Journal of Bursa Faculty of Medicine

Volume 1 · Issue 1 · January 2023

Available at https://dergipark.org.tr/tr/pub/bursamed

Journal of Bursa Faculty of Medicine

Available at https://dergipark.org.tr/tr/pub/bursamed

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What are the methods used in postcoital emergency contraception, positive and negative effects, limitations?

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Journal of Bursa Faculty of Medicine

e-ISSN:

Letter to the Editor

Obstetrics and Gynecology

Received
December 20, 2022
Accepted
December 29, 2022
Published online
January 04, 2023

J Bursa Med 2023;1(1) 1-2

Dear Editor,

Postcoital emergency contraception (EC) refers to contraceptive options that can reduce the risk of pregnancy after sexual intercourse but before pregnancy occurs. It is not a primary method of contraception, sexually active patients of all ages can use it. Emergency contraception, prevention of unintended pregnancies, that supports families to have as many children as they want, when they want. EC can be a solution for elective curettage, which is an important public health problem. The use of oral drugs without a doctor's prescription is still a controversial issue.

Patients can administer emergency contraception in the form of oral preparations or intrauterine devices (IUDs). Administration of the copper IUD in the first five days after coitus was associated with 0% pregnancy in the next cycle [1]. However, Canadian guidelines set this period as 7 days [2]. The advantage of the IUD over other methods is that its effectiveness is independent of the timing of the menstrual cycle. It is the most effective EC method, but a visit to a healthcare facility is required. The success of IUD containing levanorgestrel is similar to that of copper [3]. Ulipristal Acetate (UPA), a selective progestin receptor modulator, is the most commonly used oral EC. It should be started within five days after the unintended intercourse. The advantage of UPA over other oral preparations is that it can delay ovulation even if the LH peak begins. Those with more than one episode of UPA use in their cycle are at the highest risk of pregnancy. IUD is more suitable for this group. It is recommended that the patient use a sexual abstinence or barrier method for at least 5 days after taking UPA. Hormonal contraception should not be started earlier than 5 days after taking UPA. Because of exposure to progestins for 7 days before and 5 days after UPA use may reduce the ovulation-blocking effect of UPA.

Another oral preparation is pill containing 1.5 mg of levanorgestrel (LGN). This oral preparation should be started within 72 hours after intercourse. It can prevent ovulation if used only before the LH peak. The risk of pregnancy increases with increasing BMI. In the publications, serum levels similar to LGN were found in obese patients and it was shown that dual use did not prevent ovulation [4]. Therefore, the use of double-dose LGN has no place in obese patients. The Yuzpe method, on the other hand, is an older EC. It contains 100 micrograms of EE + 0.5 mg of LNG. Repeat dosing is required at 12 hours. Nausea and

How to cite this article
Yenigül NN, Yüce Bilgin E. What are the methods used in postcoital emergency contraception, positive and negative effects, limitations? J Bursa Med 2023;1(1):1-2

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vomiting is one of the most important disadvantages of using high-dose hormone. Preparations containing 4 mg Drosprenon, which are not yet available in our country but whose sales have started in Europe and America, also offer the advantage of cyclic use.

The only absolute contraindication for the use of EC is pregnancy. Current diagnosis of PID or uterine anomaly is a contraindication for IUD, and drug allergy is a contraindication for oral ECs. The lactation period is not restrictive for UPA or LNG use. Results of a study of UPA in mouse milk suggest discarding milk expressed for 24 hours [1], but no human data on UPA exposure in the newborn are available. LNG is minimally excreted in breast milk. EC has general side effects such as nausea, vomiting, spotting bleeding, and headache, but there is no significant difference between the methods in terms of these side effects. Data on side effects in repeated use are limited. In patients using oral EC, the menstrual cycle starts within an average of 1 week from the expected date.

Although emergency contraceptive methods prevent unwanted pregnancies, elective curettage rates have not decreased. This may be because they are not used after every unprotected sex, and current oral methods are only effective when used before ovulation. In order to clarify this issue, some new strategies regarding EC should be determined. The focus should be on maximizing the copper IUD in women with a history of recurrent EC use, facilitating the initiation of effective regular contraception after EC, and developing a more effective oral EC. In addition, patients who apply to the obstetrics clinic should be provided with information services to raise awareness on this issue.

Authors' Contribution

Study Conception: NNY,; Study Design: NNY,; Supervision: NNY,; Materials: EYB,; Data Collection and/or Processing: EYB,; Statistical Analysis and/or Data Interpretation: EYB,; Literature Review: NNY,; Manuscript Preparation: EYB and Critical Review: NNY.

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Strong primary care for the sustainability of the health system

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Journal of Bursa Faculty of Medicine

e-ISSN:

Review

Family Medicine

Received
December 18, 2022
Accepted
December 20, 2022
Published online
January 04, 2023

J Bursa Med 2023;1(1) 3-7

ABSTRACT

Although the name of all health systems in the changing world has changed, primary health care practices, whose central role has not changed, should take the place they deserve with determined health policies. A cost-effective health service delivery is provided in health systems where all patients are the first point of reference, with a strong door-holding family medicine practice. This is the key to sustainability in subsidizing health services. With a good primary care, nearly 90% of common diseases in the community are treated. Countries with a strong primary care structure and referral chain have lower health-related costs and higher clinical success in diseases. Providing easy preventive health services locally; If this cannot be done before the diseases appear, it allows the earliest diagnosis and clinical regulation before complications occur.

Keywords: strong primary care, family medicine practices, deficiencies in family medicine practice, family medicine

The provision of health services is generally given under three main headings as primary, secondary and tertiary care providers. With a strong primary care, nearly 90% of common diseases in the community are treated. In primary care-based healthcare settings, unit patient costs are less because less laboratory and imaging examinations are required [1].

According to many researchers, consumer groups and public advisors, there is a consensus that primary care should be the basis of providing fair health care [2]. The reason for this consensus is that family medicine is the easiest way to provide health services to a large part of the society with less cost and less workforce [3].

In countries with a strong primary care structure and referral chain, health-related costs are lower and clinical success is higher in diseases [1, 4]. Providing easy preventive health services locally; If this cannot be done before the diseases appear, it allows the earliest diagnosis and clinical regulation before complications occur. As long as there is no disease, there is a patient, every patient needs to be evaluated from a multifactorial point of view, according to the genetic burden from the family and the risk factors that may be specific to the society in which they live. In order to meet this need on time and in the most complete way, it seems to be the most correct philosophy to form the basis of family medicine health services [5].

In primary care, patients are evaluated with an inclusive approach, which is one of the most basic approaches of fam-

How to cite this article
Metin S. Strong primary care for the sustainability of the health system. J Bursa Med 2022;1(1):3-7

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ily medicine specialists. In the differential diagnosis of a patient, the diseases with the highest incidence in the community are considered in the foreground. Today, when dozens of specializations are formed in the medical profession, the need to determine which complaint of the patient will be related to which region and branch has increased. Contrary to all medical disciplines, family medicine treats patients of all ages and genders holistically, from birth to death [6].

Another basic feature of primary care is its quality of being the first point of reference. Regardless of what the complaints are, a differential diagnosis made according to the prevalence in the community, from the most common to the rarest, brings the possibility of accurate diagnosis and treatment at low cost [7]. This feature, which defines the necessity for the patient to be the entry point to the health system in every new health need, becomes active in the use of resources in health. The strength of the first step increases the effectiveness of the second and third steps. It should not be forgotten that every health need that is not met on site and locally will lead to the need to receive services at a higher level, which will make it difficult for the individual with specialty need to access health services.

It is another teaching of family medicine, with its person-oriented continuous care, to provide health services to every individual in need without discrimination in every period of human life, starting from the fetal period to death [8]. Less diagnostic examinations enable the prevention or delay of diseases with earlier diagnosis and intervention, and the continuity of health care with less treatment prescriptions and lower drug costs.

The state of primary care in the World

Medicine has existed since the first day of humanity. Renaissance was brought to the agenda by Francis Peabody in 1923, with the need for comprehensive general medicine service, where patients were left in the middle as a result of the development and branching in the scientific field and medicine, as well as many developments in the technical field, which the Industrial Revolution initiated. Family medicine, which entered the maturation process with its coming to the agenda, was first recognized as a specialty in England in 1965. It was recognized in America in 1966, and in 1969 it was determined as a specialty. The trend, which started in England and America, gained its central role in the provision of health services with the title of health for everyone in 2000 with the Alma Ata declaration in 1978. In 1995, the family medicine specialization was normalized by the European community to be obtained with a minimum of 2 years and then at least 3 years of education after graduation from medical school. In the 2000 World Health Organization report, in the "Recommendations for Creating a Health Service and Medical Education System that Considers the Needs of the Society", the articles that outline the recognition of family medicine as a specialty discipline were reported [9]. Although there are differences in general practices and naming in the world in the days we have come, Family Medicine practice constitutes the center of primary health care services, which are at the center of health service delivery.

The first practices of family medicine in the USA started in 15 pilot regions in 1969, and today they have reached the largest number of specialists after internal medicine specialists. It is the branch that takes care of the most patients in one day, and with various incentives, cooperation with primary care personnel is provided, and with this cooperation, preventive medicine is provided. In 2000, 25% of the total examinations performed in the USA belonged to family physicians [10].

The first family medicine department in Germany was opened in 1976. Since 1994, physicians who will work in primary care have been required to specialize, and primary care services have been entrusted to family physicians. The ratio of family physicians to other physicians is approximately 40-50%. In Germany, unlike other countries, it is obligatory to provide services by family physicians, who are registered 24/7 in case of emergency [11].

National health insurance in Canada covers all individuals, and family medicine is at the center of primary care. Family physicians make up half of all physicians, and their education period should be 2-3 years. Keeping this process long, geriatrics, emergency, etc. provides additional specialization opportunities in their fields. The striking difference in Canada is that family physicians follow up the patients referred to the next level [10, 11].

There is a health practice in England that is subsidized by general taxes. General medicine, which has been known since 1600 years, was named family medicine as of 1947. They are trained with a 3-year training in practice to work with family physicians who have received 2 years of theoretical and 1 year training on the faculties of family medicine, which is the current specialization in all medical faculties. In

practice in the UK, it is not possible to apply to secondary care, except for emergencies, without a primary care physician referral [12].

In Norway, the practice of family medicine was accepted in 1985 and the specialization training is 1 year theoretical and 4 years working with a family physician for 5 years. Family medicine is the center of primary care services. There are also incentive payments for protective services [13].

The first family medicine department was established in Portugal in 1982, and five years later, it was decided that all primary care physicians should receive family medicine specialization training. The training period is 3 years. It is obligatory for each individual to be registered with a family physician, and the average population per family physician is 1500 [10, 11].

In Israel, the duration of family medicine residency is 4 years, and in other countries, the difference seems to be that the medical organization has an active role in the supervision of education and family medicine practice. Effective imaging and laboratory services are also provided in primary care services, and the average population per physician is around 2500 [13].

Family medicine practice in Turkey

In our country, with the constitution of 1960, the understanding of the social state came to the fore, and with the laws of 1961, the first step was laid for the primary health care services for all citizens to benefit from general practice services. Following the primary care-based transformation all over the world, the family medicine pilot application was started in Düzce in 2005, and this practice has spread throughout Turkey with the reform called health transformation after a five-year transition period [14]. With the excuse of the transition period, family physicians were trained and included in the system with a 3-week training system in which all specialists and general practitioners can apply. There are physicians from many different branches in the system. Every citizen is obliged to register with a family doctor. In our country, family medicine specialists, which were added to the specialty charter in medicine in 1983, have been trained since 1985. The minimum duration of education is determined as 3 years [10, 15]. In our country, there is a requirement for a referral system designed according to the UK model at the planning stage of family medicine practice, and it could not be implemented due to the open door policy of the referral chain and the newness of the practice of family medicine.

Some steps should be taken to improve family medicine practices in our country. In this sense;

•Specialization training content should be integrated with trainings in Europe and the World.

•The general disease diagnosis statistics of the country should be made and the family physician specialty training curriculum should be developed to cover at least 85%.

•Different forms of purchases for family medicine specialties, such as contracted family medicine specialists, should be removed. A system that receives similar training at similar times and is exposed to the same application chosen by the exam should be established. There should be a uniform order in education.

•All physicians working in the family health center should be provided with family medicine training in all faculties in order to become family medicine specialists.

•In order to monitor professional development and competency, it should be ensured that professional scoring and trainings, congresses and continuous development, where scoring related to professional development can be made, should be followed at least once every five years. Family medicine practice of physicians who do not meet the development criteria should be suspended.

•For the sake of populist policies in the planned family medicine system, the open-door practice should be abandoned immediately, and applications to the second and third level should be stopped without a family physician referral, except for emergencies.

•After the implementation of the unfulfilled referral chain, a referral rate of 15% should be determined and the rules should be followed.

•A reasonable payment regulation should be implemented in which the importance and incentives given to preventive services and screening services are increased.

•The population per physician should be reduced to the range of 1500-2000 and each physician should be given the opportunity to evaluate all registered individuals in an inclusive way.

•The primary level of imaging services should be strengthened, and basal radiological practices such as x-ray reading and hand doppler should be added to the specialty curriculum.

•Group medicine practice should be encouraged for family health centers and establishment of family health centers where ten physicians can work together should be encouraged.

•Education In order not to have a family medicine department without a Family Health Center, planning

should be made in accordance with the number of family physician assistants in each province and practical training should be provided during the assistantship.

•Necessary training staff should be provided to the staff of the Ministry of Health and Higher Education Institution on behalf of the missing educators in the departments of family medicine.

•A dentist and a dietitian should be planned for each family health center, so that diet programs that can be applied at the beginning of chronic diseases should be planned and followed. In addition to the practice of dentistry and general medicine-based family medicine, it should be ensured that a holistic health service delivery is provided by providing oral and dental health services locally.

With the feasibility of recommendations, timely follow-up of chronic diseases, standardization of education and indexing to the developments in the world can be ensured and a sustainable health service delivery can be established in a fair way.

