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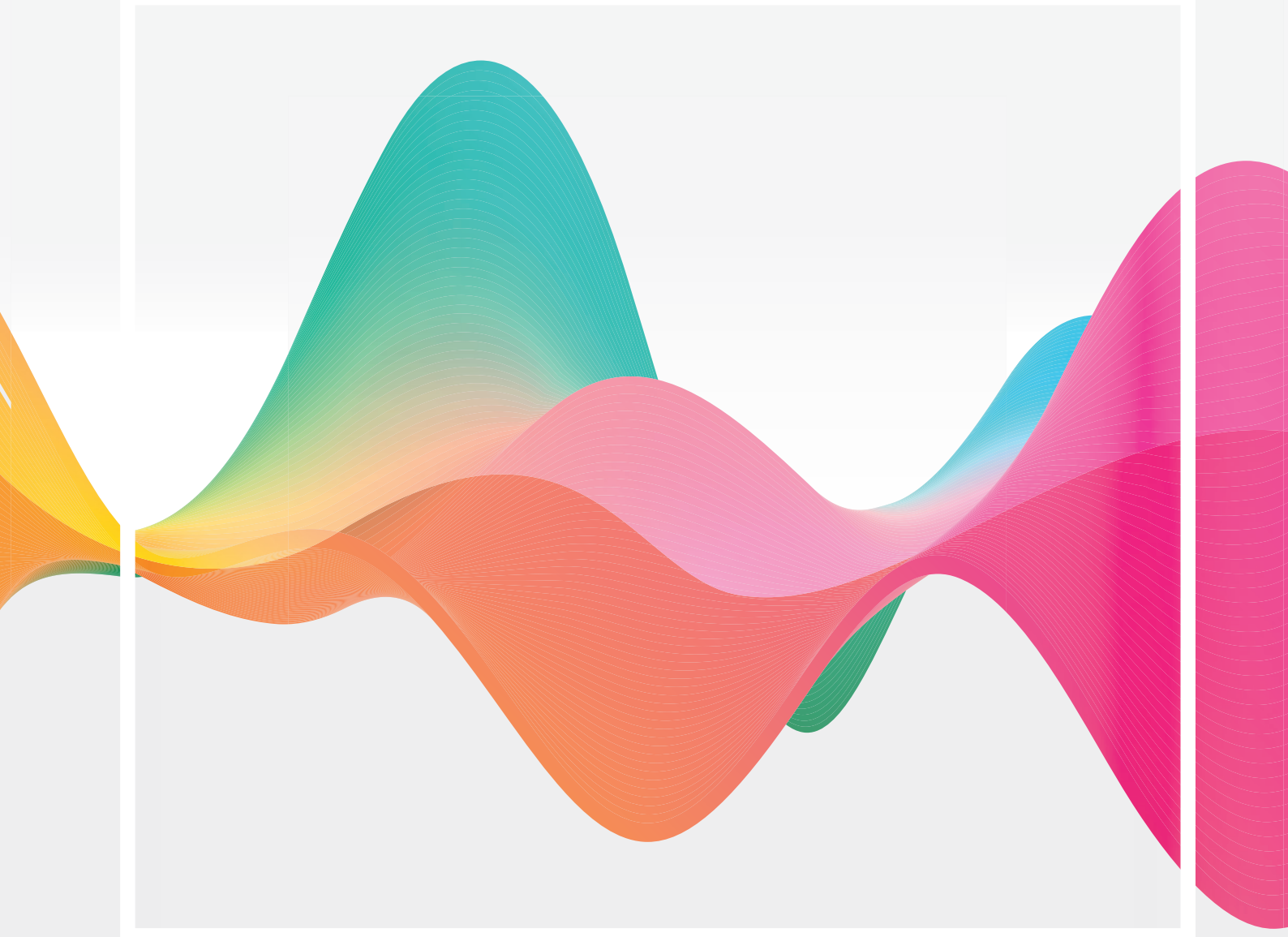

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ABSTRACTING & INDEXING

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ABOUT THE JOURNAL

About the Health Sci. Q.

Health Sciences Quarterly (Health Sci. Q.) journal as known by the name of "Journal of Scientific Perspectives" until April 2021 which has been published since 2017 is an international peer-reviewed journal of HOLISTENCE ACADEMY. It is published quarterly in January, April, July, and October. All manuscripts submitted for publication are evaluated by the editor-in-chief, section editor, editorial board, and referees. In addition, the journal provides a medium for highlighting selected articles reporting highly significant original findings, as Editor's Choice Manuscripts.

Aims and Scope

Health Sciences Quarterly (Health Sci. Q.) is an open-access journal that publishes original research papers, case reports, and reviews, clinical studies covering a wide range of subjects in life sciences and medicine as well as clinical and experimental investigations only in English.

Researchers in health sciences will find much of great use and interest in the Health Sci. Q.

HSQ aims to supply scientists of health with resources in order to provide the scientific knowledge through the publication of peer-reviewed, high quality, scientific papers and other material on all topics related to Medicine, Pharmacy and pharmaceutical sciences, Dentistry, Nursing, Bioethics, History of medicine, Health economics, Pharmacoeconomics, Medical education, Public health, and Epidemiology.

