables were used for identification of ticks [6]. Databases regarding the incidence of LD in children of Ternopil region in 2017-2021 were used to evaluate retrospective results.

This study consists of two parts : the first part describes the data from the questionnaire and clinical examination of the patients, episodes of tick bites, and the second part is serological examination of the blood by ELISA and immunoblot.

The study involved 178 children aged 1 to 18 years, who visited to the centre for Study of Lyme Disease of Ternopil National Medical University after being bitten by ticks.

The control group consisted of 30 healthy boys and girls living in Ternopil and Ternopil region. They were not bitten by ticks and did not suffer from LD previously. The age and sex distribution in the control group corresponded to that in the control group.

Ticks were identified for transmissible infections. DNA of *B. burgdorferi sensu lato (sl) (B. burgdorferi sensu stricto, B. afzelii* and *B. garinii*), *B. miyamotoi, A. phagocytophilum* were determined by real-time PCR using Vector-Best production test system (Germany).

The serological examination of the children with LD was made by two-stage diagnosis procedures, primarily using ELISA and immunoblot for confirmation of the secondary results. Antibodies to antigens of the *B. burgdorferi s.l.* complex in blood serum were determined by ELISA using test systems by Euroimmun AG (Germany): class of IgM-test system Anti-Borrelia burgdorferi ELISA (IgM), IgG – Anti-Borrelia plus VLSE ELISA (IgG).

The results were evaluated quantitatively. The indicator > 22U/ml was considered positive, 16-22 U/ml – intermediate, < 16 U / ml – negative. To detect only IgM against Borrelia antigens, a specific line of the RN-AT system was used, which contained natural purified OspC Borrelia antigens of three species *(B. afzelii, B. burgdorferi ss, B.garinii*) and antigens p 39, p 41 and VIsE.

To diagnose specific IgG a line of the RN-AT system was used, which contained VLSE antigens of Borrelia of three species (*B. afzelii, B. burgdorferi s. s*, and *B. garinii)* and other specific antigens: p18, 19, p20, p21, p58, OspC (p25), p39, p83, Lipid Ba, Lipid Bb.

Statistical processing of the results was performed using the methods of parametric and nonparametric statistics by computer programs Microsoft Office Excel and STATISTICA, estimating the absolute (n) and relative amount (%) of the indicators.

The analysis of frequency was performed using Pearson's test χ^2 and two-sided Fisher's exact test, the statistical significance of which was $p<0.05$. All the studies were performed according to the Conclusion of the Commission on Bioethics of I. Horbachevsky Ternopil National Medical University, dated September 1, 2021 (Minutes No. 65).

Results

Erythema migrans was observed in 113 (63.4%), and arthritis in 15 (8.4%) individuals. Nervous system disorders were present in 30 (16.8%) children; 18 (9.5%) children had an erythema-free form of the disease; 2 children (1.1%) complained about the cardiovascular disorders.

All children bitten by ticks were divided into the following age groups (Table 1).

Table 1. The age groups of children affected by ticks

Age categories of children (years)				
Categories	1–3	4–7	8–12	13–18
Number of children	18	39	75	46

The largest age group was children of 8-12 years old (42.1% of the surveyed). Among the surveyed, there were 83 (46.6%) boys and 95 (53.4%) girls.

Only 143 (80.3%) children had a tick bite, while others did not remember the bite. The examination of patients with an erythematous form of LD took into account the presence of a tick bite in the anamnesis and the accompanying intoxication-inflammatory syndrome, the presence of lesions of various organs and systems.

In the clinical diagnosis of an erythematous form of LD the prevalent symptoms were: primary skin lesion, which was manifested by the erythema migrans, and the epidemiological history. Subsequent examination revealed the presence of various pathogens in this category of patients. In children with erythema migrans, i.e. in 24.7% of 113 people, tick-borne infection with identified pathogens was confirmed (Fig. 1), and in children with the disseminated form of the disease only the effects of the bite were observed.

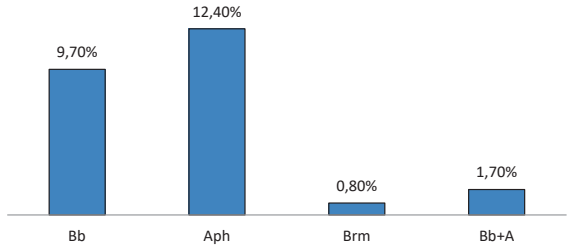

Fig. 1. *Frequency of detection of infectious agents in children with erythema migrans.*
Bbs – B. burgdorferi sensu lato; Brm – B. miyamotoi; Aph – Anaplasma phagocytophilum.

When using the western immunoblot during the first 4 weeks of the disease (an early form of LD), both immunoglobulin M (IgM) and immunoglobulin G (IgG) were determined. Since the probability of a false-positive test result for current infection is high, a positive IgM test result is not recommended when determining the active phase of the disease in people who are sick for longer than 1 month.

Verification of the presence of specific IgM antibodies was performed in the sera of 179 patients, 71 of whom had positive (56 people) or intermediate (15) results when tested by the ELISA test. (Table 2). It was found that in 56 patients with positive results, using the method of immunoblot (EUROLINE Borrelia RN-AT) also found positive results in 17 (30.4%) persons, while intermediate was not detected.

In children living in Ternopil region, a positive ELISA test was confirmed in 56 children (31.3%), an intermediate test in 15 (8.4%), and a negative test in 108 (60.3%) individuals. The results of blood screening for the presence of IgG in ELISA were positive in 28 subjects (15.6%), intermediate – in 3 (1.7%), negative – in 148 (82, 7%) (Table 2).

Subsequently, these results were confirmed by immunoblotting.

Thus, from the examined group of patients (179 people) the immunoblot confirmed the total (IgM + IgG) absolute number of positive blood results in (20 + 26) 46 children (25.7%).

To determine the etiological structure of LD, the presence of IgM antibodies to the immunogenic external surface protein OspC (a marker of the early immune response) of three species was determined: *B. garinii, B. burgdorferi, B. afzelii* separately in patients of both groups (Table 3).

Antibodies of this class to OspC *B. afzelii* were found in the sera of 11 (55%) of the 20 subjects, to OspC *B. garinii,* respectively, in 11 (55%), to OspC *B. burgdorferi s.s.* – in 6 (30%) patients.

IgM antibodies to antigens p41, p39, and VLsE were also determined in the sera of the examined patients. It was found that antibodies to antigens p41 were detected in 17 (85%) patients, to p39 antigen – in 4 (20%), respectively, to VLsE – not detected in any of the examined groups of children (Table 3).