CONCLUSION

Although the name of all health systems in the changing world has changed, primary health care practices, whose central role has not changed, should take the place they deserve with determined health policies. A cost-effective health service delivery is provided in health systems where all patients are the first point of reference, with a strong door-holding family medicine practice. This is the key to sustainability in subsidizing health services. As long as the open door policy continues, the problem of finding an appointment for all physicians in these steps will continue to be full of emergencies in secondary and tertiary hospitals. This is the biggest obstacle for the required patient to reach the relevant branch. Thanks to the execution of this system with the referral chain, the problems we have mentioned will be prevented, and together with the decrease in the patient load in the secondary and tertiary care levels, the time problem before the detailed examination of the patients referred to this level by the physicians will be overcome.

Authors' Contribution

Study Conception: SM,; Study Design: SM,; Supervision: OS, SO, LU,; Materials: SM,; Data Collection and/or Processing: SM,; Statistical Analysis and/or Data Interpretation: SM,; Literature Review: SM,; Manuscript Preparation: SM and Critical Review: SM.

Acknowledgments

I thank my dear wife Aybüke Tuğçe METİN very much for her patience and support during the writing process.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

Ethics committee approval was not required as this study was written as a reviwer.

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What are the criteria for full response to neoadjuvant treatment for oesophagus cancer? surgery or follow-up?

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Journal of Bursa Faculty of Medicine

e-ISSN:

Review

Gastroenterolojic Surgery

Received
December 14, 2022
Accepted
December 20, 2022
Published online
January 04, 2023.

J Bursa Med 2023;1(1) 8-16

ABSTRACT

Esophageal cancer is a progressive disease. Its survival rate is low compared to other tumors. The treatment strategy affects the survival of the patient. Treatment is controversial, especially in patients with complete response after neoadjuvant therapy. In our study, we investigated the criteria for complete response after neoadjuvant therapy and subsequent treatment processes.

Keywords: Neoadjuvant treatment, oesophagus cancer, surgery

In 2020, oesophagus cancers were reported to be the seventh most commonly seen cancer and the sixth cause of cancer-related deaths [1]. The incidence of oesophagus cancer is rising rapidly throughout the world. Although oesophagus cancers can generally be separated into two as squamous cell cancer and adenocancer, adenocarcinoma is seen at the rate of 90% [2]. The increase in oesophagus adenocarcinomas in recent years is thought to be affected by gastro-oesophageal reflux disease, Barret's oesophagus, and obesity [3]. In addition to being a cancer with an extremely aggressive course, close to 50% of patients are diagnosed when it is unresectable or metastatic. Despite a 5-year survival rate of > 85% in early oesophagus cancers, as diagnosis is generally made at an advanced stage, the 5-year survival rate is < 20% [4].

The application of preoperative and perioperative chemoradiotherapy (CRT) together with surgery has become a successful treatment strategy for gastrointestinal system malignancies in recent years. When compared with surgery alone, this treatment has been observed to increase overall survival (OS) in locally advanced oesophagus cancers. Neoadjuvant treatment methods decrease tumour volume and prolong survival by increasing R0 resection rates [5]. The degree of regression seen in the tumour after neoadjuvant treatment is extremely important in respect of disease-free survival (DFS), and the degree of tumour regression can be determined most accurately with histopathological examination by pathologists. However, as yet there is still no accepted definitive agreement or tumour response evaluation system for oesophagus cancers after neoadjuvant treatment [5].

In 2009, response criteria were defined, not only for oesophagus cancers but for all solid organ tumours. These are known as

How to cite this article

Durak D, Üstüner MA. What are the criteria for full response to neoadjuvant treatment for oesophagus cancer? surgery or follow-up? J Bursa Med 2023;1(1);8-16

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the RECIST criteria.

According to the RECIST criteria;

- Complete response (CR): no tumour is observed
- Partial response (PR): shrinkage of ≥ 30% in tumour size
- Progressive disease (PD): growth of ≥ 20% in tumour size
- Stable disease (SD): no change.

These response criteria are evaluated according to size using computed tomography (CT) and other imaging methods.

Evaluation of the response to neoadjuvant treatment

Although there is no clear algorithm in the evaluation of neoadjuvant response, various evaluation methods have been developed. These start with clinical evaluation together with CT, and include magnetic resonance imaging (MRI), endoscopic evaluation, biopsy, endoscopic ultrasound (EUS), positive emission tomography (PET), and histopathological grading.

Clinical Evaluation

Clinical evaluation is a method which does not present objective evidence and is insufficient in the evaluation of diagnosis response [6]. Following neoadjuvant treatment, no observation of dysphagia, the halting of weight loss, and no new symptoms (cough, hoarseness) suggest a positive response to treatment [6]. However, even if this suggests a positive response, no information is given about the degree of response.

Histopathological Response

This examination basically evaluates the relationship between the neoadjuvant response of the surgical specimen and OS and DFS. Two grading systems are at the forefront in the evaluation of response. These are the Mandard classification and the Cologne Regression Scale.

- Mandard classsification: The residual tumour is compared with the level of fibrosis formed [5].

The Mandard classification is categorised in 5 tumour regression grades (TRG).

TRG1 (pathological full response): No tumour cells. Fibrosis present in all layers

TRG2: Occasional tumour cells + fibrosis

TRG3: Many tumour cells but fibrosis is more predominant

TRG4: More cancer cells than fibrosis

TRG5: No change in regression

- Cologne Regression Scale: This evaluates changes in size from pre to post-treatment [5].

The Cologne Regression Scale is classified in 4 grades according to the response evaluation.

Grade 1: > 50% vital residual tumour cells (VTC)

Grade 2: 10-50% tumour cells

Grade 3: < 10% tumour cells (almost full response)

Grade 4: complete response

According to these classifications;

- According to the Mandard classification, TRG 4-5 are associated with a poor prognosis, and TRG1 and TRG2 with a better prognosis. This neoadjuvant response has been observed to be strongly correlated with DFS.
- According to the Cologne Regression Scale,

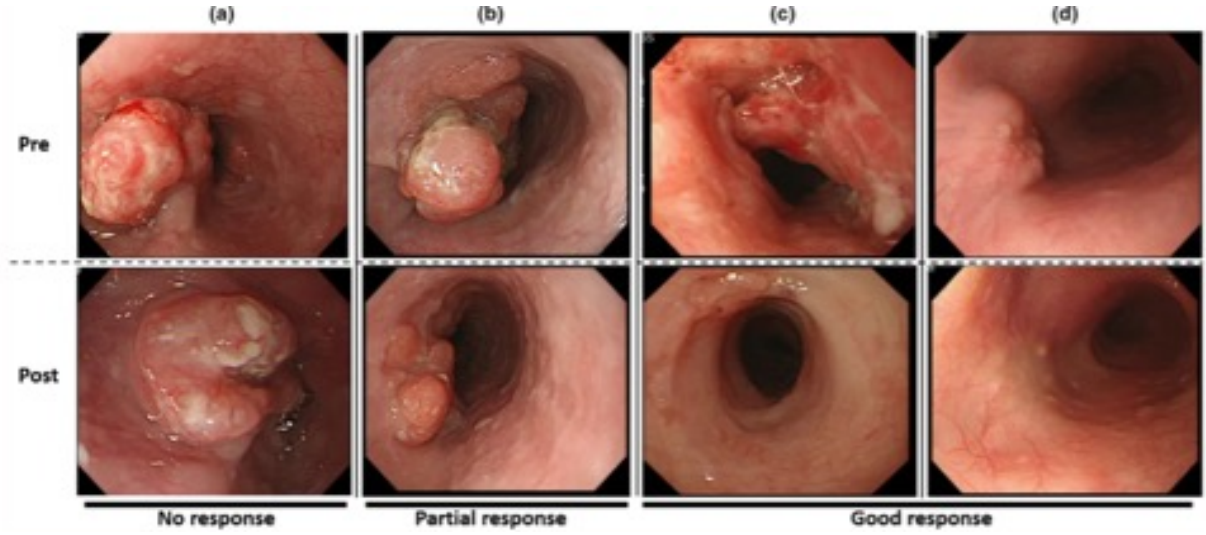

Figure 1. Endoscopic evaluation of the response to neoadjuvant treatment

patients with < 10% tumour cells, Grade 3, have a better disease prognosis [5].

Endoscopic Evaluation

Endoscopic evaluation allows macroscopic evaluation of the tumour status before and after neoadjuvant treatment.

- Endoscopic evaluation is separated into 3 categories [7]. (Figure 1)

-Endoscopic no response (eNR): No change or there is progression

-Endoscopic partial response (ePR): Despite a decrease in tumour volume, it is still present

-Endoscopic complete response (eCR): Tumour cells are not observed.

In previous studies, the prognosis has been seen to be better in patients observed with eCR and ePR. Even in patients with lymph node positivity (N1+), the prognosis and OS have been seen to be better than those of patients with no response. When the pathologies of operated patients have been evaluated, the pathological response has been observed to be correlated with the endoscopic response [7]. (Figure 1, 2)

The Japan Oesophagus Cancer Classification published by the Japanese Oesophagus Association defined evaluation criteria for the response to neoadjuvant treatment [8]. According to this classification;

- Complete response (CR): Disappearance of all target lesions
- Partial response (PR): A decrease of at least 30% in total of the largest tumour size
- Progressive disease (PD): An increase of at least 20% in total of the largest tumour size
- Stable disease (SD): No change
- According to the guidelines published by the Japanese Oesophagus Association, some criteria and findings were determined to define full response [8]. Accordingly;
- The criteria for endoscopic full response to neoadjuvant treatment [8];
- 1-The disappearance of irregular mucosa and ulcerated areas
- 2-No wounds or narrowing within the lumen
- 3-No observation of active inflammatory structures (in the form of white coating)
- 4-Negative biopsy findings
- 5-Clear visibility of the whole oesophagus
- 6-The observation of scarred areas or a smooth mother-of-pearl appearance in the oesophagus mucosa

In the evaluation of response following neoadjuvant CRT treatment, changes on the mucosa surface are evaluated with endoscopic examination. In previous studies, endoscopic evaluation has been observed to have 22-65% sensitivity and 50-85% specificity for complete response [9]. It has been recommended that biopsy is repeated after neoadjuvant treatment to increase accuracy in the evaluation of complete response [9]. In a study by Bates of endoscopic evaluation, it was reported that despite negative biopsies in 7 of 17 patients, residual cancer cells were observed [10]. Schneider repeated biopsies in 80 patients and reported sensitivity of 36% and specificity of 100% [11]. Despite these studies, the taking of biopsy has not been accepted as a rule in the endoscopic evaluation of complete response [9].

In a review of 12 studies with a total of 1281 patients, it was concluded that endoscopic biopsy has high specificity but low sensitivity. It is not surprising that endoscopic biopsy provides a high rate of false negative results because the biopsies are only taken from the superficial mucosal layer [12].

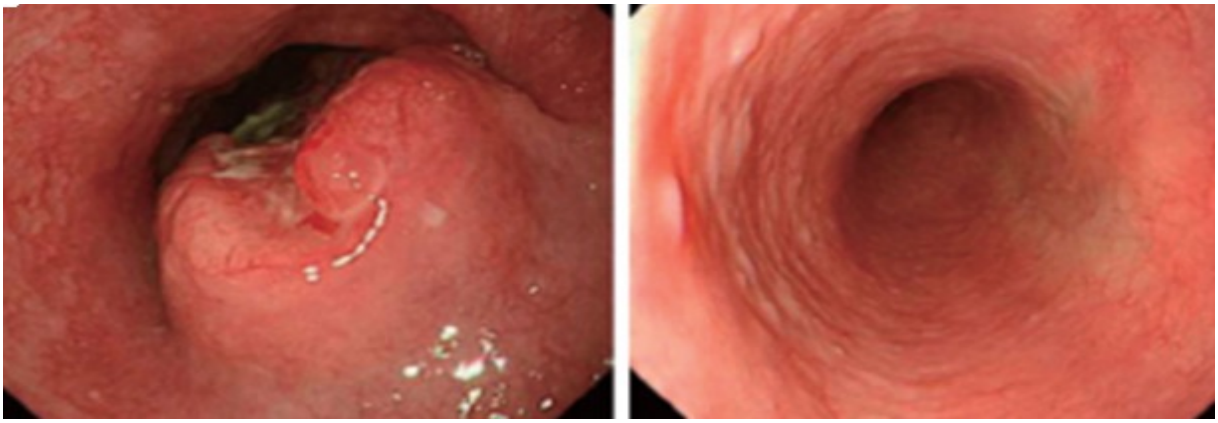

Figure 2. After neoadjuvant treatment in a patient with type 2 grade 3 oesophagus cancer before the procedure, only scar tissue was seen to remain and the patient was evaluated as complete response

In a study of 29 patients who received neoadjuvant CRT, the oesophagus wall was evaluated with biopsy taken again after the neoadjuvant CRT, and intra-epithelial lesions < 5mm in size were observed in 7 cases, and tumour nests were observed in the submucosa or m. propria in 9 cases [13].

With the deep biopsy method (bite-on-bite biopsy) an increase has been observed in recent years in the identification of submucosal residual tumour deposit. In patients with tumour negativity, 85% pCR has been observed in the surgical specimen with this method [14].

In a study by Van Rossum et al.,it was concluded that in the determination of residual oesophagus tumour in patients who had received neoadjuvant CRT, endoscopic biopsy was a specific but not absolutely sensitive method for determination [15].

Endoscopic Ultrasound (EUS) Evaluation

Tumour evaluation with EUS is frequently used, especially in oesophagus and rectum cancers. Despite the high accuracy rate of EUS in the evaluation of primary tumour depth (T) and lymph node status (N+/-), this reliability decreases after neoadjuvant treatment. The reason for this is that it remains insufficient in the evaluation of residual tissue caused by inflammation, fibrosis, oedema and scarring formed in the tissue after neoadjuvant treatment [15].