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EDITORIAL

In this October issue of Health Sciences Quarterly (Health Sci Q.), we have five original articles about cardiopulmonary resuscitation, the effect of ondansetron, some cord blood values in neonatal disease, enhanced recovery after surgery protocols and evaluating some parameters in overweight and obese children; and one review about nursing and compassion related to Covid-19.

Health Sci. Q. (formerly **Journal of Scientific Perspectives**) is an open-access, peer-reviewed journal dedicate to deliver leading-edge research in all disciplines of health sciences to publish. Health Sci. Q. encourages scientists and academicians all around the world to share their original writings in the form of original research, review, mini-review, case report, letter to the editor, commentary, news and views, editorial, as well as meeting reports. Full texts of all published articles can be downloaded for free from our website.

We especially would like to thank the authors, the referees who evaluated the manuscripts carefully and everyone (also every life form) who contributed to these studies/articles.

Hope to meet in the upcoming issues.

Kind regards.

Hasan Erbay. MD, PhD, MBGPH
Editor-in-Chief

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ORIGINAL ARTICLE

Knowledge and attitudes towards cardiopulmonary resuscitation: A cross sectional survey on health care providers in clinical practice

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Abstract

Cardiopulmonary resuscitation (CPR) is a critical, life-saving skill for healthcare professionals (HCPs) in emergency departments (EDs) and other health care settings and are expected to have a profound knowledge of the CPR guidelines. A cross-sectional study was carried out among 160 health care providers to assess the level of knowledge and attitude towards cardiopulmonary resuscitation. Data analysis were done by SPSS software version-20. Total respondents in the study were 160 health care providers (HCP) and among them 80 respondents were doctors and 80 respondents were nurses. Among the respondents, 69% were female and 31% were male. Regarding the CPR training, 51% doctors and 49% had trained in CPR. Regarding performing the CPR, 58% doctors performed CPR and 66.2% nurses had performed CPR in clinical practice. Regarding meaning of the CPR, majority (92%) respondents knew correctly as ventilation and chest compression. More than half 58% respondents correctly knew about cardiac massage as to apply strong compression to the chest wall in certain interval. Regarding component of the CPR, nearly two third (65%) respondents correctly knew as chest compression and ventilation. Regarding sequence of the CPR,71 % respondents incorrectly knew sequence of CPR as Airway-Breathing-Compression (A-B-C) and 29.38% correctly knew as Compression-Airway-Breathing (C-A-B) as the sequence of the CPR. Among the total respondents, 62.5 % respondents had average level of knowledge, 18.12% had good level and 19.38% had poor level of knowledge on CPR and CPR training were associated significantly with the CPR knowledge. Among the total respondents 70.62% had neutral attitude, 15.0% had positive and 14.38% had negative attitude to perform CPR. Doctors were more knowledgeable than nurses, and they also had more positive opinions on CPR than nurses. The study showed that CPR training was taken by both health care providers. The study also showed that nurses (53%) performed the CPR more than the doctors in clinical practice. The dissimilarity in knowledge and attitudes among the health care providers suggest that training courses on the CPR should be regularly provided to health care providers specially focusing on nurses in the country.

Keywords: *Cardiopulmonary resuscitation, knowledge, attitude, chest compression, ventilation, health care provider*

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Introduction

The able to identify and intervene in cardiac arrest early saves lives [1]. Cardiopulmonary resuscitation (CPR) is a critical, life-saving skill for healthcare professionals (HCPs) in emergency departments (EDs) and other health care settings. Although the clinical outcome of CPR depends on multiple factors, such as the initial condition of the patient and the duration of cardiac arrest, performing high-quality CPR significantly improves patient outcomes [2]. CPR has been simplified into a set of skills that can be learnt by anyone, regardless of their medical background [3]. This permits any trained hospital staff member to quickly administer this life-saving treatment [4]. CPR, in particular, is a simple maneuver which if performed correctly can greatly increase the likelihood of return of spontaneous circulation (ROSC) and survival. As healthcare professionals encounter several life-threatening emergencies on a daily basis, they are expected to have a profound knowledge of the CPR guidelines [5]. Sudden cardiac death (SCD) is the greatest cause of mortality in the world, contributing for 15–20% of all deaths [6]. Sudden cardiac death outside of the hospital accounts for more than 60% of all deaths worldwide, making cardiovascular disorders the main cause of death [7]. One of its most major concerns with SCD is that most out-of-hospital cardiac arrests (OHCAs) occur in patients who are experiencing their earliest clinical symptoms of the underlying disease or who have been diagnosed but are considered small risk [8]. An OHCA affects between 250,000 and 300,000 patients each year all around the world [9]. CPR techniques are designed to keep oxygenated blood flowing to essential organs, particularly the brain, which is extremely vulnerable to oxygen deprivation and can result in lasting brain damage in as little as a few minutes, with death occurring in less than ten minutes [10]. The benefit of resuscitation decreases by up to 10% each minute following the beginning of cardiac arrest without warning [11]. Early access, urgent high-quality CPR, quick defibrillation, basic and advanced emergency medical services, advanced life support, and post-cardiac arrest care are the five links in the chain of survival, according to the American Heart Association's 2015 guidelines [12]. Early, high-quality CPR can considerably raise the likelihood of survival for those who experience sudden cardiac arrests [13]. When patients are managed by adequately qualified health care personnel, cardiopulmonary resuscitation has been found to prevent in-hospital cardiac mortality and related mortality [14]. CPR's importance is now widely acknowledged and stressed. CPR training and familiarization with automated external defibrillators (AEDs) should be included in secondary school curricula, according to the American Heart Association [15].