Simultaneously, the presence of IgG antibodies (only positive results) to VLsE (recombinant highly immunogenic lipoprotein of the outer membrane, variable like sequence expressed) of Borrelia of different genes in the sera of 31 patients with ME LD was determined with a positive result in all children. To determine the etiological structure of LD, the presence of IgG antibodies to the immunogenic external

Table 2. The content of IgM and IgG to B. burgdorfery s.l. determined by different methods in children living in Ternopil region

IgM						IgG					
Elisa			EUROLINE Borrelia RN-AT			Elisa			EUROLINE Borrelia RN-AT		
Result	Total (n=179)		Result	Total (n=71)		Result	Total (n=179)		Result	Total (n=31)	
	Absolute value	%		Absolute value	%		Absolute value	%		Absolute value	%
Positive	56	31.3	Positive	17	30.4	Positive	28	15.6	Positive	25	89.3
			Intermediate	0	0				Intermediate	0	0
			Negative	39	69.6				Negative	3	10.7
Intermediate	15	8.4	Positive	3	20.0	Intermediate	3	1.7	Positive	1	33.3
			Intermediate	0	0				Intermediate	0	0
			Negative	12	80.0				Negative	2	66.7
Negative	108	60.3				Negative	148	82.7			

Table 3. Antigenic load to anti-*B. burgdorferi* IgM

Antigens	Absolute value (Ig M-20)	Relative value (%)
OspC Bg (*B. garinii)*	11	55
OspC Bb *(B. burgdorferi)*	6	30
OspC Ba (*B. afzelii)*	11	55
P39	4	20
P41	17	85
VLsE	0	0

Table 4. Antigenic load to *B. Burgdorferi* IgG

Antigens	Absolutely value (IgG-31)	Relative value (%)
OspC *B. afzelii*	0	0
VlsE *B. burgdorferi ss*	16	51,6
VlsE *B. afzelii*,	13	41,9
VlsE *B. garinii*	12	38,7
p39	0	0
P41	21	67,7
Lipid Ba	4	12,9
Lipid Bb	2	6,4
P21	4	12,9
P18	3	9,6
P58	3	9,6

surface protein VLsE (a marker of the early immune response) of three species was determined: *B. garinii, B. burgdorferi, B. afzelii* separately in the patients of both groups (Table 4).

OsC B. *garinii* antigens of IgM immunoglobulin predominated over OspC *B. afzelii*, OspC *B. burgdorteri* in Ternopil region.

Vlse *B.burgdorteri* antigens of immunoglobulin IgG prevailed over Vlse *B.afzelii*, Vlse *B. garinii* in Ternopil region.

Discussion

Lyme disease (LD) is an endemic disease in many countries. In Europe, North America, and Asia, it is the most common vector disease [8,9]. It is caused by *B. burgdorferi sensu lato* and is transmitted to humans by ticks of the Ixodes ricinus mite complex; up to 20% of them are infected with this bacterium. Only 2-4% of bites are clinically manifested that is one of the diagnostic challenges [10, 11].

In the presence of erythema migrans, there was a significant difference in the ELISA results for immunoglobulin M, in particular a significant predominance of negative IgM values. At the same time, the erythematous form of ME was characterized by positive results of IgM. In a small amount of IgM to flagellin (41 kB) and membrane protein OspC Borrelia begin to appear in the first days of the disease. Their titres increase within 4-6 weeks, and a little longer in untreated patients. During the generalization of the infectious process, IgG antibodies appear against several proteins, e.g. P39 and P58 [7]. The frequency of various pathogens that caused erythema migrans was established: the leading pathogen was *Anaplasma phagocytophilym* in (12.4%) cases, *B. burgdorferi sensu lato* in 9.7% of cases.

It is proved that if erythema migrans develops in a patient after a tick bite in an endemic area [12], treatment tactics should be suggested immediately. However, if the diagnosis of Lyme disease is uncertain, it is recommended to first determine the sensitivity of the ELISA reaction. Only ELISA-positive cases should be confirmed with a more specific immunoblot results [7].

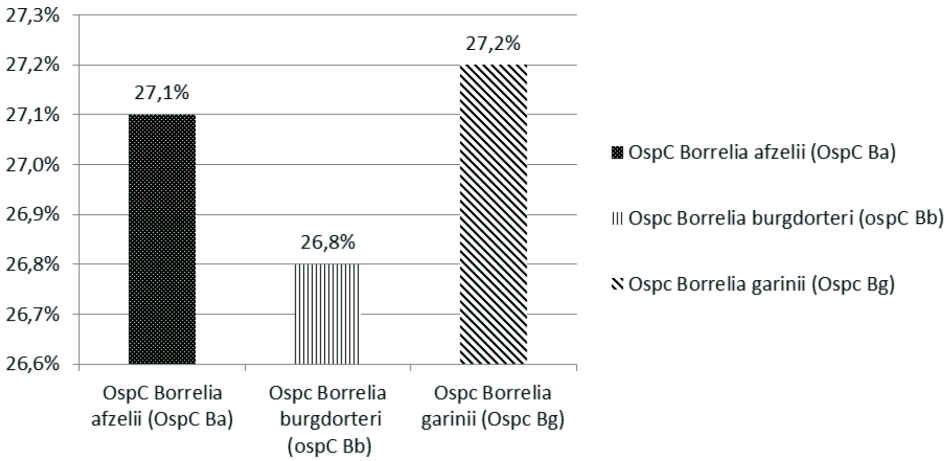

Fig. 2. *Average rate of antigenic load to anti-B. burgdorferi IgM antibodies in Ternopil region.*

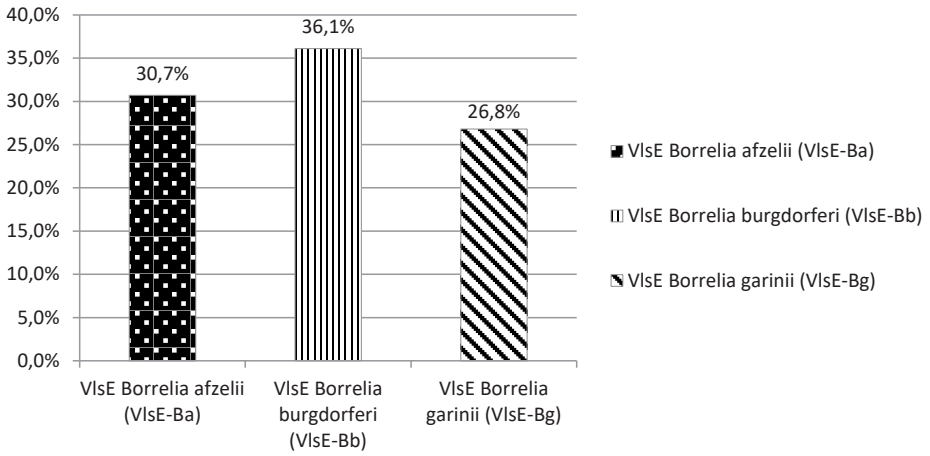

Fig. 3. *Average rate of antigenic load to anti-B. burgdorferi IgG antibodies in Ternopil.*

It is established that the differentiation between septic arthritis and Lyme arthritis in endemic areas can be a difficult task, and therefore it causes serious consequences for the treatment of the patient [14]. In the acute and late stages, Lyme disease can be difficult to distinguish from other painful processes . To establish a prediction algorithm for the differentiation of septic arthritis from Lyme disease in children with knee pain and exhaustion [13], a two-stage diagnosis is recommended. The main surface antigens of OspA, OspB, OspC proteins, which determine the difference of individual strains [14], can vary significantly; thus determining the possibility of long-term (for many years) persistence of the pathogen in the human body [14, 15].

Many antigenic determinants of the outer shell of Borrelia of different species are similar to each other and even to some bacteria of other genera, which explains the possibility of cross-immune reactions [7, 16].

Serum samples from children with disseminated or late stage LD almost always have a strong IgG response to *Borrelia burgdorferi* antigens [7, 8, 15].

In the evaluation and interpretation of serological test results, both the class of antibodies to specific *B. burgdorferi* antigenic proteins and the type of bacterial antigen, for which these antibodies are produced, are important [14]. External surface proteins (Osp) are important in the immune response to infection because they are highly immunogenic. The aantibodies to OspC are characteristic of recent infection. According to the manufacturer's recommendations, the presence of specific IgM antibodies was considered positive, intermediate, or negative, depending on the combinations of OspC antigens of three species of Borrelia (*B. afzelii, B. burgdorferi ss,* and *B. garinii*), p39, and VLsE Bb. At the same time, the presence of IgG was considered positive or negative depending on the combinations of VLsE antigens of three species of Borrelia (*B. afzelii, B. burgdorferi ss,* and *B. garinii*) and other specific antigens: p18, p19, p20, p21, p58, OspC (p25), p39, p83, Lipid Ba, Lipid Bb. In our immunological study, the genotype *B. burgdorferi sensu stricto* was detected in children with erythema migrans, arthritis, and neurolaim, which have statistically significant results (Table 4).