In a study of 110 patients, T-stage was evaluated again with EUS after neoadjuvant CRT, and success was observed to be low at 39% [16]. In another similar study, complete pathological response was evaluated at low rates such as 0-25% with EUS in the evaluation of response after neoadjuvant treatment [17].

In the accurate evaluation of neoadjuvant response, EUS is more successful in the evaluation of lymph node status (N stage) than of tumour depth (T stage). In the above-mentioned study of 110 patients, the N stage accuracy rate (58.2%) was seen to be higher than the T stage accuracy rate (39.1%) [16]. The N stage accuracy rate was reported as 64% and the T stage accuracy rate as 37.3% in another study of 59 patients [18].

When lymph node size is evaluated with EUS, lymph nodes > 10mm are considered malignant. In a meta-analysis of 10 studies including 602 patients, the identification of residual lymph node metastasis > 10mm was measured as 73.5% when examined with EUS, but this rate was 31.1% in lymph nodes > 5mm [15].

Biopsy obtained with EUS has not been seen to provide any additional benefit in N stage diagnosis because of nodal necrosis and inflammation in that region. Moreover, the rate of false negative biopsies has been found to be high in biopsies taken with EUS after neoadjuvant treatment [19].

It has been attempted to define complete response criteria based on wall thickness in some studies. In a study of 66 patients, a decrease of > 50% in wall thickness and < 6mm thickness were found to be significantly associated with complete pathological response. It was observed that every 1mm increase in wall thickness reduced the probability of complete response by 31.3% [12].

Ota measured tumour diameter before and after neoadjuvant CRT, and those with response were identified with 94% accuracy. Studies have shown that the most appropriate time for re-grading with EUS is 3 weeks after the completion of neoadjuvant CRT [12].

Foci of residual adenocarcinoma after neoadjuvant treatment have been observed in biopsy taken with EUS, as in endoscopy.

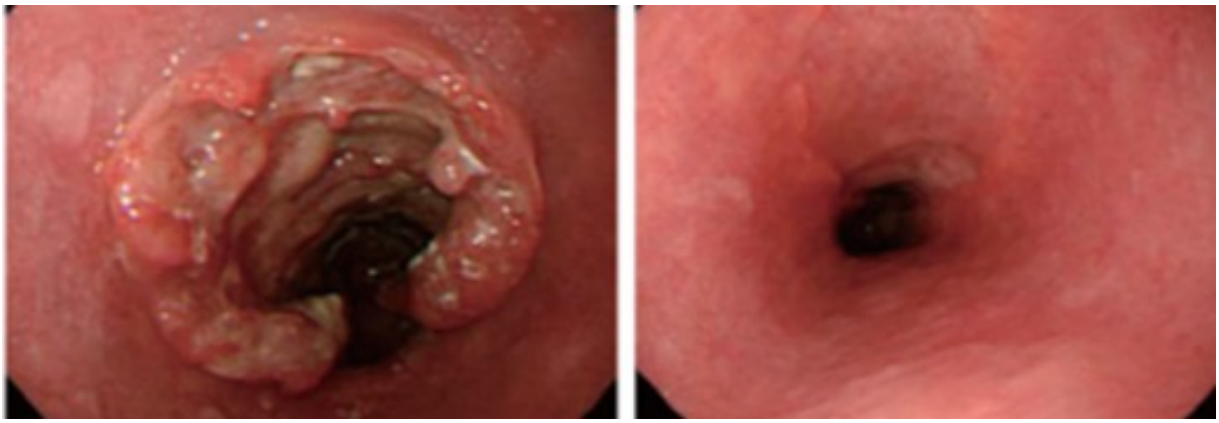

Figure 3. After neoadjuvant CRT treatment in a patient with type 2 grade 4a oesophagus cancer before the procedure, no tumour was observed in the endoscopic evaluation

Magnetic Resonance Imaging (MRI) Evaluation

In MRI evaluation, the tumour wall thickness and lymph node involvement are evaluated. MRI can evaluate the response in the early period after neoadjuvant treatment. At 10-15 days after completion of neoadjuvant treatment, the response can be evaluated with MRI [20].

Evaluation with diffusion MR has been observed to be more effective in response evaluation. Diffusion MR results are based on the information given about tissue density with contrast differences during the passage of water molecules between different tissues. The apparent diffusion coefficient (APC) is the measurement value of the free diffusion of water molecules. A high APC value shows higher diffusion. In malignancies showing a good response to treatment or in normal gastrointestinal organs the APC value is observed to be higher. Previous studies have examined APC values at 2-3 weeks after neoadjuvant treatment and have determined higher values in patients with complete response (pCR 34.6%- nonpCR 14%) [21]. In a study of 45 patients, diffusion MRI was determined to have 87% sensitivity and 58% specificity in the differentiation of good response (< 10% residual tumour cells) and poor response [20].

Computed tomography (CT) evaluation

Tumour size and oesophagus wall thickness are evaluated in evaluations made with CT imaging. In addition, metastasis and the status of lymph nodes and vascular structures can also be observed. However, CT is not a superior test in the evaluation of complete response. The accuracy rate is low in the evaluation of response in tumour cells because of the inflammation, oedema and fibrosis formed after neoadjuvant treatment. In previous studies, wall thickness of ≤ 5mm after neoadjuvant treatment is interpreted as able to show predicted complete response [22]. Perfusion CT imaging has been used in several studies in the evaluation of response to neoadjuvant CRT (23). Three perfusion parameters of blood flow (BF), blood volume (BV) and mean transit time (MTT) are used for oesophagus tissue in perfusion CT evaluation. Deng et al. reported that in 50% of patients with advanced grade oesophagus cancer who received neoadjuvant chemotherapy, BF and BV were significantly reduced and MTT increased in those with clinical response [24].

Positron Emission Tomography (PET / PET-CT) imaging evaluation

The metabolic activity of tumour cells is examined in PET evaluation. In the evaluation of metastasis and re-grading after neoadjuvant CRT, PET is extremely useful. There are a great many studies in literature showing pCR and evaluation of response with PET following neoadjuvant CRT. In those studies, a decrease in the SUVmax value has been found to be consistent with treatment response. Like the RECIST criteria, response criteria have also been defined for PET imaging. The PERCIST criteria are based on the evaluation of solid tumours with PET (25). According to these criteria;

- Complete metabolic response: Complete FDG resolution of tumour cells
- Partial metabolic response: A decrease of at least 30% FDG in tumour cells
- Stable metabolic disease: No change
- Progressive metabolic response: An increase of at least 30% FDG in tumour cells or the observation of new lesions

In a study by Wieder, a 44% decrease in the SUVmax value was found to be consistent with histopathological response (< 10% tumour cells observed in resection material) in patients with oesophageal squamous cell carcinoma who received neoadjuvant treatment [26]. In a study by Molena of patients with oesophageal squamous cell carcinoma, when the SUVmax value decreased by 70%, normal mucosa was observed in the endoscopic evaluation and no residual disease was observed in the biopsies taken, and of these patients, pathological full response was seen in 65% [27]. In another study, PET/CT was determined to have 67% sensitivity and 68% specificity in SUVmax evaluation after neoadjuvant CRT. It was attempted to determine a cutoff value for SUVmax in that study, and regression values of 30%-50%-70% were examined. All were found to be associated with 3-year OS. The strongest histopathological response was observed to be correlated with a decrease of 70% in metabolic activity [28]. Several studies have evaluated SUVmax < 4 as complete response, but a clear cutoff value has not been able to be defined [29].

In an analysis of 56 studies evaluating a total of 3625 patients, the capability of CT, PET, EUS, and MR imaging methods was examined in the evaluation of complete response. It was concluded that none of the methods provided sufficient success in showing complete response [30].

Surgery or Follow-up after Neoadjuvant Treatment?

Oesophagus cancer is a type of cancer with an extremely aggressive course. Even after surgical treatment, survival is not long. However, previous studies have shown that neoadjuvant CRT has prolonged survival. In the CROSS study, a survival benefit of 14% was observed with surgery after neoadjuvant CRT. According to the CROSS study, a pathological complete response was observed in 29% of patients (49% SCC, 23% AC) who received neoadjuvant CRT treatment. Following these high response rates, an organ-protective follow-up strategy was developed. Close follow-up is required following neoadjuvant CRT in this strategy [31]. There are great advantages to this treatment strategy, especially in respect of perioperative morbidity and mortality, and the decrease in quality of life which occurs after oesophagectomy is not observed [32].

In a study of 36 patients, in which a follow-up group was compared with a surgical group in respect of survival, no statistically significant difference was determined (58 months/51 months) [14]. In another study, when examined in respect of distant spread, the rates were observed to be similar at 31% in the follow-up group and 28% in the surgical group [33]. A study in Italy compared a follow-up group (n:38) and a surgical group (n:39) and reported similar rates of 57% in the follow-up group and 50% in the surgical group [34].

In a study that included 143 patients, surgery was applied to 43 patients following neoadjuvant CRT and definitive CRT (dCRT) to 100 patients. In respect of DFS, the rates of the surgical group were higher but the difference was not statistically significant, and no significant difference was determine between the groups in respect of OS. In the dCRT group, DFS was determined as 22.8% and OS as 17.6%. In the patients applied with dCRT+salvage surgery, the OS rates were observed to be higher than those of the patients who did not undergo surgery (35). In another study of 100 patients, the histopathological grading was calculated and pCR was observed in 45% of the patients. Survival was determined as 62.7 months in the patients with pCR and 5-year survival was found to be 58% [36].

In a study which scanned patients diagnosed with oesophagus adenocarcinoma between 2004 and 2014, patients applied with oesophagectomy were compared with those applied with neoadjuvant CRT+surgery and patients administered dCRT. Over the years there was seen to be an increase in dCRT and neoadjuvant CRT treatment methods. In the follow-up period of the patients, the best result in 5-year survival was in the patients treated with neoadjuvant CRT+surgery [37]. In an analysis of 2633 patients with grade 3 oesophagus adenocarcinoma, the 5-year survival rates were found to be dCRT 13% and neoadjuvant CRT+surgery 27%, and it was concluded that neoadjuvant CRT+surgery was statistically significant in respect of the survival benefit (38). In another meta-analysis of 4188 oesophagus adenocarcinoma patients, neoadjuvant CRT+surgery was found to be more effective in terms of survival than surgery alone [39]. In a study by Haefner, no statistically significant difference was determined between dCRT and neoadjuvant CRT + surgery in respect of 5-year survival [40]. Another study reported that of 125 patients who received neoadjuvant CRT, pathological complete response was observed in 27% [41].

A study including 130 oesophagus cancer patients examined patients treated with neoadjuvant CRT + surgery and patients treated with dCRT. Local recurrence was observed in 10.8% of the neoadjuvant CRT + surgery group and in 21.5% of the dCRT group. When evaluated in respect of survival, the period of DFS was found to be 15.6 months and OS was 20.6 months in those applied with neoadjuvant CRT, and DFS was 14.9 months and OS was 25.9 months in the patients who received dCRT. No statistically significant difference was determined between the groups in respect of these parameters [40]. In a very small study of 3 patients, surgery could not be performed in the the first patient because of the general condition, so neoadjuvant CRT was completed, and no recurrence was observed in the 4-year follow-up period. The second patient refused surgery, so neoadjuvant CRT was completed, and no local recurrence was observed in the 1-year follow-up period. In the third patient, complete response was observed but local recurrence developed in the follow-up period and the patient progressed to oesophagectomy [42].

Consequently, as there is no consensus in respect of a treatment protocol, applications are made according to the guideline recommendations.

According to the NCNN guidelines, if tumour cells are not observed in the follow-up evaluation after neoadjuvant CRT in both squamous cell carcinoma and adenocarcinoma of the oesophagus, the recommended view is that both follow-up can be applied and surgery can be performed.

According to the Japanese guidelines, endoscopy criteria have been defined in respect of complete response evaluation following neoadjuvant CRT treatment, but there is no clear consensus on a treatment

strategy.

CONCLUSION

Oesophagus cancer is a cancer which can have an extremely aggressive and mortal course. It has been attempted to prolong survival with various treatment strategies, and recently neoadjuvant treatment strategies for this purpose have become more prominent. However, there is no clear consensus about which methods can more accurately evaluate the response to neoadjuvant treatment. The survival advantage and success cannot be denied in patients with complete response after neoadjuvant CRT, but the reliability of the methods used to determine complete response to neoadjuvant treatment is not clear. No full consensus has been established on this subject.

Together with the lack of a clear answer to the question of how complete response can be evaluated, an answer is still being sought to the question of whether follow-up or surgery should be applied after neoadjuvant treatment. Two large-scale studies, the SANO study and the French ESOSTRATE study, are currently seeking an answer to this question. According to the SANO study, the follow-up strategy following neoadjuvant CRT has not produced results lower than those of the surgical strategy. The ESOSTRATE study, which includes 300 patients with oesophagus squamous cell carcinima and oesophagus adenocarcinoma, and the SANO study, which is at phase 2-3 level, are still ongoing and will be concluded in 2023 [43, 44].

Authors' Contribution

Study Conception: DD,; Study Design: DD, MAA,; Supervision: MAA,; Materials: DD,; Data Collection and/or Processing: DD,; Statistical Analysis and/or Data Interpretation: MAA,; Literature Review: MAA,; Manuscript Preparation: DD and Critical Review: MAA.

Conflict of interest

No potential conflicts of interest relevant to this article were reported.

Acknowledgements

We are grateful to all treating physicians in our center for collaboration and the data collection.

Financing

There is no source of financial support or funding.

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Are there any changes in the coagulation parameters before and after the treatment in children with hypothyroidia?

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Journal of Bursa Faculty of Medicine
e-ISSN:

Original Article

Pediatric

Received
December 18, 2022
Accepted
December 30, 2022
Published online
January 04, 2023

J Bursa Med 2023;1(1) 17-25

ABSTRACT

Objectives: Various coagulation and fibrinolysis disorders have been reported commonly in patients with thyroid dysfunction. Although it has been observed that bleeding time, protrombin time (PT), activated partial thromboplastin time (aPTT), platelet count, fibrinogen, D-dimer, Factor VIII, von Willebrand Factor have been investigated to examine the hemostatic profiles of patients with thyroid hormone disorders, studies on protein C, protein S, antithrombin 3 (ATIII), and homocysteine are rare.