Despite the fact that CPR is well-established and one of the most efficient resuscitative interventions for patients in cardiac arrest, it has been proven that medical students and younger doctors in both high- and low-income nations lack knowledge, training, and practice (LMICs) [16-20]. Furthermore, many people were afraid of contracting infectious infections if they conducted cardiac compression with mouth-to-mouth ventilation [21]. Early CPR can help individuals survive and have a better neurologic outcome. The survival for patients has increased as a result of targeted education on cardiopulmonary resuscitation for emergency medical clinicians and the general population [22]. Moreover, there is a dearth of data describing knowledge and attitude of health care providers in the direction of conducting CPR in clinical settings. Regardless of the fact that the epidemiology of cardiac arrest has been extensively researched in many industrialized nations, no studies on assessments of CPR knowledge and attitudes have been conducted in our nation. The purpose of this study was to see how well health care practitioners in clinical practice knew about cardiopulmonary resuscitation and how they felt about it. Furthermore, this research was critical in providing data for planners and programmers to use in combating cardiac arrest and its complications by promoting the adoption of CPR training and guidance in our country.

Materials and Methods

A cross sectional study which was approved ethically by ERC of BUHS was conducted among 160 health care providers and was selected purposively who were working in the respective department in the institute where data collection was taken during a period from September 2018 to December 2019. For data collection, a semi-structured questionnaire was created and used. Pretesting of the research instrument was done before finalization among ten health care providers, who were not part of the final sample. The researcher observed doctors and nurses working in hospitals that met the inclusion criteria both outside and inside. The selected respondents were informed about the study's goal. The data was then obtained via a face-to-face interview, with the responses being recorded in the questionnaire. Each respondent was given a separate questionnaire. Each day, nine to ten respondents were interviewed over the course of five days, and each

interview took about 30-40 minutes, including time to create rapport with participants. The data of this survey were input into a personal computer using the SPSS-PC version 20 application.

Results

Total respondents in the study were 160 health care providers (HCP) and among them 80 respondents were doctors and 80 respondents were nurses. Among them 49 (31%) were males and 111 (69%) were females. Regarding marital status 103 (64%) respondents were married and 57 (36%) were unmarried and their mean age was 30±5.36 years. Regarding educational status of the respondents 73 (91.2%) doctors were bachelor,7 (8.8%) were masters and majority of the nurses were diploma 70 (87.5%), bachelor 7 (8.8%), and masters 3 (3.8%). (Table 1)

Table 1. Distribution of the respondents according to the demographic status (n=160)

Variable	Number	Percentage
Age **Mean (SD) 30±5.36**		
Sex		
Male	49	31%
Female	111	69%
Total	160	100
Marital status		
Married	103	64.4
Unmarried	57	35.6
Total	**160**	**100**
Educational level of the respondents		
Doctor		
Masters	7	8.8
Bachelor	73	91.2
Diploma	0	.0
Total	**80**	**100**
Nurse		
Masters	3	3.8
Bachelor	7	8.8
Diploma	70	87.5
Total	**80**	**100**
Professional designation		
Doctor	80	50.0
Nurse	80	50.0
Total	**160**	**100.0**

Table 2. Distribution of respondents according to the training status (n=160)

Variable	Number	Percentage
CPR training of the respondent		
Doctor		
Yes	50	51
Nurse		
Yes	48	49
Training adequate to perform CPR		
Yes	80	81.6
Duration of the CPR training		
<1 Year	22	22.4
>1 Year	76	77.6
Total	**98**	**100.0**
Perform of CPR		
Doctor		
Yes	**46**	**57.5**
Nurse		
Yes	**53**	**66.2**

Table 3. Association between knowledge about step of sequence of the CPR of the respondent with training status of the respondent (n=160)

Variables	CPR training of the respondent	
Step of sequence of the CPR of the respondent	**Yes**	**No**
Compression airway breathing(C-A-B)	23(48.9%)	24(51.1%)
Airway breathing compression(A-B-C)	71(78.9%)	19(21.1%)
Don't know	4(17.4%)	19(82.6%)
Chi-square =33.441; df= 2; p<0.000		

Table 4. Distribution of the respondents according to association between total knowledge score with professional designation (n=160)

