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Peripheral blood lymphocytes apoptosis role in rheumatoid arthritis progressing

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Abstract

Rheumatoid arthritis (RA) is an autoimmune, chronic, and genetically linked inflammatory lesion of joint tissues that is accompanied by extra-articular systemic pathologies. The disease progression leads to joints immobilization, and eventually, the patient's disability occurs approximately ten years from the first clinical manifestation. RA pathogenesis involves various mechanisms: specific joint-related damage, nonspecific adaptive, and vessel-related pathological changes. Our research aimed to study the role of peripheral blood lymphocyte apoptosis in RA pathogenesis. We have analyzed research data from Google Scholar, PubMed, Web of Science, and Scopus databases to investigate the role of lymphocyte apoptosis in RA progression. Clinical manifestations in RA are caused by autoreactive T- and B-lymphocyte activity supported by humoral and cellular immune factors activity. Disease pathogenesis is caused by an imbalance in the process of programmed cell death (apoptosis): a proportion of immune cells are rapidly destroyed. In contrast, apoptosis is inhibited in the other classes of immune cells. High infiltration of the joint by autoreactive sensitized lymphocytes worsens the patient's condition. Apoptosis inhibition is especially noticeable in the early stages of RA and correlates with the concentration of the anti-apoptotic molecule Bcl-2 in the synovia. Activating the apoptotic destruction of lymphocytes (by drug action) allows a positive therapeutic effect and sustained remission. However, it should be noted that genetic factors play a significant role in the onset, progression and drug response of RA. In addition, environmental and behavioral factors can activate RA progression and influence treatment efficacy.

Key words: apoptosis, rheumatoid arthritis, lymphocytes, joint, blood serum, genetic factors, pathogenesis, treatment

Introduction

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease. It is diagnosed in over a percent of the world's population [1]. RA is one of the most common autoimmune diseases [2] and is characterised by the development of inflammation, synovitis, articular cartilage and bone damage. Its progression leads to disability and immobilisation of the patient. The effectiveness of RA treatment is around 40-70% and depends on individual patient characteristics [1,3]. However, musculoskeletal damage is not the only manifestation of RA. A chronic disease flowing can be accompanied by skin lesions (20% of patients), eye lesions (10%), gastrointestinal tract damage (hardly ever primary, more often due to drug treatment), lungs (usually asymptomatic - 50%, and 10% of patients have clinical manifestations), vascular, and cardiovascular system lesions (about 50% of patients) [4-6]. Kidney and nervous systems lesions are diagnosed as solitary, and their reasons become because of small vessel lesions (vasculitis), which lead the organ dysfunction

development such as glomerulonephritis, nephropathy, dementias, ischaemic neuropathies, and myelopathies [4,5].

RA is most commonly diagnosed at 52±15 years but can also occur in children (juvenile RA) [7]. Genetic, epigenetic and environmental factors, as well as the development of oxidative stress, must be identified as triggers for the onset and progression of RA. These factors activate cellular and molecular mechanisms associated with the progression of RA pathogenesis. Thus, the progression of joint damage is determined (Figure 1) [8,9].

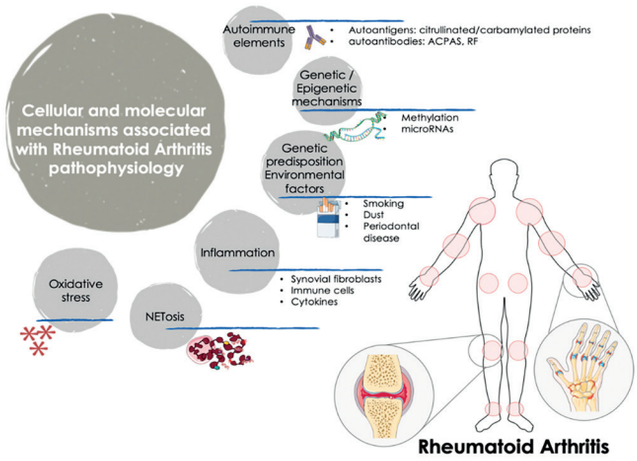

Figure 1 - Triggers for the RA pathogenesis development (according to Lopez-Pedrera et al.): inflectional, inflammation, genetic, environmental, and metabolite together with the points of the most joint damage [9].

A part of researchers associates RA with genetic factors today. Tilloeva gives data about the carriage of DRB1*0401 and DRB1*0404 complexes associated with RA development: in 50-61% and 27-37% of cases, respectively [7]. Catrina et al. declare that RA autoantigens are not tissue or organ-specific. They mark RA autoantigens as innate stimuli broad collection of post-translational modified proteins (citrullinated proteins) [10]. Almutairi K. et al. state that the global prevalence of RA (1980-2019 analysis) is 460 per 100,000. Although this pathology prevalence is heterogeneous, it may vary depending on the geographical, racial, and environmental features of a current region [11], as well as lifestyle (diet, labor type, and physical activity intensity) [8]. Rural residents are more susceptible to RA onset and progression (about 70% of diagnosed cases are fixed in Uzbekistan). Women are more predisposed to this pathology: it is recorded twice as often in this gender [2]. According to Tilloeva, the rate in women is 5.1% [7]. This disease also has a high incidence (3.5%) in first-degree relatives. We can note the connection between the RA diagnosis process and the economic state in the region: better state wealth level gives citizens an availability to have detection programs and self-ability to be checked for RA [11]. However, the link between RA pathogenesis and the humoral and cellular factors' activity in the immune system remains undisputed [8]. There is evidence that there is a close link between dysregulation of immune cell apoptosis, leading to an increase in synovial fibroblasts, inflammatory cells and cytokines, and the progression of disease signs in RA. In patients with different types of pain, such as chronic and neuropathic pain, this may be the cause of increased central hypersensitivity [12].

The aim of our study was to investigate the role of peripheral blood lymphocyte apoptosis in rheumatoid arthritis pathogenesis.

Material and methods

The current research was conducted by analysing literature sources Google Scholar, PubMed, Web of Science and Scopus databases to investigate the role of lymphocyte apoptosis in the pathogenesis of RA. Data from Kazakhstani and international clinical trial reports, analytical reviews and meta-analyses were included in our study. In this regard, the search and analysis used such keyword combinations as "rheumatoid arthritis", "rheumatoid arthritis pathogenesis", "rheumatoid arthritis prevalence", "lymphocyte apoptosis in rheumatoid arthritis", "autoreactive T-lymphocytes", "leukocytes in rheumatoid arthritis", "rheumatoid arthritis treatment". Short messages and advertisements have been excluded from the analysis.

Results and discussion

RA pathogenesis and the apoptosis role in it

Apoptosis is a programmed, controlled, specialised cell death. It is characterised by structural and functional changes in the cell's self structure. This process culminates in macrophages' phagocytosis of the destroyed cell (apoptotic cells). Apoptosis plays a significant role in inflammation development or its termination. But in the case of RA development, this process has changed. So, complex intercommunication of inflammatory and joint-damaging processes progress [13,14].

Typical, apoptosis starts with the activation of membrane "death receptors" (FasR, TNFR1, CARI, DR3, DR4, DR5), which in turn activate the Bcl-2 protein group inducing the apoptosis process and simultaneously inhibit the apoptosis antagonist protein Bcl-2 (Bak). Further, caspases (cysteine-dependent endoproteases) are involved in the process. They act as inducers and effectors of apoptosis and as pro-inflammatory components. Also, they trigger several enzymatic processes that accompany cell death and activate Ca /Mg2+2+ -dependent endonucleases (CPAN/DFF40) [13,15,16].

The early RA stages are characterised by the development of inflammation-induced synovial tissue hyperplasia with further invasion of cartilage and bone tissue, leading to the destruction of these joint structural components [17]. Synovial fibroblast-like synoviocytes (FLS) are activated and exhibit tumour-like behaviour [18]. Joint synovial tissue hyperplasia becomes due to an imbalance between the proliferation and apoptosis of fibroblasts (less subject to apoptosis) and synovial macrophages [17]. At the RA later stages, apoptosis increases with a predominance of hypertrophic joint fibroblast and chondroblast destruction [15]. In the early stages, large numbers of T cells infiltrate the synovial membrane along with synovial hyperplasia. T-lymphocytes interact with other immunocytes, such as dendritic cells, tissue macrophages, and synoviocytes, thereby releasing many inflammatory mediators. T-lymphocytes interact with other immunocytes, such as dendritic cells, tissue macrophages, and synoviocytes, releasing many inflammatory mediators. The inflammatory mediators' predominance of anti-inflammatory mediators contributes to chronic process development. Bcl-2 protein's high concentration in the joint provokes the proliferation of autoimmune T-lymphocytes [12,19]. Bcl-2 protein high concentration in the joint causes the proliferation of autoimmune T-lymphocytes [19]. Thus, the number of B-lymphocytes, whose primary function is to produce antibodies (autoreactivity proteins against RA) and inhibit memory B-cells apoptosis, is increased. Autoantibodies stimulate T-lymphocytes proliferation and release interleukins (IL-10), activating factors that promote apoptosis (caspases) and tumour necrosis factor (TNF). This process triggers abnormal T-cell autoreactivity that contributes to the exacerbation of RA symptoms [20].

Peripheral blood cell apoptosis in RA: its role and significance

Apoptosis is a general biological mechanism responsible within the immune system for eliminating activated lymphocytes that have fulfilled their function to prevent autoimmune reactions. Defects in the process of programmed peripheral lymphocyte death can cause tolerance disorders and chronic inflammation [13-17].

RA is an autoimmune disease, as evidenced by increased levels of immunoglobulins in the blood serum. And the increase in the concentration of rheumatoid factor (RF) in the blood, as well as lymphocytes sensitised to the structural components of the connective tissue, is essential [21]. The pathogenesis of the disease is determined by the state of the synovial macrophages, fibroblasts and lymphocytes. Thus, the progression of joint tissue hyperplasia in RA is diagnosed by the accumulation of synovial macrophages and fibroblasts. These cells provoke the progression of inflammation and destruction of the joints due to the release of cytokines, interleukins and proteases that initiate the inflammatory process [22]. RA progression is accompanied by increasing of the T-lymphocytes, especially CD4+ cells that concentrate on their surface activating antigens such as IA+ cells (class 2 proteins of the major histocompatibility complex), receptors for interleukins (IL-2 in particular), and TFR+ (transferrin) cells [21]. The high expansion of autoreactive T-lymphocytes into the affected joint is also noteworthy. They attack the synovial cease and destroy them. A high amount of inflammatory mediators are released, and significantly fewer anti-inflammatory mediators are produced [11]. Chronicity of the process becomes the consequence of the predominance of inflammatory mediators in the progression of the pathogenetic chain of the disease [13,22]. The degree of infiltration by lymphocytes, macrophages and FLS in the joint correlates with increased expression of the anti-apoptotic factor Bcl-2 in the synovium [23] and the increased expansion of autoimmune T lymphocytes into the affected joints due to both the tumour-like behaviour of FLS and inhibition of apoptosis by blood T cells [24].

Activated autoimmune rheumatoid-induced T-lymphocyte (B7-H1) stimulates the proliferation and apoptosis of blood lymphocytes [25]. Dong et al. (2003) report that B7-H1 boosts CD4+ T-cell proliferation and secretes interleukin IL-10, activating apoptosis-inducing ligands, caspase-3, and TNF. These processes cause abnormal T-cell responses in RA progression and exacerbate disease symptoms [24].

Peripheral blood lymphocytes (autoreactive T-lymphocytes) apoptosis in AR is activated by the CD44 protein triggering Fas ligand (FasL) on the surface of autoreactive T-cells. FasL activates Mg^{2+}/Ca^{2+}-conjugated cytokines associated with IP3 receptors. This mechanism triggers actin cytoskeleton rearrangements which induce T-lymphocyte death [13]. But there is also an undefined relationship between synovium and leukocyte survival. Zaichko et al. report that the "mortality" of T-lymphocytes in the joint cavity is lower compared to the same cells outside the joint environment (synovium) [23]. According to their study, Goltsev et al. confirm the connection between T-lymphocytes and survival in synovium. Although the characteristics of lymphocytes infiltrating the joint suggest that they are 'doomed' to the process of apoptosis (high Fas-receptor expression coupled with low Bcl-2 (an anti-apoptotic factor) activity), they are not involved in this process. The reasons for this situation are unclear, especially considering that neutrophils in the same patients undergo apoptosis in masse [21].

We have established that activating one immunocompetent cell population causes other immunocytes to become activated. Therefore, it is rather difficult to interrupt this chain. Thus, activation of CD4+ T-lymphocytes (which prevail in RA progression) is combined with activation of B-cells, production of pro-inflammatory factors, and autoantibodies to RF. B-lymphocyte apoptosis is inhibited due to a decrease in FasL activity, which induces a process of programmed lymphocyte death. Accordingly, the release of B-cell metabolites supports inflammation, the destruction of joint tissue, the release of inflammatory mediators and T-cell activation [13,19]. And the immune mechanisms' activation process in a patient with RA

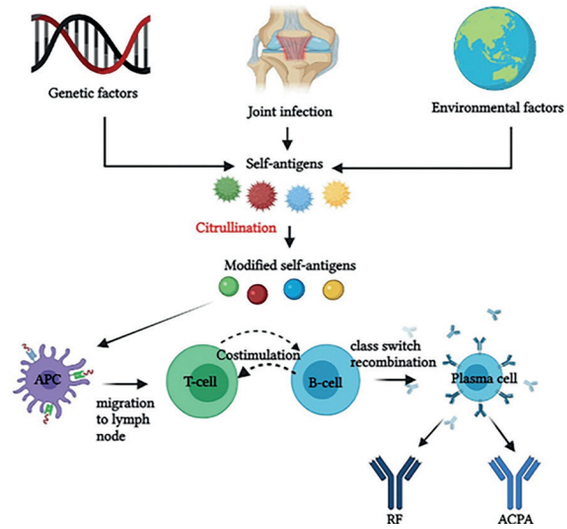

Figure 2 - Mechanism of the RA pathogenesis progression from triggers to the antibodies production by activated B-lymphocytes according to Radu and Bungau (2021) [25].

already occurs in the preclinical period of disease progression (Figure 2). So, the trigger factors (such as genetic, infectional, or environmental) activate the mechanisms of antigens reaction to body-self tissues. And this process is circle-connected to joint damage and the production of autoactivated immunocytes [26,27].

And increasing in serum levels of autoantibodies to RF, in particular - to Anti-citrullinated protein antigens (ACPA) – registered before clinical symptoms appear. Increasing antibody concentration to other post-translationally modified proteins, such as carbamylated proteins, is also detected. It is also established that in the preclinical stage of the disease some biomarkers and changes in autoreactive T-lymphocytes are observed, such as glycosylation of their variable region. This situation is considered highly predictive of future RA progression [26].

RA therapy strategy: principles and mechanisms, the significance of the lymphocyte apoptosis activation

Understanding the pathogenesis of the disease and the mechanism of the immune response is the basis for developing drug therapies to alleviate symptoms and achieve stable remission [28]. Today, an integrated approach to RA therapy is practiced, combining moderate activity, physiotherapy, symptomatic and anti-inflammatory treatment, and modifying traditional and biological anti-rheumatoid drugs [29,30]. It is subordinate to the benefit/risk assessment formula [23]. This approach can achieve remission or control the disease symptoms. But its effectiveness is not 100% guaranteed for the patient. In some cases, neither mono- nor combination therapies can achieve positive outcomes

[17,30]. However, mechanism activation of programmed autoreactive lymphocyte death, followed by the release of anti-inflammatory mediators into the bloodstream, alleviates the symptoms and stops the RA progression [13,31,32]. Genetic and environmental factors can influence therapy efficiency, including prognosis improvement [10,25]. At the same time, lack of timely therapy leads to disability in patients: 80% are diagnosed with joint damage, and 40% become disabled in 10 years [30].

One theory of therapy aimed at relieving symptoms and alleviating the patient's condition is the activation of the p53 molecule, which can affect the tumorigenic nature of cell division (suppression) and activate apoptosis [4,33]. But activating this molecule does not bring a positive therapeutic effect in the early stages of RA. Thus, a high p53 titre (+0.85) is observed in the patients' blood with active clinical RA in the early stages of the disease, which can even be considered a high disease activity predictor. In contrast, activation of the p53 molecule confers a positive therapeutic effect at the later stages of the disease. A direct correlation between apoptotic factor p53 concentration and non-erosive RA (+0.8) can be asserted. In the case of the erosive form, this relationship has been established for the anti-apoptotic molecule Mdm2 (+0.7). Therefore, activation of p53 in the RA early stages leads to worsening symptoms and can only be performed in late-stage patients [4].

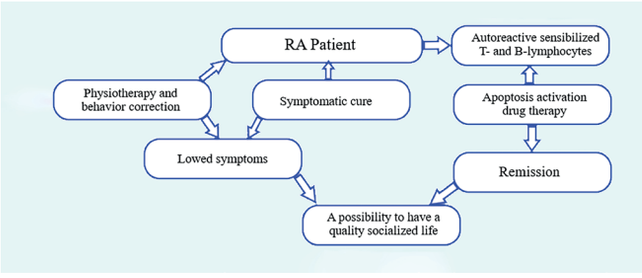

Figure 3 - Current common treatment approach in getting RA remission.

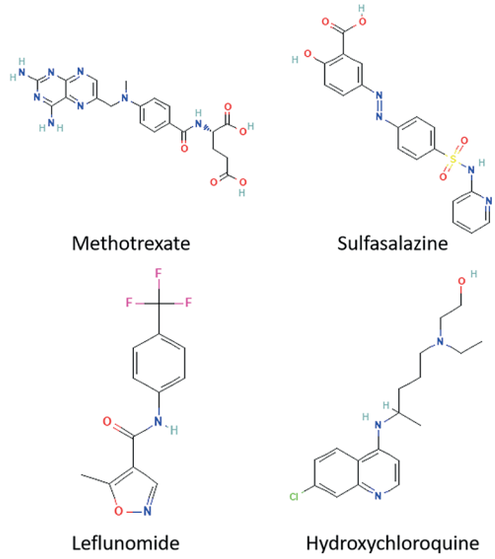

Figure 4 - Molecular structure of the most common disease-modifying anti-rheumatic drugs in the modern clinic practice.

Dedicated research into the treatment of RA has resulted in significant advances in the pharmacotherapy of RA as a chronic disease (Figure 3). This approach reduces symptoms, slows disease progression and may prevent associated complications. The European Alliance of Associations for Rheumatology [34] recommends combining treatment of symptomatic RA with disease-modifying drugs (Figure 4).

Greenblatt et al. (2020) report that a single dose of rituximab can delay the onset of RA symptoms [26]. Rituximab is essentially a chimeric monoclonal antibody. Its action is based on its mechanism of binding to the surface marker of B-lymphocytes CD20. The drug activity extends to mature (plasma) cells as well as to non-activated B-lymphocytes and memory cells. The rituximab effect is to kill target cells by activating cytotoxicity (antibody- and complement-dependent) and apoptosis [29,35]. Greenblatt et al. also hypothesise that abatacept, hydroxychloroquine and methotrexate are effective in RA treatment [26]. There is data about raising the pro-inflammatory cytokines' level due to methotrexate use in the treatment schema. According to research data, this improves the proposed cure's efficiency [36]. López-Rodríguez et al. (2018) provide evidence that the methotrexate treatment efficacy is associated with the polymorphism of the A-allele MTRR-rs1801394 in the patient [37]. It is also related to genetic variants SLC19A1-rs1051266, DHFR-rs836788 and TYMS-rs2244500 [38]. Methotrexate is an antimetabolite, similar in structure to folic acid, and its accumulation in the body provokes an antiproliferative effect by depleting the intracellular folate depot [39]. However, any therapy aimed at relieving symptoms, stabilising the patient's condition and achieving a stable remission should be accompanied by a treatment focused on repairing damaged tissue (mesenchymal stem cell therapy) [30,31].

Conclusion

Programmed cell death (apoptosis) has been extensively studied and is recognised as one of the main pathological mechanisms in RA. Its dysregulation in the pathological process contributes to RA progression and exacerbation of disease symptoms.

An imbalance of autoimmune T- and B-lymphocyte cell death enhances autoimmune and inflammatory reactions. At the same time, massive cell death of macrophages and neutrophils is fixed. Therefore, these processes contribute to the developing pathological responses associated with RA. Additionally, the increased joint structural cells death, like osteoblasts, chondrocytes, and osteoclasts, causes the destruction of articular surfaces and bone. Consequently, the unbalanced death of several cell types works in tandem, forming a vicious circle. Activation of each of its links aggravates the clinical manifestation of the disease. At the same time, genetic and environmental factors influence symptomatology development and the rate of pathology progression (flowing).

Activation of autoreactive leukocyte apoptosis (both T- and B-cells) positively affects the disease's course and prognosis, significantly alleviating the pathology symptoms. So this allows for improving the patient's life quality and delaying his disability.

Prospects for further research

Analysing the literature data, we have to fix the necessity to continue studying the intensity of lymphocyte apoptosis, taking into account the degree of RA activity and the ongoing treatment's effect on the programmed death of lymphocytes. The next planned step would become the guidelines for the RA diagnosis development and personalised therapy for RA patients.

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Does health literacy affect attitudes towards healthy eating and health anxiety in young adults?

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Abstract

Objective: The purpose of this study was to investigate the relationship between young people's health literacy, healthy eating attitudes, and health anxiety.

Material and methods: The data of this cross-sectional and descriptive study were collected by face-to-face interviews with students studying in the department of nursing, nutrition and dietetics and health management at the health sciences faculty of a university located in the Central Anatolia region of Turkey. The sample of the study consisted of 599 students who volunteered to participate in the study. In collecting the data of the study, Individual Descriptive Information Form, Turkish Health Literacy Scale (THLS-32), Attitudes towards Healthy Eating Scale (ASHN), Health Anxiety Inventory (Short Version) (HAI) used.

Results: It was determined that the total mean score of the students on the THLS-32 scale was 33.57±8.41, the mean total score of ASHN was 70.57±10.87, and the mean total score of HAI was 19.67±7.43. There was a positive relationship between students' health literacy and their attitudes towards healthy eating (r=0.258, p=0.000), a negative relationship between health anxiety (r=-0.171, p=0.000) and their attitudes towards healthy eating and health anxiety (r= -0.166, p=0.000).

Conclusion: It is important that this study is the first to examine health literacy, attitudes towards healthy eating, and health anxiety together. It is thought that improving the health literacy and healthy eating attitudes of students who will be health care professionals and reducing their health anxiety will provide significant benefits individually and socially.

Key words: health literacy, healthy eating attitude, health anxiety

Introduction

The World Health Organization defined health literacy as "cognitive and social abilities that determine an individual's motivation to acquire, interpret, and apply information for the promotion and protection of health" in 1998 [1]. Health literacy means knowing the factors that affect one's own health, the health of family and society, and how these factors affect one's health. Individuals with a sufficient level of health literacy take responsibility for their own health as well as family and community health. Moreover, having the knowledge, abilities, and motivation to choose and apply the best health practices is a component of health literacy [2].

Nutrition that is adequate and well-balanced is crucial for preserving health and leading a healthy life [3]. The fact that people's levels of health literacy vary also changes their eating habits [4]. Individuals with adequate health literacy are expected to have advanced attitudes for healthy eating, such as having basic nutritional knowledge, reading the food label, being able to control portion sizes, understanding information about nutrients and food groups, choosing and preparing healthy food [5].

Health anxiety is the concern that individuals constantly have a serious illness even though they do not have any health problems. According to the

biopsychosocial model, health anxiety is influenced by normal physiological, psychological, sociological and environmental processes. As people acquire negative information about health and illness, they perceive the changes in their bodies as symptoms of serious illnesses and their anxiety about these changes increases. People with health anxiety are always worried about their health, they are greatly affected by any news about health or illness, and they breathe and breathe. They are obsessed with their diet, heartbeat, and any minor discomfort [6].

The majority of the young population, including university students, lives far from their families and their eating habits are changing. In this period, gaining healthy eating habits, attitudes towards healthy eating and increasing health literacy levels are very important for the protection and development of health [7]. The foundations of healthy lifestyle behaviors are laid in the family; they grow in society and then change and develop with education. Health workers have a great influence on the development of these behaviors. Therefore, first of all, health professionals should review their own lifestyles and they should fix it. Health professionals set an example and are expected to be a model for the society in terms of improving health behaviors and changing behaviors that help development. In a study examining the relationship between healthy lifestyle, including healthy nutrition, and health anxiety of students studying in the health department, it was observed that as students' health anxiety increased, healthy lifestyle behaviors decreased [8]. According to a different study evaluating the relationship between healthy eating obsession and health anxiety, it was found that as healthy eating obsession increases, health anxiety also increases [9]. Health professionals, who will inform and guide individuals about healthy living behaviors, should implement every health-related knowledge and skill they have acquired and share them with patients. Considering the importance of working in a multidisciplinary environment, health science students have an important role in both individual and social level in developing health literacy and healthy eating attitudes and reducing health anxiety. However, when the literature is examined, no study has been found on the relationship between health literacy, attitudes towards healthy eating and health anxiety of young individuals studying in the health department. The aim of this study is to determine the relationship between young people's attitudes towards healthy eating, health anxiety and health literacy.

Materials and methods

Type of research

This research is cross-sectional and descriptive.

Population and sample of the research

The universe of this research consisted of 1040 students studying in the department of nursing, nutrition and dietetics and health management in the faculty of health sciences of a university located in the Central Anatolia region of Turkey. In the power analysis made in cases where the population size is certain, the required sample number was found to be 281, based on 5% error and 95% confidence level. In the study, it was tried to reach the students in the universe without using any sampling method. The sample of the study consisted of 599 students aged over 18 who volunteered to participate in the study. Students who needed a special diet program (eating disorders such as pica and anorexia nervosa, celiac, gout and cystic fibrosis, etc.) and who agreed to participate in the study but wanted to leave voluntarily were excluded from the study. The students participating in the research constituted 57.6% of the population.

Data collection method

Research data were collected by the researchers between December 2022 and February 2023. By interviewing the class representatives of the students, a suitable time for the students was determined and data collection tools were applied. Before the data collection tools were filled, the students were informed about the face-to-face study and were asked to sign informed consent if they agreed to participate in the study. It was explained to the students that they have the right to leave at any stage of the study, and it was stated that participation in the study was on a voluntary basis. It has also been stated that no fees will be charged and/or no fees will be paid from the students for research purposes. It was explained to the students that the results of the study would not affect the course grades. There is no conflict of interest between researchers and students. In collecting the data of the study, Individual Descriptive Information Form (10 questions), Turkish Health Literacy Scale (THLS-32) (32 items), Attitude Scale for Healthy Nutrition (ASHN) (21 items), Health Anxiety Inventory (Short Version) (HAI) (18 items) used.

Individual introductory information form

This form was prepared by the researchers by scanning the relevant literature. It includes questions about students' socio-demographic characteristics (age, gender, department, income status, family structure, where they live), height, weight and smoking status.

Turkish Health Literacy Scale-32 (THLS-32)

It is a 32-item scale developed based on the HLS-EU Study Conceptual Framework (HLS-EU CONSORTIUM, 2012 [10]. Turkish validity and reliability were done by Okyay and Abacıgil (2016) [11]. The scale includes two health-related dimensions (“healthcare” and “disease prevention and health promotion”) and four processes of information acquisition (access, understand, appraise, and apply) related to health relevant decision-making and practices. Each item is rated as very easy, easy, difficult, very difficult, and no idea. Values between 0-50 can be taken from the scale. Health literacy level is evaluated in four categories:

0-25: inadequate health literacy,
>25-33: problematic/limited health literacy,
>33-42: adequate health literacy,
>42-50: excellent health literacy [11].

Attitude Scale for Healthy Nutrition (ASHN)

Consisting of 21 items, this scale evaluates individuals' attitudes towards healthy eating. The scale has a 4-factor structure. These factors are: Information on Nutrition (IN), Emotion for Nutrition (EN), Positive Nutrition (PN), and Malnutrition (MP). The scale is 5-point Likert type and includes reversed items. The score that can be obtained from the scale is 21-105.The scores obtained from the scale are explained as having an attitude for healthy eating with 21 points very low, 23-42 points low, 43-63 points medium, 64-84 points high, and 85-110 points ideally high. ASHN is a valid and reliable measurement tool that can be used to measure the attitudes of university students towards healthy eating [12].

Health Anxiety Inventory (Short Version) (HAI)

The scale, which was validated and reliable in Turkish by Aydemir et al. (2013), consists of 2 factors and 18 questions. The scale is a 3-point Likert type and as the score obtained from the scale increases, the level of health anxiety increases [13].

Analysis of data

The data obtained from the research were evaluated in the Statistical Package for the Social Sciences (SPSS) 21.00 package program. Skewness and Kurtosis values were examined to ensure that the data were suitable for normal distribution, and the data between -1.5 and +1.5 were considered to be normally distributed [14]. It was observed that the obtained data had a normal distribution. Descriptive statistics are shown as mean ± standard deviation due to the normal distribution of the variables. Pearson Correlation coefficient was used in the study to examine the relationship between two variables. The t-test was used to evaluate the difference between the means of two groups, and the One-Way ANOVA test was used to evaluate the difference in the means of three or more groups. Post-hoc analyzes were evaluated with the Scheffe test when homogeneity was achieved, and with Tamhane's T2 test when homogeneity was not achieved. Confidence interval was accepted as 95.0% and significance level as $p<0.05$ in all statistical tests.

Ethical aspect of research

The ethics committee approval of the research was obtained from the ethics committee with the letter dated 09.11.2022 and numbered 99332, and the institutional permission was obtained from the faculty where the research was conducted. Informed consent principle by explaining the goal of the study's to the voluntary participations in the research, the principle of respect for autonomy by their voluntary participating in research, by ensuring the confidentiality of the information obtained, attention was paid to the principle of protecting confidentiality and confidentiality.

Results

Data on the socio-demographic characteristics of the students included in the study are in Table 1.

When the mean scores of the sub-dimensions of the THLS-32 scale of the students participating in the study were examined, the highest average score was found in the access health-related information component of the healthcare sub-dimension (36.31±9.96); it was determined that the lowest mean score was in the appraise health-related information component of the healthcare sub-dimension (29.61±10.92). When the ASHN sub-dimensions were examined, it was found that the lowest average score was found in the emotion for nutrition sub-dimension and the highest average score was in the information on nutrition sub-dimension (Table 2).

It was determined that 34.2% (n=185) of the students had problematic-limited health literacy. 62.3% (n=373) of the students have a high attitude for healthy nutrition (Figure 1).

It was detected that the total mean score of the students included in the study on the THLS-32 scale was 33.57±8.41, the mean score of the ASHN was 70.57±10.87, and the mean total score of the HAI was 19.67±7.43 (Table 3).