Methods: The study included 25 healthy children without any hematological conditions and with normal renal and hepatic functions, as well as 25 children with hypothyroidism between the ages of 2 and 18 who were diagnosed in Pediatric Endocrinology outpatient clinics between March 2020 and June 2021, who had not yet received medical treatment, and whose TSH≥10 and fT4 levels were low for age (significant hypothyroidism), thyroid autoantibodies were negative. Complete blood counts, PT, aPTT, international normalized ratio (INR), fibrinogen, D-dimer, protein C, protein S, ATIII, homocysteine tests, and thyroid function tests were investigated. Age-appropriate L-thyroxine therapy was administered to hypothyroid patients for a period of 12 weeks. The differences between the coagulation parameters before and after treatment were compared once thyroid function tests had returned to normal ranges.

Results: Pretreatment PT, INR, D-dimer, hemoglobin, mean corpuscular volume (MCV) levels were found to be statistically similar between the control and study groups ($p > 0.05$). In hypothyroid patients, PTT, fibrinogen, protein C, protein S, ATIII levels were found to be statistically significantly lower than the control group before treatment ($p : 0.001$). While there was no significant change in D-dimer and INR levels of the patients in the study group before and after treatment ($p > 0.05$), there was a significant increase in PTT, fibrinogen, protein C, protein S, antithrombin 3, hemoglobin and MCV levels ($p : 0.001$). There was no statistically significant difference between the groups in terms of PT, INR, D-dimer, hemoglobin and MCV levels before treatment ($p > 0.05$).

Conclusions: There is a general decrease in anticoagulant proteins in children with hypothyroidism. It is important to closely monitor the coagulation system and especially the anticoagulant system. Thyroid hormones should be checked and hormone replacement

How to cite this article
Çalışkan H, KAzancı EG, Kara Ö, Güven D. Are there any changes in the coagulation parameters before and after the treatment in children with hypothyroidia? J Bursa Med 2023;1(1);17-25

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therapy should be applied if necessary in patients who are followed up due to coagulation tendency.
Keywords: hypothyroidism, hemostasis, bleeding, thrombosis, childhood

Hypothyroidism is one of the most common endocrinopathies resulting from insufficiency or, rarely, ineffectiveness of thyroid hormone. It is seen in 2% of females and 0.2% of males. In children, it is seen at a rate of approximately 0.15%. Hypothyroidism can result from problems at any level of the hypothalamic-pituitary-thyroid axis. If hypothyroidism occurs in fetal life or birth, it is defined as 'congenital hypothyroidism', and if it presents in childhood and adolescence, it is defined as 'acquired hypothyroidism' [1].

In patients with thyroid dysfunction, changes are seen in both primary and secondary hemostasis and the fibrinolytic system. In individuals with hypothyroidism, prolonged activated partial thromboplastin time (aPTT) and prothrombin time (PT) as well as increased bleeding time and decreased factor VIII, von Willebrand Factor (vWF) and fibrinogen levels have been observed, but the mechanisms are still not fully clarified [2].

The most common coagulation disorder in hypothyroidism is primary hemostasis abnormalities due to vWF disease. Although the pathogenesis of acquired vWF disease due to hypothyroidism is still not fully elucidated, the most likely explanation for hypothyroidism is decreased vWF protein synthesis as a result of decreased thyroxine levels [3, 4].

There are also changes in secondary hemostasis. Studies have shown that the levels and activities of coagulation factors involved in secondary hemostasis in patients with overt hypothyroidism decreased, their fibrinolytic activities increased (low α-2 antiplasmin, TPA (tissue plasminogen activator), PAI-1 (plasminogen activator inhibitor), high D-dimer levels), and decreased fibrinolytic activity (high a-2 antiplasmin, TPA, PAI-1, low D-dimer levels) in patients with subclinical hypothyroidism [5, 6]. The common conclusion of the studies; In overt hypothyroidism, there is a bleeding tendency ranging from a mild mucocutaneous hemorrhage to bleeding after a serious trauma, depending on the decrease in coagulation [7].

Although various studies have reported that the coagulation and fibrinolytic system is impaired in patients with hypothyroidism, there are limited studies investigating protein C, protein S, homocysteine, antithrombin III (ATIII) and homocysteine levels in patients with hypothyroidism. For these reasons, our aim was to investigate the profile of coagulation/fibrinolytic activation parameters, including protein C, protein S, homocysteine, and AT III in children with hypothyroidism, in our prospective, case-control, cross-sectional study, and also to determine the changes that developed with treatment.

METHODS

This study is a prospective, cross-sectional, case-control study and was approved by the Ethics Committee of Health Sciences University Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee dated 18.03.2020 and numbered 2011-KAEK-25.

Our study included twenty-five children and adolescent patients who applied to the Pediatric Endocrinology outpatient clinic between March 2020 and June 2021, had no additional hematological disease and a history of drug use, had normal renal and hepatic functions, had Tiroid stimülan hormon (TSH) ≥ 10 and low free T4 (fT4) levels for age (significant hypothyroidism), with negative thyroid autoantibodies and have not been treated yet. The physical examination (height, weight, body mass index, pubertal status, thyromegaly) data from the files of the patients were noted. Before the treatment, laboratory measurements of TSH, fT4, PT, INR, PTT, hemoglobin (Hgb), Mean corpuscular volume (MCV), fibrinogen, D-dimer, protein C, protein S, AT-III, homocysteine were performed.

Twenty-five healthy control groups of similar age, gender, and weight to patients with hypothyroidism were included in the study. Physical examination (height, weight, body mass index, pubertal status, thyromegaly) data of the control group were also noted. Laboratory measurements of serum TSH, fT4, PT, INR, PTT, Hgb, MCV, fibrinogen, D-dimer, protein C, protein S, AT-III, homocysteine were performed.

25 patients with hypothyroidism were given age-appropriate dose of L-thyroxine for 12 weeks. Changes in PT, INR, PTT, Hgb, MCV, fibrinogen, D-dimer, protein C, protein S, ATIII, homocysteine values were examined after thyroid function tests returned to normal values in patients who came for control after 12 weeks.

Thyroid function tests, complete blood counts and

PT, aPTT, INR, fibrinogen, D-dimer, protein C, protein S, AT-III, homocysteine tests were studied from 50 patients included in the study. Patients with hypothyroidism were given age-appropriate L-thyroxine therapy for 12 weeks. After thyroid function tests returned to normal values, changes in coagulation parameters before and after treatment were examined.

For TSH, T4, blood was collected in a vacuum gel tube with a yellow cap. After centrifuging at 3500 rpm for 15 minutes, measurements were made with the 'Architect plus I2000' device using the chemiluminescence method. For the hemogram, blood was taken into a purple capped tube with EDTA (ethylenediaminetetraacetic acid) and studied with the impedance method in the 'Mindray BC 6000' device without centrifugation. Blood is taken into a sodium citrate blue capped tube and centrifuged at 3000 rpm for 10 minutes, then PT, aPTT, fibrinogen by coagulometric method with 'Sysmex CS 5100' device, D-dimer by immunoassay method with 'Sysmex CS 5100' device, protein C, protein S, Measurements were made with the AT-III 'Sysmex CS 5100' chromogenic method. For homocysteine, the blood taken into heparinized green capped tube was centrifuged at 3000 rpm for 10 minutes and studied with the enzymatic method with the 'Roche Cobas c502' device.

Statistical analysis

IBM SPSS Statistics 22 program was used for statistical analysis. The suitability of the parameters to the normal distribution was evaluated by Kolmogorov-Smirnov and Shapiro Wilk tests. While evaluating the study data, in addition to descriptive statistical methods (mean, standard deviation, median, frequency), Student's t-test was used for the comparison of normally distributed parameters between two groups, and Mann Whitney U test was used for comparisons of non-normally distributed parameters between two groups. Paired Sample T test was used for in-group comparisons of normally distributed parameters, and Wilcoxon Sign Test was used for in-group comparisons of non-normally distributed parameters. Fisher's Exact Chi-Square test and Continuity (Yates) Correction were used to compare qualitative data. Significance was evaluated at the $p < 0.05$ level.

RESULTS

The median age of the patients was 13 (12.43 ± 3.56) years for the study group and 13.3 (13.11 ± 2.21) years for the control group. Eighteen (72%) of the study group were females, 7 (28%) were males, and 14 (56%) of the control group were females and 11 (44%) were males. There was no significant difference between the study and control groups in terms of age and gender ($p > 0.05$) (Table 1).

There was no statistically significant difference between the median body weights of the study and control groups (p : 0.403). There was no statistically significant difference between the standard deviation of body weights of the control and study groups (p : 0.823). There was no statistically significant difference between the mean height measurements of the control and study groups (p : 0.218). There was no statistically significant difference between the height

Table 1. Evaluation of groups in terms of demographic characteristics

	Hypothyroidism (n = 25)	Control (n = 25)	
	Mean ± SS (median)	Mean ± SS (median)	*p*
Age (years)	12.43 ± 3.56 (13)	13.11 ± 2.21 (13.3)	0.648
Weight (kg)	52.38 ±14.42 (53.2)	55.32 ± 7.51 (55)	0.403
Weight ss	0.97 ± 0.98 (1)	0.98 ± 0.92 (1.48)	0.823
Height (cm)	153.45 ± 15.72 (160)	157.33 ± 11.60 (162)	0.218
Height ss	0.57 ± 0.61 (0.59)	0.58 ± 0.52 (0.61)	0.861
BMI (kg/m$^{2)}$	20.16 ± 3.55 (19.7)	20.22 ± 2.63 (20)	0.943
BMI ss	0.27 ± 1.14 (0.5)	0.05 ± 0.73 (0.1)	0.421
Gender*			
Female	18 (%72)	14 (%56)	0.377
Male	7 (%28)	11 (%44)	
Thyromegaly n (%)	2 (%8)	0 (%0)	0.490

ss: standard deviation, BMI: Basal metabolic index * n(%)

Table 2. Evaluation of the groups in terms of study parameters before treatment

	Hypothyroidism	Control	
Before treatment	**Mean ± SS (median)**	**Mean ± SS (median)**	***p***
TSH (µIU/ml)	20.75 ± 16.93 (14.1)	2.93 ± 0.98 (2.9)	0.001
fT4 (ng/dl)	0.92 ± 0.15 (0.9)	1.1 ± 0.16 (1.1)	0.001
PT (sn)	12.04 ± 0.6 (11.9)	11.84 ± 0.64 (11.7)	0.280
aPTT (sn)	24.22 ± 1.68 (24)	25.88 ± 1.78 (26.1)	0.001
D-Dimer (mg/L)	0.25 ± 0.1 (0.2)	0.26 ± 0.11 (0.2)	0.418
Fibrinogen (mg/dl)	276.84 ± 57.69 (276)	368.96 ± 97.14 (355)	0.001
Hemoglobin (g/dl)	12.98 ± 0.8 (13)	13.35 ± 0.79 (13.3)	0.114
MCV (fL)	81.71 ± 2.48 (82.3)	82.56 ± 2.22 (82.3)	0.351
Protein C (%)	71.57 ± 14.42 (68.6)	116.6 ± 26.59 (111.7)	0.001
Protein S (%)	72.49 ± 11.86 (71)	125.65 ± 45.43 (116.1)	0.001
AT-III (%)	33.15 ± 2.16 (33.2)	37.19 ± 2.12 (37.2)	0.001

TSH: Thyroid stimulating hormone, fT4: Free T4, PT: Prothrombin time, aPTT: Active partial thromboplastin time,MCV: Mean corpuscular volume, AT-III: antithrombin III

standard deviation of the control and study groups (*p* : 0.861). There was no statistically significant difference between the body mass index of the study and control groups (*p*:0.943). There was no statistically significant difference between the body mass index standard deviation of the control and study groups (*p* : 0.421) (Table 1). There was no statistically significant difference between the groups in terms of the incidence of thyromegaly ($p > 0.490$). While thyromegaly was observed in two children (8%) in the hypothyroidism group, it was not observed in any of the children in the control group (Table 1).

The median TSH value of the hypothyroid group was 14.1 (20.75 ± 16.93) µIU/ml, and 2.9 (2.93 ± 0.98) µIU/ml in the control group. The TSH level of the hypothyroid group was found to be statistically significantly higher than the control group (*p* : 0.001) (Table 2). The median fT4 and aPTT levels of the hypothyroid group were found to be statistically significantly lower than the control group (*p* : 0.001) (Table 2). There was no statistically significant difference between the PT levels of the hypothyroid and control groups (*p* : 0.28) (Table 2). The median D-dimer value of the hypothyroid group was 0.2 (0.25 ± 0.1) mg/L, and 0.2 (0.26 ± 0.11) mg/L in the control group. There was no statistically significant difference in D-dimer levels of the two groups (*p* : 0.4) (Table 2). The median fibrinogen value of the hypothyroid group was 276 (276.84 ± 57.69) mg/dl, and 355 (368.96 ± 97.14) mg/dl in the control group. The fibrinogen level of the hypothyroid group was found to be statistically significantly lower than the control group (*p* : 0.001) (Table 2). The median protein C value in the hypothyroid group was 68.6% (71.57 ± 14.42), while it was 111.7% (116.6 ± 26.59) in the control group. When the levels of both groups were compared, it was found that the protein C level of the hypothyroid group was statistically significantly lower than the control group (*p* : 0.001) (Table 2). The median protein S value of the hypothyroid group was 71% (72.49 ± 11.86), while it was 116.1% (125.65 ± 45.43) in the control group. When the levels of both groups were compared, it was found that the protein S level of the hypothyroid group was statistically significantly lower than the control group (*p* : 0.001) (Table 2). The median ATIII value of the hypothyroid group was 33.2% (33.15 ± 2.16), while it was 37.2% (37.19 ± 2.12) for the control group. When the levels of both groups were compared, it was found that the ATIII level of the hypothyroid group was statistically significantly lower than the control group (*p* : 0.001) (Table 2). The median Hgb value of the hypothyroid group was 13 (12.98 ± 0.8) g/dl, while it was 13.3 (13.35 ± 0.79) g/dl for the control group. When the Hgb levels of both groups were compared, it was found that there was no statistically significant difference (*p* : 0.11) (Table 2). The median MCV value of the hypothyroid group was 82.3 (81.71 ± 2.48) fL, while it was 82.3 (82.56 ± 2.22) fL for the control group. When the MCV levels of both groups were compared, it was found that there was no statistically significant difference (p : 0.35) (Table 2).