Variables	Poor		Average		Good	
Professional designation of the respondent	**Frequency (n)**	**%**	**Frequency (n)**	**%**	**Frequency (n)**	**%**
Doctor	8	10.0	50	62.5	22	27.5
Nurse	23	28.8	50	62.5	7	8.8
Total	**31**	**19.4**	**100**	**62.5**	**29**	**18.1**
Chi-square = 15.017; df=2; p<0.001						

Table 5. Distribution of the respondents according to association between total attitude score with professional designation (n=160)

Variables	Negative		Neutral		Positive	
Professional designation of the respondent	**F**	**%**	**F**	**%**	**F**	**%**
Doctor	14	17.5	47	58.8	19	23.8
Nurse	9	11.2	66	82.5	5	6.2
Total	23	14.4	113	70.6	24	15.0
Chi-square = 12.448; df=2; p<0.005						

Regarding CPR training of the respondents 51% of the doctors and 49% of the nurses had previously received CPR training. Among the respondents 22% had less than one year while 78% had more than one year of CPR training. The majority (82%) of respondents who received CPR training felt that their training was adequate to perform CPR. (Table 2)

According to the association between knowledge about step of sequence of the CPR with training status of the respondent (n=160), there is a significant association (p<0.000) between step of sequence of the CPR of the respondent with training status of the respondent. (Table 3)

According to an association between total knowledge score with professional designation showed that there is a significant association (P<0.001) between respondent's total knowledge score with professional designation of the respondents. (Table 4)

According to association between total attitude score with professional designation showing that there is a significant association (p<0.05) between respondent's total attitude score with professional designation of the respondents. (Table 5)

Discussion

In a common emergency circumstance, CPR is a commonly administered lifesaving procedure. While CPR can save a life in and of itself, its timely, effective, and high-quality administration is critical to the outcome. Healthcare personnel as well as competent bystanders, are required to respond and provide CPR. There is, however, an issue. The retention of knowledge and skills necessitates the identification and correction of outdated information.

Among the 160 respondents, 80 were doctors and 80 were nurses who worked in government and non-government hospitals in Dhaka and provided useful

information to determine the level of knowledge and attitude toward cardiopulmonary resuscitation among health care providers in clinical practice.

Among all the participants, 49 (31%) were males and 111 (69%) were females and their mean age was 30±5.36 years. The range of age was found similar with another study done in West Indies Jamaica of health care setting which was between 26 and 30 years and distribution of the respondents were 77 (55%) of female [20]. According to the findings of the study, health care providers having a high level of education in the government & non-government hospital, Dhaka, the rate of health care providers who received CPR training was found to be three fifth (61%) had previously received CPR training and two fifth (39%) had no CPR trained. This rate might be different outside of Dhaka city. Several studies have been undertaken in various nations to examine the level of knowledge, attitudes, and awareness of CPR in respective society. In this study CPR training rate seems to be low comparing to the study conducted in Slovenia which reported 69.4% had CPR training; this, according to the experts, is due to mandatory CPR training in driving schools in this country [21]. The study done in Bahrain found that 22% stated that they have not responded to a CPR event [22]. However, because 78% of the health care workers in this study had been trained in CPR more than one year, it was shown that 82% percent of them would face a situation that needed doing CPR. The study found that majority 147 (92%) respondents knew meaning of the CPR as chest compression and ventilation, only four (3%) knew as chest compression only and 9 (6%) didn't know the meaning of CPR. The study done in the Sultanate of Oman [23] shows that 62.7% of participants correctly identified the two basic components of CPR, chest compression and ventilation. This finding is nearly identical to that of a different poll conducted in the United Kingdom. [24] in which 54% of participants correctly identified the two primary components of community CPR. However, this study found a different result, with a large percentage of respondents correctly identifying the two key components of CPR, due to the fact that the respondents were doctors and nurses. In this study regarding component of the CPR nearly two thirds (65%) respondents knew the component of as both (chest compression & mouth to mouth ventilation), one fourth (27%) of the respondents knew as chest compression only (4%) of the respondents knew as ventilation and only (4%) didn't know about the component of CPR. However, according to another study, 35.5% of individuals said they could only perform cardiac compression, whereas 28.7% claimed both cardiac compression and mouth-to-mouth ventilation are used in this procedure. These low rates could be due to a lack of repeat CPR training sessions and a low rate of instruction [25]. Regarding sequence of CPR, 71% respondents incorrectly knew sequence of CPR as Airway-Breathing-Compression (A-B-C) and 29.38% correctly knew as Compression-Airway-Breathing (C-A-B) as the sequence of CPR. There is a significant association ($p<0.01$) between step of sequence of the CPR of the respondent with training status of the respondent. Reasons for the discrepancies between the doctors and nurses are unknown but may be due to a lack of clinical experience of CPR. In accordance with this, a previous study from Pakistan similarly stressed the need for continuous and regular training to improve CPR knowledge among medical students [26]. In this study 62.50% respondents had an average level of knowledge, 18.12% had good level and 19.38% had a poor level of knowledge on CPR. Another study [27] revealed that 6.7% had a good level of expertise, and another study involving nurses in Bahrain indicated that 7% had a good level of expertise [22]. This study differs markedly from this in that the respondents (61%) have received CPR training. According to the findings, 70.62% of respondents had a neutral view toward CPR, 15% had a favorable view, and 14.38% had a negative opinion toward CPR. When it comes to initiating the CPR procedure, attitude is quite important. The participants in our study had a largely neutral attitude regarding CPR. Despite their lack of knowledge, they were eager to perform CPR in an emergency. This is in line with the findings of a study that found that respondents were motivated to do CPR despite their lack of knowledge [28]. Despite the fact that a study found no link between knowledge scores and participants' self-assessment, it is maintained that a health care provider's lack of confidence would have a detrimental impact on his or her ability to lead resuscitation [29].