The difference between the mean scores of the THLS-32 scale according to the gender (t=2.360, p=0.019) and income status (F=3.414, p=0.034) of the students is statistically significant. This difference in income status stemmed from the fact that students whose income is less than their expenses and those whose income is more than their expenses have different levels of health literacy (p=0.034, Scheffe's test). ASHN total score averages differed significantly according to the department the students studied (F=13.728, p=0.000), and it was determined that the students of the nutrition and dietetics department had a significantly higher score than the nursing and health management students (p=0.000, p=0.008, Scheffe's test). A statistically significant difference was found between the total

Table 1 Socio-demographic characteristics of the students (n=599)

Socio-Demographic Characteristics		Mean±SD	Min-Max
Age (year)		20.63± 1.81	18-36
		n	**%**
Gender	Female	479	80.0
	Male	120	20.0
Income Status	Income less than expenses	211	35.2
	Income equals expense	306	51.1
	Income more than expenses	82	13.7
Family Structure	Nuclear family	517	86.3
	Extended family	64	10.7
	Scattered family	18	3.0
Department	Nursing	291	48.6
	Nutrition and Dietetics	224	37.4
	Healthcare Management	84	14.0
Grade	First year	197	32.9
	Second year	132	22.0
	Third year	116	19.4
	Fourth year	154	25.7
Living Place	State dormitory	454	75.8
	Private dormitory	20	3.3
	Home	125	20.9
If at Home with Whom	Alone	26	20.8
	With Friend	25	20.0
	With Family	70	56.0
	With Relatives	4	3.2
BMI	Underweight (<18.50)	96	16.0
	Normal Weight (18.50-24.9)	403	67.3
	Overweight (25-29.9)	85	14.2
	Obese (>30)	15	2.5
Smoking Status	Yes	110	18.4
	No	489	81.6

Mean±SD: Mean± Standard deviation, Min.-Max.: Minimum-Maximum Score

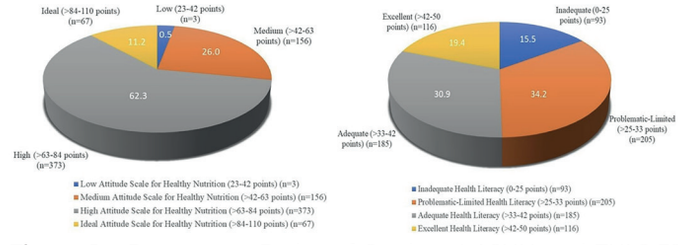

Figure 1 - Percentage Ratios of Students' ASHN and THLS-32 Categorical Score (n=599) ASHN: Attitude Scale for Healthy Nutrition, THLS: Turkey Health Literacy Scale

Table 3 Distribution of students' TSOY-32 Scale, SBITO and SAE mean scores (n=599)

Scales	Mean±SD	Median (Min-Max)
THLS- 32	33.57±8.41	33.33 (4.17-50.00)
ASHN	70.57±10.87	70.00 (33.00-103.00)
HAI	19.67±7.43	19.00 (4.17-50.00)

ASHN: Attitude Scale for Healthy Nutrition, HAI: Health Anxiety Inventory, Mean±SD: Mean±Standard deviation, Min.-Max: Minimum-Maximum Score, THLS: Turkey Health Literacy Scale.

Table 2 Students' THLS-32 and ASHN Sub-Dimensions Index Scores Mean (n=599)

	Sub-Dimension	Mean±SD	Min-Max
THLS-32	Healthcare Access health-related information	36.31±9.96	12.50-50.00
	Understand health-related information	34.58±10.18	8.33-50.00
	Appraise health-related information	29.61±10.92	4.17-50.00
	Apply health-related information	36.03±10.20	4.17-50.00
	Disease prevention and health promotion Access health-related information	34.98±10.79	4.17-50.00
	Understand health-related information	35.42±10.59	4.17-50.00
	Appraise health-related information	31.96±11.28	16.67-50.00
	Apply health-related information	29.69±12.00	12.50-50.00
ASHN	Information on nutrition	20.34±4.03	5.0-25.0
	Emotion for nutrition	16.09±4.49	6.0-30.0
	Positive nutrition	16.63±4.31	5.0-25.0
	Malnutrition	17.51±4.76	5.0-25.0

ASHN: Attitude Scale for Healthy Nutrition, Mean±SD: Mean± Standard deviation, Min.-Max: Minimum-Maximum Score, THLS: Turkey Health Literacy Scale

Table 4 Comparison of the mean scores of THLS-32, ASHN and HAI according to the socio-demographic characteristics of the students (n=599)

Socio-Demographic Characteristics		THLS- 32	ASHN	HAI
		Mean±SD	Mean±SD	Mean±SD
Gender	Female	33.97±8.21	70.50±10.98	19.73±7.29
	Male	31.95±9.02	70.85±10.48	19.47±8.00
		t=2.360 p=0.019	t=-0.308 p=0.758	t=0.337 p=0.751
Income Status	Income less than expenses	32.54±9.10	69.32±11.21	7.97±0.54
	Income equals expense	33.82±7.99	71.26±10.54	7.16±0.40
	Income more than expenses	35.27±7.84	71.23±11.05	6.98±0.77
		F=3.414 p=0.034	F=2.156 p=0.117	F=1.236 p=0.291
Family Structure	Nuclear family	33.82±8.14	70.60±10.86	19.68±7.29
	Extended family	31.99±8.95	69.98±11.27	20.01±7.62
	Scattered family	31.91±12.99	71.72±10.16	18.44±10.51
		F=1.706 p=0.183	F=0.196 p=0.822	F=0.313 p=0.731
Department	Nursing	33.08±8.65	68.65±10.10	20.42±7.60
	Nutrition and Dietetic	33.89±8.17	73.50±10.97	18.91±7.24
	Healthcare Management	34.40±8.23	69.41±11.57	19.14±7.18
		F=1.060 p=0.347	F=13.728 p=0.000	F=2.873 p=0.057
Grade	First year	32.47±8.63	69.04±10.02	20.64±7.48
	Second year	31.74±8.18	69.06±10.36	19.68±7.27
	Third year	34.20±8.48	72.50±11.91	18.99±7.50
	Fourth year	36.07±7.68	72.38±11.12	18.94±7.38
		F=4.893 p=0.002	F=8.239 p=0.000	F=1.955 p=0.120
Living Place	State dormitory	33.49±8.17	70.55±10.56	19.53±7.12
	Private dormitory	30.88±11.58	65.65±14.10	23.05±8.47
	Home	34.28±8.66	71.42±11.28	19.68±8.26
		F=1.491 p=0.226	F=2.443 p=0.088	F=2.153 p=0.117
BMI	Underweight (<18.50)	34.38±8.10	71.20±11.24	18.88±6.90
	Normal Weight (18.50-24.9)	33.30±8.31	70.59±11.03	19.85±7.65
	Overweight (25-29.9)	33.33±8.77	70.04±9.87	20.08±7.11
	Obese (>30)	36.97±10.77	68.93±10.18	17.80±6.34
		F=1.279 p=0.281	F=0.289 p=0.834	F=0.840 p=0.472
Smoking Status	Yes	32.20±9.91	66.82±11.05	18.77±8.36
	No	33.88±8.02	71.41±10.66	19.88±7.20
		t=-1.895 p=0.059	t=-4.052 p=0.000	t=-1.417 p=0.157

ASHN: Attitude Scale for Healthy Nutrition, HAI: Health Anxiety Inventory, Mean±SD: Mean±Standard Deviation, THLS: Turkey Health Literacy Scale.

score averages of the THLS-32 (F=4.893, p=0.002) and ASHN (F=8.239, p=0.000) according to the grade level of the students. It was detected that the health literacy of the fourth-year students was higher than the first and second year students (p=0.001, p=0.000, Scheffe's test). In addition, in the further analysis, it was detected that the fourth-year students' attitudes for healthy eating were higher than the first-year students' (p=0.023, Tamhane's T2 test). A statistically significant difference was found between the attitudes of smokers and non-smokers towards healthy eating (t=-4.052, p=0.000) (Table 4). A statistically significant positive correlation was found between the age of the students and their health literacy (r=0.166, p=0.000) and their attitudes for healthy eating (r=0.180, p=0.000). A statistically significant negative correlation was found between age and students' health anxiety (r=-0.112, p=0.006).

A statistically significant correlation was determined between students' health literacy and their attitudes for healthy eating, in a positive direction (r=0.258, p=0.000), and between health anxiety in a negative direction (r=-0.171, p=0.000). A statistically significant negative correlation was found between their attitudes for healthy eating and their health anxiety (r= -0.166, p=0.000).

Discussion

Health literacy, which has a role in the protection of individual health and its contribution to the health system, and the improvement of health at the social level, is affected by demographic, psychosocial, cultural and past experiences [2]. In this study, in which health literacy was evaluated with the THLS-32, 50.9% of individuals had adequate or excellent health literacy. It was seen that the mean health literacy score of the individuals was 33.57±8.41 and the highest mean score was in the component of the healthcare sub-dimension of the process of accessing health-related information. In addition, it was determined that the mean health literacy scores of female individuals, the income being higher than the expenditure, and the 4th grade students were significantly higher. In a study conducted with health science students, 55.7% of the students had adequate or excellent health literacy and the mean health literacy score was 34.53; The component with the highest mean score is the component of accessing healthy information in the healthcare sub-dimension, similar to our study [15]. In a different study involving university students, it was found that the health literacy score was 26.48±16.54 and 40.1% had adequate or excellent health literacy. When the relationship with sociodemographic data is examined, it is stated that there are significant differences according to age, gender, income status, living place, chronic disease status, department and grade level [16]. In the study of Okur et al. (2021), in which health literacy levels were examined, the mean health literacy score was 35.98±5.83, while the highest mean score was seen in the component of apply health-related information in the healthcare sub-dimension. When the relationship with demographic data was evaluated, it was stated that the difference in health literacy scores was not significant [17]. In the study of Soykan and Şengül (2021), it was detected that the average health literacy score of the students was 36.20±7.66, while the rate of participants with adequate or excellent health literacy was 62.1%. When the sub-dimensions of health literacy were evaluated, it was determined that the highest mean score belonged to the component of accessing health-related information in the healthcare sub-dimension [18]. Although this relationship between health literacy and demographic data in our study is consistent with the literature, it is thought that the higher participation of female students in this study, the increase in the level of knowledge and awareness with the health education received, and the economic difficulties experienced affect the health literacy score.

Acquiring healthy eating habits and attitudes towards healthy eating in young adulthood, a period in which eating habits change and develop, are of great importance in the protection and development of health [7]. For this reason, it is thought that it is important to determine the attitudes of university students towards healthy eating in the age group. In this study, in which the attitude for healthy eating was evaluated, the average attitude score of the individuals was 70.57±10.87, while the highest average score was seen in the information on nutrition sub-dimension when the sub-dimensions were examined. 73.5% of the participants have an attitude for high or ideal healthy eating. When the association between the attitude score for healthy eating and demographic profile is examined, the average scores of nutrition and dietetics students, fourth-year students, and non-smokers are significantly higher. In a different study examining the scores of attitudes for healthy eating, similar to our study, it was determined that the average sub-dimension with the highest score was the dimension of information on nutrition [19]. In a study that included midwifery and nursing department students, the mean ASHN score was 75.5±8.8 and no significant differences were found with gender, department, income level and smoking variables [20]. In a study evaluating the attitude for healthy eating, it was stated that the average attitude score was 75.57±10.31, 87.0% of the participants had high or ideal attitudes, and the highest average sub-dimension score was in the positive nutrition sub-dimension. When the relationship between the attitude score for healthy eating and the variables is examined, it is stated that there is a significant difference according to marital status, occupation and duration of social media use, but there is no significant difference according to gender, education level and BMI values [5]. In the study of Göral and Yıldırım (2022), it was found that male students' ASHN scores were higher, and it was stated that the sub-dimension with the highest score was the dimension of knowledge about nutrition, similar to our study [21]. In a study conducted with the participation of students from the faculty of medicine and sports sciences, it was stated that the scores of attitudes for healthy eating differ significantly according to gender, activity, smoking and the department of education [22]. Although the findings in our research are compatible with the literature, it is an expected result of the research that the students of the nutrition and dietetics department have higher attitude scores for healthy nutrition, and the higher level of knowledge and attitude of the senior grade students due to the increase in the nutrition education and education level. Smoking is an important risk factor for an unhealthy life, together with inadequate and balanced nutrition and lack of physical activity. With the behavior change interventions recommended for a healthy life, awareness and education level are increased, providing both smoking cessation and improving nutrition and physical activity [23]. In the current study, it was determined that the attitudes of smokers for healthy eating were lower.

Health anxiety is a health problem that causes individuals to worry excessively about health and cause both personal and interpersonal problems even though they do not have a serious health problem [6]. In our study, the mean health anxiety score of individuals was 19.67±7.43, and no significant correlation was found between demographic variables. In a study examining health anxiety of health students, it was found that results were similar to our study, health anxiety score was 17.85±6.36, and demographic data had no effect on health anxiety [24]. In studies examining health anxiety with university students, it was determined that the health anxiety score showed similar

results with our study and there was no significant difference in the health anxiety score according to demographic variables [8,24,25].

A positive relationship was found between students' health literacy and their attitudes for healthy eating. There are studies reporting that health literacy is important for maintaining a certain level of quality of life in individuals receiving diet therapy for diseases and in case of illness [26,27]. In addition, with the increase in the level of health literacy, reading the food label, which greatly affects the choice of healthy food, gains importance [28]. It has been determined that individuals who read the food label pay attention to their regular meal consumption and consume less unhealthy foods, while they consume more healthy foods [29]. In the study of Arslan et al. (2022) examining the food label reading behavior of university students; It has been determined that students studying in the field of health pay more attention to some nutritional information (calories, total fat, sugar) written on the label [30]. It is thought that increasing the level of knowledge about health contributes to a healthy diet.

When the relationship between students' health literacy and health anxiety was evaluated, it was found that as health literacy level increased, health anxiety decreased. Smith et al (2013) found a substantial correlation between high health literacy and low anxiety, similar to our study [31]. In the specialization study, the effect of health literacy on health anxiety, conducted in Turkey, it was found that as the level of health literacy increased, the level of health anxiety decreased [32]. It is thought that the low health anxiety of people with high health literacy is due to the fact that individuals use the ability to read, understand and apply more when making decisions about health as their level of health-related knowledge increases. In addition, it will be beneficial for individuals with adequate or excellent health literacy level to better understand and transform the education (nutrition, exercise, stress, etc.) given by health professionals into behavior. There are not enough studies in the literature examining the association between health literacy and health anxiety. The fact that this study is the first to examine health literacy and health anxiety in young adults is important in terms of contributing to the literature.

A significant inverse correlation was found between students' attitudes for healthy eating and their health concerns. Health anxiety; it adversely affects nutrition-related factors such as individuals' eating habits, meal order, healthy and balanced diet planning, and diet quality [33]. Individuals who have a health-related problem in their family or in themselves can exhibit healthy eating behaviors in order to solve the health problem or prevent the disease itself [34]. In line with this information, it is an expected result of the research that individuals with high attitudes for healthy eating have low health anxiety.

Conclusion and recommendations

This study is significant since it is the first to jointly investigate attitudes toward healthy eating, health literacy, and health anxiety. In the study, it was shown that there is a association between demographic characteristics, health literacy, healthy eating and health anxiety, and some demographic data have an effect on these variables. The increase in the health literacy of individuals in young adulthood causes a positive effect on other health-related behaviors. In addition, considering the importance of health science students working in a multidisciplinary environment, it is thought that improving health literacy and healthy eating attitudes and reducing health anxiety will provide an important benefit both at the individual and social level.

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Evaluation of the double mesh and intraperitoneal onlay mesh techniques in giant incisional hernias

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Abstract

Background: Giant incisional hernias are difficult to manage. The present study aims to comparatively evaluate the intraperitoneal onlay mesh (IPOM) technique to double-mesh repair techniques in patients with a midline abdominal wall incisional hernia larger than 15 cm (transvers width) that cannot be closed primarily.

Material and methods: Patients who underwent repair surgery with the diagnosis of incisional hernia in our hospital between January 2017 and December 2019 were retrospectively evaluated. The repair was performed with open surgery using the IPOM technique in 19 patients and the double-mesh technique in 13 patients for 2 years to evaluate for postoperative complications, pain, and recurrence.

Results: The mean age, gender distribution, body mass index, defect size, and American Society of Anesthesiologists scores were similar between the groups. The total rate of postoperative complications was 42.1% in Group A and 30.8% in Group B, with no significant difference between the groups ($p > 0.05$). Recurrence occurred in three patients (15.8%) in Group A, but it did not in Group B. Although the absence of recurrence in Group B was a remarkable finding, the difference was not statistically significant ($p>0.05$).

Discussion: The IPOM and double-mesh techniques can be used safely to perform tension-free abdominal wall reconstruction in patients with complex and giant incisional hernias. However, the double-mesh technique may be preferred owing to its lower recurrence rate.

Key words: giant incisional hernia, double mesh, IPOM

Introduction

Incisional hernia is a common surgical problem, and it occurs in 2%–10% of laparotomies [1]. According to the European Hernia Society classification, incisional abdominal wall hernias with a defect size of >10 cm (transverse diameter [width] = W3) are classified as large incisional hernias [2]. Notably, very large hernias, also referred to as giant ventral hernias, are considered in cases in which the hernia orifice is >10 cm in width with loss of domain [3]. The management of giant hernia remains a surgical challenge, and one of the main technical difficulties has been reported to be parietal closure without tension [4].

Another challenge in the management of giant hernia is the reduction of the hernia content into the abdomen. Moreover, increased intraabdominal pressure and cardiovascular and respiratory problems are expected as surgical complications [4]. Surgical correction plays an important role in the treatment of giant incisional hernias. Special techniques, such as intraperitoneal onlay mesh, double-mesh, and component, separation have been developed and employed to reduce postoperative complications as well as to decrease the likelihood of recurrence, particularly in patients with giant incisional hernias that cannot be primarily closed at the midline by suture repair [5,6].

At present, to the best of our knowledge, no technique or approach has been recognized as the gold standard for ventral incisional hernia repair. The present study aimed to evaluate the intraperitoneal onlay mesh (IPOM) versus double-mesh surgical repair techniques used for large midline incisional hernias in which the hernia defect cannot be primarily closed without tension by suture repair; moreover, we aimed to examine the two techniques in terms of recurrence and share our experience.

Material and methods

The records of patients who underwent giant incisional hernia repair surgery performed by two surgical

teams in XXX Hospital between January 2017 and December 2019 were retrospectively reviewed. The study protocol was approved by the local ethics committee (Haydarpaşa Numune Education and Training Hospital, Clinical Trials Ethics Committee, İstanbul, Turkey). The study included patients aged 18 years and older who had a midline abdominal wall defect of greater than 10 cm as evidenced by preoperative computed tomography scans or ultrasonography. Patients with recurrent hernias, those undergoing emergency surgery, those with ascites, those with metastatic disease, and those who did not attend control visits were excluded. The hospital records of 232 patients who underwent surgery with the diagnosis of incisional hernia were evaluated, and 36 patients who met the selection criteria were identified. However, two patients could not be reached, and two other patients died due to other causes. A total of 32 patients were included in the study, with 19 undergoing repair using the IPOM technique (DualMesh® [Gore®]) assigned to Group A and 13 undergoing repair using the double-mesh technique combining intraperitoneal onlay dual mesh and onlay polypropylene (PP) (Bard Ltd, UK) mesh assigned to Group B.

In addition to the findings of physical examination, ultrasonography and computed tomography were used to diagnose recurrent hernia. Chronic pain was defined as pain that lasted for >6 months and necessitated the use of analgesics. The data of patients were retrieved from the hospital records, and the patients were contacted via telephone, if necessary. Demographic data (age, gender, body mass index [BMI]), the American Society of Anesthesiologists (ASA) score, defect size (cm), operation time (minutes), length of hospital stay (days), postoperative complications, pain, and recurrence parameters were recorded.

Surgical technique

After excising the scar tissue, the hernia defect was exposed using dissection. Further, the adhesions were removed after entering the peritoneal cavity. An expanded polytetrafluoroethylene (ePTFE) dual mesh (DualMesh® [Gore®]) overlapping the defect by at least 5 cm in all directions was intraperitoneally inserted using an onlay technique and attached to the abdominal wall using transmural 2/0 prolene U-sutures. In the double-mesh technique, in addition to the ePTFE intraperitoneal onlay dual mesh placement described above, a supra-aponeurotic PP (polypropylene) mesh was placed using an onlay technique and attached with 2/0 prolene sutures. Subcutaneous aspiration drains were placed in both groups.

Statistical analysis

The IBM SPSS Statistics 22 software package was used in the statistical analysis of the study data. The Kolmogorov–Smirnov and Shapiro–Wilk tests were used to examine whether the parameters were normally distributed. Along with descriptive statistics (mean, standard deviation, and frequency), the Student's t-test was used to compare quantitative parameters with a normal distribution between the two groups, whereas the Mann–Whitney U test was used to compare parameters without a normal distribution. The Fisher's exact chi-square test, Fisher–Freeman–Halton exact chi-square test, and Yates's correction for continuity were used to compare qualitative data. A p value of <0.05 was considered statistically significant.

Results

Of the participants, 19 (59.4%) underwent repair using the open IPOM technique (Group A) and 13 (40.6%) using the double-mesh technique (Group B). The mean age was 57.58±13.66 years in Group A and 58.85±14.59 years in Group B. There was no significant difference between the two groups in terms of gender distribution, BMI, defect size, preoperative hemoglobin, albumin,and ASA scores. The demographic characteristics of the patients are presented in Table 1.

Table 1 Comparison of demographic characteristics between the groups

		Group A (n= 19)	Group B (n = 13)	Total (n = 32)	p
Age Mean ± SD		57.58 ± 13.66	58.85 ± 14.59	58.09 ± 13.82	*0.804
BMI Mean ± SD		33.34 ± 5.9	32.07 ± 4.9	32.83 ± 5.47	*0.527
Defect Size (cm) Mean ± SD		16.68 ± 2.08	16.08 ± 2.72	16.44 ± 2.34	*0.480
Preoperative Hb Mean ± SD		12.22 ± 1.31	12.64 ± 1.02	12.39 ± 1.2	*0.342
Preoperative albumin Mean ± SD		3.83 ± 0.41	3.85 ± 0.37	3.84 ± 0.39	*0.848
Length of hospital stay (day) Mean ± SD (median)		8.95 ± 3.88 (8)	8.54 ± 3.69 (8)	8.78 ± 3.75 (8)	†0.846
Gender n (%)	Male	10 (52.6%)	8 (61.5%)	18 (56.2%)	‡0.892
	Female	9 (47.4%)	5 (38.5%)	14 (43.8%)	
Comorbid Conditions n (%)	Present	15 (78.9%)	10 (76.9%)	25 (78.1%)	§1.000
	Absent	4 (21.1%)	3 (23.1%)	7 (21.9%)	
ASA n (%)	1	1 (5.3%)	1 (7.7%)	2 (6.3%)	‖1.000
	2	8 (42.1%)	5 (38.5%)	13 (40.6%)	

*Student's t-test †Mann–Whitney U Test ‡Yates's correction for continuity §Fisher's Exact test ‖Fisher–Freeman–Halton Exact test *p < 0.05* ASA, American Society of Anesthesiologists

Table 2 Comparison of operative findings between the groups

		Group A (n = 19)	Group B (n = 13)	Total (n = 32)	p
Operation time (min) Mean ± SD (median)		175.0 ± 21.8 (170)	206.92 ± 34.0 (210)	187.97 ± 31.26 (180)	*0.007*
Perioperative organ injury n (%)	Present	0 (0%)	1 (7.7%)	1 (3.1%)	†0.406
	Absent	19 (100%)	12 (92.3%)	31 (96.9%)	

*Mann–Whitney U Test †Fisher's Exact Test *p < 0.05*

The mean operation time was 175.0±21.8 (170) minutes in Group A and 206.92±34.0 (210) minutes in Group B, showing a significantly longer operation time in the double-mesh repair group (p<0.05). The comparison of operative findings between the groups is presented in Table 2. No significant perioperative hemorrhage occurred in our patients, and no patient required a blood transfusion.

When evaluated in terms of complications, the rate of seroma was 21.1% in Group A and 23.1% in Group B, the rate of wound site infection was 15.8% in Group A and 15.4% in Group B, and the rate of respiratory problems was 5.3% in Group A and 23.1% in Group B, showing no significant difference between the groups. Despite the observation of a difference in respiratory complications, no statistically significant difference was found owing to the small number of patients. No patient developed hematoma or hemorrhage, and no patient required blood replacement.

In terms of late complications, chronic pain occurred in three patients (15.8%) in Group A and one patient (7.7%) in Group B (p>0.05); recurrence was observed in three patients (15.8%) in Group A, whereas no recurrence was observed in Group B. Recurrence occurred at 9 months in one patient and 1 year after surgery in two patients. Although the absence of recurrence in the double-mesh repair group was a remarkable finding, the difference was not statistically significant (p>0.05). No mortality occurred. Postoperative early and late complications are presented in Table 3.

Table 3 Evaluation of postoperative complications

	Group A (n = 19)	Group B (n = 13)	Total (n = 32)	
	n (%)	n (%)	n (%)	p
Early Complications				
Seroma	4 (21.1%)	3 (23.1%)	7 (21.9%)	1.000
Hematoma	0 (0%)	0 (0%)	0 (0%)	-
Bands	0 (0%)	1 (7.7%)	1 (3.1%)	0.406
Wound site infection	3 (15.8%)	2 (15.4%)	5 (15.6%)	1.000
Respiratory problems	1 (5.3%)	3 (23.1%)	4 (12.5%)	0.279
Late Complications				
Chronic pain	3 (15.8%)	1 (7.7%)	4 (12.5%)	0.629
Recurrence	3 (15.8%)	0 (0%)	3 (9.4%)	0.253
Mortality	0 (0%)	0 (0%)	0 (0%)	-
Postoperative Complications (Total)	8 (42.1%)	4 (30.8%)	12 (37.5%)	0.713

Fisher's Exact Test

Discussion

The goals of surgery for incisional hernias are to perform surgical correction and to reduce complications and recurrence. In complex incisional hernias of >10 cm, suture repair is technically more difficult, and there is debate about the choice of surgical procedure owing to the increased postoperative morbidity and high recurrence rates [7,8].

Although some studies have published the advantages of laparoscopic repair over open surgery, the guidelines have recommended open repair of hernias with a defect size of >10cm [9,10]. All patients in the present study had undergone open surgery and defect size of >15 cm. There is still debate about the ideal surgical technique for the repair of incisional hernias. The Rives–Stoppa technique involving retro muscular mesh placement will gain widespread acceptance if the fascia can be closed primarily. Because the mesh is not located in the intra-abdominal cavity, this surgical method has some advantages, including low rates of surgical site infection, low recurrence rates in the long term, and low rates of intra-abdominal complications [11].

Giant incisional hernias, in which the abdominal wall cannot be closed, have prompted surgeons to seek alternative methods. Among these methods, the component separation technique has necessitated the addition of single- and double-mesh placements because the technique created new weak spots and was associated with increased postoperative morbidity. The addition of mesh placement resulted in reduced morbidity and recurrence rates [7,12]. The Expert Consensus Guided by Systematic Review has stated that the use of IPOM may be beneficial in the repair of large incisional hernias [13]. The IPOM technique is particularly recommended for patients in whom laparoscopic surgery is contraindicated, those with obesity, those with multiple previous laparotomies, and those with hernia recurrence after preperitoneal mesh placement.

Usher first reported the double-mesh technique, and several modifications have been published since [14]. An open repair using IPOM and double-mesh techniques is used to solve a complex problem caused by a large defect that cannot be closed, primarily owing to anatomical limitations. The objective of repair is to perform tension free reconstruction without compressing the abdominal compartment.

In accordance with the recommendations of these guidelines and the preferences of the two surgical teams, IPOM and double-mesh repair techniques were used in the present study to repair large incisional hernias. In a meta-analysis, obesity was reported to be a factor in the development of recurrence in many studies in which the BMI cut off value was accepted as 30 kg/m2 [8]. A study of 163 patients found that patients with a BMI of >32 kg/m2 had a higher recurrence rate 10.5%, whereas those with a BMI of <32 kg/m2 had a recurrence rate of 1.7% [15]. In the present study, there was no significant difference in BMI between the groups, and the mean BMI was 32.83±5.47 kg/m2. However, two out of three patients who developed recurrent hernia had a BMI of >40 kg/m2. The mean defect size in the

present study was 16.44±2.34 cm, which is similar to the defect sizes reported in the literature for large and giant incisional hernias that were repaired using the IPOM and double-mesh repair techniques [16].

In a meta-analysis, the risk of recurrence was reported to increase with increasing defect diameter, but no significant relationship was found between defect diameter and recurrence rate [8]. The length of hospital stay has been reported to be 5±4 days, with some studies reporting 6–60 days [16,17]. Consistent with the literature, the mean length of hospital stay in the present study was 8.78±3.75 days, with no significant difference between the groups. The mean operation time has been reported to be 60–300 minutes in the literature [16,18]; the operation times in the present study were consistent with those reported in the literature, and the operation time was significantly longer in the double-mesh repair group. It is not an unexpected result as it is already predicted that placing two meshes will increase the operation time.

Notably, postoperative complication rates in open IPOM technique are 1.6%–12.5% for seroma, 2.5% for hematoma, 2.5%–10% for wound site infection, and 3.3% to 4% for chronic pain [17,19]. In the present study, with the use of the IPOM technique (Group A), the rates of seroma, wound site infections, and chronic pain were 21.1%, 15.8%, and 15.8%, respectively. In a series of 19 patients undergoing surgical repair using the double-mesh technique, the rate of wound site infections during a follow-up period of 30 months was 5.8%,, and the rate of chronic pain was 35.3% [20]. In a study by Moreno-Egea et al. [16] involving a follow-up period of 48 months in patients undergoing repair using the double-mesh technique, the rates of seroma, skin necrosis, and wound site infections were 10%, 4%, and 2%, respectively. In another study of 43 patients in which modified double-mesh and onlay mesh techniques were compared, seroma, hematoma, wound site infection, and chronic pain were observed in 9.1%, 4.5%, 4.5%, and 4.5% of the cases treated with double-mesh technique [21].

In the present study, with the use of the double-mesh technique (Group B), the rates of seroma, wound site infections, and chronic pain were 23.1%, 15.4%, and 7.7% (one patient), respectively. Notably, the complication rates in both groups were found to be higher than those reported in the relevant literature, and this difference may be attributed to the small number of patients in our study. The rates of seroma, hematoma, and wound site infections have been reported to be higher in the onlay (supra-aponeurotic) mesh technique than in the intraperitoneal onlay mesh technique owing to the need for more extensive subcutaneous dissection during mesh placement in the onlay mesh technique [21]. In the present study, although the second mesh was placed in the supra-aponeurotic area using an onlay technique in the double-mesh group, postoperative complications were found to be similar between the two groups.

Previous studies have reported recurrence rates of 0%–61.0% (mean, 12.6%) using the IPOM Technique [16,18] and 0%–18% using the double-mesh technique [21-24]. In the present study, recurrence was observed in three patients in Group A (15.8%), whereas no recurrence was observed in Group B (0%). Despite the small number of patients and the consequent lack of a statistically significant difference between the two groups, the authors believe that the addition of a second mesh to the surgical repair procedure would reduce recurrence rates. Notably, the recurrence rates for both surgical techniques were found to be consistent with those reported in the literature.

The small number of patients and retrospective study design are limitations of the present study. However, the repair of giant incisional hernias is challenging, and there is a lack of an evidence-based research using data from large-scale randomized studies. In conclusion, the authors of the present study suggest that the IPOM and double-mesh techniques can be used safely to perform tension-free abdominal wall reconstruction in patients with complex and giant incisional hernias; however, despite the lack of a statistically significant difference, the double-mesh technique may appear to be a better option in terms of recurrence. Therefore, large-scale studies are required.