The median TSH value of the patients was found to be 14.1 (20.75 ± 16.93) µIU/ml for pre-treatment and 2.5 (2.44 ± 1.15) µIU/ml for post-treatment. When

Table 3. Evaluation of post-treatment changes in hypothyroidism group compared to pre-treatment

	Hypothyroidism		
	Before treatment	After treatment	
	Mean ± SS (median)	Mean ± SS (median)	*p*
TSH (µIU/ml)	20.75 ± 16.93 (14.1)	2.44 ± 1.15 (2.5)	0.001
fT4 (ng/dl)	0.92 ± 0.15 (0.9)	1.1 ± 0.21 (1)	0.001
PT (sn)	12.04 ± 0.6 (11.9)	12.35 ± 0.69 (12.5)	0.022
aPTT (sn)	24.22 ± 1.68 (24)	25.07 ± 1.99 (25)	0.015
D-Dimer (mg/L)	0.25 ± 0.1 (0.2)	0.24 ± 0.09 (0.2)	0.704
Fibrinogen (mg/dl)	276.84 ± 57.69 (276)	312.6 ± 66.08 (310)	0.006
Hemoglobin (g/dl)	12.98 ± 0.8 (13)	13.44 ± 0.78 (13.5)	0.001
MCV (fL)	81.71 ± 2.48 (82.3)	83.53 ± 3.1 (84.3)	0.001
Homosistein(µmol/L)	8.59 ± 1.68 (8.5)	9.48 ± 1.91 (9.1)	0.001
Protein C (%)	71.57 ± 14.42 (68.6)	85.4 ± 12.96 (84.6)	0.001
Protein S (%)	72.49 ± 11.86 (71)	85.98 ± 14.53 (80)	0.001
AT-III (%)	33.15 ± 2.16 (33.2)	34.76 ± 2.08 (34.9)	0.001

TSH: Thyroid stimulating hormone, fT4: Free T4, PT: Prothrombin time, aPTT: Active partial thromboplastin time, MCV: mean corpuscular volume, AT-III: antithrombin III

the TSH levels of the patients were evaluated before and after the treatment, it was found that the TSH levels after L-thyroxine treatment were lower than before the treatment (*p* : 0.001) (Table 3). The median fT4 value of the patients was found to be 0.9 (0.92 ± 0.15) ng/dl for pre-treatment and 1 (1.1 ± 0.21) ng/dl for post-treatment. When the fT4 levels of the patients were evaluated before and after the treatment, it was found that the fT4 levels after L-thyroxine treatment were lower than before the treatment (*p* : 0.001) (Table 3). The median PT value of the patients was 11.9 (12.04 ± 0.6) seconds before treatment and 12.5 (12.35 ± 0.69) seconds after treatment. When the PT levels of the patients before and after the treatment were evaluated, it was found that the PT levels after L-thyroxine treatment were higher than before the treatment (*p* : 0.022) (Table 3). The median aPTT value of the patients was 24 (24.22 ± 1.68) seconds before treatment and 25 (25.07 ± 1.99) seconds after treatment. When the aPTT levels of the patients were evaluated before and after the treatment, it was found that the aPTT levels after L-thyroxine treatment were higher than the pretreatment period (*p* : 0.015) (Table 3). D-dimer median value of the patients was 0.2 (0.25 ± 0.1) mg/L for pre-treatment and 0.2 (0.24 ± 0.09) mg/L for post-treatment. When the D-dimer levels of the patients were evaluated before and after the treatment, no significant change was found in the D-dimer levels after L-thyroxine treatment (*p* : 0.07) (Table 3). The median fibrinogen value of the patients was found to be 276 (276.84 ± 57.69) mg/dl before treatment and 310 (312.6 ± 66.08) mg/dl after treatment. When the fibrinogen levels of the patients were evaluated before and after the treatment, it was found that the fibrinogen levels after L-thyroxine treatment were higher than before the treatment (p : 0.006) (Table 3). The median protein C value of the patients was determined as 68.6% (71.57±14.42) before treatment and 84.6% (85.4 ± 12.96) after treatment. When the protein C levels of the patients were evaluated before and after the treatment, it was found that the protein C levels after L-thyroxine treatment were higher than before the treatment (*p* : 0.001) (Table 3). The median protein S value of the patients was 71% (72.49 ± 11.86) before treatment and 80% (85.98 ± 14.53) after treatment. When the protein S levels of the patients were evaluated before and after the treatment, it was found that the protein S levels after L-thyroxine treatment were higher than before the treatment (*p* : 0.001) (Table 3). AT III median value of the patients was found as 33.2% (33.15 ± 2.16) for pre-treatment and 34.9% (34.76 ± 2.08) for post-treatment. When the AT III levels of the patients were evaluated before and after the treatment, it was found that the AT III levels after L-thyroxine treatment were higher than before the treatment (*p* : 0.001) (Table 3). The median Hgb value of the patients was found to be 13 (12.98 ± 0.8) g/dl before treatment and 13.5 (13.44 ± 0.78) g/

dl after treatment. When the Hgb levels of the patients were evaluated before and after the treatment, it was found that the Hgb levels after L-thyroxine treatment were higher than before the treatment (p : 0.001) (Table 3). The median MCV value of the patients was found to be 82.3 (81.71 ± 2.48) fL for pre-treatment and 84.3 (83.53 ± 3.1) fL for post-treatment. When the MCV levels of the patients were evaluated before and after the treatment, it was found that the MCV levels after L-thyroxine treatment were higher than before the treatment (p : 0.001) (Table 3). The median homocysteine value of the patients was 8.5 (8.59 ± 1.68) µmol/L for pre-treatment and 9.1 (9.48 ± 1.91) µmol/L for post-treatment. When the homocysteine levels of the patients were evaluated before and after the treatment, it was found that the homocysteine levels after L-thyroxine treatment were higher than before the treatment (p : 0.001) (Table 3).

DISCUSSION

Various coagulation and fibrinolysis disorders have been commonly reported in patients with thyroid dysfunction. However, what type of coagulation disorder the thyroid disorder causes, the type, and the mechanism behind these links are confusing and controversial.

The relationship between thyroid disorder and the hemostatic system was first described by Kaliebe in 1913 [8]. Kaliebe stated that cerebral thrombosis may be related in a patient with Graves' disease, and a later study by Squizzato *et al*. supported that there was a relationship between thyroid hormone and venous thrombosis [9]. Later studies focused on changes in the levels of coagulation factors in patients with thyroid disease, and it was shown that hyperthyroidism is mostly associated with prothrombotic changes. Although the exact mechanism is still unproven, the most recommended is increased vWF and FVIII levels [10, 11]. Bleeding tendencies with possible platelet dysfunction or autoimmune development have also been reported in hyperthyroidism [12, 13]. Individuals with reduced thyroxine levels had prolonged aPTT and PT, as well as increased bleeding time and decreased FVIII, vWF, and fibrinogen levels. However, reports from previous literature on hypothyroidism are still controversial.

Although there are many studies on bleeding time, PT, aPTT, platelet count, fibrinogen, D-dimer, FVIII, vWF to examine the hemostatic profiles of patients with thyroid hormone disorders, only a few studies have reported protein C, protein S, ATIII, and homocysteine. has been studied.

Gao *et al*. showed that aPTT, PT, and INR levels were prolonged in 53 adult patients with different degrees of hypothyroidism (14). Gullu *et al*. reported that PT and aPTT values were prolonged in their study in adult patients with overt hypothyroidism and low platelets [15]. It was observed that each of the above-mentioned parameters returned to normal values after levothyroxine treatment. Contrary to the studies mentioned, in our study, pre-treatment PT and aPTT levels of the hypothyroid group were found to be lower than those of the control group, while a significant increase was observed after the treatment. This can be explained by the fact that the platelet count was within the normal range in our patient group and only pediatric patients with overt hypothyroidism were included in the study.

Chadarevian *et al*. studied the fibrinolytic system in patients with overt hypothyroidism and observed a different fibrinolytic pattern depending on the severity of hypothyroidism [16, 17]. It was found that fibrinolytic activity was increased in patients with overt hypothyroidism (low α-2 antiplasmin, TPA, PAI-1, fibrinogen and high D-dimer levels), and decreased fibrinolytic activity in patients with subclinical hypothyroidism (high α-2 antiplasmin, TPA, PAI-1, low D-dimer levels) were observed. Ozcan *et al*. found that patients with various thyroid disorders, the fact that TFPI (tissue factor pathway inhibitor) level was found to be higher in patients with overt hypothyroidism compared to patients with subclinical hypothyroidism supports this study [18]. In overt hypothyroidism, mean fibrinogen levels were increased by 14.2% after treatment. They also confirmed that coagulation factor abnormalities were corrected upon levothyroxine replacement therapy.

In the study of Gürsoy *et al*. in patients with hypothyroidism, fibrinogen and D-dimer levels were found to be significantly higher than in controls, and the results after treatment were similar to those of patients with hypothyroidism [19]. Cantürk *et al*. were give LT4 treatment 35 patients with subclinical hypothyroidism for 6 months; it was determined that the fibrinogen levels of patients with subclinical hypothyroidism were higher than those of healthy individuals in the control group, but did not change despite LT4 treatment [20]. Çakal *et al*. reported that the fibrinogen levels of patients with overt hypothyroidism were higher than those in the control group [21]. In a study

by Erem C. it was reported that the fibrinogen levels of patients with subclinical hypothyroidism were not different from those in the control group [22]. In our study, after a 12-week follow-up with the overtly hypothyroid patients who received LT4 treatment, it was discovered that the pre-treatment fibrinogen level was statistically significantly lower than the control group (p : 0.001). However, the increase seen after the treatment compared to the pre-treatment fibrinogen level was statistically significant (p : 0.006). These findings also support studies conducted with other patients with overt hypothyroidism. However, there was no statistically significant change in D-dimer levels between the hypothyroid and control groups after treatment ($p > 0.05$). The common conclusion of these studies is that there is an increased bleeding tendency in overt hypothyroidism, while patients with subclinical hypothyroidism are predisposed to thrombosis.

Balci *et al*. located that MCV values were significantly higher in their study of patients with subclinical hypothyroidism when compared to the control group [23]. There was no statistically significant difference between the Hgb and MCV values of the hypothyroid patients and the control group in our study of patients with overt hypothyroidism. However, after treatment, the hypothyroid patient group's hemoglobin and MCV levels increased in a statistically significant way (p : 0.001).

Elevated homocysteine is a cause of thrombophilia that has been shown to cause both arterial and venous thrombosis [24]. High homocysteine levels can also be observed in cases where thyroid hormone levels are low [25]. However, the number of studies on the relationship between overt hypothyroidism and homocysteine is very limited. In 7 of 8 studies evaluating homocysteine levels in patients with subclinical hypothyroidism, it was found that homocysteine levels of patients with subclinical hypothyroidism were not different from the control groups. Sengul *et al*. found that homocysteine levels increased in patients with subclinical hypothyroidism and that existing homocysteine levels decreased with LT4 treatment [26].

Jackal *et al*. found that homocysteine levels in 20 patients with overt hypothyroidism were higher in 15 patients with subclinical hypothyroidism than in healthy individuals in the control group, and homocysteine levels decreased with LT4 treatment [21]. In our study, the increase in homocysteine levels of hypothyroid patients who were given LT4 treatment after 12 weeks of follow-up was found to be statistically significant (p : 0.001). Although our result is consistent with the results of the studies conducted by Şengül and Çakal, our patient group consists of individuals with overt hypothyroidism. The results of other studies show that individuals with subclinical hypothyroidism have a tendency to hypercoagulability, while the results of our study support the results of other studies in the literature showing the tendency of patients with overt hypothyroidism to bleed.

It is known that a decrease in the activity of anticoagulant proteins AT III, protein C, and protein S may lead to thromboembolic events. These proteins have been evaluated within the scope of the relationship between hypothyroidism and hemostasis in previous studies. Erem *et al*. found in their study on 20 hypothyroid patients that protein C and protein S activities were similar between the overt hypothyroid and control groups, whereas AT-III activity was higher in the patient group [22]. Müller *et al*. found that ATIII, protein C, and protein S activities were similar between the patient and control groups in another study they conducted with 42 female patients with subclinical hypothyroidism [27]. Kilic *et al*. found that ATIII, protein C, and protein S activities were lower in the hypothyroid patient group compared to the control group in their study with 54 overt hypothyroid patients and 55 healthy children [28]. In our study, ATIII, protein C, and protein S activities were lower than the healthy controls, and the increase in these values after treatment was statistically significant (p : 0.001). Although our study is consistent with the results of Kılıç *et al*., it supports other studies showing that patients with hypothyroidism have a high tendency to thrombosis.

Limitations of the Study

The small number of patients and the need for studies with larger series are one of the limiting factors of the study. In addition, the fact that we could not study parameters such as PAI and TFPI, which are more sensitive in terms of fibrinolytic system, is another limiting factor.

CONCLUSION

In conclusion, in the light of all these findings, it shows that there is a general decrease in anticoagulant proteins in children with hypothyroidism and the risk of thrombosis may be related to many factors. For this reason, we would like to emphasize that patients followed up with a diagnosis of hypothyroidism should be followed up for thrombosis. However, the

improvement of this condition with treatment reveals the importance of early diagnosis and treatment of hypothyroidism. In addition, thyroid hormones should be checked in patients followed up for thrombosis, and thyroid hormone replacement therapy should be administered if necessary. In addition, studies with larger series are needed to investigate the effects of hypothyroidism on the coagulation system.