The diagnosis of Lyme disease should be established by a laboratory (serological tests (ELISA and Western blot) investigations, indicating the presence of specific anti-*B. Burgdorferi* IgM / IgG antibodies), which confirms clinical manifestations of the disease. This is very important because physicians often seek serological evidence of *B. burgdorfery* infection in patients with undefined diffuse complaints [15,18].

According to the list of symptoms compatible with Lyme disease, the most common symptoms in children of Ternopil region were erythema migrans (84.9%). This corresponds to the results of other studies [19, 20].

Conclusions

It was estanlished that *B. burgdorfer*i sensu lato; *B. miyamotoi*; and *A. Phagocytophilum* are pathogens that cause erythema migrans in children of Ternopil region. The presence of specific IgG (only positive results) to *B. Burgdorferi* s.l. was confirmed by immunoblotting in 83.8% of individuals who had positive and intermediate results in the ELISA test.

Conflict of Interests
Authors declare no conflict of interests.
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Author's Contributions
Svitlana Oleksiivna Nykytyuk – formal analysis, writing – original draft, writing – reviewing and editing; *Sergiy Ivanovych Klymnyuk* – conceptualization, writing – original draft, writing – reviewing and editing; *Ivan Mykolayovych Klishch* – methodology, writing – reviewing and editing; *Sofia Sergiivna Levenets* – investigation, formal analysis.

ОЦІНКА РЕЗУЛЬТАТІВ ІМУНОБЛОТУ ДЛЯ ВИЗНАЧЕННЯ АНТИТІЛ ДО ПАТОГЕНІВ ХВОРОБИ ЛАЙМА У ДІТЕЙ ТЕРНОПІЛЬСЬКОЇ ОБЛАСТІ

***С.О. Никитюк, С.І. Климнюк, І.М. Кліщ, С.С. Левенець**
ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ, ТЕРНОПІЛЬ, УКРАЇНА

Вступ. *Вступ. Лайм бореліоз (LD) є мультисистемним захворюванням, спричиненим Borrelia burgdorferi та іншими подібними кліщовими Borrelia.*

Мета. *Визначити і порівняти серологічних результатів крові при різних формах хвороби Лайма у дітей.*

Методи. *Під нашим спостереженням знаходилась група дітей (n=178) у віці від 1 до 14 років, укушених кліщами. Контрольна група становила 30 здорових дітей. Кліщів ідентифікували за допомогою стереомікроскопічної системи SEO та визначника. Фрагменти ДНК B. burgdorferi sensu lato (sl) (B. burgdorferi sensu stricto, B. afzelii та B. garinii), B. miyamotoi, A. phagocytophilum визначали у крові методом ПЛР в реальному часі. Кліщів ідентифікували за допомогою стереомікроскопічної системи SEO. Були проведені базові дослідження, пов'язані з клінічними та імунологічними дослідженнями, включаючи дані Elisa та Immunoblot.*

Результати. *Опитування охопило 178 батьків дітей, на яких напали кліщі. Виявлено Borrelia burgdorferi sensu lato (B. afzelii, B.burgdorferi sensu stricto та B. garinii), B. miyamotoi та A. phagocytophilum. Проведено порівняння серологічних результатів крові при різних формах хвороби Лайма у дітей.*

Висновки. *Встановлено, що B. burgdorferi sensu lato; B. miyamotoi; та A. Phagocytophilum є збудниками, які викликають у дітей мігруючу еритему.*

Наявність специфічних антитіл IgG (тільки позитивні результати) до B. Burgdorferi s.l. імуноблотинг був підтверджений у 83,8% осіб, які мали позитивні та проміжні результати в тесті ІФА.

КЛЮЧОВІ СЛОВА: хвороба Лайма; бореліоз ; ІФА; імуноблот; укус кліща.

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HISTOPATHOLOGICAL PROFILE OF GASTROINTESTINAL NEUROENDOCRINE TUMORS IN A TERTIARY CARE HOSPITAL

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Background. *Recently there has been a lot of discussion about the terminology and classification of neuroendocrine tumours of the gastrointestinal tract. The WHO has recommended a change of terminology and classification of these tumours. In 2019 a significant update was done in the WHO classification of neuroendocrine tumours of GIT in which neuroendocrine carcinomas (NECs) are all considered high-grade tumours. Previously, grade 1 and 2 tumours were regarded as neuroendocrine tumours (NETs) and grade 3 neoplasms as NECs. The new classification avoids confusion between these two clinically and molecularly distinct notions.*

Objective. *The aim of the research was to study GI neuroendocrine neoplasms and classify them as per location and Histopathological classification of GI neuroendocrine neoplasms according to the recent WHO classification. To use IHC whenever and wherever required for categorization of GI NET's.*

Methods. *Over a period of 15 years, a total of 85 cases of neuroendocrine neoplasms of GIT were studied. The histopathological material of patients was reviewed and histopathological diagnosis confirmed. Paraffin embedded tissue blocks were used to study and review the material. Sections from tissue blocks were stained. Five-micron sections were cut and stained. The sections were stained using DAKO LSAB-2® system HRP glass slides coated with 0.5% poly-lysine.*

Results. *Out of 85 cases 40 involved male and 45 female patients. The mean age was 46.4 years; age range 9-85 years. In our study, appendix 24 (28.23%) and stomach 11 (12.95%) were the commonest sites of primary involvement followed by colon (10), ileum (10), duodenum (5), GE junction (5), jejunum (3), oesophagus (2), rectum (2) and gall bladder (1). Metastasis to the liver were observed in 12 patients with known and unknown primary diagnosis. Based on the latest WHO classification 5 patients were classified under NECs and the rest under NETs.*

Conclusions. *Neuroendocrine tumours (NETs) are uncommon malignancies of GIT. Appendix followed by stomach was the most common anatomical site. NET Grade 1 was the most common histological type. IHC markers NSE, Synaptophysin and Chromogranin can be used in diagnosis of NETs.*

KEYWORDS: carcinoid; neuroendocrine tumours; neuroendocrine carcinoma; IHC; histopathology.