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The role of repeat computerized cranial tomography in pediatric blunt head trauma

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Abstract

Introduction: Computed cranial tomography (CCT) is commonly used in emergency departments (EDs) for pediatric blunt head injury (BHI) management. Cranial tomography is also repeated often unnecessarily due to physicians' concerns about detecting the early onset of a possible new injury or progression of an existing one. This study aims to evaluate whether routine RCCT provides a significant change in patient management.

Material and methods: The study was performed as a 2-year retrospective analysis in the ED of a tertiary hospital. The medical records of pediatric BHI patients were reviewed, and the study included accessed data of 104 patients who underwent at least two CCT during their stay in the ED.

Results: The study included 104 out of 533 BHI patients. The mean age of these 104 patients was 6.2 years (median=4.5 years), and the majority were male (n=82, 78.9%). When the initial CCT results of the patients were analyzed, it was found that 51% (n=53) of the tomography results were normal. While there were substantial changes in 7 of the RCCTs, there were no significant changes in 97. Only 4 of these 7 patients who had significant changes were taken to the emergent operating room. None of these patients belonged to the group of patients whose CCT was classified as "normal" on admission ($p<0.05$).

Conclusion: According to our results, routine RCCT for BHI in pediatric patients did not result in a significant change in patient management.

Key words: blunt head injury, computed tomography, pediatric emergency medicine, radiation exposure

Introduction

Non-contrast computed cranial tomography (CCT) is often the preferred imaging modality for the rapid and early identification and treatment of pediatric patients with blunt head injury (BHI) in our country and around the world [1,2]. Although pediatric head injury management is well established by pediatric trauma life support guidelines and some clinical decision rules in the ongoing management of patients with a BHI in the emergency department (ED), mostly the general approach is to request routine repeat computed cranial tomography (RCCT) and evaluate it for the possibility of the occurring of a new injury or progressing the old ones [3]. The most commonly used general clinical decision-making rules for assessing pediatric blunt head trauma are Pediatric Emergency Care Applied Research Network (PECARN), the children's head injury algorithm for the prediction of important clinical events [CHALICE], and Canadian assessment of tomography for childhood head injury [CATCH] rules [4-6]. The main reason for requesting RCCT outside the rules of these clinical decision algorithms is that routine imaging could detect a potential new or progressive injury early, allowing for intervention before lasting neurologic damage occurs [7,8]. However, with recent advances in imaging quality and technology, we now know that CCT scans are not free from ionizing radiation risk [1]. These tomography scans' potential harm is clear, particularly from the perspective of the pediatric population. As a result, a 1-year-old child's lifetime risk of dying from cancer from a single CCT is 10 times higher than the risk of an adult [9]. Radiation exposure also increases the risk of developing cataracts in children and negatively affects cognition in adulthood [9,10].

To the date, we have no clear evidence that the benefits of RCCT outweigh the risks. If RCCT does not

provide a clinically meaningful benefit, this implies potential future harm for this patient population. For the adult group, RCCTs have been reported to rarely lead to changes in medical care and treatment in patients whose neurological status does not change [11,12]. A study on children reported that only 4-8% of all CCTs had a traumatic brain injury finding, and only 0.5% of pediatric patients with a Glasgow Coma Scale (GCS) score of 14-15 required neurosurgical intervention [13].

Few studies in pediatric patients with BHI have addressed the routine use of RCCT, and most of them have emphasized the need to change current standards of care [7,14,15]. This study aims to (1) evaluate the characteristics and course of BHI at our center in the pediatric age group and (2) attempt to determine whether routine RCCT produces a change in patient management.

Material and methods

Patients

This 2-year retrospective study was conducted between January 1, 2019, and January 1, 2021, in the city center's ED of a tertiary training and research hospital in Ankara, in Turkey. The medical records of all patients with blunt head injuries aged 18 years and younger (with ICD-10 codes for head injury) were reviewed at the appropriate dates. Patients discharged from ED without CCT after receiving a physical examination (PE), family information, and explanations of emergency conditions were excluded from the study. In addition, patients admitted to neurosurgery, to the intensive care unit or admitted to the operating room for an emergent neurosurgical procedure according to admission PE and trauma characteristics, or initial CCT results were excluded from the study. In our center, the PECARN algorithm was generally used by emergency medicine physicians and neurosurgeons in the evaluation of pediatric blunt head trauma. Patients with a single CCT result, and patients whose admission to ED longer than 24 hours also excluded. The study included patients examined with at least two CCTs during their stay in the ED and whose data were available. Patient age and sex characteristics were recorded, as well as trauma mechanisms, any concomitant injuries, initial CCT pathologies, if there was a significant change in RCCTs, time durations between two CCTs, and discharge and hospitalization or mortality rates. A new or different pathology in RCCTs compared to patients' initial CCT scans was defined as a "significant change" between the two scans. This was generally caused by pathologies such as a new intracranial hemorrhage or contusion, a skull fracture, edema, or an increase in intracranial hemorrhage or a clearly visible non-displaced fracture line compared with the first CCT. It is not the formal policy of the hospital to repeat CCT after admission to determine significant interval changes but clinicians sometimes may order repeat CCT. Informed consent was obtained from participants in the study and the Ethics Committee of Ankara Training and Research Hospital approved the study (decision no: E-21-806, date: 24.11.2021).

Statistical analysis

The Kolmogorov-Smirnov test was used to fit the data to the normal distribution. To compare categorical data, the Chi-square test was performed. For comparisons where the expected numbers in any cell were less than 5, Chi-square analysis with Fisher's exact test was conducted. For data that did not confirm to the normal distribution, the Mann-Whitney U test, a nonparametric test, was performed. For data with a normal distribution, the t-test was performed. Values with a p-value of < 0.05 were considered statistically significant. All analyses were conducted using SPSS for Windows version 18.0 (Chicago, IL, USA).

Results

A total of 110 patients met the inclusion criteria of the study. Six patients were excluded from the study group because the period between the first CCT and the RCCT could not be determined. The remaining 104 patients constituted our patient group. The flow chart of the study group is shown in Figure 1.

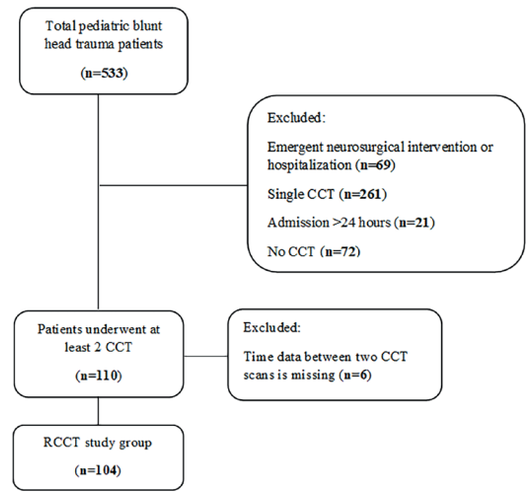

Figure 1 - Flow chart of the study population

The average age of our patients was on 6.2 years (median=4.5 years), and the majority of them were male (n=82, or 78.9%). Patients younger than 10 years old accounted for 74% of the study group (n=77). When the concomitant injury characteristics of the patients were examined, 39.4% (n=41) were found to have at least one concomitant trauma in other organ system. The most common first three associated traumas were trauma to the cervical spine, extremities, and thoracic region. When examining the trauma mechanisms causing BHI, the most common cause was a fall from height (n=84, 80.8%). Motor vehicle accidents, both inside and outside the vehicle, followed the falls (Table 1).

Table 1 Demographics and characteristics of the patients.

Variable	n (%)
Number of patients	104 (100)
Age, mean, SD, in years	6.2 (4.9)
Under 10 years old	77 (74)
Male	82 (78.9)
Concomitant trauma	41 (39.4)
Trauma mechanism, falls	84 (80.8)

Table 2 Initial CCT findings* (*Some patients have more than 1 pathology).

Variable	n (%)
Normal	53 (51)
Skull fracture	28 (26.9)
Soft tissue swelling	17 (16.3)
Contusion	6 (5.8)
Subarachnoid hemorrhage	6 (5.8)
Subdural hemorrhage	5 (4.8)
Intraparenchymal hematoma	3 (2.9)
Epidural hemorrhage	3 (2.9)

CCT, Computerized cranial tomography

Table 3 Significant change on RCCT and prognosis of the patients.

Variable	n (%)
Significant change on RCCT (+)/(-)	7/97 (6.7/93.3)
Time duration to RCCT, minute, min-max, SD	247.5 (60-1337, 175)
Prognosis, hospitalization/discharge	35/69 (33.7/66.3)

RCCT, Repeat computerized cranial tomography

In terms of trauma mechanism, there was no statistically significant difference between patients younger than 10 years of age and patients older than 10 years of age (p=0.123). When the first CCT results of the patients were evaluated, it was revealed that 51% (n=53) of the tomography results were normal. Skull fracture was the most prevalent pathology found in the first CCT scans (n=28, 26.9%). Extracranial soft tissue swelling, contusions, and intracranial hemorrhage were the other most common pathologies (Table 2). Following an average of 247.5 minutes (min:60-max:1337) after the first CCT scans, RCCT scans were performed on the patients. While there were substantial changes in 7 of the RCCTs, there were no significant changes in 97 patients. Only 4 of the 7 patients who had significant changes were taken to the operating room. Of 66.3% (n=69) the total patient group were discharged from the ED (Table 3). Repeat CCT was performed for the third time in 1 patient. This patient was in the discharged group. None of the patients in the study group was died. There were no patients who were referred to another center. All patients with significant changes according to RCCT results also had pathologic findings in their first admission CCT. Repeat CCTs of these 7 patients were not routine and scheduled, but because they clinically deteriorated (vomiting and change in consciousness). None of these patients belonged to the group of patients whose initial CCT was classified as "normal" on admission (p<0.05). There was no statistically significant difference in age, sex, or trauma mechanism between patients who had significant changes based on RCCT results and those who did not (Table 4).

Table 4 Patients with significant changes on RCCT scans

	Significant change (-) (n=97)	Significant change (+) (n=7)	p
Initial CCT Normal	53	0	0.005
Initial CCT Abnormal	44	7	
Fall from height	80	4	0.255
MVA, out of vehicle	12	2	
MVA, in vehicle	3	1	
Domestic violence	2	0	
<10 years	72	5	0.585
≥10 years	25	2	
Female	20	2	0.637
Male	77	5	

RCCT, Repeat computerized cranial tomography; MVA, Motor vehicle accident

Discussion

The care of patients with blunt head trauma requires intensive resource use and effort for both the ED and neurosurgical clinics and requires evaluation for general trauma care and neurosurgical intervention. In addition, clinicians who keep the number of CCT scans to a minimum may reduce both the cost of treatment and the potential radiation damage to patients [1]. Routine RCCTs rarely change patient management in patients with stable neurological status and no new complaints or examination findings, according to the adult head injury literature [11,12]. The benefit of repeat imaging has been shown to be minimal, especially in mild traumatic brain injury (GCS score ≥13) [8]. Because of the different trauma mechanisms than in adults, the more difficult collaboration of the physician with the patients, and the greater anxiety, concern, and expectations of the parents and the patient, management of pediatric head injury patients in the ED is more difficult, and imaging techniques may be used more liberally [16,17]. Therefore, the literature on pediatric BHI has also focused on the consequences of the use of ionizing radiation in children and the development of some screening criteria to minimize the number of CCT scans requested to reduce these negative consequences [9,16,17]. However, the evidence on the follow-up of patients with pediatric BHI without CCT, particularly on managing children with pathology at their first CCT, is not clear [1].

Compared to adults, the mechanism of pediatric BHI may be different. While falls [1] and motor vehicle accidents [15] ranked first in various studies, in our study, about 80% of our patients were caused by falls. Given our patient group's relatively young average age (7.9 [1], 10 [15], and 12.5 [7] in some studies in the literature), it is reasonable to conclude that the cause is falling from pushchairs, strollers, cradles, and beds. In our patient group, motor vehicle accidents consisted of a very small proportion of the trauma mechanism. Because very young children cannot yet communicate verbally, the levels of consciousness and neurological examinations in these children are fundamentally different from those of older children and adults. Because of the retrospective nature of our study, we were unable to determine the value of RCCT in the group without verbal communication, but prospective studies may be designed, especially for patients < 2 years old.

In a retrospective 5-year cohort of 95 patients with a head injury, of whom about 70% underwent RCCT, conducted by Hill et al. [1], the authors reported that no significant change in approximately 2/3 of the patients who underwent RCCT. According to the authors, RCCT changed the management of only one patient (the need for surgical intervention emerged), but this was already apparent from the patient's neurological examination [1]. The authors reported RCCT scans should be taken if new or worsening neurological symptoms or GCS score changes were present [1]. Similarly, in the study by Aziz et al. [7], in which they examined RCCT imaging of 191 patients, the authors concluded that routine RCCT for mild to moderate traumatic brain injury did not cause any management change (in terms of neurosurgical intervention). Repeat neurological examinations have been reported to be a safe and cost-effective alternative to routine RCCTs especially in pediatric BHI patients with a GCS score of 8 and above [1,7]. Howe et al. [2] also do not recommend routine use of RCCT in pediatric patients with BHI with a GCS score of 14 and above without clinical deterioration. The authors noted that in their study, which examined the RCCT of 106 patients, only 7 patients developed worsening changes in re-images, and only 2 of them required surgery [2]. In the 10-year retrospective cohort of Bata et al. [15], in which they evaluated the routine RCCT imaging of 36 patients, the authors reported that the RCCT scans did not reveal the need for craniotomy in any of the patients and made the decision for longer-term ICP monitoring in only 2 patients. Only 7 of the 104 patients who underwent RCCT in our study had a significant radiological change, and more importantly, these 7 patients had already pathology in the first CCT. No new pathology occurred in the RCCT of any patient who did not have an acute pathology on admission CCT. This

is a statistically significant result. Neurosurgical intervention was required in only 4 of these 7 patients. Therefore, new CCT scans enabled a change in patient management in only 4 of 104 RCCT patients. Considering that the population of BHI included 533 patients at first, we consider this a relatively low rate. The fact that about half of our study group had "normal" CCTs at initial admission and about two-thirds of them were discharged from ED may suggest that our patient group is mild to moderate head injury. Furthermore, as a limitation, the fact that we did not record the GCS scores of patients makes it difficult for us to make a judgment on this issue. In our patient group, intracranial hemorrhages are also generally less frequent than described in the literature. This situation may justify the criticism that RCCT in patients with mild head injuries obviously does not lead to a significant change in patient management, but it remains to be discussed why such an intensive RCCT scans were used in such a mildly traumatized group. Other authors also reported RCCT scans in pediatric head trauma do not provide evidence for changes in patient management [18,19]. Again, in a study of 50 pediatric patients with mild to moderate head trauma under 2 years of age, it was investigated whether RCCT affected clinical management and treatment and the authors reported that RCCT did not change patient management without clinical deterioration [20]. On the other hand, there are publications suggesting that RCCT in infants may provide more significant changes, but the authors recommend further validation of this study with a larger number of studies [21].

In some studies in the literature [1,7,15], the meantime for the control image series after the first CCT is 12, 21, and 24 hours, respectively, whereas, in our study, it was about 4 hours (247.5 minutes). We consider that a significant change will not occur in such a short time, or even if it does, it may not yet have a chance to being visible on CCT. In this regard, we believe that an approach like routine RCCT 4-6 hours after the first imaging in the pediatric or adult head injury patients, which has become a classic in our ED and many hospitals in our country, may be changed.

Limitations

We would be able to present clearer data regarding whether RCCT has varied different value for these different groups if we could record the GCS scores of the patients in the study group and divide them into mild-moderate and severe head injury. This is due to data loss, and retrospective nature of the study. So we may have the opportunity to talk about a group that would benefit greatly from RCCT scan or a group that should not have RCCT at all. A prospective study may provide stronger control for these variables. Second, hemorrhage volumes of patients on CCT scans, whether there was an increase in these volumes, length of hospital stay of the patients, number of patients required mechanical ventilation (if any), and length of intensive care unit stay could not be evaluated because of the loss of retrospective data. We consider that these data are also important for such a group. Finally, our data was dependent to hospital data recording systems. We also consider that data on what happens in these patients during follow-up is also important. Further studies may be needed to determine whether a particular type or size of intracranial hemorrhage or skull fracture requires special control imaging.

Conclusion

According to our results, routine RCCT for a BHI in pediatrics does not result in a significant change in patient management. When the entire patient population is considered, the rate of significant change noted in these scans is quite low. Compared to the literature, the duration between repeating CCT is relatively short, which may prevent relevant changes from being reflected in the imaging scans. We believe that repeat CCT decisions of the clinicians deserve a careful consideration in the pediatric population in terms of high radiation exposure. Routine RCCT may be applied to patients more selectively and that well-designed prospective studies are required to determine the time and indications for RCCT in pediatric BHI.

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No-reflow phenomenon and triglyceride-glucose index in acute myocardial infarction

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Abstract

Objective: The objective of this research was to evaluate the association between the measured triglyceride/glucose index (TyG) and the occurrence of no-reflow phenomena in patients with acute ST-elevation myocardial infarction (STEMI) following primary percutaneous coronary intervention (PCI).

Material and methods: This study comprised 242 patients who were treated with primary PCI for acute STEMI. The values of triglycerides and glucose at the time of admission were derived from the patient's file. Using coronary angiography records, the grade of post-procedural thrombolysis in myocardial infarction (TIMI) flow was determined.

Results: After PCI, patients were divided into two groups based on their TIMI flow grade: the normal coronary flow group (n=202) and the reduced coronary flow (no-reflow) group (n=40). The group with no-reflow had a poorer left ventricular ejection fraction and a higher prevalence of diabetes compared to the group with normal coronary flow. Individuals with a lower grade of TIMI flow had a substantially higher TyG index (9.7±0.25 vs. 8.8±0.5, p=0.001). The receiver operating characteristic (ROC) curve revealed that the optimal cut-off point of the TyG index for predicting no-reflow was >9.2 with specificity of 72.8% and sensitivity of 97.5% (area under the curve = 0.884; 95% confidence interval, 0.837-0.921; p=0.001).

Conclusion: At admission, patients with STEMI who experienced no reflow after primary PCI had a higher TyG index. In such cases, the TyG index can be utilized as a predictor of no-reflow.

Key words: acute myocardial infarction, percutaneous coronary intervention, no reflow phenomenon, triglyceride-glucose index

Introduction

Despite advancements in mechanical and pharmacologic reperfusion treatment, acute myocardial infarction (AMI) continues to be one of the primary causes of mortality. AMI is most effectively treated with primary percutaneous coronary intervention (PCI) [1]. The advancement of myocardial necrosis is prevented by balloon angioplasty of the epicardial coronary artery responsible for infarction. Thus, acute mechanical problems and readmissions resulting from heart failure can be reduced. Unfortunately, achieving epicardial coronary artery patency does not necessarily result in acute and long term advantages. In many patients with AMI after primary PCI efficient myocardial perfusion is not really obtained. This is one of the most important reasons for this. The failure to achieve adequate myocardial perfusion despite the patency of the epicardial coronary artery is known as no-reflow. While reported in non-ST-elevation myocardial infarction and elective PCI, specifically saphenous vein grafting, no-reflow occurs more frequently in AMI. It has been demonstrated that the "no-reflow" phenomenon, a significant complication following PCI, is related to a poor prognosis in patients [2].

Although the reasons for no-reflow creation are debatable, a number of studies have linked it to coronary artery spasm, atherosclerotic plaque embolization, and severe abnormalities of glucose metabolism [3-5]. Many investigations have shown that the triglyceride/glucose (TyG) index is a new measure of insulin resistance and

is also connected with coronary atherosclerosis, glucose and lipid metabolism problems, and microvascular endothelial dysfunction [6–10]. The establishment of the "no-reflow" syndrome after PCI is also facilitated by these pathologic pathways. In this study, we sought to determine the association between the TyG index and the "no-reflow" phenomenon in AMI patients who underwent PCI.

Material and methods

Study population

Between June 2021 and June 2022, 390 patients hospitalized with AMI at the Kahramanmaraş Sutcu Imam University Faculty of Medicine Hospital were enrolled in the retrospective-cohort study. 34 patients with a history of previous myocardial infarction, 29 patients with a history of previous PCI, 31 patients with a history of coronary artery bypass grafting, 2 patients with confirmed familial hypertriglyceridemia, 11 patients receiving statin and triglyceride-lowering therapy prior to admission, 9 patients with hepatic failure, 17 patients with renal failure, and 15 patients receiving glycoprotein IIb/IIIa antagonists during PCI were excluded from the study (Figure 1).

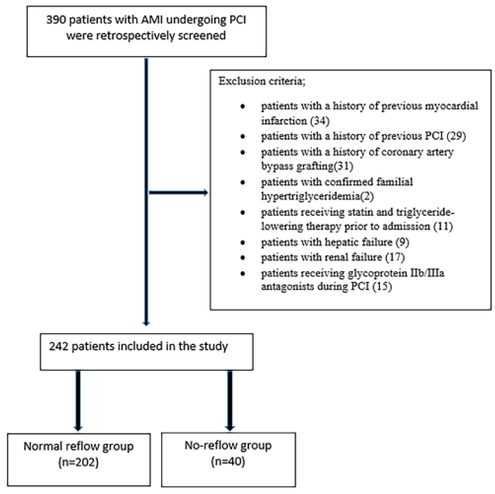

Figure 1 - Flowchart shows the patient selection process.

The study included 242 AMI patients with applying to our center. The research group comprised patients who received acetylsalicylic acid, additional antiaggregant loading (clopidogrel, prasugrel, or ticagrelor), and anticoagulant treatment (unfractionated heparin or low molecular weight heparin) prior to PCI. In accordance with the degree of TIMI blood flow after PCI, the patients included in the research were classified into two categories: no-reflow and normal coronary flow. There were 40 patients in the no-reflow group and 202 individuals in the normal blood flow group.

Exclusion criteria

Individuals having PCI or coronary artery bypass grafting with a previous history of myocardial infarction or decompensated heart failure, patients with verified familial hypertriglyceridemia; patients taking statins and triglyceride-lowering treatment prior to admission, patients with significant hepatic and renal impairment (transaminase equal to or higher than 2 times the normal value, GFR<60ml/ minx1. 73m), utilizing glycoprotein IIb/IIIa antagonists during PCI were excluded. The study procedures were evaluated and approved by the local medical ethics commission and adhered to the Declaration of Helsinki's recommendations.

Diagnostic criterion

Acute myocardial infarction was characterized as chest discomfort accompanied by new ST-segment alterations and myocardial necrosis markers that were at least twice the upper normal value [11]. TIMI flow grade; TIMI 0 (no flow after lesion), TIMI 1 (flow after lesion but partial filling of the distal vascular bed), TIMI 2 (flow after lesion with complete but delayed vascular distal bed filling), and TIMI 3 (normal coronary flow after lesion) [8]. Normal coronary flow was defined as TIMI 3 flow after PCI, while the no-reflow phenomenon was defined as angiographic blockage of coronary flow in the absence of dissection and thrombus and TIMI 2 flow [12].

Research methods

Examining patient information and patient files registered in the hospital's digital records enabled the collection of the fundamental features of the research population. By looking at the patient information and patient files in the hospital's digital records, it was possible to determine whether the patients had hypertension or diabetes mellitus if they smoked, and if they had been to the hospital before.

Blood samples were collected from the patients during hospitalization before coronary angiography. During hospitalization, laboratory data, including basic biochemistry tests and hemogram parameters were collected. The TyG index was computed with the method Ln [fasting triglycerides (mg/dl) x fasting glucose (mg/dl)/2] [13]. The left ventricular ejection fraction (LVEF) values of the research population were retrospectively evaluated using the modified biplanar Simpson technique. Two competent cardiologists who were blinded to the research data assessed the coronary angiography images of the study group and reported TIMI flow grades.

Statistical analysis

For data administration and analysis, version 24 of the SPSS program (SPSS Inc., Chicago, IL, USA) was utilized, and a p value of 0.05 was considered statistically significant. Continuous variables are reported as mean standard deviation (SD) or median and interquartile ranges (IQR) where applicable for categorical variables. The independent sample t test and, in the absence of a normal distribution, the median Mann-Whitney U test were utilized to compare the means. When applicable, the chi-square test was employed to evaluate categorical data. For regularly distributed variables, the Pearson correlation test was employed in correlation analysis, whereas the Spearmen correlation test was utilized for non-normally distributed variables. ROC (Receiver Operating Characteristics) curve analysis was used to determine the appropriate cutoff point of the TyG index for no-reflow prediction. Area under the curve (AUC) was computed using a 95% confidence range for the prediction of no-reflow. Using univariate analysis, the correlation between factors and no-reflow was determined. In a multivariate logistic regression model with a backward stepwise approach, statistically significant univariate variables and other possible confounders were employed to discover independent prognostic determinants of no-reflow.

Results

After the registry data were reviewed, the study group was split into two groups, those with normal coronary flow (patients with TIMI 3 flow, n: 202), and those with no-reflow (patients with TIMI 0, 1, and 2 flow, n: 40). Table 1 displays the baseline parameters, laboratory results, and vessel characteristics of both groups receiving PCI.

Table 1 Comparison of basic characteristic parameters between groups

	Patients with no-reflow (n:40)	Patients with normal coronary flow (n:202)	p
Basic characteristics			
Age, ± SD, years	67 ±12	64 ±12	0.921
Male/Female, n	28/12	136/66	0.854
Atrial Fibrillation, n (%)	10 (%25)	37 (%18.3)	0.374
Diabetes Mellitus, n (%)	23 (%57.5)	57 (%28.2)	0.002
Hypertension, n (%)	34 (%85)	182 (%90)	0.837
Smoking, n (%)	19 (%47.5)	88 (%43.5)	0.654
LVEF, mean ± SD, %	41±8	44 ±8	0.043
Laboratory findings			
Glucose, median (IQR), mg/dL	191 (171.25-209.75)	111 (95-157.25)	<0.001
Total cholestrol, (IQR), mg/dL	180 (158-206.5)	174 (149-205.25)	0,348
Triglyceride, (IQR), mg/dL	185.5 (168.25-193)	143 (95-174.25)	<0.001
LDL, mean ± SD, mg/dL	118.7 ±39.3	127.0±41.0	0.232
HDL, mean ± SD, mg/dL	36.7 ±9.9	41.9 ±9.6	0.003
Creatinine, mean ± SD, mg/dL	1.10 ± 0.69	1.43 ±6.0	0.451
BUN, median (IQR), mg/dL	20.6 (15.25-32)	17 (13.75-22.25)	0.037
Sodium, mean ± SD, mmol/L	137.8 ± 6.3	137.9 ±5.1	0.884
Potassium, mean ± SD, mmol/L	4.4±0.7	4.3±2.7	0.978
Hemoglobin, mean ± SD, g/dL	13.5±4.1	13.0±1.9	0.195
Hematocrit, mean ± SD, (%)	40.1±9.2	39.3 ±5.4	0.439
Platelet, median (IQR), 109/L	222 (173.75-309.25)	221 (186-272)	0.508
RDW, mean ± SD, %	44.3±6.3	44.1±5.6	0.863
MPV, mean ± SD, fL	10.4±0.9	10.9±2.3	0.022
TyG index	9.7 ±0.25	8.9±0.5	<0.001
Vessel undergoing percutaneous coronary intervention			
LAD, n (%)	15 (%37,5)	96 (%47.5)	0.298
CX, n (%)	10 (%25,0)	60 (%29.7)	0.703
RCA, n (%)	15 (%37,5)	46 (%22.7)	0.071
Stent diameter, mean ± SD, mm	2.98±0.23	2.93±0.28	0.211
Stent length, mean ± SD, mm	28.3±6.6	25.8±4.9	0.090

Continuous variables are presented as mean ± SD or median (IQR), categorical variables are presented as frequency (%). LVEF: left ventricular ejection fraction; LDL: low density lipoprotein; HDL: high density lipoprotein; BUN: blood urea nitrogen; RDW: red cell distribution width; mean platelet volüme; TyG: Triglyceride-Glucose; LAD: left anterior descending artery; CX: circumflex artery; RCA: right coronary artery.

In terms of age, gender, atrial fibrillation, presence of hypertension, and smoking, there was no significant difference between the no-reflow group and the normal coronary flow group. Regarding the coronary artery in which PCI was done and the diameter-length ratio of the stent, there was no difference between the two groups. Diabetes mellitus (DM) was more prevalent in the no-reflow group [23 (57.5%) vs 57 (28.2%), p=0.002]. Comparing the LVEF values acquired from transthoracic echocardiography reports for each patient revealed that the no-reflow group had lower LVEF values (41.8 vs. 44.8, p = 0.043).

When the laboratory results of both groups were examined, the group with no-reflow had higher glucose levels [191 (171.25-209.75) vs. 111 (95-157.25), p=0.001]. In the group with no-reflow, triglyceride levels were higher [180 (158-206.5) vs. 143 (95-174.25), p=0.001] In the group with normal coronary flow, BUN levels were lower than in the group with no-reflow (17 (13.75-22.25) vs. 20.6 (15.25-32), p=0.037). MPV was lower in the no-reflow group (10.4±0.9 vs. 10.9±2.3, p=0.022). The TyG index was greater in the no-reflow group (9.7±0.25 vs. 8.9±0.5, p=0.001).

In all patients, the TyG index was favorably correlated with fasting glucose, total cholesterol, and hemoglobin, and negatively correlated with HDL (Table 2). TyG index was negatively correlated with TIMI flow grade obtained from the evaluated coronary angiography images (r=-497, p<0.001).

Table 2 Correlation coefficients for TyG index

Variables correlated with the TyG index	R	p
Glucose	0.743	<0.001
Total cholesterol	0.142	0.028
HDL	-0.175	0.006
Hemoglobin	0.155	0.016

TyG: Triglyceride-Glucose; HDL: high density lipoprotein.

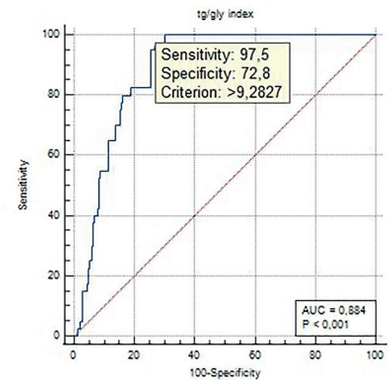

Figure 2 - Receiver operator characteristic (ROC) Curve of TyG Index to predict no-reflow.

Table 3 Univariate and multivariate logistic regression analysis results for no-reflow phenomenon

Variables	Univariate analysis						Multivariate analysis					
	B	S.E	WALD	P	OR	CI	B	S.E.	WALD	P	OR	CI
Stastistically significant variables												
TyG index	0.361	0.550	4.282	<0.001	1.819	1.698-1.767	0.013	0.678	4.996	<0.001	1.915	1.837-1.921
LVEF	0.046	0.220	4.306	0.038	1.047	1.003-1.093	0.071	0.030	5.543	0.019	1.073	1.012-1.138
BUN	0.027	0.011	5.694	0.017	1.028	1.005-1.051	0.035	0.017	4.249	0.039	1.036	1.002-1.071
MPV	0.375	0.179	4.360	0.037	0.687	0.484-0.977	0.529	0.260	4.136	0.042	0.589	0.354-0.981
Glucose	0.020	0.004	30.638	<0.001	1.020	1.013-1.028						
Diabetes Mellitus	1.229	0.356	11.914	0.001	3.418	1.701-6.868						
Triglyceride	0.015	0.004	16.543	<0.001	1.015	1.008-1.023						
HDL	0.059	0.020	9.027	0.003	0.943	0.908-0.980						

TyG: Triglyceride-Glucose; LVEF: left ventricular ejection fraction; BUN: blood urea nitrogen; MPV: mean platelet volüme; HDL: high density lipoprotein.