Ethical considerations

Ethics Review Committee of Bangladesh University of Health Sciences issued the Ethical clearance (Memo no: BUHS/Bio/EA/19/196) and ethics was maintained strictly throughout the study. A letter of cooperation written from the respective department to the institute where data collection was taken prior to the data collection period. Personal information of the participants was kept confidential. Each participant was given an informed consent statement in Bengali to read, which was also explained by the investigator and signed by the individual. Throughout the research, rigorous ethical standards were followed.

Conclusion

This study indicated that doctors had higher levels of expertise than nurses and that doctors had more positive attitudes on CPR than nurses. It also revealed that both health-care workers had completed CPR training. This study also found that nurses (53%) were performing more than the doctors in clinical practice. However, given the disparity in knowledge and attitudes among health-care providers, frequent CPR training should be provided to all health-care workers, with a special focus on nurses in the country. According to the findings, government and non-government organizations should increase educational activities concerning CPR and enhance training and recertification to improve physician and nurse understanding that would contribute to improvement CPR efficiency in hospitals.

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Conflict of interest

The authors confirm that they have no competing interests to disclose.

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ORIGINAL ARTICLE

Effect of ondansetron application on neural tube development in 48-hour chick embryos

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Abstract

The study aims to show that ondansetron, which is used safely in pregnant women, can cause serious side effects. Neural tube defects are among the most common congenital malformations of the central nervous system. It is known that genetic predisposition, environmental factors, and some drugs play an important role in the development of neural tube defects. Ondansetron is a selective 5-hydroxytryptamine-3 receptor antagonist used in the treatment of cancer, nausea, and vomiting during pregnancy and after anesthesia. In the literature studies, it was not found that developmental anomalies were observed. Seventy-five free specific pathogen eggs were incubated for 32 hours and divided into five groups of 15 eggs each, including a control group. Ondansetron was administered to these five groups by sub-blastoderm route in 4 different doses with a Hamilton microinjector. At 48 hours of incubation, the embryos were dissected and examined morphologically and histopathologically. At the end of the study, a significant dose-dependent decrease was observed in crown-rump lengths, somite numbers, and mean the number of silver-dyed nucleolar regulatory regions (AgNOR) and total AgNOR / nuclear area ratios. Statistically significant differences were observed between the experimental groups in terms of neural tube closure ($p < 0.05$). Ondansetron has been shown to affect neuronal development and vertebral growth in chicken embryos depending on increasing doses.

Keywords: *Chicken embryo, ondansetron, mRNA, neural tube defect*

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Introduction

Ondansetron is a fast-acting and safe antiemetic drug. It is often used after chemotherapy, in the first trimester of pregnancy, and due to nausea and vomiting associated with anesthesia. It exerts its pharmacological action as a 5-hydroxytryptamine receptor antagonist. It has a superior efficacy, safety, and pharmacoeconomic profile compared to other antiemetic groups. There are many different usage forms; which makes it a useful candidate for the treatment of women with persistent vomiting [1]. The most common side effects of pregnancy are nausea and vomiting [2]. It is most common in the first trimester, where organogenesis is most frequently affected.

Ondansetron is one of the most commonly used drugs for the treatment of pregnancy nausea and vomiting [3]. Ondansetron stands out because of its less sedation and superior antiemetic properties [4, 5]. Ondansetron use has been increasing, but unsafe data are still available [1].

Today, many different congenital malformations are encountered. Many factors are effective in the etiology. Environmental factors, genetic causes, and drug use during pregnancy are most common. Although the pregnancy categories of the new generation drugs used during pregnancy are certain, it is not known exactly whether they cause malformation due to their low use [6, 7]. It is the chick embryo that is most similar in development to the human embryo [7]. Animal studies on the use of ondansetron in pregnant women are not sufficient, and there is no information about neural tube defects in human use. Therefore, this study was designed to overcome this information gap in the literature.

Materials and Methods

This study was conducted after obtaining ethics committee approval (AKUHADYEK-49533702/45). 75 SPF eggs were divided into 5 groups. When creating groups: group 1; control group (No drug injection), group 2; ondansetron 0.08 mg / kg, group 3; ondansetron 0.16 mg / kg, group 4; ondansetron 0.32 mg / kg and group 5; ondansetron was determined to be 0.64 mg / kg.