Introduction

Gastrointestinal endocrine tumours currently referred to as gastrointestinal neuroendocrine tumours (GI-NETs), were known as carcinoids previously [1-4]. Accumulation of evidence has given way for newer and updated classification [4-6]. NENs account for about 0.5% of newly diagnosed neoplasms [7]. An increase in frequency of carcinoids is being noticed possibly as a result of increased ascertainment of cases from the ever-increasing use of diagnostic techniques [8]. The majority are well-differentiated neoplasms that can be diagnosed easily by traditional light microscopy and routine immunohistochemistry, but a small proportion can cause diagnostic difficulty. Gastrointestinal neuroendocrine tumours (GI-NETs) are currently sub-classified on morphologic grounds into Well differentiated NETs (WD-NETs) that have an indolent clinical course and the poorly differentiated ones that, on account of their outspoken malignant characteristics and aggressive clinical behaviour, are designated as poorly differentiated neuroendocrine carcinomas (PD-NECAs). In this classification, tumours that were referred to as carcinoids would correspond to the WD-NETs. In routinely processed tissue sections, these neuroendocrine cells can be conveniently identified histochemically by their argentaffin or argyrophil properties or immunohistochemically by staining for such generic neuroendocrine markers as chromogranins, synaptophysin,

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neuron-specific enolase (NSE) and PGP9.5 etc. that relate to their neurosecretory granules, cytosol, or vesicles. Specific cell types such as serotonin-producing EC cells, histamine-producing ECL cells, gastrin-producing G cells, or Somatostatin producing D cells, etc. are similarly best identified by the immunohistochemical localization of their secretory products in their cytoplasm. Previously neuroendocrine tumours were classified on the basis of site which led to divergence in terminologies and criteria. So, in 2010 a new WHO classification was published for neuroendocrine neoplasms. The main feature of this new classification system is the distinction between well-differentiated NETs and poorly differentiated NECs. Although NETs and NECs are not closely related neoplasms, they share the expression of neuroendocrine markers [1-3]. In this classification NETs are graded into G1, G2, and G3 based on mitotic rate and/or Ki-67 proliferation index. The mitotic rates used for grading NETs are expressed as the number of mitoses/mm^2, which is assessed by counting in 50 fields of 0.2 mm^2. Although the mitotic rate yields an accurate assessment, it may be unreliable for small samples. To determine the Ki-67 proliferation index, at least 500 cells in the regions of highest labelling, known as "hotspots", are counted. These areas are identified via scanning magnification. When areas with two varying proliferation indices are present in a particular sample, the area with higher proliferation index is selected for grading purposes [3, 9-13]. NECs are subtyped into small-cell NEC (SCNEC) and large-cell NEC (LCNEC). By definition, NECs are always high-grade neoplasms. Hence, as per the new WHO classification, NECs are not assigned any grade to avoid any confusion with neuroendocrine tumours in the G3 category (Table 1). In this single centre study, our objective was to study GI neuroendocrine neoplasms and classify them as per location. The tumours according to the recent WHO classification were further classified. We used IHC whenever and wherever required for categorisation of GI NET's.

Methods

The study period was 15 years. The histopathological material of patients was reviewed and histopathological diagnosis was confirmed.

Table 1. The 2019 World Health Organization (WHO) classification for neuroendocrine neoplasms (NEN) of the digestive tract

Well-Differentiated NEN	Ki–67 Index (%)	Mitotic Index (HPF)
NET G-1 (low-grade)	<3	<2/10
NET G-2 (intermediate-grade)	3–20	2–20/10
NET G-3 (high-grade)	>20	>20/10
Poorly differentiated NEN		
NEC G-3 Small-cell type, Large-cell type	>20	>20/10
Mixed Neuroendocrine–nonneuroendocrine neoplasm (MiNEN)		

Notes: NEN – neuroendocrine neoplasms, HPF – high-power fields, NET – neuroendocrine tumours, NEC – neuroendocrine carcinomas.

Table 2. Distribution of cases as per location

Site	Number
Appendix	24
Stomach	11
Colon	10
Ileum	10
Duodenum	5
GE Junction	5
Jejunum	3
Oesophagus	2
Rectum	2
Gall bladder	1
Secondaries to liver	12
Total	85

The medical records of patients were reviewed and primary site of involvement of GI tract was confirmed. The specimens preserved in the Department of Pathology were used to study the gross appearance of the tumours and further material obtained from specimens and processed as and when needed. Paraffin embedded tissue blocks were used to study and review the material. Sections from tissue blocks were stained for immunostains and hematoxylin and eosin (H&E). The corresponding slides for the respective cases were used to study and classify the cases based on morphology. For the prospective material the specimens received fresh were fixed in 10% formalin. After adequate fixation representative bits were given. The tissue bits were processed and embedded in paraffin for pathological examination. Five-micron sections were cut and stained. Immunohistochemical studies were carried out using 5-micron paraffin sections. The sections were stained using DAKO LSAB-2® system HRP glass slides coated with 0.5% poly-lysine.

Results

A total of 85 cases were found, out of which 40 were males and 45 were females. Mean age was 46.4 years with age ranging 9-85 years old. Table 2 gives the details of tumours origin.

Gastric neuroendocrine tumours were further classified into type 1, 2 and 3 on the basis of endoscopic and histology findings. Among 11 cases, 8 were type 1, 2 were type 2 and 1 case was type 3 (Fig. 1 and 2). Fig. 3-5 show histopathology and immunohistochemical details using different stains employed in our study.

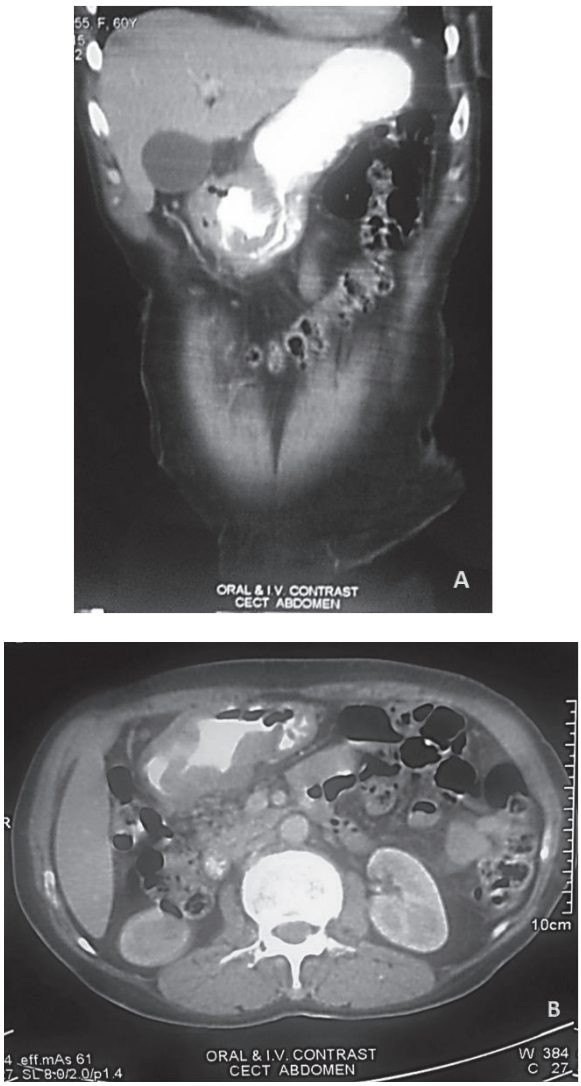

Fig. 1. *Distended stomach showing circumferential thickening and mass within gastric wall with peri-gastric fat infiltration and lymphadenopathy on CECT.*