In multiple regression analysis with forward stepwise method, TyG index, LVEF, BUN and MPV remained to be associated with an predictor of no-reflow occurence after adjustment for variables found to be statistically significant in univariate analysis and correlated with TyG index (Table 3).

The receiver operating characteristic (ROC) curve indicates that the ideal cut-off point of the TyG index for predicting no-reflow is >9.2 with a specificity of 72.8% and a sensitivity of 97.5% (area under the curve =0.884; 95% confidence interval [CI], 0.842-0.926; p=0.001) (Figure 2). ROC curve analyses comparing the predictive values of TyG index, glucose and triglyceride showed that the sensitivity of TyG index was higher (Figure 3).

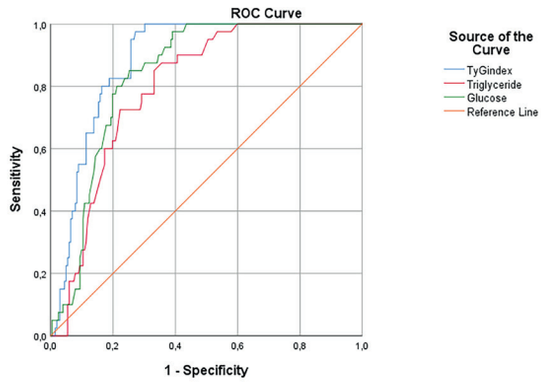

Figure 3 - ROC curve analyses comparing the predictive values of TyG index, glucose and triglycerides

Discussion

In our investigation, the TyG index was considerably higher in AMI patients who exhibited no-reflow phenomena following primary PCI. Furthermore, diabetes mellitus was more prevalent among individuals with no-reflow.

Insulin resistance plays a crucial role in the pathogenesis of the metabolic syndrome, a significant cardiovascular disease risk factor, by causing reduced glucose metabolism, impaired insulin action, and changes in hepatic lipid metabolism. The TyG index can be used to inexpensively test insulin resistance in clinical settings [6, 14, 15].

High fasting glucose is seen as a sign of insulin resistance originating in the liver, while elevated triglyceride levels are regarded as the source of insulin resistance originating in fat cells. Hence, the TyG index is a crucial indication of insulin resistance [16]. Insulin resistance is known to enhance vulnerability to thrombosis through several pathways, particularly endothelial dysfunction; there is evidence that plasminogen activator inhibitor-1 level is elevated in atherosclerotic lesions of type 2 diabetes patients [17].

In addition to its detrimental effects on endothelial function, hyperglycemia is known to promote thrombosis susceptibility [18]. In plasma, triglycerides are quickly changed from very low density lipoprotein cholesterol (VLDL) to low density lipoprotein cholesterol (LDL). LDL cholesterol is quickly glycosylated under conditions of high blood glucose to create the advanced glycation end products-LDL (AGE-LDL) complex, an advanced glycation end product [19]. It has been demonstrated that AGE-LDL has a high atherogenic impact and is related to no-reflow in patients following PCI [20, 21].

The TyG index is a novel composite score that incorporates two risk indicators, fasting glucose and triglycerides. Many studies have demonstrated the association between the TyG index and cardiovascular diseases (CVD), stroke, and CVD risk factors [21, 22]. In STEMI patients having PCI, a greater TyG index has been associated with an increased risk of significant adverse cardiac and cerebrovascular events [23, 24]. Based on these research, the TyG index, an indication of insulin resistance, can be used as a marker for atherosclerosis. In the era of reperfusion, many efforts have been made to limit the magnitude of myocardial infarction by early reperfusion with primary PCI or thrombolytic drugs; yet, while door-to-balloon timings have improved dramatically, gains in in-hospital mortality have lagged.

The success of reperfusion is governed by variables such as the severity of ischemia, the duration of reperfusion, the patency of the epicardial artery connected with the infarct, distal thromboembolism, and inadequate microvascular flow [25]. It has been demonstrated that no-reflow phenomena in the cardiac microcirculation is related to a bad long-term prognosis [26]. Recent investigations suggest that inflammation, vasospasm, and thrombosis in the microvascular bed may be among the reasons for the no-reflow phenomenon, even if its mechanism is not entirely understood [27, 28]. Diabetes mellitus is considered to be an immunologic reaction rather than a metabolic problem, and inflammation is implicated in the pathogenesis of DM patients' common microvascular consequences [29].

The no-reflow has been associated with hyperglycemia, hypercholesterolemia, and thrombus load [30, 31]. In our study, the fact that glucose levels were higher, HDL cholesterol levels were lower, and the number of patients with a diagnosis of DM was greater in the group with no-reflow supported the influence of the risk variables listed. Tartan et al. demonstrated that individuals with metabolic syndrome were more likely to have no-reflow than those without metabolic syndrome [5]. In this study, we found that the TyG index was favorably connected with fasting glucose and total cholesterol, but negatively correlated with HDL. The study by Tartan et al. is supported by metabolic syndrome components such as triglycerides, fasting blood glucose, and HDL levels in the no-reflow group [5]. In

accordance with the findings of the study by Park et al., TyG indices of 8.50 or higher are related to an elevated cardiovascular risk [32]. In our study, the no-reflow group had a higher TyG index.

There are some limitations in this study. First, our study was retrospective in method. Second, it included a relatively small number of patients and was performed in a single center. Third, clinical variables such as total ischemic time before hospital arrival, Killip scores, and MI severity according to troponin levels were not measured. The results of the study cannot be generalized to other populations and patients undergoing PCI.

Conclusion

According to the findings of our investigation, the TyG index was related to no-reflow in AMI patients receiving PCI. The TyG score shows considerable predictive value in patients with no reperfusion after AMI and can be used to stratify individuals at high risk of no reperfusion before PCI. This suggests that the TyG index could be a useful tool for identifying patients who are at a higher risk of no reflow before undergoing PCI, allowing for earlier intervention and potentially improving outcomes. It is potential as a predictor of no-reflow in patients undergoing PCI warrants further investigation in larger and more diverse patient populations.The TyG index is a simple and cost-effective measure that can be easily calculated from routine laboratory tests, making it a feasible tool for clinical use. It is potential as a predictor of no-reflow in patients undergoing PCI warrants further investigation in larger and more diverse patient populations.

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Comparison of the efficacy of LigaSure and laser for grade 2-3 hemorrhoids

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Abstract

Aim: The aim of this study is to compare the efficacy of LigaSure and LH procedures in the treatment of grade 2-3 hemorrhoids.

Material and methods: Demographic and clinical data of the patients were recorded retrospectively. A visual analogue scale (VAS) was used to evaluate the pain intensity of the patients after the procedure and a Likert-type scale was used to evaluate patient satisfaction surveys 6 months after the procedure.

Results: Of the 66 patients, (mean age: 42.12±11.92 years, %72,7 male) 34 underwent LH procedure whereas 32 underwent LigaSure procedure. Spinal anesthesia was applied for 64 patients and general anesthesia was applied for 2 patients. Procedure time and time to return to work were significantly shorter in the LH group compared to the LigaSure group (900 vs. 1200 seconds, p<0.001, and 3.64±1.29 vs. 14.46±3.73 days, p<0.001). Late complications (abscess, relapse, pruritus, and seromucous discharge) were more common in the LH group, but the difference was not statistically significant (23.5% vs. 6.3%, p=0.08). VAS pain scores were significantly lower in the LH group (p<0.001). Although there was no significant difference between the treatment groups in terms of patient satisfaction, relapse was significantly less common in the LigaSure group (p=0.045).

Conclusion: In patients with grade 2-3 hemorrhoids, LH may be preferred over LigaSure due to greater patient comfort, higher satisfaction rates, and fewer early complications. However, close follow-up of these patients is important due to the higher incidence of late complications with LH.

Key words: hemorrhoidal disease, visual analog scale, Likert measurement system, LigaSure, laser

Introduction

Hemorrhoidal disease is the most common disease of the anorectum [1]. Its prevalence is 27.9% worldwide [2]. Hemorrhoids may become symptomatic in 50 percent of patients due to pregnancy, pushing, conditions causing increased intra-abdominal pressure, and weakening of the connective tissue, smooth muscle, and vascular structures in the anal area [3].

According to the Goligher system, grade 1 hemorrhoids do not prolapse outside the anal canal, and grade 2 hemorrhoids prolapse distally during defecation but retract spontaneously. Grade 3 hemorrhoids protrude from the anal opening during defecation and require manual reduction. Grade 4 hemorrhoids have permanent prolapse that cannot be reduced [4].

In the treatment of hemorrhoidal disease, LigaSure, an electrothermal device for cutting and sealing vessels, is now being used in addition to classical surgical procedures to reduce postoperative pain, bleeding, infection, anal stenosis, incontinence, and relapse. Moreover, minimally invasive procedures such as sclerotherapy, rubber band ligation, infrared coagulation, Doppler-guided hemorrhoidal artery ligation, cryotherapy, and laser techniques are also popular [5-7].

Laser hemorrhoidoplasty (LH), another treatment option for hemorrhoidal disease, coagulates the vascular structure in the submucosal area within the hemorrhoidal pouch with thermal energy and allows the hemorrhoidal pads to shrink and become obliterated [8,9].

LigaSure is an electrothermal and hemostatic device that causes minimal damage to surrounding tissues. It allows the complete coagulation of the vessels with radiofrequency and the closure of vessels with a combination of pressure sources. Once LigaSure has achieved coagulation of the vascular structure, the electric current is automatically interrupted. With this limited

spread of electric energy, LigaSure enables effective, bloodless hemorrhoid excision with minimal tissue damage [10,11].

There is limited evidence for the effectiveness of procedures used in the treatment of hemorrhoidal disease and patient satisfaction [12,13]. In this study, it was aimed to compare the efficacy and postoperative complications of LigaSure and LH procedures, which have recently been growing in popularity compared to the traditional Milligan-Morgan and Ferguson surgical treatment options, for patients with grade 2-3 hemorrhoids.

Material and methods

The study was retrospective in design. All the patients between the ages of 18 and 70 years who underwent LH or LigaSure treatment with a diagnosis of grade 2-3 hemorrhoids in a single center between June 2021 and April 2022 were recorded. Patients who had a the American Society of Anesthesiologists physical status classification (ASA) score above II, diabetic patients, pregnant women, patients with other anorectal diseases (fistula, abscess, rectal carcinoma, inflammatory bowel disease, etc.), and patients with a history of previous anal surgery were excluded. Finally, a total of 66 patients were included in the study.

LH was performed for 34 patients with a radial 1.470-nm diode laser and LigaSure (Aesculap Caiman, 17 cm, small jaw open sealer/divider) was applied for 32 patients. All procedures were performed by an experienced colorectal surgeon. Demographic and clinical characteristics of the patients and early / late postoperative complications were recorded from patients' data. In addition, pain levels as measured for all patients with a visual analogue scale (VAS) at the 6th, 12th, and 24th postoperative hours were also recorded (Table 1).

Table 1 Visual Analog Scale (VAS)

0	1	2	3	4	5	6	7	8	9	10
0: No pain at all 10: Unbearable pain										

Table 2 Likert's 5-choice measurement system

I absolutely approve	I approve	I am undecided	I Disapprove	I absolutely do not approve

The VAS was scaled from 0 to 10, with 0 representing no pain and 10 representing the most severe unbearable pain [14]. The patients of both groups were called 6 months after treatment and information was obtained about their satisfaction levels using a 5-point Likert-type scale that included questions with 5 possible answers: strongly agree, agree, neither agree nor disagree, disagree, and strongly disagree [15] (Table 2). All patients underwent a detailed physical examination. Grade of hemorrhoids was determined by anorectal examination with the help of anoscope and flexible rectosigmoidoscopy.

General anesthesia was administered for two of the patients who underwent LigaSure treatment, and spinal anesthesia was administered for the other 30 patients in the LigaSure group. An anoscope was placed in the lithotomy position. Hemorrhoidal pockets were excised with the LigaSure device over the internal sphincter muscle, leaving the anoderm, including the submucosal vascular network structures. Bleeding was controlled by electrocautery. Spongostan was routinely inserted into the anal canal of each patient.

Spinal anesthesia was administered for all patients who underwent LH treatment. An anoscope was placed in the lithotomy position. With the help of the anoscope, a 1470-nm diode laser probe was inserted in the submucosal region from the distal of the hemorrhoidal pockets, and 3-5 shots were made in a standard crowbar pattern starting from the proximal and advancing toward the distal of the hemorrhoidal pouch (3-5 shots of 3 seconds each with 3-second pauses at 10 W). At the end of each laser treatment, ice in gloves was applied to the treated pocket for 1 minute. Spongostan was routinely inserted into the anal canal of each patient.

Two enemas (250 mL) were administered to all patients preoperatively, the evening before the procedure and early in the morning of the day of the procedure. Antibiotic prophylaxis (sephazolın 1×1, 1 gram intravenously) was routinely administered 30 minutes before the procedure. Painkillers (paracetamol, 3×1, 500 mg orally) were administered to all patients postoperatively. Laxative syrup (667 grams of lactulose 2x1 orally in 1000 ml of aqueous solution) was recommended to all patients for 7 days after discharge. In addition, routine examinations were performed in the outpatient clinic by a specialist surgeon in the 1st week and 1st, 3rd, and 6th months after the procedure. In these follow-up visits, flexible rectosigmoidoscopy was performed for patients with complaints of persistent rectal bleeding, discharge, or pain. Patients with recurrence were identified by anorectal examination and flexible rectosigmoidoscopy. Edema, urinary retention and thrombosis were considered postoperative early complications whereas abscess sero-mucous discharge, recurrence and itching were considered postoperative late complications.

Ethical approval

Ethical approval of this study was granted by the Ethics Committee of the University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, with decision number 2011-KAEK-25 2022/05-26 on May 18, 2022. The study was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

IBM SPSS Statistics 21.0 (IBM Corp., Armonk, NY, USA) was used for statistical evaluations in this study. Compliance with normal distribution was evaluated by Kolmogorov-Smirnov test. Measurable parametric data were given as mean±standard deviation, and distributions were defined as median (minimum-maximum) for measurable data that did not satisfy parametric conditions. Categorical variables were given as numbers and percentages. In comparisons of data between two groups, independent samples t-tests were used for data that satisfied parametric conditions and Mann-Whitney U tests were used for non-parametric data. Chi-square tests were used for the comparison of categorical variables. Values of $p<0.05$ were considered significant in all statistical evaluations.

Results

Of the 66 patients included in the study (mean age: 42.12±11.92 years, % 72.7 male), LH was applied for 34 patients (%51.5) and the LigaSure procedure was applied for 32 patients (%48.5).In terms of age , gender and body mass index , there was no statically difference between the groups. Fifteen patients (%22.7) had edema, 2 patients (%3) had urinary retention, and 1 patient (%1.5) had thrombosis. The patient who experienced thrombosis underwent surgical thrombectomy in another clinic. No postoperative bleeding or hematoma was observed in any

Table 3 Comparison of the complications and satisfaction of the patients based on the groups

Variables	Ligasure group (n: 32)	Laser group (n: 34)	p
Early postoperative complication, n (%)			
Edema	13 (41)	2 (6)	**0,001**
Urinary retention	2 (6)	0 (0)	0.141
Trombosis	0 (0)	1 (3)	0.332
Late postoperative complication, n (%)			
Abscess	0 (0)	1 (3)	0.334
Sero-mucous discharge	2 (6)	1 (3)	0.526
Recurrence	0 (0)	4 (12)	**0.045**
Itching	0 (0)	1 (3)	0.331
Likert scale answers, n (%)			
Very unsatifsfied	0 (0)	0 (0)	**0.002**
Unsatisfied	0 (0)	5 (15)	
Neutral	0(0)	1 (3)	
Satisfied	13 (41)	22 (65)	
Very satisfied	19 (59)	6 (18)	

Table 4 Comparison of the demographic and clinic characteristics of the patients based on the group

Variables	Ligasure group (n: 32)	Laser group (n: 34)	p
Age, mean ± SD	40±10	44±14	0.201
Gender, Male, n (%)	24 (75)	28 (71)	0.683
BMI (kg/m^2), mean ± SD	26,00 ± 4,97	25,73 ± 5,28	0,835
Smoking, n(%)	15 (47)	15 (44)	0.822
Hemorrhoids grade, n (%)			
Grade 2	6 (19)	10 (29)	0.313
Grade 3	26 (81)	24 (71)	
Mean operating time, second*	1200 (900-6000)	900 (540-1800)	**<0.001**
Hospitalisation, day mean + SD	1,31 + 0,47	1,14 + 0,35	0,116
Return to work, day mean + SD	14,46 + 3,73	3,64 + 1,29	**<0.001**
İntroperatif hemorrhage, n (%)	25 (78)	11 (32)	**<0.001**
Postoperatif VAS score*			
6. hour	6 (2-10)	3 (0-6)	**<0.001**
12.hour	6 (1-9)	2 (0-7)	**<0.001**
24. hour	2 (0-7)	0.5 (0-3)	**0.001**

*BMI: body mass index, SD:standard deviation, *: Median (minimum-maximum), VAS:Visual Analog Scale*

case. Early complications (edema, thrombosis, urinary retention) were significantly more common in the LigaSure group (%46.9 vs. %8.8, p=0.001). This difference between the groups was due to significantly more edema complications in the LigaSure group (%40.6 vs. %5.9, p=0.001). When late complications were evaluated at the 6-month follow-up period, the following were determined: abscess in 1 case (%1.5), discharge in 3 cases (%4.5), relapse in 4 cases (%6.1), and pruritus in 1 case (%1.5). The patient with abscess developed a perianal fistula after drainage. Anal incontinence or stenosis was not observed in any of the patients during the six-month follow-up. No relapse was observed in any patient in the group treated by LigaSure, while relapse was seen in 4 patients (%11.8) in the group treated by LH (p=0.045). Other late complication rates (abscess, pruritus, seromucous discharge) did not differ significantly between the groups. When all late complications were compared, it was observed that late complications were more common in the LH group, but the difference was not statistically significant (%23.5 vs. %6.3, p=0.08) (Table 3). When the clinical and demographic data of the patients were compared, operation time was significantly shorter in the LH group (p<0.001). Pain levels as evaluated by VAS at 6, 12, and 24 hours postoperatively were significantly lower in the LH group (p<0.001 for all). The time to return to work was significantly shorter in the LH group than the LigaSure group (p<0.001). Comparisons of the demographic, clinical, and procedural results of the patients according to type of procedure are shown in Table 4.

In the Likert-type satisfaction survey administered in the 6th month of follow-up, all 32 patients (%100) in the LigaSure group stated that they were satisfied or very satisfied with the operation, while in the LH group, 28 patients (%83) were satisfied or very satisfied (p=0.002). Comparisons of complication and satisfaction rates of the patient groups are shown in Table 3.

Discussion

In the last 50 years, new procedures have been developed to replace traditional surgical approaches for hemorrhoidal disease in order to improve patient satisfaction and minimize complications [16-18]. However, there has been no study to date comparing the outcomes of LH and LigaSure procedures in the treatment of hemorrhoidal disease. In this respect, our study can be considered the first of its kind in the literature.

In some previous studies, it was found that the operation time, postoperative pain levels, and postoperative length of hospital stay were significantly lower with the LigaSure procedure compared to the Milligan-Morgan procedure [19,20]. Upon comparing the LigaSure procedure with the Ferguson

procedure, intraoperative bleeding and postoperative pain were found to be significantly lower [21,6]. These procedures did not yield significant differences in terms of early and late postoperative complications in comparison to the LigaSure approach [22,6].

While LH has been found to provide statistically significantly lower operation times, hospitalization times, and rates of urinary retention, anal stenosis, postoperative pain, and intraoperative bleeding compared to the Milligan-Morgan procedure, no difference in relapse rate was observed [23,24]. There are no studies in the literature comparing the results of LH and Ferguson procedures. However, according to an evaluation of the results of the Milligan-Morgan and Ferguson procedures, there was no statistically significant difference in terms of hospitalization time, operation time, postoperative pain level, or urinary retention [25].

In previous studies, it was observed that male patients significantly predominated among cases of both LH and LigaSure treatment for hemorrhoidal disease compared to female patients [26,27]. In the present study, it was similarly found that more male patients were treated by both LigaSure and LH compared to female patients.

In previous studies, the mean duration of surgery was 900 seconds for the LigaSure procedure and 600 seconds for LH [27,19]. In our study, the mean duration of surgery was 1200 seconds for LigaSure and 900 seconds for LH. For these patients with grade 2-3 hemorrhoids, the mean duration of surgery was thus significantly shorter with LH compared to LigaSure.

In our study, none of the patients in either group had early postoperative bleeding. In the literature, this rate was reported to be % 0-3 for LH and 0.4% for LigaSure [28,29]. Mean postoperative VAS pain levels on the 1st day were previously reported as 3.7 after LigaSure treatment and 2 after LH [29,30]. In our study, VAS scores on the 1st day after surgery were 2 in the LigaSure group and 0.5 in the LH group. In previous studies, the mean time to return to work was 11.1 days after LigaSure and 2.8 days after LH [31,32]. In our study, mean time to return to work was 14.46 days after LigaSure and 3.64 days after LH.

In previous studies, the postoperative relapse rate at 6 months was % 0 after LigaSure and 0-% 8.8 after LH [33,34]. In those studies, % 80-90 of the patients had grade 3 hemorrhoids. However, no information was provided in those studies about whether the patients who experienced recurrence had grade 2 or grade 3 hemorrhoids [8,30,34]. In our study, the recurrence rate was % 0 after LigaSure and % 12 after LH. Thus, the recurrence rate after LigaSure was statistically significantly lower than that for LH among our patients, and % 75.7 of our total patients had grade 3 hemorrhoids. All of our patients who experienced postoperative recurrence were patients with grade 3 hemorrhoids. None of our patients with grade 2 hemorrhoids had recurrence at 6 months postoperatively.

We administered a satisfaction survey to our patients in the 6th postoperative month, and % 100 of patients treated by LigaSure and % 83 of those treated by LH reported being satisfied or very satisfied. In previous studies, % 98.9 of patients treated by LigaSure and % 98 treated by LH reported being satisfied or very satisfied [27,35].

Limitations

The limitations of this study include its retrospective nature, the small number of patients, and the relatively short follow-up period.

Conclusion

For patients with grade 2-3 hemorrhoids, LH could be the preferred treatment choice compared to LigaSure due to higher levels of patient comfort, better satisfaction rates, and fewer early complications. However, close follow-up of these patients is important due to the higher incidence of late complications following LH.

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The effect of virtual reality glasses on reducing pain during chest tube removal

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Abstract

Background: The studies that generally investigate the effectiveness of pharmacological and non-pharmacological methods in reducing chest tube removal related pain are remarkable. However, new studies need to expand the use of virtual reality glasses and evaluate its effectiveness.

Aim: This study aims to determine the effect of distraction with virtual reality glasses on pain during chest tube removal in patients undergoing tube thoracostomy.

Material and methods: This quasi-experimental study with a pre-test post-test control group design was performed with the participation of 40 patients. The patients in the intervention group (n=20) watched the video with virtual reality glasses throughout procedure. Pain measurements were evaluated before, during, and after chest tube removal. The patients in the control group (n=20) received standard care.

Results: In the intervention group, it was revealed that the pre-procedure pain score decreased compared to the pain score obtained during the procedure (p=0.002). After the chest tube removal procedure, a statistically significant decrease was observed in pain score in favor of the intervention group. In the intervention group, the pre-procedure pain score was found to decrease statistically significantly in the measurement at the 10th min of the procedure (p=0.000). The pain score of the intervention group 10 min after the chest tube removal procedure was lower than that of the control group (1.80 vs 2.95 and p=0.028).

Conclusion: The virtual reality glasses assisted chest tube removal procedure can help reduce pain. Surgical nurses should benefit from the use of virtual reality glasses for pain control.

Key words: chest tube removal, pain, virtual reality

Introduction

Chest tube (ChT) insertion is a minimally invasive surgical procedure applied for indications such as pleural effusion, pneumothorax, and hemothorax. Its objective is to provide the drainage of the fluid, air, or blood in the pleural space. During follow-ups, a ChT is removed in cases where the chest X-ray is expanded, the air leak stops, and the daily drainage is less than 200 mL [1]. Increased pain and anxiety can usually be observed in patients during chest tube removal (ChTR) [2,3].

In the literature review, studies that generally investigate the effectiveness of pharmacological and non-pharmacological methods in reducing ChTR-related pain are remarkable [4-6]. Distraction techniques (20.6%), relaxation (20.6%) and deep breathing exercises (11.7%) have been reported as the methods most commonly used by patients after thoracic surgery [7]. Distraction methods act on patients by enhancing the effect of analgesic methods and ensuring energy to increase pain tolerance. Healthcare professionals contribute to reducing pain-related fatigue and mood changes using distraction methods [5]. Furthermore, it increases self-confidence and self-control in coping with pain and reduces the fear of recurrent pain. Distraction methods, which are non-pharmacological

interventions, are inexpensive and safe auxiliary methods that can be easily accepted by patients and provide good cooperation between patients and healthcare professionals. Moreover, possible side effects and complications of pharmacological interventions are out of the question for distraction [5].

Virtual reality (VR) glasses are an advanced technology allowing users to create a three-dimensional computer environment for themselves [7]. Owing to VR glasses, attention is directed to the virtual world, and patients' thinking and feeling of pain decrease [8-10]. The distraction provided by VR glasses can inhibit pain particularly effectively, considering its inherently immersive and interactive properties. Using this technology ensures the interaction of patients with the virtual environment at many levels [11]. Patients, who use their multiple senses with VR glasses, leave the environment they live in for a while and transition to the virtual world. Thus, VR technology provides an effective environment for the method of attracting attention in pain control [10]. Some studies have reported that VR glasses, one of the distraction methods, effectively reduces pain [12,13]. VR is estimated to be a promising technological method due to its low cost and the absence of side effects [14]. Furthermore, it has been reported that using VR glasses in hospitalized patients can provide cost savings ($5.39 per patient) for the hospital system [15].

Pain management techniques are required for patients' recovery, and nurses assume many responsibilities in non-pharmacological pain interventions. Hence, nurses must be aware of innovative pain relief tools and be able to provide counseling to patients on new treatment modalities in the future [16]. There is a need for future studies to expand the use of VR glasses, an easy-to-use, inexpensive, and harmless method, by healthcare professionals and investigate its effects in patients who have undergone tube thoracostomy. This study aims to determine the effect of distraction with VR glasses on pain during ChTR in patients undergoing tube thoracostomy.

Materials and methods

A quasi-experimental study involves the comparison of groups that are already naturally exposed to different conditions or interventions. This quasi-experimental study with a pre-test post-test control group design was performed with the participation of 40 patients receiving inpatient treatment in the thoracic surgery ward of a university hospital between March 2020 and May 2023. After including the first case in the study, the study was interrupted when the first case of the new coronavirus disease was detected in March 2021. Cases were started to be included in the study again as of January 2022.

The study sample was calculated to be at least 40 people using an effect size of 0.95, a confidence level of 95%, a margin of error of 5%, and a power of 80%. Patients who agreed to participate in the study, to whom a standard single ChT was applied with the diagnosis of pneumothorax without surgery, had no history of disease that could cause chronic pain, had no neuro/psychiatric problems, did not use any analgesic agents in the last 12 hours before the ChTR procedure, had an American Society of Anesthesiology (ASA) score of <3, and had no biological and cognitive problems that could prevent the use of VR glasses were included in the study.

Patients who received care in an isolated room, had facial trauma, claustrophobia, a history of epileptic seizures, neuro-psychiatric problems, had a ChT inserted for traumatic and operative reasons, had multiple ChTs inserted, to whom a ChT had been inserted before, had a fear of underwater or underwater creatures and who did not agree to participate in the research were excluded from the study.

For data collection “Patient Identification Form” and “Visual Analog Scale” (VAS) were used. Patient Identification Form created by the researchers in line with the literature [5] comprises 7 questions, including the descriptive characteristics of patients (age, sex, education level, smoking status, chronic disease, and day of stay of the ChT) and pre-ChTR anxiety score (numeric 0-10). VAS consists of a 10 cm line (0-10 cm). A line of 0 means “no pain,” while a line of 10 means “unbearable pain.” The patient is requested to mark the place that expresses his/her degree of pain. The patient’s pain degree is determined by the number marked by the patient as the pain level [5]. The patients’ VAS scores were evaluated immediately before ChTR (preprocedural), immediately after ChTR (pain during the procedure-intraprocedural), and 10 min after ChTR (postprocedural).

On the morning of the day when the ChTR procedure would be applied, the researcher received written informed consent from the individuals after the researcher informed the patients about the study. The ‘Patient Information Form’ was applied to the patients in the control and intervention groups. Pain measurements were evaluated before, during, and after ChTR. Pain during the procedure was questioned immediately after the procedure. Post-procedure pain was assessed 10 min after the procedure. The same physician researcher applied the ChTR procedure to all patients. The procedure was performed in the patient's room with the participation of the patient, the physician researcher, and the nurse researcher. The patients in the control group received standard care without any pharmacological or non-pharmacological interventions for pain relief during ChTR. The patients in the intervention group were informed about using VR glasses before the procedure, and the patient tried the use of VR glasses. Prior to the ChTR procedure, the researcher placed VR glasses on the patient's head, and the patient watched the video throughout the procedure. The video contained the undersea view and lasted 10 minute (https://www.youtube.com/watch?v=cC9r0jHF-Fw&feature=youtu.be). Due to the short duration of the procedure, the recording was shortened (first 10 min.) using a video editing program. A longer video was not selected because the time of the procedure was short. During ChTR, patients in both the intervention and control groups were asked to take a deep breath and hold their breath, and the ChT was removed by the physician researcher and nurse researcher at this time. While the physician researcher tied the suture left ready while the ChT was being inserted, the nurse researcher quickly pulled the thoracic drain and closed the dressing. After the ChT was removed, chest radiography was taken, and no iatrogenic pneumothorax was observed in any patient. In this study, deep breathing and holding methods were used in both groups during ChTR.

After use, the inner and outer surfaces of the VR glasses were disinfected with separate gauzes and then left to dry before continuing with the next patient. After the VR glasses dried up, it was kept in a clean, sealed, and disposable bag [17,18].

This study was approved by the Noninvasive Scientific Research Ethics Committee of Trakya University (Date: 02.03.2020, No: 2020/98, Decision: 05/30). Prior to the study, all the participants were informed about the study, and written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki and the ethical committee.

Statistical analysis

IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. was used to evaluate the data from 40 patients. Data are presented as the mean, standard deviation, number, and frequency. The normality of data was checked using the Shapiro−Wilks test. The data analysis used the Independent sample t-test, Mann-Whitney U test, and Kruskal Wallis test. Wilcoxon signed rank test was used to evaluate the difference between measurements within the group. Statistical significance was defined as a p-value .05.

Results

Of the participants (n=40), 90% were male, 37.5% were primary school graduates, and 80% were comprised of patients without chronic diseases. The mean age of the patients was 45.57±18.82 years. The intervention group and the control group were similar in respect of sociodemographic characteristics (p>0.05) (Table 1). The mean day of stay of the drains was 5.00±1.91 days in the intervention group and 5.65±2.75 days in the control group.