Authors' Contribution

Study Conception: EGK,; Study Design: ÖK,; Supervision: HÇ,; Materials: ÖK,; Data Collection and/or Processing: HÇ,; Statistical Analysis and/or Data Interpretation: HÇ,; Literature Review: DG,; Manuscript Preparation: DG, HÇ and Critical Review: EGK.

Conflict of interest

The authors declare that they have no conflicts of interests.

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Demographic, etiological, clinical features, and laboratory features of hepatocellular carcinoma; a single center experience

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Journal of Bursa Faculty of Medicine
e-ISSN:

Original Article

Hematology

Received
November 30, 2021
Accepted
December 24, 2021
Published online
January 04, 2023

J Bursa Med 2023;1(1) 26-32

ABSTRACT

Objectives: Hepatocellular carcinoma (HCC) is our country's most commonly encountered cancer. This study examined demographic, etiologic, clinical characteristics, and biochemical and serological findings of patients with HCC.

Methods: We retrospectively analyzed 207 HCC patients followed by gastroenterology and medical oncology departments.

Results: It was established that, in the demographic analysis, HCC was more common in the elderly population, especially in men. The positive hepatitis B virus surface antigen rate was 65.5%, anti-delta was 2%, and hepatitis C virus antibody was determined to be 15%. The rate of alcohol users was 11.1%, and that of tobacco users was 68.2%. Serum alkaline phosphatase, gamma-glutamyl transferase, and serum alpha-fetoprotein (AFP) levels were above average in 75.6%, 86.3%, and 72.6% of patients, respectively. Approximately 63% of patients had cirrhosis at presentation. Ultrasonography (USG) was the primary diagnostic method in 57% of the patients. Histopathological diagnosis was made by ultrasound-guided biopsy in 67.6% of the patients.

Conclusion: Chronic hepatitis B was the most common etiological factor for HCC, and chronic hepatitis C was observed at a significant rate of 15%. The majority of the patients developed HCC on the cirrhotic ground. Most of the patients had high levels of AFP. In 58% of patients, the tumor was located in the right lobe. Routine liver tests and clinical findings varied. Radiologically, it was concluded that USG, computed tomography, and magnetic resonance imaging techniques were complementary and equivalent methods in terms of tumor diameter

Keywords: Hepatocellular carcinoma, Hepatitis B virus, Hepatitis C virus, Alpha-fetoprotein.

Hepatocellular carcinoma (HCC) is a malignant tumor of the liver which originates from hepatocytes. HCC is the fifth most common cause of cancer worldwide and the second leading cause of cancer death, accounting for nearly more than 500,000 deaths annually. HCC is the fifth most common malignancy in men and the eighth in women. The 5-year overall survival rate is below 5% [1]. HCC frequently occurs in the setting of chronic liver disease or cirrhosis. Hepatitis B virus (HBV), hep-

How to cite this article
Ersal T, Lika Karabulut F. Demographic, etiological, clinical features, and laboratory features of hepatocellular carcinoma; a single center experience. J Bursa Med 2023;1(1):26-32

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atitis C virus (HCV), alcoholic liver disease, exposure to toxic chemicals and probably non-alcoholic steatohepatitis are considered amongst the major causes of cirrhosis in patients with HCC. Rarer causes include hereditary hemochromatosis, alpha-1 antitrypsin deficiency, autoimmune hepatitis and some types of porphyria. Globally, HBV is the most common cause of HCC [2]. Most of patients are asymptomatic during the early period. In patients with compensated cirrhosis, acute development of liver failure signs such as ascites, encephalopathy, jaundice or variceal bleeding is important with regard to HCC. These signs may indicate the tumoral invasion of hepatic or portal vein or arteriovenous shunting [3]. The physical examination in HCC patients reveals the findings related to the underlying liver disease (splenomegaly, ascites, jaundice or other findings of decompensated cirrhosis) [4]. 4 Laboratory tests are often non-specific. Thrombocytopenia, hypoalbuminemia, hyperbilirubinemia and hypoprothrombinemia can be identified in most cirrhotic patients with HCC. Serum aminotransferases, alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) levels are often abnormal but are non-specific [5].

In 10-20% of patients, metastatic dissemination is evident at the time of initial diagnosis. Extrahepatic metastasis generally occurs in patients with a tumor size of more than 5 cm in diameter. The most frequent metastasis sites involve lungs, intraabdominal lymph nodes, bone, brain and adrenal glands [6, 7].

The diagnostic delay is common in HCC due to lack of specific pathognomonic signs as well as the presence of a large liver functional reserve, and therefore many patients experience delay in receiving appropriate treatment at the time of diagnosis [8, 9]. The average survival time after the diagnosis ranges from 6 to 20 months [10]. Large tumor size, vascular invasion, deterioration in functional status and nodal metastases are poor prognostic indicators [9, 11]. American Association for the Study of Liver Diseases (AASLD) guidelines recommend further investigation for HCC in patients with underlying liver disease (i.e., cirrhosis, chronic viral hepatitis) who have concomitantly elevated serum alpha-fetoprotein (AFP) levels [11]. In these patients, computed tomography (CT) screening and/or magnetic resonance imaging (MRI) of liver should be performed as the first-line modalities of diagnosis [12]. The definite diagnosis of HCC is often based on the presence of hyper-vascular lesion with T2 hyperintensity and venous invasion characteristics or accompanied with AFP elevation.

AFP levels are commonly used as a marker in HCC. The elevation of AFP levels in cirrhotic patients is suggested to be important in terms of HCC development. Although AFP levels > 500 ng/ml (normal reference range: 10-20 ng/ml) in high-risk patients are considered to be diagnostic for HCC, [13] patients with low AFP levels are also diagnosed with HCC through screening studies [14, 15].

Several imaging modalities such as Ultrasonography (USG), CT, MRI and angiography are used in the diagnosis of HCC. USG, often together with AFP levels, is used for screening purposes.

Cancer staging is of utmost importance for determining the disease prognosis and the appropriate treatment options. Severity of underlying liver disease, tumor size, tumoral invasion to surrounding structures and metastasis status are the four key factors in terms of survival among HCC patients [16-19].

Predicting survival is challenging in HCC due to concomitant presence of cirrhosis and tumor as the two underlying diseases. The residual hepatic functional reserve has been reported to be directly correlated with prognosis in several studies. This indicates the stronger role of cirrhosis rather than tumor size as a main predictor of survival outcome. In newly diagnosed untreated HCC patients, survival is limited to weeks or months [20].

Several factors have been associated with poor survival outcome including male gender, advanced age, etiological factor (poorer prognosis in HCV vs. HBV), presence of multiple risk factors, number and volume doubling time of nodules, vascular invasion and distant metastasis [21].

Liver transplantation is considered a curative treatment for HCC. Curative resection is one of the treatment options in HCC [22, 23]. However, in most of cases, the tumor is beyond the resection limits at the time of diagnosis along with failure to meet inclusion criteria for transplantation programs. In such cases, nonsurgical treatment modalities can be utilized such as local ablation (ethanol, acetic acid, radiofrequency, cryoablation), trans-arterial chemoembolization, radioactive iodine and lipiodol therapy [24-26].

In patients with advanced HCC, routine use of chemotherapy is not possible due to several reasons. HCC is a relatively chemotherapy-resistant tumor. Chemotherapy cannot be tolerated by patients with severe hepatic dysfunction, while efficacy of chemotherapy is also low among patients with significant cirrhosis. Comparative efficacy of several chemotherapeutics including doxorubicin, tamoxifen, megestrol, interferon

alpha, antiandrogens and sorafenib have been reported in the randomized controlled studies. Apart from sorafenib, use of these agents caused marked toxicity with no significant survival benefit or improvement in complete response rates [27, 28].

In this study, we aimed to evaluate patients diagnosed with HCC in our hospital in terms of etiological, demographic, clinical and laboratory characteristics.

METHODS

A total of 207 patients diagnosed with HCC based on clinical, radiological and pathological findings were included in this retrospective study conducted at tertiary care gastroenterology and oncology clinics of ***** Training and Research Hospital in 2010.

Data on patient demographics (age, gender), biochemical and serological parameters, etiology, symptoms and physical examination findings at initial admission, presence of paraneoplastic syndrome, diagnostic and screening tests and final diagnosis after biopsy and tests were retrieved from hospital records. Smoking status and alcohol consumption as well as the concomitant medications such as oral contraceptive, androgen or steroids were also recorded.

RESULTS

Overall, 77.29% of patients were males. Median patient age in males and females were 58 years and 64 years, respectively. HBV positivity was noted in 68.2% of patients, while 16.6% of patients were HCV positive. History of regular alcohol consumption and smoking were noted in 11.1% and 62.8% of patients, respectively. Alcohol was considered the isolated risk factor only in 3 patients. The most frequent symptoms on initial admission were abdominal pain (30%), weight loss (19%), fatigue (16%) and jaundice (11%). Physical examination on initial admission revealed hepatomegaly and splenomegaly in 61.84% of patients, while ascites was noted in 70% of patients. Paraneoplastic syndrome was evident in 73 patients at the time of initial admission. The most common laboratory abnormalities included hyperlipidemia (65%) followed by hyperuricemia (17%), hypoglycemia (8%) and hypercalcemia (5%). Chronic hepatitis and cirrhosis were evident in 78% and 64% of patients, respectively at the time of initial diagnosis, while HCC was the first diagnosis in 33 patients without chronic hepatitis or cirrhosis. USG was the first diagnostic test used in 54% of patients. Assessment regarding the localization of the tumor revealed the tumor to be

Table 1. Demographic and clinical characteristics

Patient characteristics	n	%
Total	207	100
Gender		
Male	160	77.29
Female	47	22.71
Age		
Median	59	
Min-max	17-84	
Clinical Presentation		
Stomachache	103	30
Weight loss	65	19
Weakness	55	16
Jaundice	36	11
Swelling	28	8
Nausea-vomiting	16	5
Fever	14	4
Anorexia	10	3
Other (anorexia, constipation, itching, bone pain, cough)	14	4
Physical examination findings		
Hepatomegaly	128	61.8

Table 1 *contunied*. Demographic and clinical characteristics

Splenomegaly	107	51.7
Ascites	63	30
Icterus	39	18.8
Palmar erythema	32	15.4
Spider angioma	11	5.3
Venous collateral	10	4.8
Gynecomastia	3	1.5
Hepatitis serology		
HBV	120	58
HCV	23	11.1
HBV+HCV	7	3,4
HBV+HDV	4	1.9
Negative	46	22.2
Paraneoplastic syndrome		
Hyperlipidemia	48	65
Hyperuricemia	13	17
Hypoglycemia	11	15
Hypercalcemia	6	8
Hypokalemia	5	7
Gynecomastia	5	7
Hypothyroidism	3	4
Alcohol abuse	23	11.1
Tobacco abuse	130	62.8
OS (month)		
Median	7	
Min-max	0.25-48	

Abbreviations: HBV: hepatitis B virus, HCV: hepatitis C virus, HDV: hepatitis D virus, TNM: Tumor, lymph node, metastasis, OS: Overall survival.

located in the right lobe in 85% of cases. The HCC was diagnosed pathologically with biopsy in 68% of patients, while 32% of patients were diagnosed on the basis of clinic and radiological findings. According to TNM staging, 34% of patient had stage 3A disease, followed by stage 4A (17%), stage 3C (13%), stage 1 (12%), stage 4B (11%), stage 2 (9%) and stage 3B (4%) (Table 1). Excluding the 18 patients with no data available on AFP levels, AFP levels were found to be higher than normal in 78.8% of patients. AFP levels were > 100 ng/mL in 114 patients, > 400 ng/mL in 69 patients and > 1000 ng/mL in 39 patients (Table 2).

DISCUSSION

Although decrease in the incidence of HCC has been expected in relation to improved living standards in certain societies, the studies revealed paradoxical results indicating the incidence of HCC to be still on the unpreventable rise. In an autopsy study from Japan, assessment of 19357 autopsies revealed HCC rates to increase from 1.91% in years 1958-1959 to 7.66% in years 1986-1987 [29]. HBV infection is the etiological factor in nearly 80% of HCC cases and

HCC incidence correlates with HBV carrier rates [30].

In the current study, HBV positivity was noted in 68.2% of patients. Overall, 9 patients were HBsAg negative anti-HBc IgG positive. In a study by Matsuzaki *et al*. among Japanese patients with no serological findings related to HBV and HCV in the recent past, HBV-DNA was demonstrated to be integrated to the host genome, indicating that previous history of

Table 2. Baseline laboratory results of patients

Variables	Median	Min-max	Standard deviation
ALP (mg/dL)	389	33-3500	459.8
GGT (mg/dL)	221	16-1295	228.4
Bilirubin (mg/dL)	2.6	0.2-48	5.2
Albumin (g/dL)	3.2	1.2-5.1	0.9
LDH (U/L)	455.4	2-2215	294.5
AFP (ng/mL)	4376	0.6-54000	12912.3

Abbreviations: ALP: alkaline phosphatase, GGT: gamma glutamyl transferase, LDH: lactate dehydrogenase, AFP: fetoprotein.

HBV infection may also have a role in the neoplastic development [31].

HCV positivity was noted in 16.6% of our patients. This rate seems to emphasize a need for further investigation on HCV positivity, given that it represents the second most common risk factor in developing HCC, while in a study with 54 patients with primary liver tumor, none of patients had HCV positivity [32].

In our study, regular alcohol consumption rate was 11.1%. However, only 6 patients reported heavy alcohol consumption with at least 60 g daily alcohol consumption for more than 10 years. In addition, of 22 cirrhotic patients with alcohol consumption, alcohol was the isolated risk factor only in 3 patients who were also heavy alcohol consumers, while HBV positivity was evident in 16 patient, HCV positivity in 2 patients and HBV plus HCV positivity in 1 patient. Accordingly, on the basis of this rate, alcohol should be considered as a severe risk factor which also has a synergistic effect, in combination with the other concomitant etiologic factors, in progression to cirrhosis.