All eggs were incubated at 37±0.5°C and turned automatically. Eggs removed from the incubator at the 32nd hour of the study were perforated in a sterile manner and appropriate doses of drugs were injected. The eggs, the holes of which were resealed, were placed in the incubator and removed from the device at the end of the 48th hour. Embryos removed with appropriate hand tools were examined with a light microscope. At this stage, the fore and aft length of the embryos in all groups, the number of somites, and whether the neural tubes were closed or not were determined. Embryos were then followed up histologically. Embryos passed through appropriate alcohol series were embedded in paraffin. Then, sections with a thickness of 5 μm were cut and subjected to AgNOR and Hematoxylin-Eosin staining [Figure 1].

The average AgNOR number and Total AgNOR region / Nuclear region (TAA / TNA) ratio were calculated for each nucleus [Figure 2]. mRNA threshold cycle values were calculated for genetic analyses.

Statistical analysis

While NT closures were analyzed with the chi-square test, Kruskal-Wallis tests were used for the analysis of other data. $p<0.001$ was considered significant. REST 2009 V2.0.13 software was used for genetic data analysis. Analysis of histological findings was done with IBM SPSS 22.0 software.

Results

In our study, neurological development retardation was investigated on embryos of 48-hour chicken eggs of ondansetron, which was given in four separate doses.

In the control group, the eggs in group 1 were not injected with ondansetron and the neural tube was closed in all 10 embryos and no developmental delay was observed. When the embryos were evaluated macroscopically under the light microscope, the mean crown-rump length was found to be 678.86±103.60. The mean number of somites was found to be 16.6±2.8. The mean TAA/NA ratio was 0.35 ±0.07, while the mean of AgNOR number was 17.5±1.8 (Table 1).

Group 2; The neural tube was found to be open in 7 of 10 embryos. The mean crown-rump length of the embryos was 650±98.46. The mean number of somites was found to be 15.5±2.4. When cell proliferation was evaluated by the AgNOR staining method in histological sections of embryos, the mean TAA/NA ratio was 0.30±0.05, while the average AgNOR number was 16.2±1.6 (Table 1).

Group 3; It was observed that the neural tube was open in 8 out of 10 embryos. The mean crown-rump length was found to be 609.81±80.54. The mean number of somites was found to be 13.9±2.2. The mean TAA/NA ratio was 0.28±0.03, while the average AgNOR number was 15.6±0.9 (Table 1).

Group 4; It was observed that the neural tube was open in 8 out of 10 embryos. The mean crown-rump length was 606.18±62.24. The mean number of somites was found to be 13.2±2.0. When the histological sections of the embryos were evaluated, the mean of the TAA/NA ratio was 0.25 ±0.02, while the average of the AgNOR number was 14.8±1.4 (Table 1).

Group 5; It was observed that the neural tube was open in 9 out of 10 embryos. The mean crown-rump length was 588.04±48.86. The mean number of somites was found to be 12.9±1.6. When the histological sections of the embryos were evaluated, the mean of the TAA/NA ratio was 0.24 ± 0.02, while the average of the AgNOR number was 14.3 ±1.0 (Table 1).

When NT closures were compared, significant differences were found between the groups ($p < 0.05$). While NT closure increased in a dose-dependent manner, all other parameters decreased in a dose-dependent manner. A dose-dependent neural tube defect was observed. As a result of the study, it was determined that fore and aft length, somite numbers, TAA / NA ratios, and AgNOR number averages decreased depending on the dose (Table 1).

A significant decrease was observed between group 1 and group 5 in the crown-rump length comparison (p=0.008). When the somite counts were compared, a significant decrease was observed between group 1, group 2, and group 5 (p=0.005). When AgNOR numbers were compared, a significant decrease was observed between group 1 and group 5 (p=0.015).

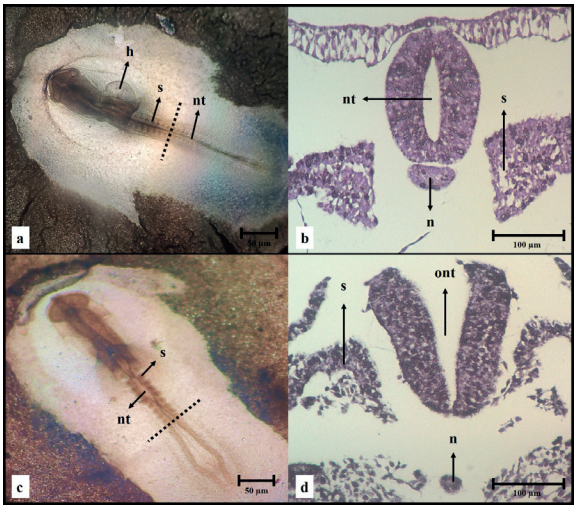

Figure 1. Effects of ondansetron on chick embryo development. Light microscope image of chick embryo in control (a), tissues stained with Hematoxylin and Eosin staining (H&E) in control (b), light microscope image of chick embryo with open neural tube (c), tissues stained with H&E in open neural tube (d), h, heart; n, notochord; nt, neural tube; ont, open neural tube; s, somite.