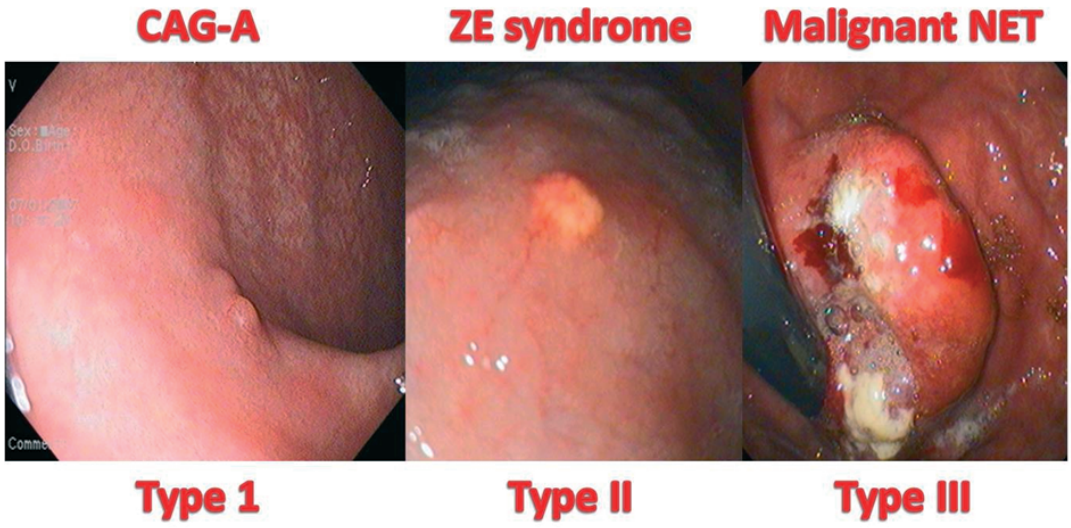

Fig. 2. *Showing endoscopic picture of gastric neuroendocrine tumours*

Table 3. Distribution of cases as per grading

Grade	NO. OF CASES
Well-Differentiated NEN	
NET G-1 (low-grade)	38
NET G-2 (intermediate-grade)	32
NET G-3 (high-grade)	10
Poorly differentiated NEN	
NECG-3 Small-cell type, Large-cell type	5
Mixed Neuroendocrine-nonneuroendocrine neoplasm (MiNEN)	

Notes: NEN – neuroendocrine neoplasms, HPF – high-power fields, NET – neuroendocrine tumors, NEC – neuroendocrine carcinomas.

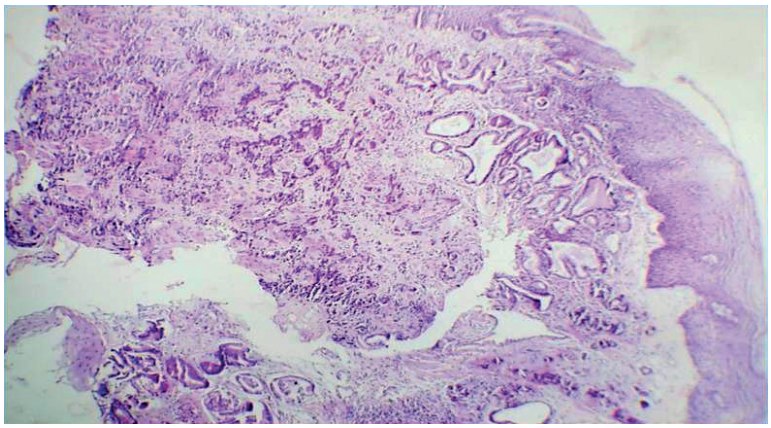

Fig. 3. *Low power view of a neuroendocrine tumour in esophagus.*

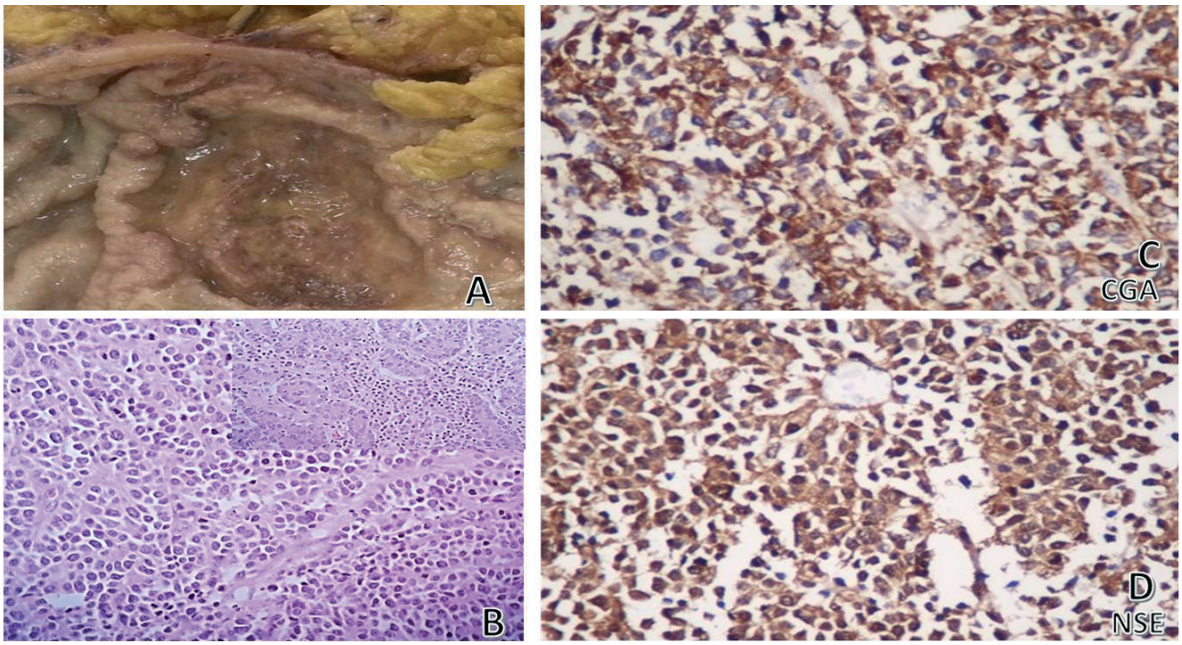

Fig. 4. A. *Gross photomicrograph of gastrectomy specimen showing a large ulcerated growth infiltrating into serosa.*
B. *(H&E 400X): Small to medium sized tumour cells with scant to moderate cytoplasm, salt and pepper chromatin with tumour cells arranged in sheets trabeculae and rosettes (inset).*
C. *(Chromogranin A; CGA): Tumour cells stained strongly positive for chromogranin A.*
D. *(neuron specific enolase; NSE): Tumour cells stained strongly positive for NSE.*