Although at initial admission, chronic hepatitis and cirrhosis diagnoses were noted in 78% and 64% of our patients, respectively; further clinical, laboratory, radiological and endoscopic evaluation after hospitalization of patients revealed the cirrhosis rate of 80.6%. This seems in accordance with the literature findings indicating 80-90% of HCC cases to be due to underlying cirrhosis.

Considering the localization of the tumor, our findings revealed the tumor to be located in the right lobe in 85% of cases. This finding is in agreement with distribution of tumor localization reported in a study by Özdemir *et al*. [32]

The USG was the first diagnostic test used in 54% of our patients, while CT and MRI were used as supportive diagnostic modalities. Amongst diagnostic tests, USG seems to be effective method in initial diagnosis, as a simple, cost-effective imaging modality with no side effects. When used as a screening test, USG has been associated with specificity of > 90% and sensitivity of 65-80% [33].

CT and MRI are used as complementary imaging modalities when USG alone is not sufficient. Despite the remarkable advances in imaging technology, there is no ideal method that can be used alone in HCC screening and to discriminate malignant and benign nodules. In such nodules, with inability to make malignant vs. benign discrimination, USG-guided liver biopsy is considered an important method supporting the diagnosis. In a study by Caturelli *et al*. on USG-guided fine needle aspiration biopsy of 294 newly detected nodules, findings revealed HCC diagnosis in 87.6% of patients who had < 2 cm nodules and could not be diagnosed via AFP, while in those with nodules smaller than 1 cm HCC diagnosis rate was 68.7% [33].

Elevated AFP levels have been reported in approximately 60-70% of patient with HCC across USA and Europe [34].

CONCLUSION

Our findings related to retrospective evaluation of 207 patients with HCC revealed the higher incidence of HCC at an advanced age and particularly in males, while the viral etiology, HBV (68.2%) and HCV (16.6%) in particular, remains to be the most important risk factor in our country. Chronic liver parenchyma disease at cirrhotic stage was evident in 64% of our patients, while imaging on tumor localization and size revealed the right lob location and a tumor size of > 7 cm in majority of patients. AFP levels, which were significantly over the normal range, may be a complementary marker aiding in diagnosis but have no significant impact on disease progression or survival. Other laboratory findings seem to be abnormal

but nonspecific. Metastasis sites involved lung (35%), lymph node (21%), bone (21%), abdominal wall (4%) and adrenal glands (4%).

Despite the provision of all treatment options, survival was poor with 7 months on average, while the longest and shortest survival time was 48 months and 1 week, respectively. As recommended, patients at high risk of HCC development should be included in a follow up program and be assessed in terms of USG findings and AFP levels every 6-12 months.

Authors' Contribution

Study Conception: FLK,; Study Design: FLH, TE,; Supervision: FLK,; Materials: TE,; Data Collection and/or Processing: TE,; Statistical Analysis and/or Data Interpretation: FLK, TE,; Literature Review: TE,; Manuscript Preparation: TE and Critical Review: FLK, TE.

Acknowledgement

The authors thank all those who participated in the recruitment of patients and helped to gather

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What do the pregnant women in our hospital know and think about complementary medicine methods in childbirth?

Journal of Bursa Faculty of Medicine
e-ISSN:

Original Article

Obstetrics and Gynecology

Received
December 24, 2022
Accepted
December 31, 2022
Published online
January 04, 2023

J Bursa Med 2023;1(1) 33-38

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ABSTRACT

Objectives: Pregnancy is a very special and challenging process for women. Especially in the third trimester, as the birth approaches, some concerns may increase. Especially normal birth can scare many women. Since women do not dominate the birth process in their first pregnancies, they have some concerns for both their baby and themselves. In recent years, complementary medicine methods have been used to support normal birth and for the comfort of the patient. In this study, we evaluated the knowledge and thoughts of pregnant women hospitalized in the delivery room about complementary medicine methods in childbirth.

Methods: This prospective survey study was conducted at Bursa Yüksek Ihtisas Training and Research Hospital from 01 March 2022 to 30 April 2022. The study consists of 57 patients aged 18-40 who gave birth in our hospital. Consent was obtained from all participants and archived before starting the study.

Results: Although only nine pregnant heard about complementary medicine methods in childbirth; 100% of the patients thought that these techniques would reduce the mother's stress during childbirth. While 54.4% of these patients were in pain, they were trying to take deep breaths as breathing and relaxation exercises, while 21.1% were praying. None of the patients wanted to try the hypnosis method because they thought it was too scary. 68.4% of the patients thought that relaxing music in labor and 63.2% of them thought that aromatherapy would be successful. In addition, none of the patients had heard of homeopathy.

Conclusions: Complementary medicine methods such as aromatherapy, relaxing music therapy or lumbar massage will increase the place of these methods in childbirth, as pregnant women demand it as much as doctors. We can achieve this by providing training on complementary medicine to patients from the early stages of their pregnancy. The increase in the number of patients receiving support from complementary medicine at birth will also diversify the scientific studies that can be done on this subject. In this way, we may have the opportunity to re-evaluate complementary medicine methods with the scientific data we have.

Keywords: Complementary medicine, Labor, Aromatherapy

How to cite this article
Yenigül NN, Yüce Bilgin E. What do the pregnant women in our hospital know and think about complementary medicine methods in childbirth? J Bursa Med 2023;1(1):33-38

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Pregnancy is a very special and challenging process for women. Especially in the third trimester, as the birth approaches, some concerns may increase. Especially normal birth can scare many women. Since women do not dominate the birth process in their first pregnancies, they have some concerns for both their babies and themselves. They have a lot of questions and wonders especially about normal birth. A pregnant woman who does the appropriate physical exercises for this process from the first weeks of her pregnancy, goes to the maternity school and prepares herself mentally will feel much more comfortable during childbirth [1]. The process will be much more successful and seamless.

In recent years, complementary medicine methods have been used to support normal birth. Hypnosis, aromatherapy, the relaxing effect of music during labor or homeopathy are the supports methods that increase comfort of the patient [2]. Although scientific evidence for its operability is low [3], it is important for women to be aware of these supportive treatments. Because a woman who feels more comfortable and safer in labor may increase the probability of having a normal vaginal delivery [4]. This may be an important support for the decreasing normal vaginal delivery rates in our country [5].

In order to make this process more comfortable, obstetricians in many institutions started to support the birth process with complementary medicine methods. However, many methods still cannot be used actively during childbirth. One of the reasons for this may be the lack of knowledge of the patients on this subject. In this study, we evaluated the knowledge and thoughts of pregnant women hospitalized in the delivery room about complementary medicine methods in childbirth.

METHODS

This prospective survey study was conducted at Bursa Yuksek Ihtisas Training and Research Hospital from 01 March 2022 to 30 April 2022. The study consists of 57 patients aged 18-40 who gave birth in our hospital. Consent was obtained from all participants and archived before starting the study.

Patients between 37-41 weeks of gestation who were alive, had cephalic presentation and were admitted to the delivery room for normal vaginal delivery coming from the vertex were included. Gestational weeks of the patients were calculated according to their last menstrual period and 9-12 weeks old ultrasound. Inclusion criteria of the study: low-risk pregnant women, patients who has sufficient sociocultural level to answer the survey questions, and pregnant women whom labor induction can we applied. High-risk pregnancies (i.e., preeclampsia, IUGR, poor obstetric history), patients with previous uterine surgery, patients at high risk of postpartum bleeding, women with serious disease such as heart, kidney or liver disorders diagnosed during the study or previously and hospitalization in the delivery room. Pregnant women with less than an hour interval between delivery, placenta previa, invasion anomaly or a diagnosis of abruptio placenta were excluded from the study. In addition, patients who did not speak Turkish or wanted to leave the study during the evaluation were not included in the study. These patients were excluded according to their anamnesis and laboratory values.

Bishop scoring and detailed anamnesis were taken for all women who met the study criteria when they were admitted to the delivery room. Demographic and obstetric characteristics of the included pregnant women were recorded. A survey was conducted on these patients who had normal delivery or cesarean section, about how much they knew about complementary medicine methods and which one they would like to apply more in childbirth.

Dinoprostone insert was placed in the posterior fornix of patients with a Bishop score of ≤ 6 on admission to the delivery room, and the application time was recorded. The application time of this insert was determined as a maximum of 24 hours [6]. Patients whose cervix did not open despite a dinoprostone swab for 24 hours were performed cesarean section with the diagnosis of failed induction and were excluded from the study. Oxytocin infusion was started when necessary, in patients with a Bishop score of >6 or a Bishop score of >8 at admission. It was prepared as 5U in 500 ml of saline and started at a dose of 4 mU/min, increasing by 2 mU/min in 20 minutes. The dose was not increased in patients with contractions of 200 Montevideo units every 10 minutes [7]. The maximum dose was defined as 20 mU/min. All patients were followed up with continuous fetal heart monitoring after uterine contractions started.

Primary outcome was the level of knowledge of the pregnant women hospitalized in our delivery room about complementary medicine methods. The secondary outcome was which of these complementary methods they wanted to apply during childbirth.

Statistical analysis

SPSS v23 package programs were used in the analysis of the data. The conformity of the data to the normal distribution was examined with the Shapiro-Wilk test. When the data were normally distributed, comparisons between the two groups were made with Student's t-test and descriptive statistics were mean ± standard deviation; When the continuous data did not show normal distribution, the comparison of the continuous data was made with the Mann-Whitney U test and the descriptive statistics were given as the Median (Minimum-Maximum) value. The comparison of categorical data between two groups was made with chi-square and Fisher's exact chi-square test, and descriptive statistics were given as frequency and percentage. In statistical analyzes, $\alpha = 0.05$ was taken as the level of significance.

RESULTS

At the time of the study, an average of 1350 pregnant women gave birth. Approximately 650 of these patients were taken directly to cesarean section. Only 112 of the patients followed for normal delivery agreed to participate in the survey. Excluding patients with increased contractions or those who could not complete the questionnaire, 57 patients met the study criteria.

Demographic characteristics of the patients are given in Table 1. The median age of the patients was 29, and the body mass index was 25. 38.6% of the patients were secondary school graduates and 29.8% were high school graduates. The obstetric results of the patients were evaluated in Table 2. Their gestational week was 39 weeks. Only 7% were diagnosed with preterm labor. 84.2% of the patients were admitted to the delivery room with the complaint of pain and most of them had normal vaginal delivery. Fetal outcomes were evaluated in Table 3.

In Table 4, patient data about complementary medicine methods are shared. Although only nine pregnant heard about complementary medicine methods in childbirth; 100% of the patients thought that these techniques would reduce the mother's stress during childbirth. While 54.4% of these patients were in pain, they were trying to take deep breaths as breathing and relaxation exercises, while 21.1% were praying. None of the patients wanted to try the hypnosis method because they thought it was too scary. 68.4% of the patients thought that relaxing music in labor and 63.2% of them thought that aromatherapy would be successful. In addition, none of the patients had heard of homeopathy.

DISCUSSION

The women who gave birth in our hospital did not know the complementary medicine methods that could be applied during delivery. Although they did not know, they believed that these methods could enable more active participation in childbirth. In addition, although they did not know at all, they were afraid to practice because of the name of some methods.

According to a study conducted by family physicians [3], 82% of the sources that pregnant women obtained information about complementary medicine methods were from family members, while 34% were from friends. In another study conducted in our country,

Table 1. Demographic characteristics of the patients

	Values (n = 57)
Maternal age, years(min-max)	29 (20-40)
Gravida, n (min-max)	2(1-7)
Parity, n (min-max)	1(0-4)
BMI (kg/m^2), median (min-max)	25(21-29)
Education status	
Primary school, n (%)	9 (15.8)
Middle school, n (%)	22 (38.6)
High school, n (%)	17 (29.8)
University, n (%)	9 (15.8)

BMI: Body mass index

Table 2. Obstetric and fetal outcomes of the patients

	Values (n = 57)
Gestational week, median (min-max)	39 (31-41)
Reason for hospitalization	
Labor pain, n (%)	48 (84.2)
PPROM, n (%)	5(8.8)
Fetal distress, n (%)	4 (7)
Contraction	
Yes, n (%)	53 (93)
No, n (%)	4 (7)
Type of birth	
Vaginal birth, n (%)	48(84.2)
Ceserian, n (%)	9 (15.8)
Fetal weight, n (%)	3200 (1840-3835)
1.min. APGAR, median (min-max)	9 (7-9)
5.min. APGAR, median (min-max)	10 (9-10)

PPROM: Preterm premature rupture of membranes , min: minute

the rate of obtaining information from close friends, family and relatives is around 76.9% [8]. In another study conducted on patients who applied to family medicine, it was found that the media (64%) and family members (34.6%) were the most common [9]. According to a study conducted with individuals with breast and gynecological cancer in Germany, the rate of obtaining complementary medicine information from friends and family members is 31.6% [10]. As can be seen, women get this information mostly from their close circles. It is necessary to change this situation, which has a very low scientific level, and to facilitate access to information.

Complementary medicine applications, which are widely used today, are also used in the treatment of problems experienced during pregnancy. When we look at the literature, women used at least one type of complementary medicine method in order to reduce the symptoms they experienced during pregnancy in the early stages of pregnancy and stated that the methods were effective [1,5]. In a review published in recent years [11], the successful results of massage therapy and foot reflexology for edema, which is common in late pregnancy, were mentioned.

Aromatherapy which is defined as the use of oils obtained entirely from plants [3], can be used to control blood pressure in hypertension [12]. These oils, which are used during labor, are mostly used by massage, bath, foot bath and inhalation. Aromatherapy application during childbirth is usually used with rose, lavender, neroli, sage etc. It is applied in the form of rubbing or inhalation of essential oils on the skin of the mother in labor. In the second phase of the baby's descent and birth, peppermint oil is recommended for the mother as it gives a feeling of strength, lavender oil reduces the sense of panic and strengthens contractions [13, 14]. More than half of the women participating in our study stated that they could try aromatherapy during labor. They've probably heard of this method before. They thought positively about the back massage to be applied with aromatherapy.