Table 1 Patients' sociodemographic characteristics (n = 40)

Characteristics		Intervention Group (n = 20)	Control Group (n = 20)	t-test, U-test or χ2	P - value
Age (year)		46.2 ± 19.7	44.9 ± 18.3	t = -0.224	p = 0.824
Sex (male)		19 (95.0)	17 (85.0)	U = 180.000	p = 0.602
Education level	Primary school	10 (50.0)	5 (25.0)	χ2 = 1.847	p = 0.174
	High school	8 (40.0)	13 (65.0)		
	University	2 (10.0)	2 (10.0)		
Smoking status (yes)		16 (80.0)	13 (65.0)	U = 170.000	p = 0.429
Chronic diseases (yes)		4 (20.0)	4 (20.0)	U = 200.000	p = 1.000

The data are presented as: number (n), percent (%), mean and standard deviation (SD).
t: Independent sample t test, **U:** Mann-Whitney U test, **χ2:** Kruskal Wallis test

In the intervention group, it was revealed that the pre-procedure VAS score decreased compared to the VAS score obtained during the procedure (p=0.002), and the pre-procedure VAS score of the control group increased right after the procedure (p=0.056). After the ChTR procedure, a statistically significant decrease was observed in pain score in favor of the intervention group (p=0.000). Moreover, the decrease in the post-procedure VAS score in favor of the intervention group was found to be statistically significant (p=0.000) (Table 2).

Table 2 Comparisons of patients' preprocedural and intraprocedural pain scores according to groups (n = 40)

Pain score	Intervention Group (n = 20)		Control Group (n = 20)	
	Median	25th-75th percentile	Median	25th-75th percentile
Preprocedure	4.00	4.00 - 5.00	4.00	4.00 - 4.75
Intraprocedure	2.00	1.25 - 3.00	5.00	4.00 - 6.00
Mean difference	-2.00	-3.00 – -2.00	0.00	0.00 – 2.00
Value of statistical	Z = -3.151	p = 0.002	Z = -1.912	p = 0.056

The data are presented as: number (n), percent (%), mean and standard deviation (SD). **Z:** Wilcoxon signed rank test

Table 3 Comparison of patients according to pain scores 10 minutes after the procedure and before the procedure (n = 40)

Pain score	Intervention Group (n = 20)		Control Group (n = 20)	
	Median	25th-75th percentile	Median	25th-75th percentile
Preprocedure	4.00	4.00 - 5.00	4.00	4.00 - 4.75
Postprocedure	2.00	1.00 - 2.00	3.00	1.25 - 4.00
Mean difference	-2.50	-3.00 – -2.00	-1.00	-3.00 – 0.00
Value of statistical	Z = -3.962	p = 0.000	Z = -2.812	p = 0.005

The data are presented as: number (n), median and percentiles.
Z: Wilcoxon signed rank test

In the intervention group, the pre-procedure VAS score was found to decrease statistically significantly in the measurement at the 10th min of the procedure (p=0.000). Likewise, the pre-procedure VAS score was determined to decrease in the control group in the measurement at the 10th min of the procedure (p=0.005).

The higher decrease in the VAS score in favor of the intervention group 10 min after the procedure was found to be statistically significant (-2.75 vs -1.45 and p=0.017) (Table 3).

No significant difference was identified between the groups in terms of anxiety scores before the procedure (p=0.301) (Table 4).

Table 4 Comparison of patients' anxiety scores according to groups (n = 40)

Anxiety	Intervention Group (n = 20)		Control Group (n = 20)		Value of statistical
	Median	25th-75th percentile	Median	25th-75th percentile	
Preprocedure	2.00	1.00 ± 4.75	2.00	0.00 ± 3.00	U = 161.000 p = 0.301

The data are presented as: number (n), median and percentiles.
U: Mann Whitney U test

Discussion

Local anesthesia and moderate sedative agents are mostly used to relieve pain during ChT insertion [19]. This may cause the patient to feel pain at some stages because of the nature of the procedure. The pain felt during ChT insertion increases the feeling in patients that pain may also develop during ChTR. Many methods are employed to reduce pain during the ChTR procedure [4,5,6,20]. It is possible to divide them into two as pharmacological and non-pharmacological methods [20,21]. However, there is no standard method or guide in this matter. In this study, the effects of VR glasses, which were used to decrease the level of pain during the ChTR procedure, were investigated and discussed in line with the literature.

In this study, the pre-procedure baseline pain scores of the intervention and control groups were found to be similar. Similarly, it is reported in the literature that there is no significant difference between the groups in terms of pain score before ChTR [20-27].

In this study, there was a significant decrease in pain score during the procedure compared to the pre-procedure in favor of the intervention group. Yarahmadi et al. [28] reported that cold treatment and combined (cold+musicotherapy) method interventions effectively decreased ChTR-induced pain. In other studies investigating the effectiveness of cold application on pain, it was stated that the intervention group had lower pain score than the control group immediately after ChTR [20,25]. Elmetwalyl and Sayed [22] elucidated that pain score during the procedure was lower in the intervention group undergoing cold application and relaxation exercise compared to the control group (1.23 versus 3.60). Similar results were obtained in other studies in the literature [21,24,26]. In another study, Başak et al. [29] found that procedural pain resulting from peripheral intravenous catheterization was lower in patients who used VR glasses and distracting cards compared to the control group. It is reported that VR glasses are effective in ensuring pain control during different acute interventions [30,31]. According to the study results, it can be said that non-pharmacological methods can be effective in ensuring pain control during the procedure.

It was revealed that the pre-procedure VAS score decreased in the intervention group 10 min after the procedure (p=0.000), and the pre-procedure VAS score of the control group decreased 10 min after the procedure. Ten min after the ChTR procedure, the pain score of the intervention group was found to be lower than that of the control group (1.80 versus 2.95 and p=0.028). The fact that the VAS score decreased more in favor of the intervention group 10 min after the procedure was found to be statistically significant (2.75 versus 1.45 and p=0.017). The study by Soydan and Uğraş [32] reported that the VAS scores before ChTR decreased significantly in the intervention groups concurrently before and after the ChTR procedure. The same study found that the highest pain score of patients in the control group was during the procedure, and the VAS scores 15 min after the procedure were significantly higher in the control group than in the intervention groups. In the study by Ceylan and Rızalar [20], it was observed that pain was at the lowest level during the ChTR procedure in the intervention groups undergoing relaxation and cold application. In the same study, the pain score was the highest during the ChTR procedure in the control group. In their study, Sheykhasadi et al. [5] reported that distraction using the voice of a loved one during ChTR after open-heart surgery was effective in reducing pain. Jahani Shoorab et al. [31] stated that the VR technique reduced pain in patients who underwent episiotomy repair. The study results in the literature show that nursing interventions are effective in reducing pain during ChTR.

While there was no difference in the anxiety scores of the groups before the procedure, Aktaş and Karabulut [33] reported in their study that there was no difference between the pre-procedure anxiety scores of the groups treated with cold therapy, music therapy, and lidocaine spray during the ChTR procedure and the control group. Elmetwalyl and Sayed [22] found that anxiety scores were similar in the intervention cold application and relaxation exercise) and control groups before the ChTR procedure. Similar results were obtained in other studies in the literature [21,27]. In parallel with the literature, no significant difference was identified between the pre-procedure anxiety scores of the groups in this study.

Conclusion

The ChTR procedure, which is frequently used in the daily practice of thoracic surgery, can cause painful processes in patients. To solve this problem, pharmacological and non-pharmacological methods can be used. The VR glasses assisted ChTR procedure appears to be an easy, reliable, and side-effect-free technological intervention that can help reduce pain. Nonetheless, there is a need for future multi-center studies involving larger case series on the subject.

Limitations

The prospective case-controlled nature of the article, and the search for an easy, and safe solution to a clinical problem can be considered the strengths of this study. However, the research has some limitations. First, the low number of samples and the single-center design of the study restrict the generalization of the results. Second, in the study, patients' VAS scores related to the ChTR procedure were evaluated subjectively based on the patients' self-reports. Behavioral and physiological responses to pain were not included in the evaluation. Third, the economic dimension of the use of VR glasses per patient has not been analysed. Studies including calculations of the cost per patient of VR glass use should be planned. Finally, another limitation of the study is that the sample consisted only of patients who were not operated on but underwent ChT insertion due to the diagnosis of pneumothorax.

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Evaluation of early functional outcome of arthroscopic decompression in chronic primary sub-acromial impingement syndrome

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Abstract

Background: Sub-Acromial Impingement Syndrome (SAIS) spectrum ranges from acute inflammation to chronic degeneration of the bursa and of rotator cuff tendons in sub-acromial space. It may lead to a full-thickness tear of rotator cuff tendons and degenerative joint disease of the shoulder girdle leading to functional loss and disability if not treated early and adequately. This study aimed to determine the early functional outcome of arthroscopic sub-acromial decompression in chronic SAIS due to mechanical causes.

Material and methods: This was a prospective cohort study. Patients were operated on arthroscopically for sub-acromial decompression between September 2018 and March 2020. Thirty-five patients with a range of 20 to 65 years of age diagnosed clinically with primary chronic sub-acromial impingement syndrome meeting the inclusion criteria were included in this study. All the patients under study were initially kept for at least four weeks of a course of conservative treatment and persisted in having symptoms were treated surgically with arthroscopic sub-acromial decompression. The UCLA (The University of California at Los Angeles) shoulder rating scale was used to assess shoulder function. The assessment was done in the pre-operative period, four weeks, 12 weeks, and 16 weeks post arthroscopic sub-acromial decompression surgery.

Results: Compared to pre-operative UCLA shoulder function score at the end of non-operative conservative treatment, the patients under study showed a statistically significant improvement at the end of the 16th week of post-arthroscopic subacromial decompression ($p<0.0001$).

Conclusion: This study concludes that arthroscopic sub-acromial decompression provides a good functional outcome in patients having primary shoulder impingement due to extrinsic mechanical causes such as shape and slope of the acromion in the absence of significant (total or near total) rotator cuff tear after 16 weeks of follow-up.

Key words: sub-acromial impingement syndrome, shoulder arthroscopy, sub-acromial decompression

Introduction

Shoulder pain is complicated and causes include subacromial impingement syndrome (SAIS), glenohumeral problems, acromioclavicular illness, and referred pain [1, 2]. Soft tissue encroachment into the sub-acromial space narrows the sub-acromial space, which contains the supraspinatus tendon, subacromial bursa, and long head of biceps tendon and capsule of the shoulder joint [3,4]. Depending on the location of causative variables, two hypotheses have been proposed for SAIS: the extrinsic theory and the intrinsic theory. Neer et al. popularised the idea of extrinsic impingement by defining it as the impingement of the anterior acromion, coracoacromial arch and acromion-clavicular joint on the sub-acromial bursa, rotator cuff, and biceps tendon [4]. Furthermore, he concluded that impingement of the rotator cuff against the undersurface of the acromion was primarily anterior and not lateral; therefore, anterior decompression rather than total or lateral acromionectomy (which results in deltoid injury followed by abduction weakness) is the appropriate operative approach for SAIS associated with rotator cuff degeneration. Codman et al. were among the first to introduce the idea of secondary or intrinsic impingement

[5]. They hypothesised that an inherent degenerative degeneration of the rotator cuff tendon was crucial for the development of SAIS. Several microvascular procedures have provided support for this theory [6–9]. The resultant discomfort and weakening of the supraspinatus weakens its function as a humeral head depressor and permits upward humeral migration, which is amplified by the deltoid's upward abduction force. This divergence from normal shoulder biomechanics is pathogenic for shoulder impingement [10, 11]. During the time of clinical examination, Neer's SAIS stages are essential for identifying the chronic stage of SAIS. Stage 1 is characterised by joint swelling, tendinitis-like symptoms, and a locally elevated temperature in patients younger than 25 years old. There is no indication of a tear in the Rotator Cuff tendon, however. Individuals may have moderate pain during exercise, although there is no decrease of Rotator cuff muscular strength. There is evidence of permanent scarring and tendinitis of the rotator cuff tendons, but there is no sign of a torn rotator cuff or loss of mobility. Stage 2 is typically diagnosed in individuals aged 25 to 40 years. Stage 3 is frequently observed in patients older than 40 with a partial Rotator Cuff tear, whereas stage 4 is associated with a complete or near-complete Rotator Cuff rupture. The initial treatment consists of conservative measures (NSAIDs, physiotherapy, steroid injections) that modify inflammation, muscular dyskinesia, and altered shoulder biomechanics without removing the primary underlying pathology. Patients who do not respond satisfactorily to conservative treatment should be considered for surgical intervention. Ellmann et al. [12] were among the first surgeons to employ arthroscopes. The majority of subsequent research has detailed the inconsistent functional outcome of Arthroscopic sub acromion decompression (ASAD) in long-term follow-up, with few studies reporting good outcomes and others demonstrating no superiority over conservative therapy [13-18].

The purpose of this study was to evaluate the functional result of ASAD in patients with chronic primary SAIS of Neer type 2 without considerable rotator cuff pathology in order to demonstrate the efficacy of this common therapy. The primary objective was to determine the improvement in The University of California at Los Angeles (UCLA) score at 16 weeks postoperatively. The secondary objectives were to estimate the duration of the surgery and any complications that may arise.

Material and methods

This was a prospective cohort study at a tertiary care centre. This research was approved by an institutional review board (2018-225). From September 2018 through March 2020 patients with significant subacromial pain for more than one month without relief from non-operative means (physiotherapy, NSAIDs, corticosteroid injections & rest) and symptoms and signs indicating primary impingement syndrome due to extrinsic mechanical causes (clinically diagnosed by pain provoked by abduction, positive painful arc sign and Positive impingement test - Neers test, Hawkins Kennedy test) were included in the study. These patients were scanned with an MRI. Exclusion criteria included complete thickness/High-grade partial thickness tears of the Rotator Cuff tendon, concomitant secondary impingement signals, glenohumeral and/or acromioclavicular joint osteoarthritis, and extensive calcific deposits in the Rotator Cuff tendon.

Additional exclusion criteria included a history of previous surgical procedures on the afflicted shoulder and signs of shoulder instability (positive apprehension/positive sulcus sign). Only patients with primary impingement as indicated on MRI were included in the research. Patients were informed of their rights and provided with information about the treatment procedure. All patients gave their informed consent in writing. Patients ranging in age from 20 to 65 years old and clinically diagnosed with chronic SAIS (Neer's stage 2) were included in the study.

Patient satisfaction
0 Patient feels procedure was not successful
5 Patient feels procedure was a success
Active forward flexion range of motion
0 Less than 30°
1 30°-45°
2 45°-90°
3 90°-120°
4 120°-150°
5 Greater than 150°
Strength of forward flexion
0 No active contraction
1 Evidence of slight muscle contraction, no active elevation
2 Complete active forward flexion with gravity eliminated
3 Complete active forward flexion against gravity
4 Complete active forward flexion against gravity with some resistance
5 Complete active forward flexion against gravity with full resistance
Pain
1 Present always and unbearable, strong medication frequently
2 Present always but bearable, strong medication occasionally
4 None or little at rest, present during light activities; salicylates frequently
6 Present during heavy or particular activities only, salicylates occasionally
8 Occasional and slight
10 None
Function
1 Unable to use limb
2 Only light activities possible
3 Able to do light housework or most activities of daily living
6 Most housework, shopping, and driving possible; able to do hair and to dress and undress, including fastening brassiere
8 Slight restriction only, able to work above shoulder level
10 Normal activities
Total
Excellent: 34-35
Good: 28-33
Fair: 21-27
Poor: 0-20

Figure 1 - Detailed University of Los Angeles (UCLA) Shoulder Score.

The University of California and Los Angeles (UCLA) shoulder rating scale was utilised to evaluate shoulder function, and the pain score was determined from a preoperative history [12] (Figure 1). According to this scale, a score greater than or equal to 27 indicates a satisfying outcome, whereas a score less than or equal to 27 indicates a fair or bad performance (unsatisfactory result). The maximum score is 35 points. The UCLA score total outcome has been rated as poor (0-20), acceptable (21-27), good (28-33), and exceptional (34-35), with the outcome steadily improving. The UCLA scoring system questionnaire incorporates both objective criteria evaluated by professionals and subjective characteristics reported by patients. Active forward elevation and strength (physician-reported), discomfort, contentment, and function make up these five sub-scales (patient-reported). All elements of the UCLA score may not improve at the same time; for instance, the patient may report a reduction in pain prior to an increase in joint range of motion. Seldom have other research indicated this sub-categorical improvement in numerous metrics; instead, they have typically described the sum of all parameters. Knowing which parameters improve and which do not improve after subacromial decompression can help surgeons select patients more carefully. In our study, we evaluated the early functional result (each parameter of the UCLA score) of arthroscopic sub-acromial decompression in patients with primary chronic sub-acromial impingement syndrome.

General anaesthesia was administered during the operation. All surgeries were done by single senior surgeon trained in arthroscopy. With the patient in the lateral decubitus position, the surgical arm was placed in a Chinese finger trap sleeve and attached to the traction device. According to Gross and Fitzgibbons [19], it was in 45 degrees of abduction and 15 degrees

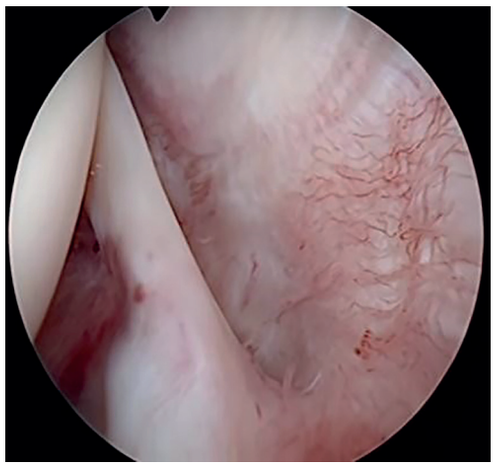

Figure 2 - 30 degree arthroscopic view showing rotator interval.

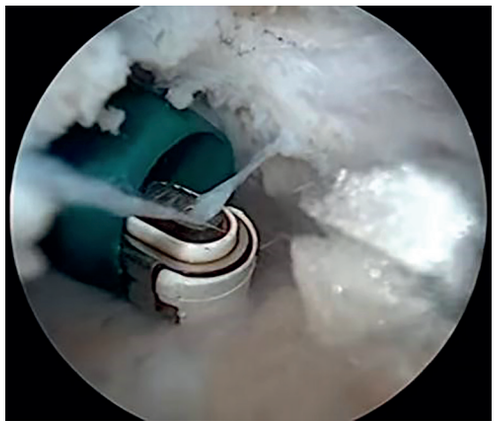

Figure 3 - Arthroscopic view showing subacromial space during process of debridement.

of forward flexion. Using a pulley, around five to six kg of weight were used to distract the arm. During diagnostic arthroscopy, the fluid pressure within the glenohumeral joint was kept close to 30 mm Hg, but it was occasionally elevated to between 40 and 70 mm Hg in the sub-acromial area to facilitate appropriate vision of structures and facilitate intervention. For diagnostic arthroscopy and ASAD, a three-portal method (posterior, anterosuperior, and lateral) was utilised. The posterior portal was created initially, 2 centimetres inferior and 1 centimetres medial to the posterolateral corner of the acromion soft spot, in order to facilitate the placement of the remaining portals and provide adequate visual acuity. The anterosuperior portal was created under the guidance of arthroscopic illumination via the posterior portal, which was positioned approximately 1 cm inferior and medial to the anterolateral corner of the acromion and lateral to the coracoid process (Figure 2) for improved visualisation of the anteroinferior and posterior portions of the glenohumeral joint. For end-on instrumentation and visibility of the subacromial area, a lateral portal 2 to 3 cm distal and parallel to the acromion's anterior margin was required [20]. A motorised shaver or radiofrequency ablation device was introduced by the lateral portal at the sub-acromial space to perform resection and decompression of hypertrophied synovial tissue of the sub-acromial bursa, and any loose body was removed (Figure 3). Via the posterior portal, the bur was used to remove 5 to 8 mm of the inferior surface of the acromion, including osteophytes extending from the ceiling of the sub-acromial area from the anterolateral corner to medially up to the lateral end of the clavicle [21]. For acromioplasty decision-making, preoperative X-ray shoulder outlet view [to rule out Bigliani [22] type 2-curved and type 3-hooked acromion] and intraoperative arthroscopic image of the acromion's undersurface were necessary. Using the cutting block technique, acromion resection was performed. In 1991, Sampson et al. [23] introduced a method, the "cutting block" approach (Figure 4), to shorten the procedure's steep learning curve and reduce the risk of insufficient decompression. Once the patient is positioned, it is necessary to sketch bone landmarks such as the clavicle, AC joint, acromion, and scapular spine as a requirement for this procedure. According to this technique, the scope was positioned laterally to view the acromial arch, and shaving and burring instruments were introduced through a posterior portal on the undersurface of the posterior half of the acromion; using this as a cutting block, the bur was advanced anteriorly and swept from medial to lateral. Both the lateral and posterior portals were used to examine the anterior hook and undersurface of the acromion. With an arthroscopic rasp, the surface was smoothened.

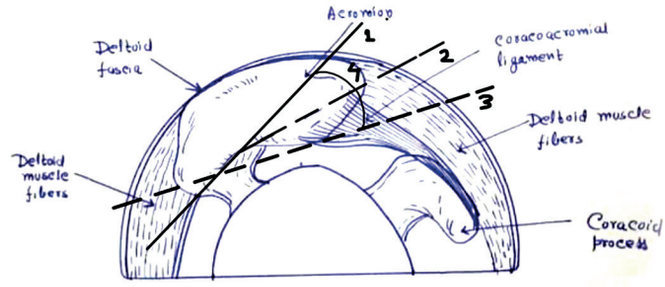

Figure 4 - End on view of subacromial space showing cutting block technique. Line 1 showing original cutting block line which is inappropriate for this curved acromion. Line 2 showing modified anterior hook resection per Ellman technique [12], preserving deltoid fascia and not producing a type 1 flat acromion. Line 3 showing the two extreme point of acromion. Curved line showing approximate amount of resection.

The day after surgery, patients were sent home with their arms immobilised in arm pouches. patients were evaluated at four, twelve, and sixteen weeks after arthroscopic sub-acromial decompression. Throughout the postoperative phase, physical therapy was performed in accordance with South Shore Hospital's [24] shoulder exercise guidelines.

Statistical evaluation

A qualified statistician calculated the sample size with following variables. Effect size expressed as a standardized mean difference (Cohen's d) with a value of 0.5. This means that the mean improvement in the UCLA score in the treatment group is expected to be 0.5 standard deviations higher than the control group. Significance level (α): It was set at 0.05, representing a 5% chance of incorrectly rejecting the null hypothesis. Power (1 - β): It was assumed to be a power of 0.80, indicating an 80% chance of detecting a significant difference if it truly exists. Dropout rate: Assume a dropout rate of 10%, meaning that 10% of participants may drop out or be lost to follow-up during the study. Plugging these values into the formula: $n = [(Z\alpha/2 + Z\beta) * \sigma / \Delta]^2$ a sample size of 35 was regarded adequate in comparison to previously published research [14]. Categorical variables were reported as numbers and percentages, whereas continuous variables were provided as means standard deviations (SD) and medians. The Kolmogorov-Smirnov test was used to examine the data's normality. The non-parametric test was employed when the assumption of normality was rejected. Quantitative variables were compared across follow-up using paired t-tests/ Wilcoxon tests (where data sets were not normally distributed). A p-value of less than 0.05 was deemed statistically significant. The data were entered into an MS EXCEL spreadsheet, and SPSS version 21.0 was used to conduct analysis.

Results

During the study period, 35 individuals were operated on. Thirty patients were male (85.71%) and five were female (14.29%). The range of ages was between 23 and 50 years, with a mean age of 36.1 years. In this study, the UCLA shoulder scale was used to evaluate shoulder function. We compared both the total Scores and the scores of each component. Table 1-5 displays the specific component-by-component variations in the UCLA scores during the evaluation period. After surgery, all components improved dramatically.

The pre-operative mean total UCLA score was 12.66±3.01. In the fourth week following surgery. At the 12th postoperative week mean UCLA was 24.80±3.96 and at the 16th week it was 29.14±3.05. The improvement in mean total UCLA scores at fourth, twelfth, and sixteenth weeks after surgery were statistically significant (p=0.0001) when compared to the pre-operative status.

According to this scale, a score greater than or equal to 27 indicates a satisfying outcome, whereas a score less than or equal to 27 indicates a fair or bad performance (unsatisfactory result).

Table 1 Comparison of pain component of UCLA score between pre-operative and follow up.

Pain	Pre-operative (n=35)	4th week (n=35)	12th week (n=35)	16th week (n=35)	P value	Test performed
Mean ± Stdev	2.86 ± 1.09	3.83 ± 1.22	5.66 ± 1.14	7.83 ± 1.12	Pre-operative vs 4th week:0.0001 Pre-operative vs 12th week:<.0001 Pre-operative vs 16th week:<.0001	Wilcoxon Signed Ranks Test
Median(IQR)	2 (2-4)	4 (4-4)	6 (5-6)	8 (8-8)		
Range	1-4	2-6	4-8	6-10		

Table 2 Comparison of function component of UCLA score between pre-operative and follow up.

Function	Pre-operative (n=35)	4th week (n=35)	12th week (n=35)	16th week (n=35)	P value	Test performed
Mean ± Stdev	3.03 ± 1.1	5.03 ± 1.01	6.74 ± 1.2	8.06 ± 1.24	Pre-operative vs 4th week:<.0001 Pre-operative vs 12th week:<.0001 Pre-operative vs 16th week:<.0001	Wilcoxon Signed Ranks Test
Median(IQR)	4 (2-4)	6 (4-6)	6 (6-8)	8 (8-8)		
Range	1-4	4-6	4-8	6-10		

Table 3 Comparison of active forward flexion component of UCLA score between pre-operative and follow up.

Active forward flexion	Pre-operative (n=35)	4th week (n=35)	12th week (n=35)	16th week (n=35)	P value	Test performed
Mean ± Stdev	2.89 ± 1.08	3.51 ± 0.78	4.2 ± 0.58	4.54 ± 0.61	Pre-operative vs 4th week:0.0001 Pre-operative vs 12th week:<.0001 Pre-operative vs 16th week:<.0001	Wilcoxon Signed Ranks Test
Median(IQR)	3 (2-4)	4 (3-4)	4 (4-5)	5 (4-5)		
Range	0-4	2-5	3-5	3-5		

Table 4 Comparison of strength of forward flexion between pre-operative and follow up.

Strength of forward flexion	Pre-operative (n=35)	4th week (n=35)	12th week (n=35)	16th week (n=35)	P value	Test performed
Mean ± Stdev	3.89 ± 0.58	3.89 ± 0.58	3.97 ± 0.62	4.14 ± 0.55	Pre-operative vs 4th week:1.00 Pre-operative vs 12th week:0.257 Pre-operative vs 16th week:0.007	Wilcoxon Signed Ranks Test
Median(IQR)	4 (4-4)	4 (4-4)	4 (4-4)	4 (4-4)		
Range	3-5	3-5	3-5	3-5		

Table 5 Comparison of satisfaction component of UCLA score of the patient between pre-operative and follow up.

Satisfaction of the patient	Pre-operative (n=35)	4th week (n=35)	12th week (n=35)	16th week (n=35)	P value	Test performed
Mean ± Stdev	0 ± 0	2.71 ± 2.53	4.29 ± 1.78	4.57 ± 1.42	Pre-operative vs 4th week:<.0001 Pre-operative vs 12th week:<.0001 Pre-operative vs 16th week:<.0001	Wilcoxon Signed Ranks Test
Median(IQR)	0 (0-0)	5 (0-5)	5 (5-5)	5 (5-5)		
Range	0-0	0-5	0-5	0-5		

The maximum score is 35 points. The UCLA score total outcome has been rated as poor (0-20), acceptable (21-27), good (28-33), and exceptional (34-35), with the outcome steadily improving. In the pre-operative phase, all evaluated patients (35, 100%) were graded as bad. After the fourth week of postoperative follow-up, the majority of patients (23, 65.71%) were still rated as poor. In addition, in the 12th week of postoperative follow-up, the majority of patients were graded as fair (23, 65.71%), and in the 16th week, the majority of patients were graded as good (27, 77.14%). The difference in total UCLA score between the preoperative stage and the fourth week of postoperative follow-up was extremely significant ($p<0.0001$), as was the difference between the preoperative UCLA score and that at the 12th and 16th weeks after surgery ($p<0.0001$). From the pre-operative period through the 16th week of postoperative follow-up, the total UCLA score showed a significant and ongoing trend of improvement.

The average duration of surgery was 49 minutes (range: 38-69 minutes), and no notable complications were seen during the course of the trial.

Discussion

The study demonstrates that arthroscopic sub-acromial decompression is an effective and reliable procedure for improving short-term functional outcomes in carefully selected patients with primary sub-acromial impingement (chronic type 2 primary impingement) who have failed to respond to conservative treatment. Aside from the tight patient selection criteria and prospective nature, another strength of the present study is that it describes changes in each of the five components of the UCLA shoulder score, which has seldom been done previously.

The results of subacromial decompression are inconsistent in the medical literature, likely due to improper diagnosis, failure to treat the associated rotator cuff pathology adequately, performing surgery in Neer's type 3 impingement, and technical errors such as under resection of the acromion [13-18]. Checroun et al. examined 34 studies (1,935 patients) between 1970-1996. Arthroscopic Sub-Acromial Decompression (ASAD) was indicated as the initial treatment of choice, with open surgery reserved for arthroscopic failure [13]. Although technically more rigorous, ASAD allowed for faster recovery. In recent literature, however, ASAD's efficacy has been called into question. Health Economists in Denmark have documented a poor and delayed rate of return to work for SAIS patients treated with ASAD [14]. They say that because to the low incidence of return to employment, there are no financial benefits for the government. Surgeons assert that patients who undergo ASAD obtain excellent pain alleviation and a high level of activities of daily living (ADLs). Owing to the aforementioned disparities, the current study was designed to include only individuals with type 2 main impingement. About fifty percent of acromioplasty failures have been ascribed by several researchers to a wrong or missed diagnosis. Unrecognized shoulder instability with secondary rotator cuff symptoms, glenohumeral arthritis, periarthritis of the shoulder, suprascapular neuropathy, and glenohumeral internal rotation deficiency are the most common causes of failure. Under these conditions, arthroscopic subacromial decompression and debridement exacerbate an already weakened shoulder, leading in many cases to recurrent dislocation and a positive postoperative apprehension test [25-29]. Arthroscopic subacromial decompression is the preferred treatment for patients with chronic type 2 primary impingement syndromes who have not responded to conservative treatment [30]. Dom et al. published a five-year follow-up analysis of 52 patients with advanced (stage 2) rotator cuff illness who underwent arthroscopic sub-acromial decompression. From six months to five years postoperatively, a total of 45 (out of 52) patients demonstrated progressive improvement and symptom alleviation [25]. Ellman et al. performed subacromial decompression on 65 patients who were assessed two to five years after surgery. According to the UCLA shoulder assessment scale, 89% of the cases in the research had an acceptable outcome [12]. Esch et al. assessed the outcomes of arthroscopic subacromial decompression based on the degree of rotator cuff tear in 71 patients with at least one year of follow-up (average 19 months). 82% of patients with stage 2 illness were pleased, regardless of whether they had a rotator cuff tear (9 of 11) or not (28 of 34). Eighty-eight percent (23 of 26) of patients with stage 3 illnesses (rotator cuff tears) were happy. 82% (9 of 11) of the patients without a rotator cuff tear, 76% (26 of 34) of those with a partial tear, and 77% (20 of 26) of those with a total tear had an acceptable objective UCLA shoulder rating > 28. Four patients with full tears less than one centimetre in length achieved excellent outcomes. The objective success rate of 77% and the total patient satisfaction rate of 85% are comparable to those of open rotator cuff repair [30]. Ravikiran et al. found that a total of 20 patients diagnosed with primary shoulder impingement due to secondary mechanical reasons and undergoing decompression surgery had a mean UCLA shoulder rating scale score greater than or equal to 27, indicating a good/excellent (satisfied) outcome [31]. Consistent with the aforementioned findings, the current investigation demonstrates similar outcomes. The study also indicates that arthroscopic sub acromion decompression is effective for a carefully selected group of patients with Neer's type 2 primary impingement with rotator cuff scarring/tendinitis and no signs of rotator cuff tear.