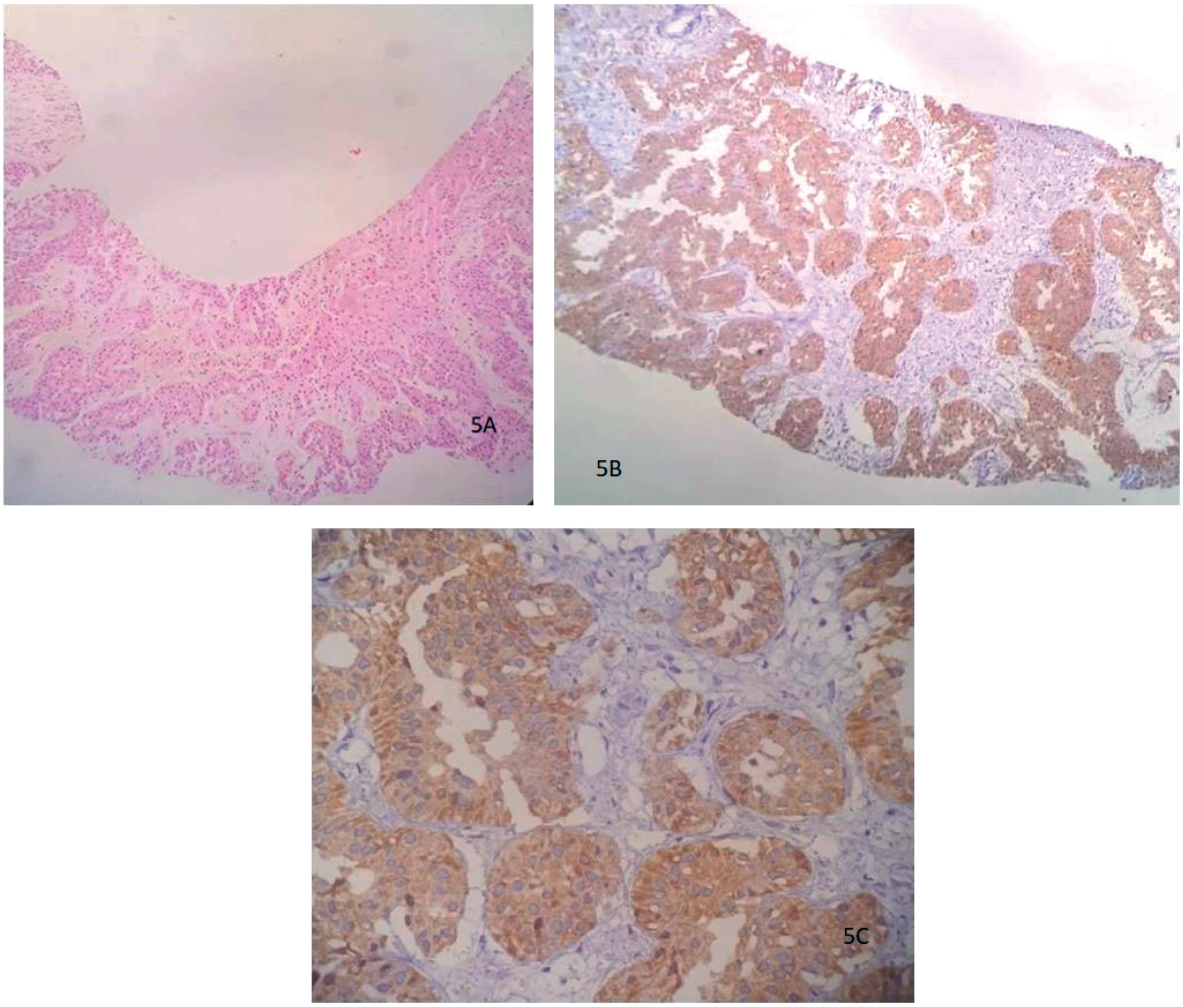

Fig. 5. A. *(H&E): Shows deposits of a tumour in liver with cells arranged in acinar and nesting pattern.*
B. *(neuron specific enolase NSE): Tumour cells show positivity for synaptophysin.*
C. *(synaptophysin): Tumour cells show positive staining for synaptophysin.*

Discussion

Neuroendocrine tumours of the gut have been also called as carcinoids ever since Oberndorfor coined this term to designate tumours that resembled carcinomas but behaved as if they were benign. Using 'carcinoid' as a collective term has certain limitations that this term does not differentiate benign from malignant tumours, morphologically identical tumours at different sites can show divergent prognosis and the cell of origin can be different in all tumours. The tumours arising from these cells differ in their respective locations, etiological factors, pathogenesis and also prognosis. The mean age at diagnosis of NET of GIT in the present study was 46.4 years. Similar results were observed in studies by Rothenstein J et al [14] Bruna Estrozi et al [15] and Amarapurkar DN et al [16] where the mean age at diagnosis was 56, 52.8 and 53 respectively. The studies by Rothenstein J et al and Amarapurkar DN et al showed that males were more commonly involved with neuroendocrine tumours of GIT as in our study [14,16]. Most of the patients presented with nonspecific symptoms of abdominal pain and vomiting. Similar findings have been noted by Amarapurkar et al, who reported 74 cases of NETs of GIT-pancreas [16]. It was found out that the appendix was the most common site of primary NENs followed by the stomach, however in the study by Klimstra et al the ileum and appendix have been reported as the most common sites for NET [17]. Maggard et al found the small intestine to be the most common site accounting for 44.7% [18]. Amarapurkar et al found that the stomach (30.2%) was the most common site followed by the pancreas (23.3%) [16]. In our study NET G1 was the most common histologic type followed by NET G2 and neuroendocrine carcinomas

respectively that correlated with the literature where Rothenstein J et al and Amarapurkar et al also found NET G1 as the most common tumour [14,16]. Similarly, according to Matsui K et al [19] and Okita NT et al [20], neuroendocrine carcinoma is a rare tumour with highly malignant biological behaviour exhibiting aggressive growth that leads to vascular invasion, distant metastasis and poor prognosis [19,20]. Our results were similar to the study by Amarapurkar et al in which Metastasis was seen in 18.9% of cases and Yamaguchi et al. who reported metastatic deposits in 7 out of the 45 cases (15.5%) [16,21]. Immunohistochemical studies were used to confirm the diagnosis of neuroendocrine tumours. Our study also showed that NSE and synaptophysin were expressed by most of the tumours compare to chromogranin. Anna Fen-Yau Li et al also found that NSE and synaptophysin were useful markers in confirming Neuroendocrine tumours. [22].

Conclusions

Neuroendocrine tumours (NETs) are uncommon malignancies of GIT. The appendix followed by the stomach was the most common anatomical site. NET Grade 1 was the most common histological type. IHC markers NSE, synaptophysin and chromogranin can be used in diagnosis of NETs.

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Conflict of interests

Authors declare no conflict of interest.

Authors contributions

Dr. Farhat Abbas and Dr. Mehnaaz Sultan Khuroo – conceptualization, methodology, formal analysis, writing – original draft, writing – reviewing and editing; *Dr. Ambreen Beigh and Dr. Summyia Farooq* – data curation, writing – reviewing and editing; *Dr. Naira Sultan Khuroo and Dr. Shagoofa Tazeen* – investigation, formal analysis.

ГІСТОПАТОЛОГІЧНИЙ ПРОФІЛЬ НЕЙРОЕНДОКРИННИХ ПУХЛИН ШЛУНКОВО-КИШКОВОГО ТРАКТУ В МЕДИЧНИХ ЗАКЛАДАХ ТРЕТИННОГО РІВНЯ

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Вступ. *Останнім часом ведеться багато дискусій щодо термінології та класифікації нейроендокринних пухлин шлунково-кишкового тракту. ВООЗ рекомендувала змінити термінологію та класифікацію цих пухлин. У 2019 році було внесено значне оновлення в класифікацію ВООЗ нейроендокринних пухлин шлунково-кишкового тракту, в якій усі нейроендокринні карциноми (NEC) вважаються новоутвореннями високого ступеня тяжкості. Раніше пухлини 1 і 2 ступеня вважалися нейроендокринними пухлинами (NET), а новоутворення 3 ступеня – NEC. Нова класифікація дозволяє уникнути плутанини між цими двома патологіями різними на клінічному та молекулярному рівнях.*

Мета. *Вивчити нейроендокринні новоутворення шлунково-кишкового тракту та класифікувати їх за локалізацією та гістопатологічною класифікацією нейроендокринних новоутворень шлунково-кишкового тракту за останньою класифікацією ВООЗ. Для категоризації нейроендокринних новоутворень шлунково-кишкового тракту використовували імуногістохімічний метод.*

Методи. *Протягом 15 років досліджено 85 випадків нейроендокринних новоутворень ШКТ. Вивчався гістопатологічний матеріал пацієнтів та підтверджувався гістопатологічний діагноз. Для вивчення та перегляду матеріалу використовувалися тканинні блоки просочені парафіном. Зрізи товщиною 5 мікронів фарбували на предметному склі покритому 0,5% полілізином за допомогою системи HRP DAKO LSAB-2®.*

Результати. *З 85 випадків 40 були чоловіками та 45 жінками. Середній вік становив 46,4 року; віковий діапазон 9-85 років. У нашому дослідженні апендикс 24 (28,23%) і шлунок 11 (12,95%) були найчастішими місцями первинного ураження, за ними слідували товста кишка (10), клубова кишка (10), дванадцятипала кишка (5), гастроезофагальне з'єднання (5), тонка кишка (3), стравохід (2), пряму кишку*

(2) і жовчний міхур (1). У 12 пацієнтів з відомим і невідомим первинним діагнозом спостерігалися метастази в печінку. На основі останньої класифікації ВООЗ 5 пацієнтів були віднесені до NEC, а решта – до NET.