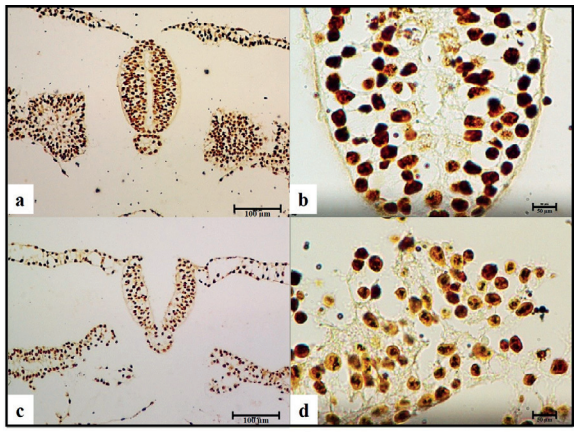

Figure 2. Counting nucleoli by determining random areas in tissues stained with AgNOR Staining Method. NT is closed (a-b), NT is open (c-d).

Table 1. Statistical analyses embryonic development in control and experimental groups (48-hour embryos)

Parameters	Group 1, Control	Group 2, Ondansetron 0.08 mg/kg	Group 3, Ondansetron 0.16 mg/kg	Group 4, Ondansetron 0.32 mg/kg	Group 5, Ondansetron 0.64 mg/kg	Significant P Values
Somite number	16.6±2.8	15.5±2.4	13.9±2.2	13.2±2.0	12.9±1.6	G5-G1 (P=0.005) G5-G2 (P=0.005)
Crown-rump length, mm	678.86±103.60	650±98.46	609.81±80.54	606.18±62.24	588.04±48.86	G5-G1 (P=0.008)
AgNor number	17.5±1.8	16.2±1.6	15.6±0.9	14.8±1.4	14.3 ±1.0	G5-G1 (P=0.015)
TAA/NA rate	0.35 ±0.07	0.30±0.05	0.28±0.03	0.25 ±0.02	0.24 ± 0.02	G5-G1 (P=0.002) G4-G1 (P=0.002) G3-G1 (P=0.002)
Open NT/closed NT	0/10	7/3	8/2	8/2	9/1	
Stage of embryo	13	12	11	11	11	

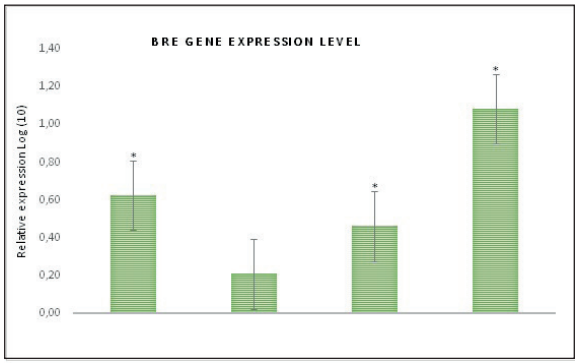

Figure 3. Relative mRNA expression of BRE in chick embryos exposed to different doses of ondansetron, given as fold regulation levels. GAPDH is the reference gene for normalization. * Represents the significance of $p < 0.05$.

When the TAA/NA ratios were compared, a statistically significant decrease was observed between the group and group 3, group 4, and group 5 (p=0.002).

BRE gene expression was observed to increase in embryos at each dose of ondansetron (group 2, 3, 4, 5) compared to the control group (group 1) (4.21; 1.61; 2.89; 12.11 fold regulation value, respectively). This increase was found to be statistically significant between groups 2, 4, and 5 when compared with the control group ($p < 0,05$). In addition to this result, the BRE gene expression was found to be increased in all embryos exposed to ondansetron in terms of mRNA levels compared to control (3.92; regulation value folds; $p<0.05$) [Figure 3].

Discussion

Today, ondansetron, which is used by many branches in the treatment of persistent nausea and vomiting, is a fast-acting and reliable 5-HT 3 receptor antagonist. The mechanism of action in controlling vomiting and nausea is not fully known. The effect of ondansetron in controlling nausea and vomiting caused by cytotoxic chemotherapy and radiotherapy is likely due to blocking 5-HT3 receptors in neurons in both the peripheral and central nervous systems.

According to the US Food and Drug Administration drug classification, the pregnancy category of ondansetron is designated as B. Ondansetron multiple hepatic cytochrome P-450 enzymes are metabolized by CYP3A4, CYP2D6, and CYP1A2. There is still timidity in terms of usage of ondansetron in human pregnancy.

Ondansetron is the most commonly used prescription oral antiemetic drug in pregnancy in the United States and was ranked as the fifth most commonly used oral drug in pregnancy in the Slone Epidemiological Center Birth Defects Study [3]. Compared to alternatives, ondansetron has been shown to have fewer side effects with less sedation and superior antiemetic effects [4, 5]. Regarding hyperemesis gravidarum treatment, half of the women receiving treatment in some emergency departments receive intravenous ondansetron [9].

Ondansetron crosses the placental barrier, therefore, concerns have been raised that its use in the first trimester of pregnancy may increase the risk of major congenital malformations. In this context, the findings from a meta-analysis of 6 cohorts and 2 case-control studies show that early pregnancy exposure to ondansetron increases the risk of increased heart defects and orofacial defects [10].