The present study has several limitations. The study participants were mostly males, and the sample size is small. Second, the period of follow-up is brief, and long-term outcomes are being tracked. In addition, no control group was included in the study. Despite these limitations, the study has major clinical implications for patients with mechanical sub-acromion impingement, demonstrating that surgical decompression is associated with a considerable improvement.

Conclusion

This study suggests that arthroscopic sub-acromial decompression produces a favourable functional outcome in patients with primary shoulder impingement due to extrinsic mechanical factors, such as the shape and slope of the acromion, in the absence of rotator cuff tear, after 16 weeks of follow-up.

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Side effects after first and second doses of Covid-19 vaccine among health care providers in tertiary care hospital

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Abstract

Background: Acceptance of Covid-19 vaccination among the general population is one topic that has been discussed worldwide. Large number of doses of vaccine has been administered throughout the world, but, concerns about safety of Covid-19 vaccination still persists. There have been reports of adverse effects with Covid-19 vaccination which are mild and resolve spontaneously. This study was done to evaluate the side effects after first and second doses of Covid-19 vaccine among health care providers in tertiary care hospital.

Material and methods: This cross-sectional, questionnaire based study was done among health care workers after first and second dose of vaccine in Teerthanker Mahaveer Medical College & Research Center, Moradabad, India between January 2021 to July 2021. In this survey, post Covid-19 vaccination questionnaire was designed using Google Forms and was shared to vaccinated participants through social media and mail. Snowball sampling method was used for gathering a total of 485 responses. Informed consent was obtained from all research participants and the study was approved by the Institutional Review Board (IRB)

Results: The respondents were health care professionals which included Physician, Surgeons, and Other Health Care Workers. The most common adverse effects reported after both doses of vaccination were fever, chills and rigor, headache, myalgia, malaise and pain at site of injection. The results showed that 65% (n=338) of participants had mild symptoms like headache, fever, pain at injection site, malaise, myalgia, dizziness, nausea and vomiting after first dose of vaccination. In comparison 39% (n=190) of participants reported mild symptoms after the administration of second dose of vaccination. A total of 63% (n=330) and 41% (n=197) participants took medication for relief of symptoms during post-vaccination period after the first and second dose of vaccine with slight female preponderance.

Conclusion: The most prevalent adverse effects following vaccination were nausea and vomiting, headache, dizziness, fever, chills, fatigue, including pain, redness and swelling at the injection site with more female preponderance. The adverse effect encountered were higher in number after the first dose of vaccination.

Key words: vaccination, adverse effects, Covid-19, health care workers

Introduction

Nowadays, Covid-19 vaccine is being discussed wildly worldwide. Large number of doses of vaccine has been administered throughout the world [1]. But, some concerns about safety and adverse effects related to COVID-19 vaccination is still there [2]. However according to WHO, Covid-19 vaccines also can cause some side effects. Mostly these reactions to vaccine are mild and they went away on their own. The probability of any side effects following vaccination varies according to specific vaccine. Many initiatives were taken by the government, at different levels (central, state, etc). While vaccination is best and important option in this pandemic condition to boost

immunity and staying healthy. In various randomized clinical trials related to COVID-19 vaccines, It has been reported that some local adverse effects like pain, redness and swelling at injection and few systemic side effects like headache, dizziness, malaise, myalgia with rare but few severe adverse effects [3-6]. About 50% to 90% of participants experienced only mild side effects [3,4,6]. Emergence of data on adverse effects related to Covid-19 vaccine reported through various reporting systems e.g. government-sponsored reporting systems [7-11].

The objectives of this prospective study were to identify and compare various adverse effects (adverse drug reaction) encountered after receiving first and second dose of vaccination for COVID-19 among health care professionals. These results may help the population in gaining a confidence and better understanding of side effects after COVID-19 vaccination.

Material and methods

Study design

This observational, cross-sectional study was based on self-administered online survey, which was done using questions pertaining to the post vaccine experience after first and second dose of vaccine in a tertiary care hospital of Western Uttar Pradesh of India. In this survey, post Covid-19 vaccination feedback form was designed using Google Forms platform and questions were formatted in the binary fashion to the extent possible. In this questionnaire few questions were descriptive in which respondents can put their own experiences in addition to other options. There was also provision of "others" as an option to collect more descriptive and versatile data. Then this Google form was shared to vaccinated persons in Teerthanker Mahaveer Medical College & Research Center, Moradabad, India between January 2021 to July 2021 through what's app and mail. Snowball sampling method was used for gathering a total of 485 responses. All the respondents were informed regarding their voluntary participation. In this survey, only those were included who were 18 years and above. The data was thereafter transferred into Excel sheet for its analysis. Informed consent was obtained from all research participants and the study was approved by the Institutional Review Board (IRB). Questionnaire was formed in Goggle forms. Participants were asked to fill the questionnaire after first and second dose of vaccine. All the participants enrolled in the study received either Covaxin or Covishield. Questions were framed in such a way to collect the data of adverse effects. To answer those questions there were options like pain at injection site, headache, fever, chills and rigor, malaise, myalgia, dizziness, hypersensitivity reaction, any other, and none of the above. These response options were identified because similar symptoms had been reported earlier in different clinical studies. This questionnaire as Goggle Form link was shared with all the vaccinated participants. To prevent problem of missing data, it was mandatory to respond all questions to submit the form otherwise submission of this questionnaire would not be complete. For precipitation in this survey no incentive was given. The primary objective of the study was to evaluate and assess differences, as well as severity of symptoms after 1st and 2nd dose of COVID-19 vaccine and various symptoms appeared in different time interval among health care workers in Medical College.

Statistical analysis

The baseline characteristics of data transferred from goggle form to Microsoft Excel and were analyzed using Descriptive statistics. All quantitative variables were presented as mean and percentage, and the qualitative variables are presented as percentages and frequency. Chi-Square test was used for comparison of categorical data.

Results

After thorough literature search and various guidelines from the WHO and MoHFW on the various adverse reactions after COVID-19 vaccine this study was designed. The questionnaire was in English language. This questionnaire was shared two times, firstly after 1st dose of Covid-19 vaccine and secondly after 2nd dose of Covid-19 vaccine. However, Total 2 groups were formed, Group 1 – those participants who had received first dose of Covid-19 vaccine and group 2 – after receiving 2nd dose of Covid-19 vaccine. Total respondents who filled the google form were 522 after 1st dose (group1) and 485 after 2nd dose (group2) of Covid-19 vaccine. The respondents in the survey were health care professionals which included Physician, Surgeons, and Other Health Care Workers (Staff Nurses, Paramedical Staff, Students and Administration Staff). The analysis showed that in group 1 (after 1st dose) 52.5% (275) were male, 47.3% (247) were females and in group2 (after 2nd dose) 48.24% (234) were male, 51.75% (251) were females. Among those who were surveyed, In group 1 - students 79.5% (415), Doctors 17.24% (90), paramedical staff 2.10 % (11), administrative staff 0.5 % (3), others 0.5 % and in group 2- students 82.68% (401), Doctors 13.40% (65), paramedical staff 1.03% (5), administrative staff 0.41 % (2), others 2.47 %. Age of participants were from 19 to 65 years. After both doses (i.e. First and Second Dose) of vaccination most common side effects were fever, chills and rigor, headache, myalgia, malaise and pain at site of injection.

During first 30 minutes, in group 1- 82% (429) had no symptom, but there was fever 4%, headache 3.6%, body ache1.7%, and nausea and vomiting 1.3%. (Table 2) However in group 2 – 82% (401) did not experience any symptom, 0.8% developed nausea and vomiting 1.4% developed myalgia and malaise, 2.2% developed dizziness, 3.2 % developed pain at injection site, 2.47% developed headache and 3% developed fever (Table 1 and Figure 1). There was no difference in adverse effects based on gender distribution.

Table 1 Adverse effects in the first 30 minutes after vaccination (n (%))

Symptoms in first 30 min	After 1st dose	After 2nd dose
No	429(82%)	401(82.68%)
Nausea/ vomiting	7(1.34%)	4(0.82%)
Myalgia	9(1.7%)	7(1.44%)
Dizziness	22(4.2%)	11(2.26%)
Pain at injection site	19(3.6%)	16(3.29%)
Headache	19(3.63%)	12(2.47%)
Fever	21(4.01%)	15(3.09%)

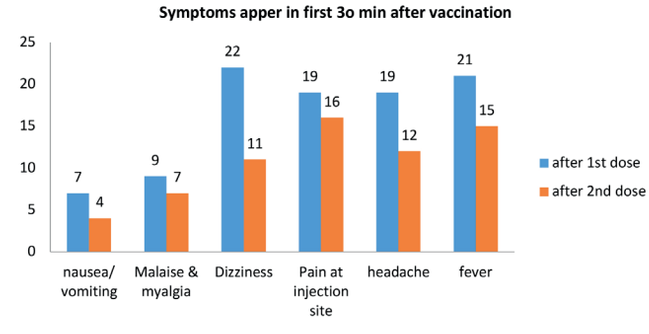

Figure 1 - Symptoms reported by patients in first 30 minutes' post vaccination

On data analysis of the side effects in post vaccination period that started from 30 minute after vaccination to 24 hours (1 day) after vaccination, in group 1, a total 10.5% (55) participants had not reported any symptoms but there was fever 42.5%, pain at injection site 33% (171), headache 14.3% (75), body ache 12.5%(65), nausea/vomiting 3%. However, in group 2 total 30.72% (149) respondents were having no symptoms while remaining respondents experienced symptoms like nausea/vomiting 18(3.7%), malaise and myalgia 130(26.80%), dizziness, pain at site of injection 179(36.90%), headache 86(17.73%), fever 130 (26.80%) and chills and rigor 47(9.69%) (Table 2 and Figure 2).

Table 2 Adverse effects from 30 minutes – 24 hours after vaccination (n (%))

Symptoms from 30 min - 24 hours	After 1st dose	After 2nd dose
No	55 (10.53)	149 (30.72%)
Nausea/ vomiting	14 (2.68%)	18 (3.71%)
Myalgia	69 (13.215)	130 (26.80)
Dizziness	0	0
Pain at injection site	171 (32.75%)	179 (36.90)
Headache	75 (14.36)	86 (17.73%)
Fever	222 (42.52%)	130 (26.80%)
Chills and rigor	57 (10.91%)	47 (9.69%)

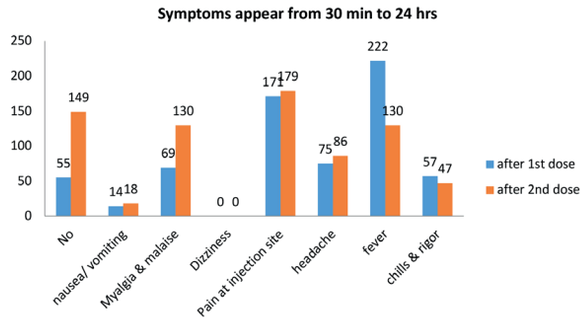

Figure 2 - Symptoms reported by patients after 30 minutes to 24 hours post vaccination

Also, on analysis of symptoms appear after 24 hours of vaccination, it was found that group 1 - 187(35%) respondents had no any symptom. But, there were 338 (65%) participants who reported mild symptoms like headache, fever, pain at injection site, malaise, myalgia, dizziness, nausea and vomiting. However, the analysis of participant showed that in group 2 - 295 respondents (60.82%) did not reported any symptom. But total 190 respondents (39.17%), reported few mild symptoms which are shown in Table 3 and Figure 3. There was no difference in adverse effects based on gender distribution.

Table 3 Adverse effects after 24 hours of vaccination (n (%))

Symptoms after 24 hours	After 1st dose	After 2nd dose
No	187 (35.82%)	295 (60.82%)
Nausea/ vomiting	34 (6.51%)	2 0.41%)
Myalgia	130 (24.90)	18 (3.71%)
Dizziness	0	6 (1.23%)
Pain at injection site	103 (19.73)	26 (5.36%)
Headache	101 (19.34%)	22 (4.53%)
Fever	160 (30.65%)	68 (14.02%)
Chills and rigor	60 (11.49%)	6 (1.23%)

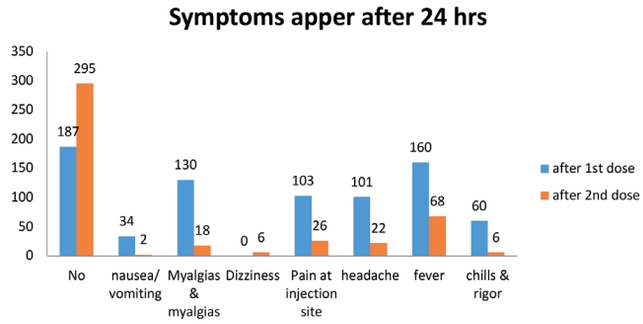

Figure 3 - Symptoms reported by patients after 24 hours post vaccination

In group 1 – a total of 330 (63.2%) participants took medication for relief of symptoms in vaccination period, whereas, 192 (36.7%) participants took no medication following first dose of Covid-19-19 vaccine. However, in group 2 - only 197 (40.61%) had medicine for relief of symptoms in post vaccination period while 288 (59.38%) did not have any kind of medication following vaccine administration. Most of the participants either took paracetamol as a drug for pain relief or NSAIDS. We also performed the data analysis of vaccination procedure, and it was found that more than 75% of respondents were vaccinated by maintaining social distance, explanation of vaccination procedure, hand sanitization and proper disposal of syringe at vaccination centre except monitoring of body temperature (Table 4).

Table 4 Analysis of vaccination procedure (n (%)

	After 1st dose	After 2nd dose
Maintenance of Social distancing	423 (81%)	335 (69.07%)
Recording of body temperature	339 (65%)	162(33.40%)
Any waiting period to get vaccination.	398 (76.3%)	372(76.70%)
Explanation of procedure before vaccination	394 (75.5%)	342 (70.51%)
Proper hand sanitization	407 (77.9%)	353(72.78%)
Proper disposal of syringe	477 (91%)	430(88.65%)
Rest of 30 min after vaccination in observation room	516 (98.8%)	412(84.94%)

In this study side effects were reported more in females, during the period post vaccination i.e. 30 minutes to 24 hours (1 day), in comparison to males (Table 1). There was no difference in adverse effects based on gender distribution.

All the participants also rated their encounter with the vaccination team for Covid-19-19 vaccination center. The rating scale adopted for this study had scores in the range of 1 to 5. Majority of the participants (> 2/3rd participants) (n=377) rated their experiences as very satisfied with the vaccination process (A score of ≥ 4 on 5 point Likert scale). A limited number of participants (n=37) rated their experience as not happy with their experience (A score of ≤ 2 on 5 point Likert rating scale).

Discussion

Data of symptoms was collected by giving questionnaire following the first and second dose of vaccination. Our study compared data of same vaccine to evaluate the severity and incidences of adverse reactions between the first and second doses to more accurately after each inoculation. Most of the respondents presented with the complaint of following symptoms following vaccination like malaise, myalgia, pain

at site of injection, dizziness and fever within 24 hours of vaccination. Results of this study are in consistent with studies conducted by Mennic et. al, and Haya Omeish et. al. that demonstrated following side effects after administration of vaccination for COVID-19, which included pain at the site of injection as reported by majority of patients, followed by flu-like symptoms and Gastrointestinal symptoms were more following first dose of COVID-19 vaccination [12,13]. It was also noticed in this study that as compared to males, females experienced more symptoms. This could be due to better immunity and higher formation of antibodies in response to vaccination among males than females. Other studies also showed similar results of gender dependent association with vaccine related side effects especially fatigue, headache, myalgia and chills after both the doses. [12-14].

In this study, symptoms like nausea/vomiting, malaise, myalgia, dizziness, pain at site of injection, headache, fever, chills and rigor were more frequent after first dose of vaccine as compared to second dose in first 30 min and after 24 hrs of vaccine except in 30 min -24 hrs, where nausea/vomiting, malaise, myalgia, pain at site of injection and headache was more frequently encountered after the administration of second dose in comparison to the first dose. But fever, chills and rigor was reported more often after the administration of first dose in comparison to the second dose in first 30 min, 30min- 24 hrs and even after 24 hrs. However, there was marginal difference in these symptoms after first and second dose. Results of this study were similar to studies done by Omeish et al. [13]. On comparison of data of adverse effects (Adverse drug reaction) following first dose of vaccination as compared to the second dose, studies conducted on the administration of vaccine developed by BNT162b2Mrna, Pfizer and AstraZeneca reported more frequent local and systemic adverse effects were more after receiving second dose as compared to first dose [15]. In contrast, data of this study was not in alignments with results observed in these studies, as adverse effects were more frequent following administration of the first dose as compared to the second dose, with the exception for enlargement of lymph node, some sexual disturbance and chills. In their study pain at injection site and fever was the most common symptom in 30 min to 24 hrs after first and second dose of vaccine. This observation was similar to another cross-sectional study which showed that other local site adverse effects were far too lass as compared to participants complaining of pain at the site of injection which was reported in 88.04% of participants [13,16].

Gastrointestinal symptoms, especially nausea, was reported more after first dose as compared to second dose in first 30 min as well as after 24 hrs of vaccination. But it was found that incidences of nausea were reported more after second dose as compared to the first dose in 30 min to 24 hrs after vaccination. These results are partly in consistent with other studies as well as the reports of WHO of AstraZeneca vaccine.

In our study on analysis it was found that headache was more common after 24 hrs of first dose of vaccination in comparison to the second dose of vaccine [17-19]. However there was marginal difference in headache in first 30 min and 30 min -24 hrs after first and second dose of vaccine. These results are in consistent with other study that showed that about half of all the participants who were administered vaccine of either AstraZeneca or Pfizer vaccines ad complaint of headache [16,18,21]. Study done by Kadali et.al. which considered the manifestation of neurological symptom showed that they were rarely encountered in participants following vaccination is consistent with results of our study where dizziness was the only neurological symptom. No single serious symptom was reported by any of the respondent in post vaccination period. Our study revealed that most of the side effects were only mild and do not require any hospitalization and the adverse effects encountered by the participants subsided few days following vaccination. The similar results were shown in other study also where side effects were in the category of mild to moderate in severity and were resolved within days following vaccination. However, this survey was done within a span of few days following vaccination. Hence, delayed side effects were not reported.

Limitations

There are certain limitation of this study, firstly in this study all the participants were from the same center as well as the size of the sample. Another limitation was that all the respondents received only Covishield so there was no comparative data of adverse effects after the administration to two set of vaccines.

Conclusion

The frequent adverse effect for Covishield vaccination were nausea/vomiting, dizziness, headache, fever, chills, fatigue. The other adverse effects encountered included pain at the site of injection along with redness and swelling with Covishield vaccine. The adverse effects were reporter frequently by females as compared to males. To summarize the adverse effects reported were well-tolerated, but, long-term study is required to investigate for long-term side effects and safety profiles of the vaccine. It was also concluded through this study that the majorly side effects after second dose were less as compared to the vaccine by first dose of Covid-19 (Covishield). However all side effects were mild. There was no serious adverse reaction after administration of Covid-19 vaccine in study participant. All the vaccination safety protocol issued by the government was followed at the vaccination centre.

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The role of artificial intelligence in colonoscopy imaging and colonic diseases: A scientometrics analysis and visualization study

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Abstract

Introduction: Artificial intelligence (AI) has made a big difference and is used in many different sectors also in medicine. We sought to identify the areas of interest and potential future directions for AI in the field of colonoscopy imaging and colonic diseases by utilizing bibliometrics to analyze the previous 50 years' worth of changes on this topic.

Material and methods: Using the Web of Knowledge (WOS) database, we searched for articles published from 1970 to 2021 using the keywords related to colonoscopy imaging/colonic diseases and AI. The retrieved articles were analyzed with bibliometric methods.

Results: A total of 278 documents were analyzed in this study. The earliest article was published in 1997 and the vast majority of the documents were published in 2021 (n=81). There was a growth in publications number in the last 5 years. The documents were cited 3054 times in total and had 10.99 citations per document. The main Hirsch (H) index of the documents was 27. A total of 41 countries contributed to the literature. The United States of America (USA), the People's Republic of China, and England were the leading countries on this topic. Also, England had the highest number of citations (total of 974 citations, 31.42 per document) and the USA publications had the highest H index.

Discussion: Artificial intelligence facilitates diagnosis and treatment possibilities, especially in the field of health. Especially the use of artificial intelligence in colonoscopic imaging reduces the risk of missing a possible polyp or a mucosal pathology. The integration of artificial intelligence into imaging methods has been the most in the last 5 years. Most studies on this subject have been done in the USA.

Conclusion: Our research may offer a historical perspective on the development of AI in colorectal diseases. The documents were limited to some developing countries.

Key words: artificial intelligence, colorectal diseases, colon, colonoscopy, machine learning, bibliometric analysis

Introduction

The definition of artificial intelligence (AI) is an intelligence displayed by machines as opposed to the natural intelligence exhibited by humans and other animals [1]. It was made of leather, wood, and artificial organs [2]. AI is projected to fill a number of jobs currently filled by humans [1].

There are two key applications of AI in medicine: both imaginary and physical. Firstly, AI has increased and continues to encourage advancements in genetics and molecular offering machine learning algorithms and knowledge administration [3]. AI and its use in medicine have advanced significantly since 2010 [4]. The use of AI-based medicine in gastroenterology practice is anticipated in the near future [1]. In gastroenterology, AI is being investigated for endoscopic lesion analyzed, cancer detection, and for making it easier to analyze inflammatory lesions or gastrointestinal bleeding using wireless capsule endoscopy. It is challenging to compare the findings of various research due to variations in performance indicators. AI appears to be especially useful for endoscopy, where it might improve the identification

of inflammatory lesions, small-bowel hemorrhage, malignant and premalignant lesions, and pancreaticobiliary illnesses [4-6]. Additionally, these studies may be able to forecast the onset of GI illness before symptoms appear, increasing the likelihood of prevention or pre-treatment. Additionally, computer vision offers the intriguing possibility of automated lesion detection during endoscopy and colonoscopy [7,8].

An accepted colonoscopy quality indicator is the adenoma detection rate. For instance, a 1 % increase in the adenoma diagnosis rate was linked to a 3 % decrease in the risk of interval colorectal cancer [8]. A prior meta analysis, however, revealed that about 26% of neoplastic diminutive polyps were missed during a single colonoscopy [9]. Blind spots and human mistakes are thought to be two variables that influence this rate. A wide-angle scope or distal attachments might address the first issue, but human error is difficult to eliminate. AI has drawn interest as a way to alleviate human mistakes [10,11]. Systems that use a computer's capacity to learn and carry out certain tasks include computer-aided detection (CADe) and computer-aided diagnostic (CADx). Machine learning and deep learning advancements have made it possible for computers to learn and carry out certain endoscopic activities that were previously the duty of the endoscopist. CADe and CADx have the potential to change endoscopy, albeit in its early stages. The use of CADe and CADx during colonoscopy, with an emphasis on three main points: (1) the effectiveness of the mucosal inspection, (2) the identification of polyps, and (3) ocular biopsy. Imaging, robotic surgery, and genomics are just a few of the numerous possible uses for CADe and CADx in the healthcare industry [10].

We sought to identify the areas of interest and potential future directions for AI in the field of colonoscopy imaging and colonic diseases by utilizing bibliometrics to analyze the previous 30 years' worth of changes on this topic.

Materials and methods

In this retrospective bibliometric design study, the Web of Science (WoS) database was used to gain the dataset. Subscribers to the WOS database gain access to a range of databases that offer comprehensive citation data for a wide range of academic disciplines. It was originally developed by the Institute for Scientific Information (ISI). It is currently owned by Clarivate, formerly known as the Intellectual Property and Science division of Thomson Reuters. The Scientific Information Institute (ISI) initially developed the service, which is now run by Clarivate Analytics [12].

There are two search options available for this database: a simple search and an advanced search, which enables users to construct intricate and comprehensive search queries to accomplish the desired objective. Customers can access words in the database's titles, abstracts, journal/author names, and affiliations [13]. In this study, authors, affiliations, nations, publication numbers, journals, H-index, and citation bursts were only a few of the parameters that were noted.

We used the keywords related to AI (artificial intelligence; computer-aided detection; computer-aided diagnosis; convolutional neural network, deep learning; machine learning; computer-aided diagnostic; computer-aided detection) and colonic diseases or colonic diagnostic methods (colonoscopy; colonic diseases; colon; colonic diseases, colonoscopy, colonic polyps) in the "title" as a search item in our study.

The following were the exclusion criteria: (1) Articles written in languages other than English; (2) Articles covering a variety of topics but not only colorectal diseases.

The WOS database's maximum timeframe for searches was June 25, 2022, so this was the timeframe covered. In order not to cause bias, the search in the study was carried out in a single day. The information was gathered on June 26, 2021, by pre-analyzing retrieval outcomes from the core collection's online version in the WOS database. All published documents were examined without making any distinction between documents.

Finally, the collected information was extensively studied for its applicability to the research presented in the study.

Statistical analysis

Microsoft Word and Microsoft Excel were used to create the tables and graphs, respectively. Based on the frequency of keywords in titles and abstracts, data visualization was done using the VOSviewer 1.6.18 software (Leiden University, Leiden, The Netherlands) approach to produce scientific networks and landscapes.

Results

A total of 278 documents were analyzed in this study. Regarding study type, there were articles (n=100), meeting abstracts (n=75), proceedings papers (n=42), reviews (n=32), editorial materials (n=23), early access (n=5), letters (n=4), news items (n=3), corrections (n=2) and book chapters (n=1). There were no guidelines, respectively. Most of them were from gastroenterology/hepatology (53.957%) and surgery (15.827%) research areas (Table 1).

Table 1 Publishing Categories

Web of Science Categories	Record Count	% of 278
Gastroenterology Hepatology	150	53.957
Surgery	44	15.827
Engineering Biomedical	24	8.633
Robotics	21	7.554
Radiology Nuclear Medicine Medical Imaging	20	7.194
Engineering Electrical Electronic	17	6.115
Automation Control Systems	16	5.755
Medicine General Internal	14	5.036
Computer Science Artificial Intelligence	13	4.676
Engineering Mechanical	12	4.317

Showing 10 out of 47 entries

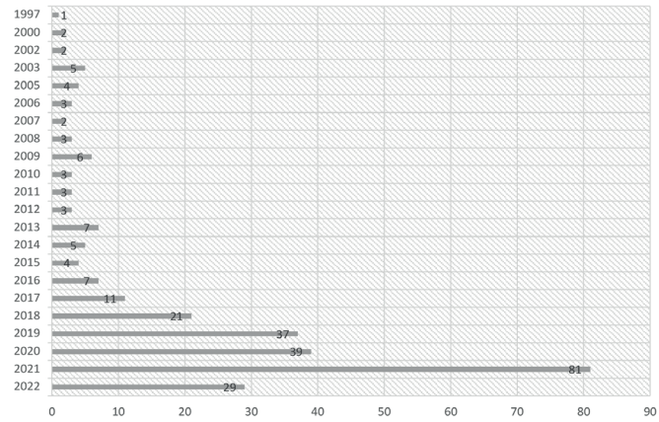


Figure 1 - The number of published documents by the years

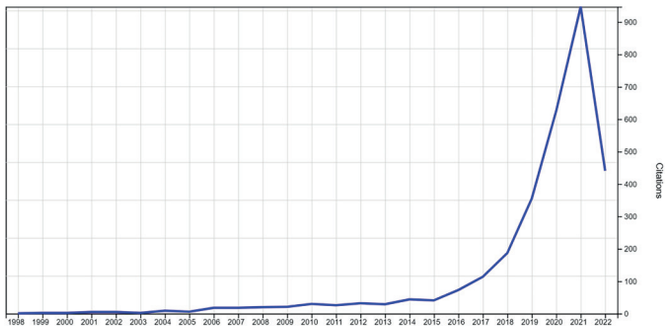


Figure 2 - The number of citations of the documents by the years

The earliest article was published in 1997 and the vast majority of the documents were published in 2021 (n=81). There was a growth in publications number in the last 5 years (Figure 1). The documents were cited 3054 times in total and had 10.99 citations per document. The main Hirsch (H) index of the documents was 27. Figures 1 and 2 display the number of papers and citations per year (Figure 1,2). The article had the highest citation number published by Sirinukunwattana et al. [13] in 2016. This article [17] was cited 563 times.

The European Commission (n=9), the National Institutes of Health Nih United States of America (USA) (n=9) and, the United States Department Of Health Human Services (n=9) were the leading funding agencies (Figure 3).

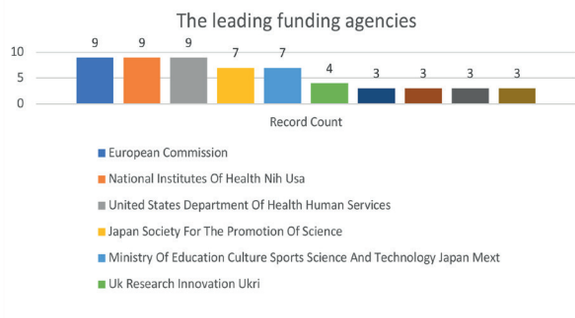


Figure 3 - The leading funding agencies
*Showing 10 out of 133 entries;196 record(s) (70.504%) do not contain data in the field being analyze

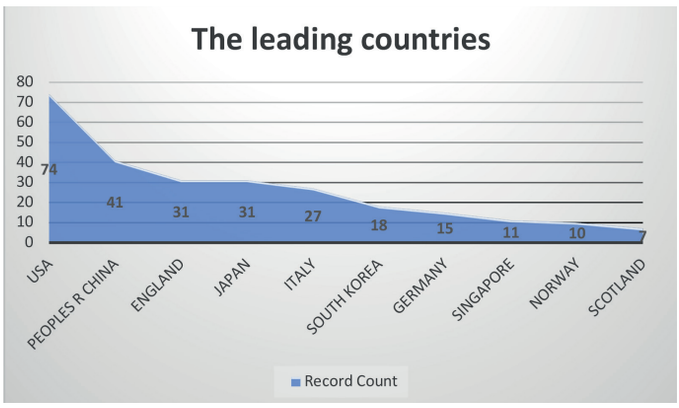


Figure 4 - The leading countries on the AI&colon literature
*Showing 10 out of 41 entries

A total of 41 countries contributed to the AI&colon literature. The USA, the Peoples' Republic of China, and England were the leading countries in the AI&colon literature (Figure 4). Also, England had the highest number of citations (total of 974 citations, 31.42 per document) and the USA publications had the highest H index (Table 2).