Висновки. *Нейроендокринні пухлини (NET) є рідкісними злоякісними новоутвореннями шлунково-кишкового тракту. Апендикс і шлунок уражалися найчастіше. NET 1 ступеня були найпоширенішим гістологічним типом. Імуногістохімічні маркери NSE, Synaptophysin і Chromogranin можуть бути використані в діагностиці NET.*

КЛЮЧОВІ СЛОВА: карциноїд; нейроендокринні пухлини; нейроендокринна карцинома; імуногістохімічний метод; гістопатологія.

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THE EFFECT OF MICROCRYSTALLINE CELLULOSE ON THE MICROFLORA OF THE COLON

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Background. *Nowadays, much attention is paid to enterosorption methods that allow cleansing the internal organs and removing extraneous substances out of the body of a sick person.*

Objective. *The aim of the research was to study the effect of microcrystalline cellulose on the microflora of the large intestine.*

Methods. *The study was performed on 50 white laboratory Wistar rats weighing 180-270 g, which were divided into control and experimental groups. The experimental group was daily administered with microcrystalline cellulose at a dose of 500 mg/kg. The study followed ethical standards and recommendations for the humanization of work with laboratory animals according to the "European Convention for the protection of vertebrate animals used for experimental and other purposes" (Strasbourg, 1986, 2010), as well as the requirements of the Commission on Bioethics of I. Horbachevsky Ternopil National Medical University (Minutes No. 66, dated November 01, 2021). The first group involved the intact rats on standard diet, the second – the rats, which received normal feeding of microcrystalline cellulose.*

Results. *In the feces of the experimental white rats treated with microcrystalline cellulose, the level of Escherichia coli in the large intestine decreased by 22 and 25%. The number of these microorganisms increased by 20% in 7 days and by 14% in 14 days. The content of epidermal staphylococci in the stool decreased by 10% on the 7th day of administration. Microcrystalline cellulose increased the number of Staphylococcus aureus by 12%, but decreased the number of enterococci in the feces by 28%. In 7-14 days of the experiment, the content of these bacteria did not change significantly in the colon. In relation to anaerobic microorganisms – bacteroides and clostridia, this supplement caused a slight increase in the number of bacteroides – by 8.64% and the number of clostridia – by 11.54% on the 14th day. The content of fungi of the Candida genus on the 7th and 14th day increased by 8.3%.*

Conclusions. *In the 2nd period of the study, the microbiome of intestinal contents worsened: the process of dysbacteriosis increased, which was manifested by a significant increase in the number of Proteus spp., Staphylococcus aureus, anaerobes (bacteroides, clostridia) and Candida spp., as well as decreased Escherichia coli and Enterococci.*

KEYWORDS: enterosorption; microcrystalline cellulose; colon microflora; enterosorbents.

Introduction

These days the incidence of the large intestine disorders due to various microorganisms is increasing. Therefore, it is important to study the mechanisms of its development, features of early diagnosis, prevention and treatment. The large intestine is the main reservoir of the human microbiota in general and the digestive tract in particular; it is always dominated by characteristic groups of microorganisms, the number of species of which is small, but in quantitative terms they form the basis of the biocenosis [1,4]. The main microflora of the colon contains obligate anaerobic bacteria of the *Bifidobacterium, Bacteroides, Lactobacillus, Propionibacterium, Peptostreptococcus* genera, as well as additional anaerobic and aerobic bacteria of the *Escherichia, Enterococcus* genera. Additional colon microflora includes anaerobic bacteria of the *Peptococcus, Clostridium, Eubacterium, Fusobacterium* genera and additional anaerobic and aerobic bacteria of the *Staphylococcus, Citrobacter, Proteus, Enterobacter, Edwardsiella, Klebsiella* and other genera [1,5]. Enterosorption is an important method based on the binding and excretion of toxic substances from the gastrointestinal tract for therapeutic and prophylactic purposes. Microcrystalline cellulose is of particular interest. The supplement

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gently cleanses the intestinal wall, absorbs toxins, poisons and other dangerous accumulations. For active sorption of toxins, re-administration of enterosorbents should last at least two weeks, so an important factor for their effective and safe use is the preservation or restoration of physiological parameters of gastrointestinal function, in particular normal intestinal microbiocenosis [6,9].

The aim of the research was to study the effect of microcrystalline cellulose on the microflora of the large intestine.

Methods

The study was performed on 50 white laboratory Wistar rats weighing 180-270 g, which were divided into control (20 rats) and experimental (30 rats) groups. The experimental group was daily administrated with microcrystalline cellulose at a dose of 500 mg/kg.

The study was carried out following ethical standards and recommendations for the humanization of work with laboratory animals according to the "European Convention for the protection of vertebrate animals used for experimental and other purposes" (Strasbourg, 1986, 2010), as well as requirements of the Committee on Bioethics of I. Horbachevsky Ternopil National Medical University (Minutes No. 66, dated November 1, 2021). The study protocol was approved by the university review boards and ethics committees of the participating centers.

Sampling was performed from the rectum with a disposable sterile cotton swab to remove feces. Disposable cotton swabs by Copan (Italy) were used. Before and after material collection, the tampon was weighed on torsion scales. The difference in weight was taken as the mass of stool. Then the swab was placed in 1 ml of 0.1% solution of Triton X-100 in 0.075 M phosphate buffer pH 7.9, and shaken thoroughly for 10-15 minutes. The prepared ten-fold dilutions of the material, inoculated on nutrient media of MPA, YSA, Endo, Sabouraud, Blaurock, MRS, agar-EDDS, was incubated at the optimum temperature of 37 °C.

In 24-96 hours of incubation the number of colonies was counted and the result was expressed by the number of colony-forming units per 1 gram of feces according to the formula: $X1 = 20 \cdot M \cdot N / t$, where X1 is the number of CFU/ml; 20 is the constant coefficient, when 0.1 ml of the sample is inoculated; M is the number of colonies that grew; N is the dilution (in 10, 100, 1000 times etc.); t is the mass of feces. Since the number of microbes per unit can reach tens of thousands, we used the decimal logarithm of this indicator – log CFU/m.

The arithmetic mean and standard error (M±m) were used to describe the data in the normal distribution. Since the data obtained as a result of the clinical study had deviations from the normal distribution of the variation series, nonparametric statistical methods to compare groups – the Mann – Whitney U-test (for independent groups) was used. The software and mathematical complex for the personal computer Microsoft Excel 2016 was used for processing of the results of the study.

Results

The groups were statistically comparable at the beginning of the study. During the experiment, no significant changes of the microbiome of feces of the control rats on a fiber-free diet were evidenced, when comparing the two terms of the study (Tables 1 and 2). However, in the control group of animals, the composition of feces showed degree 1 dysbacteriosis (the concentration of normal microflora was below standard levels).

Microcrystalline cellulose reduced the level of *Escherichia coli* in the large intestine of the experimental rats up to 5.3±0.2 and 5.2±0.2 log CFU/g (by 22 and 25%, respectively), by 20% in 7 days, and by 14% in 14 days. On the 7th day of microcrystalline cellulose administration, the content of epidermal staphylococci in feces decreased by 10%. However, the microcrystalline cellulose increased the number of *Staphylococcus aureus* by 12%.