In a recent study [15], it was emphasized that nurses and midwives could use music therapy in the care and follow-up of pregnant women with preeclampsia in obstetric units. The majority of the patients in our study were also positive towards music therapy during delivery. With scientific evidence, pregnant women can be relieved by the application of music that has a relaxing timbre in delivery rooms. Thus, a pregnant woman who can cope with contractions more easily may have a higher chance of having a normal delivery. Another method known and favored by most of the patients is water birth. The fact that water delivery rooms have been established and actively working in delivery rooms in some hospitals cannot be denied.

Most of the patients did not research complementary medicine methods before delivery. The reason can be the low sociocultural levels of the pregnant. But the

Table 3. Patient data on complementary medicine modalities

	Values (n=57)
Have you heard of complementary medicine methods in childbirth?	
Yes, n (%)	9 (15.8)
No, n (%)	48 (84.2)
Do these methods enable the mother to participate more actively in the birth?	
Yes, n (%)	39 (68.4)
No, n (%)	18 (31.6)
Do these methods reduce the mother's stress during childbirth?	
Yes, n (%)	57 (100)
No, n (%)	-
Do these methods provide a more positive outcome of the birth?	
Yes, n (%)	53 (93)
No, n (%)	4 (7)
Do you want to listen to relaxing music during labor?	
Yes, n (%)	39 (68.4)
No, n (%)	18 (31.6)
Would you like to apply aromatherapy?	
Yes, n (%)	36 (63.2)
No, n (%)	21 (36.8)
Do you think that the back massage applied during labor will reduce the pain?	
Yes, n (%)	30 (52.6)
No, n (%)	27 (47.4)
Would you like to give birth in water?	
Yes, n (%)	31 (54.4)
No, n (%)	26 (45.6)
Do you think complementary medicine methods will relieve the mother physically and psychologically?	
Yes, n (%)	47 (82.5)
No, n (%)	10 (17.5)

majority of the patients prefer lumbar massage and music therapy during labor pains. Thus, priority would be informing pregnant about these new methods and studies. The creation of more isolated rooms where complementary medicine methods can be applied, may contribute to normal birth rates.

CONCLUSION

Complementary medicine methods such as aromatherapy, relaxing music therapy or lumbar massage will increase the place of these methods in childbirth, as pregnant women demand it as much as doctors. We can achieve this by providing trainings on complementary medicine from the early stages of pregnancies. The increase in the number of patients receiving support from complementary medicine at birth will also diversify the scientific studies. In this way, we may have the opportunity to re-evaluate complementary medicine methods with the scientific data.

Authors' Contribution

Study Conception: NNY,; Study Design: NNY,; Supervision: NNY,; Materials: EYB,; Data Collection and/or Processing: EYB,; Statistical Analysis and/or Data Interpretation: EYB,; Literature Review: NNY,; Manuscript Preparation: EYB and Critical Review: NNY.

Conflict of interest

The authors declare that they have no conflicts of interests.

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Post-Covid 19 arrhythmia? Wolf parkinson white syndrome case report

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Journal of Bursa Faculty of Medicine

e-ISSN:

Case Report

Emergency Medicine

Received
December 14, 2023
Accepted
December 19, 2023
Published online
January 04, 2023

J Bursa Med 2023;1(1) 37-40

ABSTRACT

The purpose of this case report is to emphasize the very rare association of COVID-19 with Wolf-Parkinson-White (WPW) syndrome and the emergency management of this clinical condition.

A 30-year-old female patient with a diagnosis of COVID-19 applied to our emergency department on the 6th day with complaints of increasing fever, shortness of breath and tachycardia for two days. ECG showed sinus tachycardia, short PR interval and delta wave, which was consequent with WPW syndrome.

With this case report, we emphasized that WPW should be considered in the differential diagnosis of patients with COVID-19 who applied to the emergency department with complaints such as tachycardia and shortness of breath, although it is rare.

Keywords: Wolf Parkinson White, arrhythmia, COVID-19

On December 31, 2019, the World Health Organization (WHO) was informed about cases of pneumonia with unknown cause identified in Wuhan City, Hubei Province, China. On January 12, 2020, it was reported that a new coronavirus had been identified in the samples acquired from the cases, and as a consequence of the study, the virus was determined to be the source of the pandemic. This virus was identified as SARS-CoV-2, and the associated disease was COVID-19. The clinical picture encompasses a broad spectrum, ranging from asymptomatic illness or mild upper respiratory tract disease to severe pneumonia that will result in respiratory failure and even death [1, 2]. Fever, lethargy, muscle and joint discomfort, headache, nausea and vomiting, diarrhea, cough, and shortness of breath are some frequent symptoms. In COVID-19, acute respiratory failure, septic shock, acute respiratory distress syndrome (ARDS), and multiple organ failure syndrome (MODS) are the leading causes of mortality and hospitalization [3] In addition to respiratory involvement, which causes high mortality and morbidity, it has recently attracted the attention of researchers due to the high rate of extra respiratory involvement such as cardiac, hematological, neurological, renal, hepatic, gastrointestinal, and immunological systems [4-6]

Wolff-Parkinson-White (WPW) syndrome is a kind of ventricular pre-excitation that affects the accessory

How to cite this article
Çalışkan FB, Yüksel M, AY MO, Kaya H, Ayan İ, OCAK U. Post-Covid 19 arrhythmia? Wolf parkinson white syndrome case report. J Bursa Med 2023;1(1):39-42

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conduction pathway and affects between 0.1% and 3.0% of the population. Wolff, Parkinson, and White first defined the syndrome in 1930 as comprising paroxysmal tachycardia episodes, a short PR interval, and bundle branch block in young, healthy persons with normal heart anatomy. The estimated prevalence of a WPW pattern on electrocardiography (ECG) in the general population is 0.13 to 0.25 percent. The traditional WPW ECG pattern is characterized by two primary characteristics: a short PR interval and a broadened QRS complex due to a delta wave [7, 8]

This case report aims to highlight the extremely rare relationship between COVID-19 and WPW, as well as the emergency room management of this condition.

CASE REPORT

A 30-year-old female was presented to our emergency department on the sixth day after her COVID-19 diagnosis with complaints of two days of growing fever, shortness of breath, and palpitations. It was discovered that she was admitted to an external facility for COVID-19 pneumonia, discharged two days ago, and did not have a chronic condition. The patient's medical history included the usage of methyl prednisolone and clarithromycin.

Her overall status was fair, and she was conscious and dyspneic. Vital signs; fever 38.5 °C, blood pressure 110/80 mmHg, heart rate 103 beats/min, and SpO_2 95%. Respiratory sounds revealed broad rales in both lungs, but no abnormal signs were observed in other system investigations. Laboratory values were WBC:26500/mL, Lymphocyte 3100/mL, CRP 3.43 mg/L, BUN 17 mg/dL, creatinine 0.7 mg/dL. On thorax CT, both lungs have a diffuse ground glass appearance. The patient's ECG revealed sinus tachycardia, a short PR interval, and a delta wave, consistent with Wolf-Parkinson-White syndrome (Figure 1).

Chest diseases and cardiology consultation was requested from the patient. Medical treatment was arranged for the patient, who was evaluated by cardiology, and outpatient control was recommended for ablation planning. COVID positive hospitalization was given by pulmonologists for the treatment of covid pneumonia.

DISCUSSION

The majority of patients with a WPW ECG pattern are asymptomatic. As part of the WPW syndrome, a small proportion of patients with a WPW pattern experience arrhythmias. The majority of people with arrhythmia may exhibit symptoms including palpitations, dizziness, syncope/presyncope, chest discomfort, and cardiac arrest [9]. Patients with a WPW pattern who are asymptomatic do not require emergency care. To establish the patient's risk of getting tachyarrhythmia, it may be beneficial

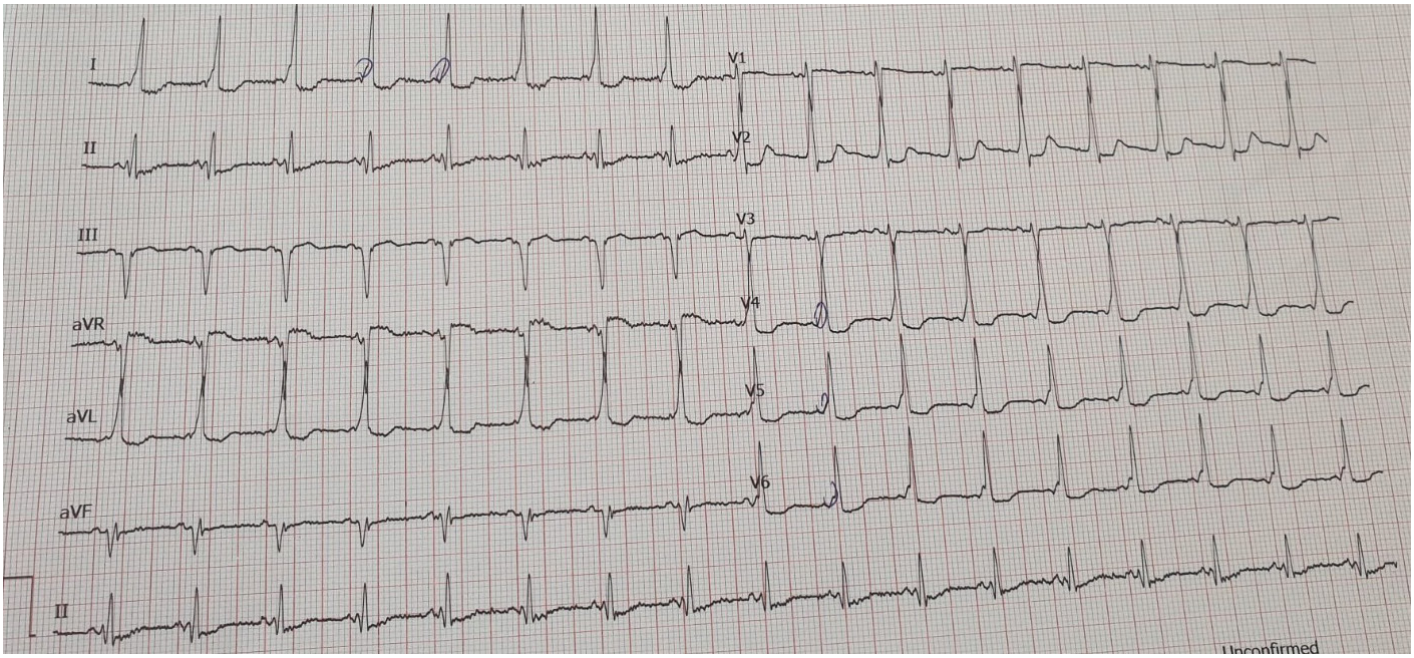

Figure 1. ECG of the case

to have them evaluated by a cardiologist or electrophysiologist. Depending on their level of risk, type and characteristics of the accessory route, cardiac comorbidities and other medical problems, high-risk patients may benefit from preventative antiarrhythmic medications or prophylactic accessory pathway ablation [10]. Many regard transcatheter ablation to be the first-line treatment for WPW due to its definite treatment potential. Radiofrequency ablation (RFA) and cryoablation are procedures included in transcatheter ablation. Due to its higher success rate and reduced recurrence in quelling accessory pathways, RFA is regarded the gold standard for invasive management [8]

Palpitations are a common symptom, especially in patients without fever and cough. In a research involving 137 patients admitted for COVID-19 infection, 7.3% of patients presented with palpitations [11]. The incidence of cardiac arrhythmia (atrial or ventricular) in COVID-19 may be attributable to myocardial injury or inflammatory stress, neurohormonal, fever, hypoxia, metabolic dysregulation, sepsis, or electrolyte imbalance; however, this is unclear. Even numerous antivirals and antibiotics used to treat the condition can produce arrhythmias [12, 13].

At the onset of COVID-19, azithromycin (AZM) and hydrocycloquine (HCQ) were commonly used in combination. It has been observed that there are significant cardiac hazards connected with the use of these two medicines, and that cardiac arrhythmias produced by prolonging of the QT interval may enhance the risk of death in patients receiving this combination [14, 15]

In a study of COVID-19 patients, sinus tachycardia was found to be the most common type of arrhythmia, especially in severe and critical cases, whereas ventricular tachycardia and atrioventricular block are uncommon and occur mostly in the critical state and terminal stage of the disease [16]

It has been reported that several medicines (AZM, HCQ) used to treat COVID-19 can cause cardiac arrhythmias [14, 15, 17]. In our circumstance, neither AZM nor HCQ were used. She had previously utilized methyl prednisolone and clarithromycin. We found no cases of WPW in the literature related to the usage of methyl prednisolone and clarithromycin.

As far as we are aware, the literature does not contain any references to the cohabitation of COVID-19 and WPW. We believe that this is the first case reported in the literature. Although uncommon, we stressed in this case report that WPW should be evaluated in the differential diagnosis of COVID-19 patients presenting to the emergency room with complaints such as palpitations and shortness of breath

CONCLUSION

Authors' Contribution

Study Conception: FBÇ, MY, MOA, HK, İA, UO,; Study Design: FBÇ, MY, MOA, HK, İA, UO,; Supervision: FBÇ, MY, MOA, HK, İA, UO,; Materials: FBÇ, MY, MOA, HK, İA, UO,; Data Collection and/or Processing: FBÇ, MY, MOA, HK, İA, UO,; Statistical Analysis and/or Data Interpretation: FBÇ, MY, MOA, HK, İA, UO,; Literature Review: FBÇ, MY, MOA, HK, İA, UO,; Manuscript Preparation: FBÇ, MY, MOA, HK, İA, UO and Critical Review: FBÇ, MY, MOA, HK, İA, UO.

Conflict of interest

No potential conflicts of interest relevant to this article were reported.

Acknowledgements

We are grateful to all treating physicians in our center for collaboration and the data collection.

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