Table 2 The number of citations and H indexes according to countries

Ranking	Country	Total citations	Mean of citations per document	H index
1	The USA*	689	9.31	14
2	The Peoples Republic of China	278	6.78	8
3	England	974	31.42	10
4	Japan	846	27.29	11
5	Italy	429	15.89	12

*USA: United State of America

Table 3 The leading institutions

Name of institutions	**n**	**% of 278**
SHOWA UNIVERSITY	18	6.475
MAYO CLINIC	11	3.957
UNIVERSITY OF LONDON	11	3.957
NAGOYA UNIVERSITY	10	3.597
UNIVERSITY OF OSLO	10	3.597
KOREA AEROSPACE UNIVERSITY	9	3.237
UNIVERSITY COLLEGE LONDON	9	3.237
SCUOLA SUPERIORE SANT ANNA	8	2.878
UNIVERSITY OF CALIFORNIA SYSTEM	8	2.878
POLIAMBULATORIO NUOVO REGINA MARGHERITA	7	2.518

Table 4 Journals in which the AI&colon articles were published

The publishing journal	n	% of 278
GASTROINTESTINAL ENDOSCOPY	41	14.748
ENDOSCOPY	15	5.396
AMERICAN JOURNAL OF GASTROENTEROLOGY	14	5.036
GASTROENTEROLOGY	13	4.676
GUT	9	3.237
ENDOSCOPY INTERNATIONAL OPEN	7	2.518
LANCET GASTROENTEROLOGY HEPATOLOGY	7	2.518
JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY	6	2.158
PROCEEDINGS OF SPIE	6	2.158
SURGICAL ENDOSCOPY AND OTHER INTERVENTIONAL TECHNIQUES	6	2.158
DIGESTIVE AND LIVER DISEASE	5	1.799
WORLD JOURNAL OF GASTROENTEROLOGY	5	1.799
CANCERS	3	1.079
DIAGNOSTICS	3	1.079
DIGESTIVE ENDOSCOPY	3	1.079
IEEE ROBOTICS AND AUTOMATION LETTERS	3	1.079
2003 IEEE INTERNATIONAL CONFERENCE ON ROBOTICS AND AUTOMATION VOLS 1 3 PROCEEDINGS	2	0.719
ADVANCED MATERIALS RESEARCH	2	0.719
ANNALS OF INTERNAL MEDICINE	2	0.719
ANNALS OF TRANSLATIONAL MEDICINE	2	0.719
APPLIED SCIENCES BASEL	2	0.719
CLINICAL ENDOSCOPY	2	0.719
COLOPROCTOLOGY	2	0.719
COMPUTERS IN BIOLOGY AND MEDICINE	2	0.719
IEEE INTERNATIONAL CONFERENCE ON ROBOTICS AND AUTOMATION	2	0.719

Showing 25 out of 149 entries

With regard to institutions, the Showa University from Japan (n=18), The Mayo Clinic from the USA (n=11), and the University of London (n=11) published the largest number of documents (Table 3).

Showing 10 out of 452 entries; 35 record(s) (12.590%) do not contain data in the field being analyzed.

The vast majority of the articles (n=41) were published in the Gastrointestinal Endoscopy journal (Table 4). The summary of the journals were given in Table 4.

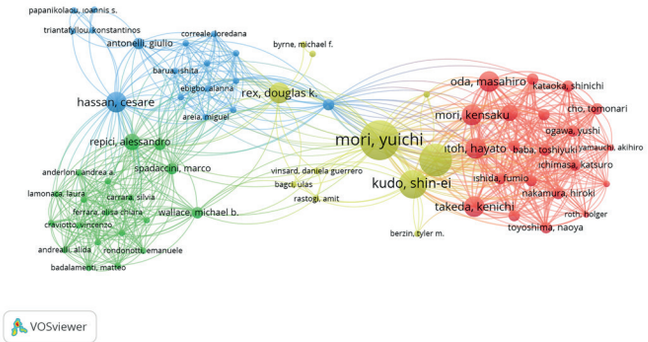
Mapping

Figures 5-9 define the mapping of co-authorship analyzis between authors (Figure 5), keyword analysis (Figure 6), citation analyzis among countries (Figure 7), co-citation analysis among authors (Figure 8), and bibliographic coupling among countries (Figure 9).

Discussion

Recent years have seen an upsurge in the prevalence of colorectal disorders across the world, particularly inflammatory bowel disease and colorectal cancer [15]. One of the most prevalent cancers in the world is colon cancer, which often begins as localized changes in the colon epithelial tissue that progress to a malignant polyp as a result of genetic abnormalities that accumulate over the course of cancer development [15,16]. As an outcome, several studies on colorectal illnesses have been conducted in the fields of pathophysiology, epidemiology, genetics, and immunology [17]. The abundance of information may overwhelm researchers, making it challenging to identify areas of interest for further study. Therefore, there is a pressing need to investigate strategies for facilitating researchers' efficient access to relevant papers in their areas of study [15]. However, no research on colorectal diseases has examined the relationship between AI and colonic diseases. To do this, we used bibliometrics to examine the developments over the preceding 30 years in the field of colonoscopy imaging and colonic disorders to determine the areas of interest and potential future avenues for AI.

The bibliometric analysis has been used by several medical disciplines to determine the most significant papers in their area [18-30]. In the past few years, a wide range of bibliometric analysis techniques have begun to appear in the medical literature, and techniques like mapping and graphing can enhance analysis research on this topic. These studies can be conducted using a variety of techniques, including content analysis, comparisons of scientific productivity across years, nations, and citation counts. Databases that offer quick and thorough data analysis, such as Pubmed, EBSCO, Scopus, Pro-Quest, and Web of Science, are often used for the bibliometric study.



VOSviewer

Figure 5 - Co authorship analysis between authors
*Author with 1 article

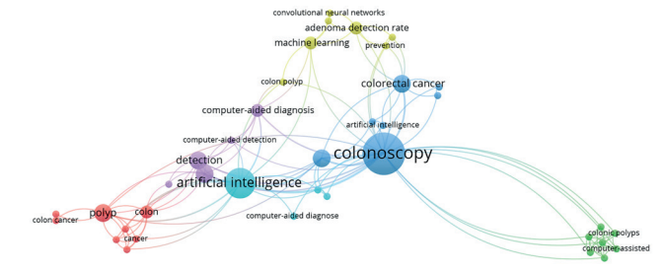


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Figure 6 - Keyword analysis
*41 keywords total with 1 occurrence

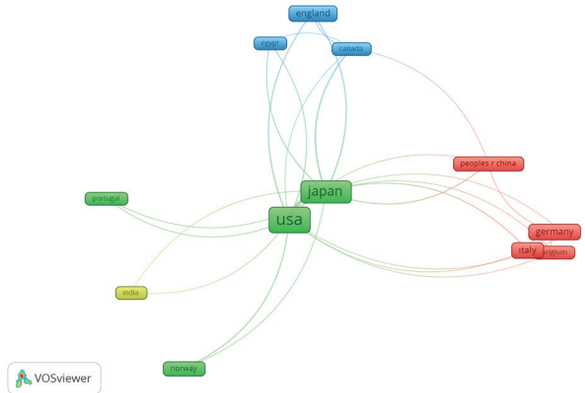

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Figure 7 - Citation analysis among countries

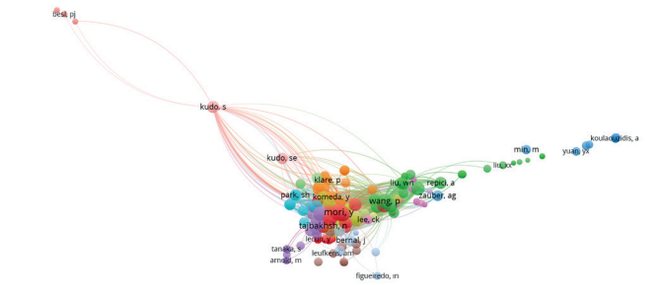

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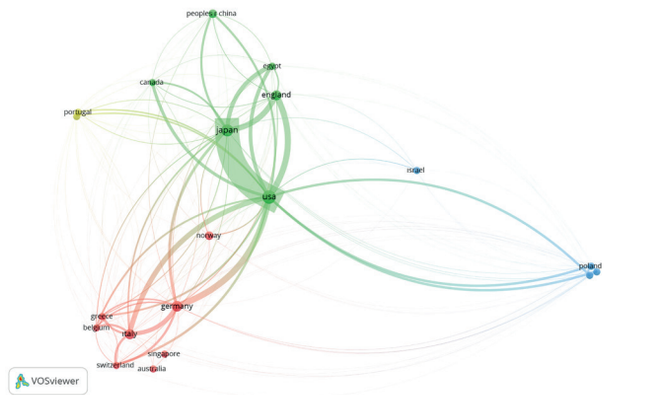
Figure 8 - Co-citation analysis among authors



VOSviewer

Figure 9 - Bibliographic coupling among countries

But other sources, including any database, theses, journals, conferences, etc., can also be examined using this technique [18-30]. In our study, we preferred the WOS database as this database indexes highly quality studies. And our findings revealed that scientific output was rising, especially in the last 5 years. Leading nations, journals, and funding agencies were found to be the main contributors to the discipline. The top contributing nations were the United States, the People's Republic of China, England, Japan, Italy, South Korea, Germany, Singapore, Norway, and Scotland.

The bibliometric method refers to the quantification of general trends and the identification of links or relationships that may be concealed in vast amounts of data [22-25]. In this current study, the mapping results stated the co-authorship analysis between authors (Figure 5), citation analysis among countries (Figure 7), co-citation analysis among authors (Figure 8), and bibliographic coupling among countries (Figure 9).

The thickness of the links and the size of the node reflect the degree of international collaboration; the larger the node, the more important the country or area, and the thicker the line, the tighter the cooperation ties between the countries/regions/authors (Figure 5-9). In our study, it was determined that there was an intense bibliographic coupling between USA and Japan (Figure 9).

An article's impact and legitimacy are shown by how many times it has been cited, and the number of citations also reflects the author's academic success [31]. Also, H-index is an author-specific statistic that measures a scholar's publications in terms of productivity and citations. It is also known as the Hirsch index or Hirsch number [32]. Jorge Hirsch made the initial suggestion to measure the relative academic contribution of different theoretical physicists [33]. England had the highest number of citations (total of 974 citations, 31.42 per document) and the USA publications had the highest H index.

Analysis of keywords offered a special hint about this field's potential future directions (Figure 6). Over this time, there was a clear dynamic change in the top terms with burst citations, showing a transfer of research resources and interests.

Misawa et al. studied AI using 546 short videos from 73 full-length videos, which were divided into two groups of training data (105 polyp-positive videos and 306 polyp-negative videos) and test data (50 polyp-positive videos and 85 polyp-negative videos). The researchers showed the possibility of the automate detection of colonic polyps in real time, and the sensitivity and specificity were 90.0% and 63.3%, respectively [34].

Urban et al also used a AI to identify colonic polyps. They used 8641 hand-labeled images and 20 colonoscopy videos in various combinations as training and test data. The AI model detected polyps in real time with an AUROC of 0.991 and an accuracy of 96.4% [35].

This study has certain limitations. The data were obtained from a single database (WOS), thus there may have been some missing articles and the number of citations was inflated, although the authors think this is unlikely. The content analyses weren't put into practice enough. This manuscript's biggest flaw is the likelihood of many sorts of prejudice, which might bias the findings. Disproportionate citation can be caused by institutional prejudice, linguistic bias, self-citation, or bias against powerful people. Additionally, older journals might get more citations. The restriction to just first and senior writers, as well as the first author's institution, is another one. Several of the first writers could have contributed to additional studies.

Conclusion

Our research may offer a historical perspective on the development of AI in colorectal diseases. The documents were limited to some developing countries.

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Computer-aided evaluation of targets and biological activity spectra for new piperidine derivatives

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Abstract

Background: The unique ability of piperidine to combine with various molecular fragments makes it possible to use its chemical structure to create new drugs with potential pharmacological effects. However, preliminary studies are required to predict the activity of new compounds in order to determine the direction of further preclinical studies.

Aim: This study aims at determining the potential targets and spectrum of biological activity of new piperidine derivatives by the in silico method.

Material and methods: Prediction of the effects on targets and the spectrum of biological activity of three new piperidine derivatives synthesized at the Bekturov Institute of Chemical Sciences JSC was analyzed in this study. The chemical structures of these compounds were studied in silico using the web tool SwissTargetPrediction to identify the most likely protein targets. PASS (Prediction of Activity Spectra for Substances) online tool was used to predict the possible pharmacological activity of the studied compounds.

Results: New modified piperidine derivatives are able to affect different enzymes, receptors, transport systems, voltage-gated ion channels, thereby providing a wide range of biological activities applicable in various fields of medicine. These substances represent interest in the treatment of cancer, central nervous system diseases, as local anesthetic, antiarrhythmic and antimicrobial agents, and are promising for pharmacological activity demonstration in preclinical studies.

Conclusion: A comprehensive analysis of the above results leads to the conclusion that the compounds under study should be considered as potential substances for the design of new highly effective medicinal agents with a wide range of practical applications.

Key words: piperidine derivatives, computer prediction, biological activity spectra, SwissTargetPrediction, PASS, in silico

Introduction

The search and study of low-toxic compounds that can serve as a basis for the development of new drugs is a very relevant area of modern research. New compounds of piperidine derivatives represent a particular interest in this field. Piperidine derivatives have been intensively studied for a long time as promising substances for the development of new drugs. The chemical structure of piperidine has a unique ability to combine with other molecular fragments. This fact allows its extensive use as an effective base and heterocyclic system for the development of new compounds and derivatives thereof [1]. Due to this reason, piperidine fragments are now widely used for the development of new drugs. Over the last decade, several thousand different piperidine derivatives have been reported in preclinical and clinical studies [2]. Numerous studies confirm that many substituted piperidine derivatives can exhibit a broad spectrum of pharmacological activity, including antineoplastic, antimicrobial, antiviral and antifungal, anti-inflammatory and central nervous system activities [3-5]. The chemical structure of piperidine is found

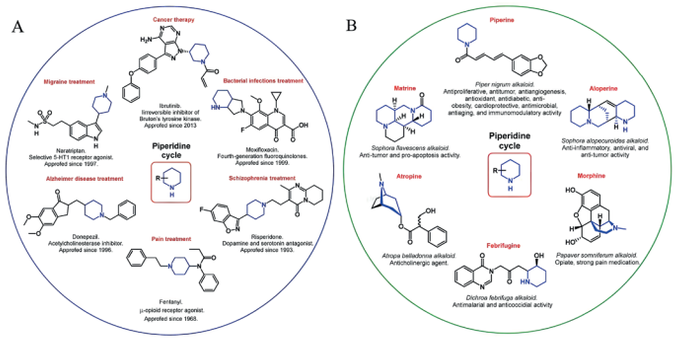

Figure 1 - Piperidine derivatives used in medical practice: A, Synthetic piperidine derivatives. B, natural piperidine derivatives. Reprinted from "Piperidine Derivatives: Recent Advances in Synthesis and Pharmacological Applications" by Frolov N.A. and Vereshchagin A.N., 2023, International journal of molecular sciences, 24(3), 2937

in various groups of drugs (Figures 1a) and many biologically active alkaloids used in medicine (Figures 1b) [6]. The piperidine ring is one of the constituent parts of the chemical structure of the local anesthetics bupivacaine and ropivacaine widely used in clinical practice [7]. Piperidine derivatives with analgesic activity, such as promedol, fentanyl, are widely used in various fields of medicine nowadays. Haloperidol and risperidone are the most commonly used antipsychotics from the group of piperidine derivatives. Tiagabine containing this structural component is actively used as an antiepileptic agent [8].

Research on active substances has long been carried out independently of the purpose and mechanism of action and in most cases has been based on available knowledge and intuitive or empirical approaches. Advances in technology have transformed drug discovery into a targeted, multidisciplinary, hypothesis-driven approach in which exposure to specific targets is of primary importance [9]. Determining the spectrum of biological activity plays an important role in drug development. The spectrum of biological activity depends directly on the chemical structure and reflects not only different pharmacological effects but physiological, biochemical mechanisms of action, including specific toxicity [10].

The development and research of new medicines is a time-consuming and costly multi-stage process [11, 12]. The use of automated and computerized laboratories facilitates research, but excludes completely high drop-out rates for various reasons [13]. Thus, researchers may be faced with a loss of invested resources and time in the preclinical and clinical trial phases. The search for strategies to reduce costs and shorten development times for potential medicines is therefore currently required direction [14].

One of the solutions is the application of computer modelling (in silico) based on artificial intelligence (AI). Using AI computational models to process, manage and integrate large amounts of data from various fields will enable target recognition analysis and identification of new compounds. Thus, the use of chemical structure of compounds for drug design and subsequent pre-screening becomes an important tool for experimental research. Performing virtual screening before starting experiments has great potential. Computer-aided prediction will speed up the process, increase efficiency, optimize costs and reduce drop-out in the early stages of research. The strategy of computer prediction of atomic and molecular properties of compounds is now widely used, making it possible to predict physical and chemical characteristics, pharmacokinetic properties and search for correlations between them and toxicological activity [14-17]. Computer modelling can be used as an initial step in selecting the safest substances from the vast array of chemical compounds. The online resource PASS (Prediction of Activity Spectra for Substances) is one of the platforms used to identify BAS (Biological Activity Spectrum) [10]. The SwissDrugDesign project includes a number of web-based tools for drug design and analysis [18].

The prediction results validity of this software is reflected in the results of a number of preclinical studies. Thus, the high efficiency of pharmacological screening through the use of computer predictive spectrum prediction was established in the study of A. Dairov et al. on the anti-inflammatory and analgesic effects of the new acanthosterone steroid compound. Earlier *in vivo* experimental studies of the arglabin derivative on its anticancer effect also prove the validity of the computer prediction data [19, 20]. The spectrum of biological activity of chicory herb extract determined by the *in silico* method according to G. Adamov correlates with the literature data on experimental studies of anti-inflammatory properties, antioxidant and immunomodulatory effects [21]. According to a study by M. Basanagouda et al. of coumarin-4-acetic acid derivatives showed a high likelihood of anti-inflammatory and analgesic effects in prediction, confirmed by experimental work on appropriate models [22]. In a study by Jiawen Han et al. the results of SwissADME (absorption, distribution, metabolism and excretion) and SwissTarget showed the potential activity of Curculigoside A with target identification, which provided an explanation for the mechanism of therapeutic effects in osteoporosis and rheumatoid arthritis [23].

In present investigation, we were interested in deeper *in silico* analysis of the chemical structure of three new piperidine derivatives, not previously studied. Therefore, the chemical formulas of these compounds were tested using special web tools of Swiss and PASS computer programs. Since piperidine derivatives have been reported to exhibit various pharmacological effects, we needed to identify a number of potential target classes and assess the probability of the presence of certain types of activity in this series of compounds. In addition, the obtained prediction results will play a key role in the further stage of selecting experimental models of the detected effects at the level of preclinical studies. That's why; the aim of the study was to determine potential targets and the spectrum of biological activity of new piperidine derivatives by *in silico* method.

Material and methods

Three new derivatives of azaheterocycles LAS-250, LAS-251 and LAS-252 (LAS is a laboratory code for local anesthetic substance) were identified as objects of study. This group of compounds was synthesized at the A.B. Bekturov Institute of Chemical Sciences JSC. The studied substances belong to the derivatives of hexamerous saturated heterocycles. One compound is a substituted piperidine (one nitrogen atom in heterocycle), two others have two nitrogen atoms (derivatives of 1,4-piperazine). In addition, the molecules have aromatic substituents (two phenyl substituents or α-naphthalene ring). The identification of potential targets and types of activity was determined by analyzing the chemical structure using the *in silico* method.

The identification of potential targets was performed on the SwissDrugDesign software platform (developed by SIB - Swiss Institute of Bioinformatics), using the online web tool SwissTargetPrediction in version 2023 (http://www.swisstargetprediction.ch/). After entering the chemical structure of the substance under study, this resource predicts the most likely targets of the protein structure with a selection of the expected

species (*Homo sapiens, Mus musculus, Rattus norvegicus*). The prediction principle is based on searching for ligand and descriptor similarities with similar molecules entered into the program. The database consists of experimentally active 376342 compounds and 3068 macromolecular targets. The predictive ability of this computer model has been validated on an external test suite of experimentally active compounds [24, 25].

Prediction of the biological activity spectrum of the studied compounds was carried out using the online PASS software on the Way2Drug platform in version 2023 (http://way2drug.com/). This web- resource was designed by a multidisciplinary team of researchers in drug search and development at the Research and Development Institute of Biomedical Chemistry named after V.N. Orekhovich (Russia, Moscow). The chemical structures of the compounds under study were entered into the online program, followed by processing of the entered information using a prediction algorithm based on a Bayesian approach. The software uses the data from the training sample and ensures high prediction accuracy. Evaluation of the biological activity spectrum is based on the analysis of the chemical structure of the substance with the training sample and then the results of the analysis are displayed as an ordered list of expected activities. The probabilities of presence (P_a) and absence (P_i) for each type of intended effect are used to judge its potential presence. The results of the prediction are arranged by default in descending order of the P_a-P_i difference. The spectrum generated by the software includes those types of activity for which the condition $P_a>P_i$ is met. It should be noted that a prediction of $0.3<P_a<0.7$ will indicate the highest probability, and $P_a>0.7$ will indicate a sufficiently high chance of detecting the activity in the following stages of the survey [26, 27].

Results

Potential targets prediction

A SwissTargetPrediction web tool analysis of the prediction of virtual structures of the compounds under study highlighted the main classes of putative targets in preclinical studies in laboratory rats (*Rattus norvegicus*). As can be seen in the results presented (Figures 2, 3, 4), all the compounds studied can affect a wide range of targets, including enzymes (proteases and kinases), families A and C G-protein-coupled receptors, voltage-gated ion channel and electrochemical transporter.

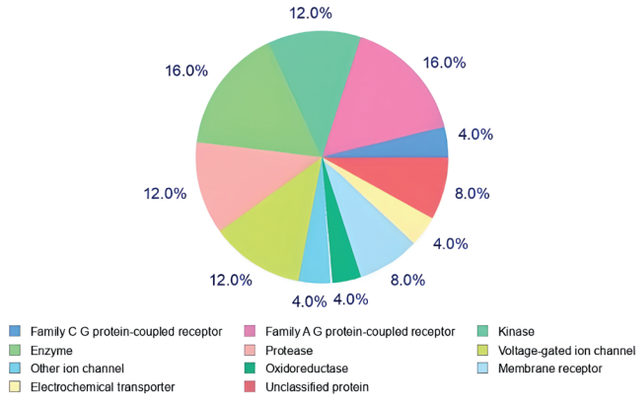

Figure 2 - The target classes of LAS-250 in preclinical research on laboratory rats identified by SwissTargetPrediction web tool

It should be noted that a significant part of the probable target classes of all compounds are enzymes. The highest activity on kinases was detected in LAS-250 and is 12%. LAS-251 has a smaller effect on kinases (6%). LAS-252 has the lowest efficiency (4%). However, LAS-252 may have a more pronounced effect on proteases (16%) in comparison with other compounds. The new piperidine derivatives LAS-250 and LAS-251 have an equal probability of acting on the oxidoreductase. Based on the evidence found, a number of targets should be identified for each compound individually. For example, the enzymes phosphatase and hydrolase were identified among the predicted targets for LAS-252. The predicted target enzyme typical only for LAS-251 was lyase.

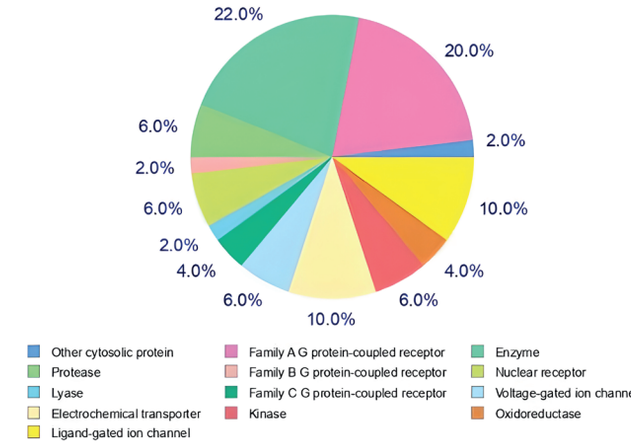

Figure 3 - The target classes of LAS-251 in preclinical research on laboratory rats identified by SwissTargetPrediction web tool

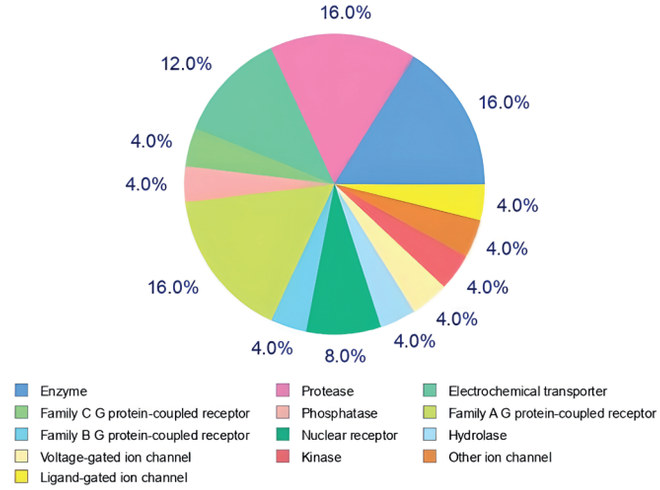

Figure 4 - The target classes of LAS-252 in preclinical research on laboratory rats identified by SwissTargetPrediction web tool

During the analysis of the possible effect on the receptors we found similar classes. The predicted effect on the receptors is not significantly different. The compounds studied have little difference in effect on family A G-protein-coupled receptor with a slight 4% advantage in LAS-251. The effect on the family C G-protein-coupled receptor is absolutely equal for all piperidine derivatives is 4%. LAS-251 and LAS-252 are also slightly possible to influence the family B G-protein-coupled receptor. In addition, LAS-250 differs from other compounds by the presence of some membrane receptors as a target. While LAS-251 and LAS-252 classes of nuclear receptors have been identified.

Evaluation of target prediction revealed 2 classes of ion channels for a series of compounds. LAS-250 has a higher affinity to the voltage-gated ion channel, which is 2 and 3 times higher than LAS-251 and LAS-252, respectively. According to the results received on the effect on ligand-gated ion channel, piperidine derivatives differ slightly from each other, and the difference is 6%.

Compounds LAS-251 and LAS-252 have almost equal effect on electrochemical transporter in contrast to the MAV-250 showing the lowest level of prediction.

Pharmacological activities prediction

Since a biological action spectrum is predicted for the compounds studied, those effects and mechanisms were selected from the data set whose probability of occurrence met the condition $P_a \geq 0.5$ (Figures 5, 6, 7). Probabilities "to be active" (P_a) did not exceed 0.8 (80%). The highest probability of having effects was found for LAS-251 ($0.799 < P_a < 0.554$). The predicted activity probability for LAS-250 was $0.804 < P_a < 0.480$. The lowest activity values were observed for LAS-252, where the maximum value of $P_a = 0.642$ and the minimum was 0.498.

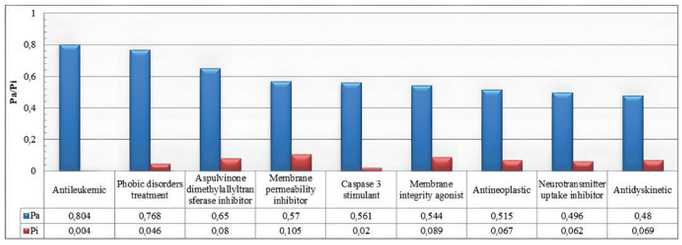

Figure 5 - Biological activity spectra of LAS-250 with the probabilities "to be active" (Pa) and "to be inactive" (Pi) evaluated by PASS

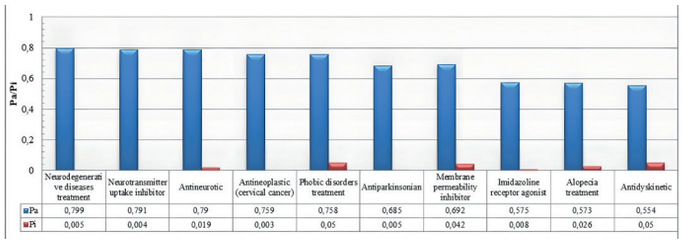

Figure 6 - Biological activity spectra of LAS-251 with the probabilities "to be active" (Pa) and "to be inactive" (Pi) evaluated by PASS

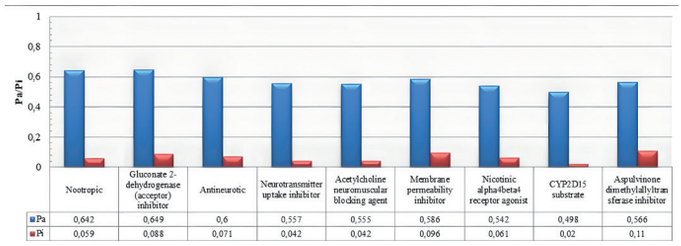

Figure 7 - Biological activity spectra of LAS-252 with the probabilities "to be active" (Pa) and "to be inactive" (Pi) evaluated by PASS

All the chemical structures of the studied compounds showed activity in the inhibition of membrane permeability and neurotransmitter uptake to varying degrees. By the identified mechanisms of action, LAS-251 outperformed the remaining compounds in terms of predicted activity ($P_a \sim 0.7$). Compounds LAS-250 and LAS-252 showed little difference in these values ($0.496 < P_a < 0.586$). The inhibition of membrane permeability by piperidine derivative LAS-250 is probably responsible for the membrane stabilizing effect ($P_a = 0.544$) revealed by the results prediction.

Pharmacological effects affecting the central nervous system, where the highest probability of prognosis was observed, made up a large proportion. LAS-251 has sufficiently high probability of antineurotic ($P_a = 0.79$) and antiparkinsonian ($P_a = 0.685$) activities, can be used for the treatment of neurodegenerative diseases ($P_a = 0.799$). Also, this piperidine derivative probably stimulates imidazoline receptors ($P_a = 0.575$) located in the brain and in the periphery. The predictive data showed that LAS-250 and LAS-251 had the highest and almost equal Pa values for use in the treatment of phobic disorders ($P_a \sim 0.76$) and a lower probability of antidyskinetic effect ($0.48 < P_a < 0.554$). The piperidine derivative LAS-252 also has a potential antineurotic effect ($P_a = 0.6$) and differs from other compounds in the presence of nootropic action ($P_a = 0.642$).

Probability analysis revealed the presence of antitumor activity for LAS-250 and LAS-251. It should be noted that the chemical structure of LAS-250 suggests a high chance of detecting an antileukemic effect ($P_a = 80\%$) in subsequent studies, in contrast to LAS-251, where significant efficacy is possible in the treatment of cervical cancer. The antineoplastic activity of LAS-250 may be related to the process of apoptosis activation due to the detected stimulatory effect on caspase-3 ($P_a = 0.561$).

The detected mechanism of aspulvinone dimethylallyltransferase inhibition is common to LAS-250 and LAS-252, with 65% and 57% probability of their presence, respectively.

A number of significant pharmacological effects should be noted, the prediction of which is unique to each compound. LAS-252 can be used as a gluconate 2-dehydrogenase inhibitor ($P_a = 0.649$), acetylcholine neuromuscular blocking agent ($P_a = 0.555$), nicotinic alpha4beta4 receptor agonist ($P_a = 0.542$), CYP2D15 substrate ($P_a = 0.498$). Potential application of LAS-251 is of interest in the treatment of allopecia ($P_a = 0.573$).