Microcrystalline cellulose reduced the number of enterococci in the feces by 28%. In contrast, after taking microcrystalline cellulose in 7-14 days of the experiment the content of these bacteria did not change significantly in the colon. In relation to anaerobic microorganisms: bacteroides and clostridia, this supplement caused a slight increase in the number of bacteroides – up to 8.8±0.3 log CFU/g (8,64%) and a more significant increase in the number of clostridia – 8.7±0.2 log CFU/g (11.54%) on the 14th day. After taking microcrystalline cellulose, the content of fungi of the *Candida* genus on the 7th and 14th day slightly increased by 8,3%.

Discussion

The effect of crystalline microcellulose on the intestinal microbiota has not been studied comprehensively. According to the literature,

Table 1. Effect of microcrystalline cellulose on the microflora of the large intestine of white rats, log CFU/g (on the 7th day of the study)

Types of microorganisms	Control (n=20)	Microcrystalline cellulose (n=30)
Escherichia coli	6.79±0.2	5.3±0.2 p<0.01
Enterobacteriaceae spp.	5.34±0.49	6.4±0.2 p<0.01
Staphylococcus epidermidis	5.44±0.2	4.9±0.3 p<0.05
Staphylococcus aureus	5.0±0.0	5.5±0.34 p<0.05
Streptococcus faecalis	5.53±0.2	4.0±0.2 p<0.002
Lactobacillus spp.	6.10±0.4	6.2±0.3 p<0.1
Bifidobacterium spp.	6.3±0.23	6.4±0.3 p<0.1
Bacteroides spp.	7.3±0.22	8.4±0.3 p<0.02
Clostridium spp.	7.3±0.12	7.4±0.3 p<0.1
Candida spp.	3.61±0.2	3.91±0.26 p<0.05
Proteus vulgaris	2.5±0.1	3.0±0.1 p<0.01

Table 2. Effect of microcrystalline cellulose on the microflora of the large intestine of white rats, log CFU/g (on the 14th day of the study)

Types of microorganisms	Control (n=20)	Microcrystalline cellulose (n=30)
Escherichia coli	6.9±0.2	5.2±0.2 p<0.01
Enterobacteriaceae spp.	5.6±0.3	6.4±0.2 p<0.02
Staphylococcus epidermidis	5.4±0.2	4.9±0.3 p<0.05
Staphylococcus aureus	5.0±0.2	5.6±0.34 p<0.05
Streptococcus faecalis	5.5±0.2	4.2±0.2 p<0.01
Lactobacillus spp.	6.1±0.4	6.2±0.3 p<0.1
Bifidobacterium spp.	6.3±0.2	6.4±0.3 p<0.1
Bacteroides spp.	8.1±0.2	8.8±0.3 p<0.05
Clostridium spp.	7.8±0.2	8.7±0.2 p<0.05
Candida spp.	3.6±0.2	3.9±0.26 p<0.05
Proteus vulgaris	2.5±0.1	3.5±0.1 p<0.001

concomitant therapy in patients with various pathologies shows significant effectiveness [10, 11]. The results of various studies prove a positive effect of enterosorbents on the manifestations of oxidative stress; it normalizes prooxidant-antioxidant balance [12,13]. However, no studies have been presented on the effects of enterosorbents on the microflora of the colon, especially in its prolonged administration.

Enterosorbents are biomaterials that "work" in the lumen of the gastrointestinal tract and have only local pharmacokinetics. However, in cases of sorption detoxification of the body, they act not only locally, but also have remote long-term effects [14]. The sorption of toxic metabolites and compounds relieves the main organs of metabolism and excretion. This explains the positive effect of enterosorbent in many comorbid pathologies. The effect of enterosorption on the intestinal microflora is also positive [15].

Conclusions

Microcrystalline cellulose entering the stomach has the ability to swell when absorbing fluid and is used to mechanically achieve a feeling of satiety and suppress appetite. Mechanical cleaning of the intestinal mucosa and effective absorption of harmful substances when passing through the gastrointestinal tract allows using it in poisoning by chemicals, toxins and salts of heavy metals. However, in the 2nd period of the study, the microbiome of intestinal contents worsened: dysbacteriosis developed, which was manifested by a significant increase in the number of *Proteus vulgaris*, *Staphylococcus aureus*, anaerobes (*Bacteroides spp., Clostridia spp*.) and *Candida spp.,* as well as decreased intestinal and intestinal bacteria.

Limitations of the study are the restricted number of laboratory animals and the limited range of methods for studying the large intestine microflora.

Conflict of Interests

Authors declare no conflict of interest.

Authors Contributions

Dmytro B. Koval, Hanna R. Malyarchuk – conceptualization, methodology, formal analysis, writing – original draft, writing – reviewing and editing; *Dmytro B. Koval, Hanna R. Malyarchuk* – data curation, writing – reviewing and editing; *Dmytro B. Koval, Hanna R. Malyarchuk, Olexandr O. Levenets* – investigation, formal analysis.

ВПЛИВ МІКРОКРИСТАЛІЧНОЇ ЦЕЛЮЛОЗИ НА МІКРОФЛОРУ ТОВСТОЇ КИШКИ

Д.Б. Коваль, *Г.Р. Малярчук, О.О. Левенець

ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО МОЗ УКРАЇНИ, ТЕРНОПІЛЬ, УКРАЇНА

Вступ. *У наш час велика увага надається методам ентеросорбції, які дозволяють очищати внутрішнє середовище та виводити з організму хворої людини чужорідні речовини.*

Метою *дослідження було вивчення впливу мікрокристалічної целюлози на мікрофлору товстого кишечника.*

Методи. *Дослідження проведено на 50 білих лабораторних щурах лінії Вістар масою 180-270 г, які були розділені на контрольну і експериментальну групи. В експериментальній групі шляхом щоденного введення мікрокристалічної целюлози з розрахунку 500 мг/кг. Роботу із піддослідними тваринами виконували згідно з правилами Європейської конвенції про гуманне ставлення до лабораторних тварин (Страсбург, 1985). Першу групу склали інтактні щури, годування яких було стандартним, другу – щури, які при звичайному годуванні отримували мікрокристалічну целюлозу.*

Результати. *У випорожненнях дослідних білих щурів, які отримували мікрокристалічну целюлозу знижувався рівень кишкової палички в товстому відділі кишечнику на 22 і на 25%. Збільшилася кількість цих мікроорганізмів на 20% через 7 днів і на 14% – через 14 днів. Зменшувався вміст епідермальних стафілококів у випорожненнях на 10% після 7-го дня прийому. Прийом мікрокристалічної целюлози*

збільшував кількість золотистих стафілококів на 12%, проте зменшував кількість ентерококів у фекаліях на 28%. В товстій кишці через 7-14 днів експерименту зміст цих бактерій не зазнав помітних змін. По відношенню до анаеробних мікроорганізмів – бактероїдів і клостридій цей препарат викликав незначне збільшення кількості бактероїдів – на 8,64% і кількості клостридій – на 11,54% після 14-го дня. Вміст грибів роду Candida після 7-го та 14-го дня збільшувалася на 8,3%.

Висновки. *В 2-й термін дослідження мікробіологічний краєвид кишкового вмісту погіршувався: збільшувався процес дисбактеріозу, що виражалося в істотному збільшенні кількості протея, золотистих стафілококів, анаеробів (бактероїдів, клостридій) і грибів роду Candida, а також зниженням змісту кишкової палички та ентерококів.*

КЛЮЧОВІ СЛОВА: ентеросорбція; мікрокристалічна целюлоза; мікрофлора товстого кишечника; ентеросорбенти.

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