Discussion

The development and release of new medicines in today's world is time-consuming and capital-intensive because of the various risks involved from the discovery to the later stages. The experience of the global pharmaceutical industry shows a low success rate of drug design in all therapeutic areas [28]. A recent study of 21143 compounds found an overall success rate of only 6.2% [29]. The key to solving these problems is to develop mechanisms to maximize the use of information derived from basic science. Advances in basic biological and chemical research, as well as in bioinformatics and artificial intelligence, represent great potential for the production of new drugs. Artificial intelligence has transformed drug design and development over the past decade [28-30]. Nowadays, it is a fair assumption to say that heterocyclic compounds play a significant role in the pharmaceutical industry. Among them, one of the most important and widely used for drug design is the piperidine cycle. The piperidine cycle is present in more than twenty pharmacological groups as well as alkaloids. A review of scientific studies in the last five years found more than 7000 publications related to piperidine [6].

This article describes the results of a study, based solely on the structural formula of the substance, on the computer prediction of targets and variations in biological activities of previously unexplored new piperidine derivatives, using computer software. The use of computer prediction at the initial stage will enable researchers to identify the most promising areas of preclinical research and select experimental *in vivo/in vitro* models in accordance with the detected targets and types of activity. The results obtained predicting potential targets and the spectrum of biological activity have in most cases been confirmed in the results of many scientific *in vivo* or *in vitro* studies of compounds from the piperidine derivatives group.

The results of our study revealed many classes of targets, including various enzymes, receptors, channels and transport

systems. The prognostic data of the compounds presented in this article demonstrate the presence of significant effects on enzyme which correlates with the world research data. As well as in our study piperidine derivatives are capable of affecting various enzymes including kinases [31-34], viral proteases [35-37], hydrolases [38-40] and others [41-45], thereby realizing a wide range of activities. Based on the facts presented, the data obtained in the study may indicate the possible influence of compounds on the processes of inflammation, carcinogenesis, enzymatic activity of viruses, neuroprotection and other functional changes in the cardiovascular system and metabolism [31-45].

A number of publications have reported the discovery of piperidine transporters [46-49], voltage-gated potassium, calcium, sodium ion channels [50-52] and membrane [53-55] and G-protein-coupled receptors [56, 57] as targets, which is also consistent with the SwissTargetPrediction data in this investigation. Accordingly, the probable effect on target classes in our case may cause the presence of both peripheral antiarrhythmic and local anaesthetic effects, and central effects such as anticonvulsant and antidepressant [58].

SwissTargetPrediction results are consistent with many of the pharmacological effects and mechanisms identified by the PASS web resource. Numerous studies confirm the antitumor activity of piperidine derivatives through their action on various enzymes, receptors of paramount importance [59]. The above-mentioned target enzymes (kinases, protein kinase, proteases, polymerase, reductase, aromatase) are the key points of application of drugs incorporating this chemical fragment as an antitumor agent [59]. Also supporting the probable presence of antineoplastic action according to PASS results of LAS-250 compound is undoubtedly the identified effect on caspase-3, which is known to be the most abundant and important member of the family of cysteine proteases involved in apoptosis [60]. The targets of voltage-gated ion channels identified in the analysis as a predictor of pharmacological activity confirms the probability of an inhibitory effect on membrane permeability and consequently the provision of membrane stabilizing action. Effects on ion channels have been shown to provide local anaesthetic, antiarrhythmic, anticonvulsant, antidepressant, neuroprotector and other effects [61-63]. The compounds studied have a high probability of developing pharmacological effects of central nervous system. The probable ability to inhibit neurotransmitter uptake by piperidine derivatives is promising for the treatment of some central nervous system diseases [64-66]. PASS analysis of the compounds predicts anti-parkinsonian and anti-dyskinetic activities associated with neurodegenerative processes, which is also found in the publications of experimental and in silico studies of other piperidine derivatives [67-69]. The likelihood of antimicrobial, antiviral and anti-inflammatory effects of the studied substances has been associated with inhibition of aspulvinone dimethylallyltransferase [70, 71]. The results also revealed the ability of LAS-252 to affect the biotransformation process by using CYP2D15, which is a human orthologue (CYP2D6), leading to amino acid changes in canine liver microsomes [72]. According to the results obtained, this compound can influence neuromuscular conduction regulated by cholinergic activity through a direct stimulatory effect on nicotinic alpha4beta4 receptors responsible for neurotransmission in parts of the central and peripheral nervous system. This process promotes skeletal muscle tone and various cognitive effects in the brain [73]. LAS-251 has potential antihypertensive activity due to its stimulatory effect on imidazoline receptors [74]. Possible mechanisms of piperidine derivatives to be effective in the treatment of allopecia remain unclear and require further investigation and research.

Thus, all of the compounds in question can most likely be classified as having different types of biological activity.

Conclusion

A new line of piperidine derivatives showed promising results. Comprehensive analysis of the results presented in the article leads to the conclusion that the investigated new piperidine derivatives LAS-250, LAS-251, LAS-252 should be considered as potential substances for the development of novel highly effective drugs with a wide spectrum of practical application. The obtained prediction data are confirmed in previous studies on different series of substances from the piperidine group. The obtained by Swiss prognostic data demonstrate the most significant varying degrees effect of compounds among other targets on enzymes such as kinases, proteases, oxidoreductases, as well as a more specific effect on phosphotase, hydrolase and lyase. Both voltage-gated and ligand gated ion channels, as well as electrochemical transporters, were found as targets for the studied substances. The results of the PASS analysis showed a high probability of various effects realized by the identified targets. All the studied chemical structures of compounds showed activity in inhibiting the permeability of membranes, causing a membrane-stabilizing effect. The detected effect of neurotransmitter uptake is important in a CNS diseases development. The possible prospect of using the studied piperidine derivatives in the treatment of neurotic and phobic disorders, neurodegenerative diseases and Parkinson's disease is of particular interest. Probability analysis revealed the presence of antitumor activity for LAS-250 (antileukemic) and LAS-251 (cervical cancer). LAS-252 can be used as gluconate 2-dehydrogenase inhibitor, acetylcholine neuromuscular blocking agent, nicotinic alpha4beta4 receptor agonist, CYP2D15 substrate. Virtual screening to determine the main targets and pharmacological activity confirmed the activity of these compounds to continue further research at the level of preclinical studies. The data of this investigation allow selecting the appropriate areas of experimental work to confirm the potential effects by next *in vivo* or *in vitro* methods.

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Clinical heterogeneity in Fabry disease: A clinical case

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Abstract

Fabry disease is an orphan lysosomal storage disease characterized by progressive organ damage. Considering that the disease is rare, the low awareness of doctors about this pathology leads to late diagnosis of the disease and untimely pathogenetic therapy. Clinical case of late (relative to clinical manifestation) diagnosis of the “classical” phenotype of Fabry Disease in a male patient with cardiac and renal damage and typical early presentations such as neuropathic pain, angiokeratomas, hypohidrosis.

Key words: Fabry disease, α-galactosidase, globotriaosylceramide, agalsidase

Introduction

Over the past 20 years, there has been a scientific advance in the study of orphan (rare) diseases. Genetic diagnosis and enzyme replacement therapy have reached a new level. There are around 8,000 rare diseases worldwide. The most common are sphingolipid lysosomal storage diseases (LSDs), one of which is Fabry disease (FD). Fabry disease is inherited recessively as an X-linked disorder, so the clinical signs are more frequent and earlier in males than in females [1]. Impaired sphingolipid metabolism is associated with a GLA (α-Galactosidase A) gene mutation and disruption of the α-galactosidase enzyme synthesis, which is required for their cleavage. As a result of insufficient α-Gal A production, metabolic products accumulate in organs and tissues in the form of globotriaosylceramide, which accumulates in the vascular endothelium, smooth muscle cells, neural cells, ganglia, renal podocytes, mesangial and tubular cells, cardiac muscle and cells of the cardiac conduction system.

The spectrum of clinical manifestations is highly heterogeneous, even in members of the same family [2]. The prevalence of the clinical phenotype depends on the type of GLA gene mutation, but nevertheless, the main and most characteristic manifestations are damage to vital systems: cardiovascular, urinary and nervous systems, which determine the severity and prognosis of the disease. Manifestation can start with any leading syndrome, evolving into classical or atypical "monosyndromic" forms [3,4].

Fabry disease can be divided into three clinical phenotypes related to α-Gal A activity levels. The first is the "classical" FD (α-Gal A<3% or absent enzymatic activity, onset in childhood or puberty, multisystem involvement including acroparesthesias, angiokeratomas, sweating abnormalities, gastrointestinal symptoms, cornea verticillata, hearing disorders. Long–term disease manifestations include progressive renal failure and cardiovascular events (third decade of life). The second is "nonclassical" FD, also referred to as late-onset or atypical FD (α-Gal A activity 3-30%, disease manifestations may be limited to a single organ: brain, heart or kidney); and the third is asymptomatic female carrier (in women with a mutation in only one X chromosome, the other continues to secrete α-Gal A, which can present clinically as a less severe or asymptomatic disease) [5,6].

The aim of our publication is to describe a case of delayed diagnosis of a classical Fabry disease with a predominance of cardiovascular and urinary system involvement in order to highlight the problem of early detection of an orphan disease, Fabry disease, among doctors of different specialties.

Case presentation

Patient S, born in 1994 (age 27) in May 2021 was diagnosed with chronic nephrotic syndrome. Stage G4A3 CKD (Chronic Kidney Disease), GFR (Glomerular Filtration Rate) -25 mL/min/1.73 m2.

Presenting complaints: muscle weakness, performance impairment a month earlier after hypothermia which first changed the urine colour to red, increased blood pressure.

At physical examination there was a haemorrhagic rash on the lower half of the body, around the navel and in the groin area (Figure 1).

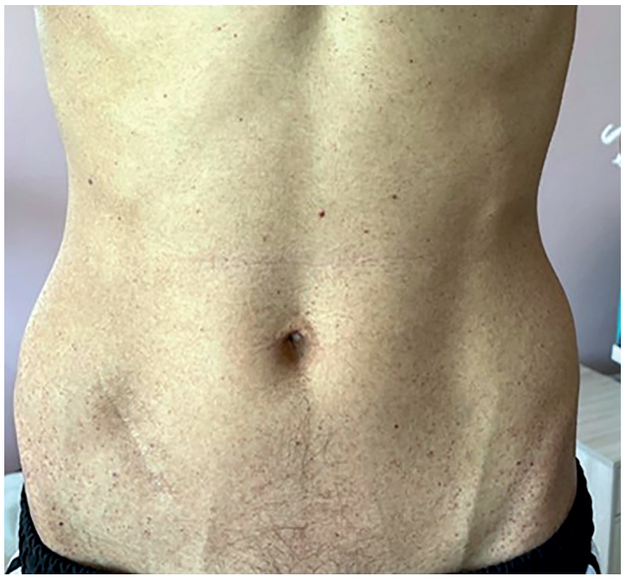

Figure 1 - Anterior abdominal wall angiokeratomas in the periumbilical area in patient S.

During the current visit the history of the present condition was clarified. Since the age of 6 years (2000) single angiokeratomas appeared in the umbilical region (angiokeratoma corporis diffusum); by the age of 16 years (2010) the rash had spread to the lumbosacral, buttocks and groin area. Associated with angiokeratomas at about the same period, the patient experienced burning pains in hands and feet occasionally with physical exertion and unexplained annual episodes of fever rising to 38-39° C, intensity of pains became less at the age of 14-15 years. A careful questioning of the patient revealed that he has a poor tolerance to heat and hardly ever sweats.

At the age of 27 (2021) he was diagnosed with nephritic syndrome, stage G4A3 CKD (GFR 25 mL/min/1.73 m2) and referred to the "Research Institute of Cardiology and Internal Medicine" for diagnosis verification. Fabry disease was suspected and tests were taken. Enzyme assay test results showed a decrease in α-Gal activity <0.8 μmol/L/h (reference, ≥ 15.0 μmol/L/h) and an increase in lyso-GL-3 levels up to 62 ng/mL (reference, ≤1.8 ng/mL).

This patient was tested positive for the hemizygous GLA mutation (NM_000169.2:c.679C>T (p.Arg227*) in a molecular genetic analysis.

From the family history, it is known that the patient's brother has a similar clinical presentation and his sister has minimal clinical symptoms. The defective gene (the GLA gene) has been inherited from the mother.

On further examination at the Research Institute of Cardiology and Internal Medicine the patient was diagnosed with a cardiac defect. Electrocardiography (ECG): sinus rhythm with a heart rate of 90 bpm; signs of left ventricular (LV) hypertrophy (Figure 2).

Electrocardiographic (ECG) changes characteristic of Fabry Disease were found: LVH, LV posterior wall thickness at end-diastole (LVPWTd) was 13mm, interventricular septal

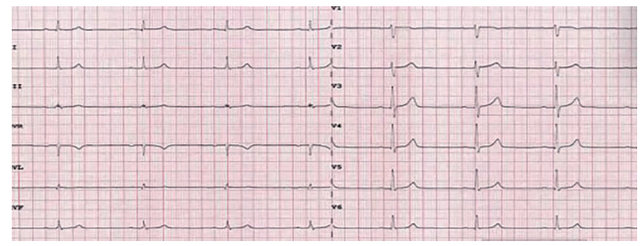

Figure 2 - ECG findings of patient S.: sinus rhythm, 90 bpm; leads V2-V6, signs of left ventricular myocardial hypertrophy. PR Interval: 0.13 sec, QRS Duration: 0.06 sec, QT Interval (QTc 0.36 sec)

thickness at end-diastole (IVSTd) was 13mm, MMI 127g/m2 (Figure 3). No reduction in global left ventricular contractility EF (Ejection Fraction), 60%; biplane Simpson's method), no regional wall motion abnormalities and no signs of ventricular diastolic dysfunction; large vessels, valve system and pericardium - no abnormalities.

Doppler echocardiography: mild (grade 1) mitral regurgitation, grade I tricuspid regurgitation. Pulmonary artery pressure was unchanged (17 mmHg). The examination revealed increased myocardial echogenicity.

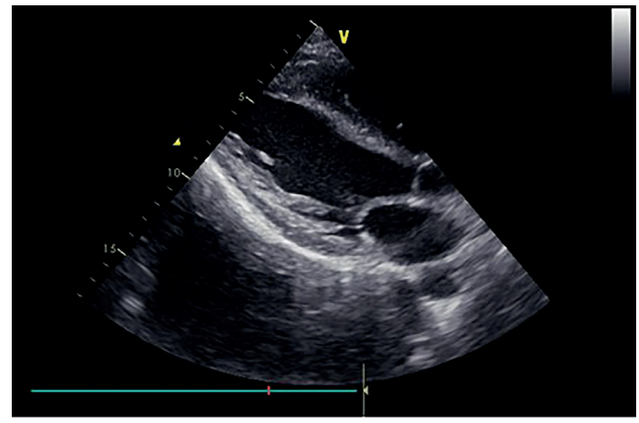

Figure 3 - TTE findings in patient S: left ventricular free wall hypertrophy

Holter ECG monitoring detected a small number of atrial premature beats, while 24-hour ambulatory blood pressure monitoring showed no evidence of hypertension.

Particular attention should be focused on renal impairment; this patient has stage G4A3 CKD (GFR 18 mL/min/1.73 m2). It should be noted that impaired renal function, up to dialysis-dependent chronic kidney disease (CKD C5d), is observed in the majority of patients with Fabry disease, making it highly suspicious in patients with CKD, especially those younger than 40 years and with morphologically unverified renal pathology [7]. In our case, the diagnosis was verified in the pre-dialysis period, which is certainly a favourable factor in our patient's treatment and prognosis.

The patient was diagnosed with Fabry disease at the age of 27 years following follow-up examination. He developed polyorganic lesions: skin lesions (angiokeratomas), peripheral nervous system lesions (peripheral neuropathy), exocrine gland dysfunction (hypohidrosis), kidney failure (CKD G4A3), cardiac damage (left ventricular hypertrophy). Inpatient enzyme replacement therapy with agalsidase alfa at a dose of 0.2 mg/kg body weight was carried out.

Discussion

Factors such as the non-specificity of most of the symptoms of Fabry disease, the difficulty of diagnosis and differential diagnosis, and the low awareness of the characteristic symptoms, mean that the disease is rarely detected de novo in the early stages. Screening is often most effective in high-risk groups, in particular in patients already receiving renal replacement therapy due to irreversible loss of renal function, early stroke survivors and patients with severe left ventricular hypertrophy. According to the Ricardo Reisin et al (2017) study, based on analysis of data from the international long-term observational registry (Fabry Outcome Survey (FOS)), in Europe and other countries the period from symptom onset to confirmation of diagnosis of FD in adults is 8 to 13 years (median 10.5 years), the period from diagnosis to initiation of enzyme replacement therapy is 0.9 to 1.1 years (median 1.1 year) [8]. Unfortunately, even in the presence of typical symptoms, the diagnosis of Fabry disease is often delayed, as in our clinical case of the **"classical" variant of FD** in a patient with polyorganic involvement (skin, peripheral nervous system, exocrine glands, kidneys and heart) and the initiation **of enzyme replacement therapy 21** years after the clinical manifestations. The onset of the disease presented with the rather characteristic symptoms of Fabry disease (peripheral polyneuropathy, angiokeratomas, hypohidrosis). In this case, the most important symptom causing the patient's discomfort was peripheral neuropathy, most likely considered to be Raynaud's syndrome, rheumatoid arthritis [9]. The decrease in pain intensity in our patient at age 14-15 years may be related to the period of puberty, when pain syndrome may be less pronounced or absent [10], due to progressive degeneration of nerve fibres [11,12]. Further involvement of the vital urinary system (stage G4A3) prompted referral to our hospital, where further examination revealed cardiovascular pathology (left ventricular hypertrophy) and the diagnosis was confirmed. In our case the diagnosis was established in the pre-dialysis period, which is clearly a favourable aspect of the treatment and prognosis of our patient. Immediate enzyme replacement therapy has been administered in order to reduce the progression of the disease [13].

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Giant prostatic enlargement: A presentation of a rare asymptomatic case

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Abstract

Benign prostatic hyperplasia is a histological diagnosis and the most frequent benign tumor in older men, and its incidence strongly correlates with advanced age. Giant prostate enlargement (GPE), also known as giant prostatic hyperplasia, is a term given for severely enlarged prostates that weigh more than 500g. GPE cases reported in literature is less than 30. We describe our experience of removing previously asymptomatic 528g prostate by open transvesical prostatectomy. According to transrectal ultrasound (TRUS) the prostate size is 482 ml and prostate-specific antigen level of 5.1 ng/ml. Histological examination showed nodular prostatic hyperplasia, an adenomatous variant with foci of cystic atrophy, chronic prostatitis. The patient's post-operative recovery went without any relapses and complications.

Key words: benign prostatic hyperplasia, lower urinary tract symptoms, giant prostatic enlargement

Introduction

Benign prostatic hyperplasia (BPH) is a histological diagnosis that refers to the proliferation of smooth muscle and epithelial cells in the transitional zone of the prostate gland [1,2]. The most frequent benign tumor in older men is BPH, and aging is a major predictor of incidence [3,4]. Patients with BPH will suffer from lower urinary tract symptoms (LUTS). Still, a significant percentage will also present with other BPH-related complications and seeking urological care [3-6]. LUTS can be divided into storage, micturition, and post-micturition symptoms [7]. Giant prostate enlargement (GPE), also known as giant prostatic hyperplasia, is a term given for severely enlarged prostates that weigh more than 500g [8]. The size of the prostate and symptoms' presence and severity are not positively correlated. A large prostate may not cause symptoms, but a small prostate may [9]. We describe our experience of removing previously asymptomatic 528g prostate by open transvesical prostatectomy.

Case presentation

Patient A., 72 years old, was admitted to the multidisciplinary city hospital №1 in Astana with complaints of nocturia and pain. According to the patient, these complaints bothered him for last one year. Based on the results of an outpatient examination (TRUS: prostate volume 482 cm3; PSA 5.1 ng/ml; uroflowmetry: obstructive type of urination), LUTS was diagnosed, and surgical treatment was recommended.

Urological profile: per rectum - the prostate gland is enlarged, spherical in shape, painful on palpation, densely elastic consistency, the interlobar sulcus is smoothed, the rectal mucosa over the gland is mobile; uroflowmetry revealed the signs of infravesical obstruction with a maximum urine flow rate (Qmax) of 9.1 ml/s; IPSS 15 points, QoL - 4 points; according to transrectal US (TRUS) the size of the gland is 482 cm3, the capsule is not thickened; residual urine volume is 200 ml when filled with 380 ml.

MRI results: On MRI T2 mode in axial (a) and coronal (b) projections, the prostate gland is significantly enlarged in size up to 100.4x93.5x108.1 mm, with clear uneven contours, heterogeneous structure due to the presence of multiple nodular formations, various shapes, up to 32.8x21.2 mm in size, without clear zonal differentiation, with signs of prolapse into the bladder (Figure 1).

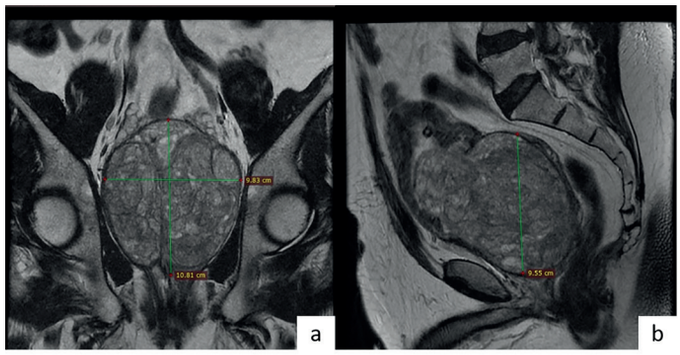

Figure 1 - MRI of the patient

Surgery: Under spinal anesthesia, a transverse incision was made, and access was made to the anterior bladder wall. A urethral catheter 22 French was inserted, and the bladder was filled. The bladder was taken on holders, between which it was opened. A finger was inserted rectally, a surgical capsule was opened, and the adenomatous tissue of the prostate gland was enucleated bluntly. A gland of dense consistency was 15-16 cm in diameter. Two hemostatic sutures were placed on the surgical capsule. The Foley catheter balloon is inflated, and the balloon is stretched. During revision of the bladder, blood clots were removed and epicystostomy was placed. The integrity of the anterior wall of the bladder was restored with a two-row suture and checked for tightness. A rubber is installed in the Reitz space. The wound is sutured in layers and aseptic bandage was placed (Figure 2).

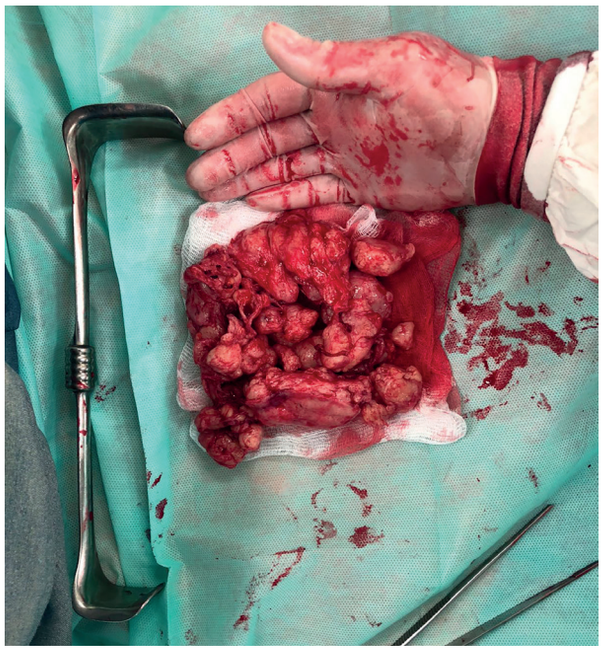

Figure 2 - The prostate after surgery

Histological conclusion: In the studied preparations were fragments of prostate tissue. The glands are located unevenly, close to each other, and separated by fibrous tissue. Some acini are lined with a single-layer prismatic epithelium of different heights; in some acini are a proliferation of the epithelium with the formation of multilayer multi-row, papillary structures. In single glands, foci of epithelial proliferation with a violation of the row. Some of the glands are cystically dilated and contain a dense protein secret. There are foci of acinar structures of various sizes, unevenly located and lined with a flattened epithelium. There is pronounced fibrosis in the stroma, and focal lymphoplasmacytic infiltration, mainly around the glands. Circulatory disorders - stasis, plethora and hemorrhages. Fragments of the prostatic part of the urethra with hemorrhages and subepithelial lymphoplasmacytic infiltration. *Histopathological conclusion:* nodular prostatic hyperplasia, an adenomatous variant with foci of cystic atrophy. Chronic prostatitis.

The postoperative period was without complications. Antibacterial, anti-inflammatory, hemostatic, infusion, and anticoagulant therapy was carried out. The urethral catheter was removed on the seventh day. Spontaneous urination was restored. The patient was holding urine, periodically noticing a slight instillation of urine (using two pads). He was discharged from the clinic for outpatient follow-up after ten days.

Discussion

LUTS is a common complaint in adult men. Understanding the lower urinary tract as a single functional compartment and the multifactorial etiology of associated symptoms implies that the current focus is on LUTS rather than benign prostatic hyperplasia (BPH). BPH is inappropriate because treatment is indicated if the clinically LUTS is a benign prostatic obstruction (BPO) [10]. BPH is almost ubiquitous in aging men, with autopsy evidence of histological prevalence worldwide, increasing from age 40–45, reaching 60% at age 60 and 80% at age 80 [4].

Inflammation is also thought to play a role in the pathogenesis and progression of BPH [10,11]. Although there are several hypotheses, BPH is likely the result of a multifactorial process, the exact etiology of which is unknown. However, the presence of functioning testicles is necessary for developing BPH. According to hypotheses, giant prostate enlargement is caused by a combination of normal stromal-epithelial paracrine communication disturbance, an imbalance between androgen, cytokine, and peptide growth signals, reduced apoptosis, and stromal and epithelial cell proliferation [12]. Particularly, inhibition of the p53 suppressor gene and mutations in proto-oncogenes such as Ras and c-erbB2 can result in aberrant and continuous cell proliferation [12].

When Fishman and Merrill reported on the successful surgical excision of a prostate weighing 526g in 1993, they introduced the term "Giant Prostate Enlargement" (GPE) to describe a prostate weighing more than 500g [8].

MRI, computed tomography (CT), and transrectal US (TRUS) can all be used to measure prostate volume. Our patient had TRUS volume of 482 cm3 and an MRI volume of 528 cm3. And he did not complain any symptoms before a year of surgery. When a patient experiences severe LUTS that is unresponsive to medical therapy, acute or chronic urinary retention, resistant gross hematuria, urinary tract infections, obstructive nephropathy, bladder stones, or urinary tract infections surgery is indicated [13]. For patients with a prostate volume between 30 and 80 ml, the European Association of Urology currently recommends transurethral resection of the prostate, and for prostate volumes greater than 80 ml, open surgery or transurethral enucleation using a holmium laser [10]. The recommended surgical method for GPE is open surgical enucleation either the suprapubic (transvesical) or retropubic approach. There haven't been any reports of GPH being successfully managed with holmium laser enucleation yet, in spite of the procedure showing satisfactory outcomes with large-sized prostates. In addition, a number of studies have shown that these minimally invasive methods are effective for treating significantly enlarged prostates. Less post-operative catheter time, a shorter hospital stay, less complications,

and comparable results to open prostatectomy are all associated with these procedures [14-16]. Even though severely enlarged prostates may be treated using minimally invasive methods, just one study showed that GPH greater than 500 g could be successfully treated [14]. A case of GPH was successfully treated using the prostate arterial embolization [17]. Bhatia et al, reported that 6 weeks after starting this treatment, the patient's bothersome LUTS had improved and prostate volume had decreased from 571 to 270 ml. They believed that this method would be appealing for men with significantly enlarged prostates who also have co-morbid conditions because it is minimally invasive and has low morbidity. It should be noted, however, that open procedure is still frequently utilized for moderately to severely enlarged prostates because laparoscopic and robotic surgeries are not easily accessible in a developing nation.

In the literature review [18], only 32 prostates met the GPE criteria, including three patients diagnosed by imaging but not offered surgical treatment. This makes the current case the 33st reported case of a giant prostate in medical history (Table 1).

Table 1 All GPE cases reported in the literature.

	Weight (g)/ Volume (cc)	Year	Treatment	Outcome
Thomson-Walker [19]	680	1920	Open surgical resection	Survived
Middleton [20]	557	1937	Open surgical resection	Survived
Wadstein [21]	705	1938	Open surgical resection	Survived
Gilbert [22]	713	1939	Open surgical resection	Died
Nelson [23]	720	1940	Open surgical resection	Deid
Ockerblad [24]	820	1946	Open surgical resection	Died
Bacon [25]	602	1949	Open surgical resection	Survived
Lantzius-Beninga [26]	705	1966	Open surgical resection	Survived
Ashamalla and Ahmed [27]	695	1972	Open simple transvesical prostatectomy	Survived
Kitagawa and Kano [28]	535	1980	Open surgical resection	Survived
Tolley et al. [29]	1058	1987	Open surgical resection	Survived
Fishman and Merrill [8]	526	1993	Open simple retropubic prostatectomy	Survived
Medina Pérez et al. [30]	2410	1997	Open surgical resection	Not mentioned
Hosseini and Safarinejad [31]	508	2004	Open simple transvesical prostatectomy	Survived
Yilmaz et al.[32]	610	2006	Open simple transvesical prostatectomy	Survived
Sood et al. [33]	522	2006	Open simple transvesical prostatectomy	Survived
Akpo and Akpo [34]	510	2010	Open simple transvesical prostatectomy	Survived
Üçer et al. [35]	734	2011	Open surgical resection	Survived
Appiah et al. [36]	800	2014	Open Simple Transvesical Prostatectomy	Survived
Maliakal et al. [12]	740	2014	Open simple transvesical prostatectomy	Survived
Khan et al. [37]	700	2014	Open simple retropubic prostatectomy	Survived
Wroclawski [38]	720	2015	Open simple transvesical prostatectomy	Survived
Lacy et al. [39]	708	2015	Open radical retropubic prostatectomy	Survived
Bhatia et al. [17]	571	2015	Prostate artery embolisation	Survived
Domínguez et al. [40]	3987	2016	No treatment required	n/a
Wang et al. [41]	800	2016	Long-term indwelling catheter	Survived
Zeng et al. [14]	524	2017	Laparoscopic simple prostatectomy	Survived
Egote et al. [42]	700	2018	Open simple transvesical prostatectomy	Survived
Anglickis M et al. [43]	800	2019	Open simple transvesical prostatectomy	Survived
Aghamir et al. [44]	1070	2020	Open simple retropubic prostatectomy	Survived
Ojewola et al. [18]	512.5	2020	Open simple retropubic prostatectomy	Survived
Cui et al. [45]	522	2022	Bipolar transurethral resection of the prostate	Survived
Our case	528	2022	Open simple transvesical prostatectomy	Survived

After the operation, we examined our patient four weeks later. He had satisfactory urination and urinary retention. Histopathology of the surgical material showed characteristic signs of BPH.

Conclusion

GPE is a rare type of enormous prostatic enlargement that only occasionally appears in case reports. In most cases, GPE associated with recurrent bleeding and LUTS. Despite the enormous size of the prostate gland, surgery should only be performed when necessary and the patient is a good candidate. The most popular type of surgical treatment continues to be open surgery. Prostatic artery embolization, laparoscopic and robotic simple prostatectomy are alternatives to open surgery when they are available. Before enucleation, careful hemostasis can help to limit intraoperative blood loss.

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