While many studies have shown ondansetron to be an effective and safe treatment in the treatment of hyperemesis gravidarum, there is still some concern about adverse effects on the fetus in a small number of studies [11].

Animal study models are very limited regarding whether there is a relationship between ondansetron and neural tube development. The first of the studies conducted on pregnant women was carried out by Anderka et al, and the increased risk of cleft palate associated with the use of ondansetron in the first trimester was found in women exposed to ondansetron [12].

Pasternak et al. compared the pregnant women who were prescribed and not prescribed ondansetron in the first trimester and reported that there was no significant major birth defect and cleft palate was not observed in women exposed to ondansetron (36 / 1,233) and those who were not exposed (141 / 4,932) [13].

In 2014, Danielson, like Pasternak and others, did not find a significant risk of malformation [14]. However, they found an increased risk of cardiovascular defects.

In their study, Damkier et al showed that ondansetron used in the first trimester of pregnancy did not increase the risk of cardiac malformation and that the oral cleft palate risk was only three for every 10,000 liveborn children exposed to ondansetron [15].

No teratogenicity has been reported regarding intravenous ondansetron therapy for hyperemesis gravidarum. When intravenously administered ondansetron and metoclopramide were compared in the treatment of hyperemesis gravidarum, it was reported that both had a generally preferred profile

in terms of side effects and showed similar clinical efficacy [4].

Animal studies on the use of ondansetron in pregnant women are not sufficient, and there is no information about neural tube defects in human use. Many models have been developed to show NT defects using chicken embryo models [16, 17]. The reason for choosing the chicken embryo model is that the first 48 hours of development are highly similar to the development of the mammalian spine. Therefore, different parameters were measured by using different doses of ondansetron in this model. The first parameter to be looked at was NT on or off, and the results showed that the use of ondansetron caused NT to remain open, depending on the dose [Table 1]. Nucleolar regulatory regions (NORs) are parts of metaphase chromosomes from which ribosomal genes are created. Throughout the interphase, NORs are linked to a large number of regulatory proteins and contain parts of the operative subunits of the nucleolus. They are where RNA organization and ribosomal gene transcription occur. NORs contain extremely acidophilic proteins, so NORs are seen sensitively and selectively by silver nitrate staining methods at the light microscope level (AgNOR). Changes in AgNOR protein levels also indicate the metabolic effects of cells. The AgNOR parameter, which was initially applied as a malignancy parameter, is useful for evaluating the prognosis of cancer [18, 19]. Our results showed that the average AgNOR number decreased in a dose-dependent situation (Table 1).

Another parameter examined was the average embryonic stages. The average embryonic stage was 13 in the control group and 11 in group 5. These results are similar to other studies [7, 20].

In our study, it was observed that the average crown-rump length and the number of somites decreased depending on the dose. This decrease was very significantly between the control group and group 5.

BRE gene is mainly detected in NT, nerve crest cells, somites, and neurites at the early embryonic development stage [21]. It has been suggested that when the BRE mRNA level decreases, somite development also decreases [20, 21]. Differently in our study, although BRE mRNA levels showed a dose-dependent increase, it was observed that somite counts decreased as the dose increased. In our study, the BRE gene was found to be significantly higher in group 5 compared to the control group and the second group. When the BRE mRNA was examined, no significant difference was observed between group 2 and the control group. BRE expression is affected by the high dosage.

Conclusion

Our study has shown that ondansetron has a direct teratogenic effect on the process of NT formation in chick embryos in a dose-dependent manner. These changes cannot be directly attributed to the human embryo. We interpreted our results according to genetic and histopathological findings. Studies with improved technical materials and larger sample sizes will be valuable in showing the possible dose-dependent toxic effects of ondansetron in the prenatal period. Findings obtained from all studies have shown that potential risks are less after the period of organogenesis and short-term treatment is always preferred. The present findings cannot be conclusive evidence of the use of ondansetron, but require caution in pregnancy use. When deciding on the use of ondansetron, it should be kept in mind that severe nausea and vomiting during pregnancy can cause significant physical and psychological morbidity to a degree suggesting termination of pregnancy in some women.

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No financial contribution has been received.

Conflict of interest

"The authors declared that they have no competing interests to disclose."

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ORIGINAL ARTICLE

The link between cord blood IL-1β, TLR4, PGE2 and TAC values with neonatal diseases

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Abstract

Premature birth is an important cause of neonatal mortality and neonatal morbidity. Most premature births are known to be induced by cytokines released for different reasons. Inadequate congenital immune response in premature infants may contribute to increased susceptibility to infection. The aim of the study is to determine the IL-1β, TLR4, PGE2, and TAC profiles in cord blood with characteristics specific to pregnancy and the correlation with neonatal complications caused by premature birth. The study included 26 neonates, 11 girls and 15 boys, born from 24-42 weeks of gestation. Of these, 13 were term and 13 were preterm . For IL-β, PG-E2, TLR4 and TAC levels, 1 mL of cord blood sample was taken from preterm and term neonates. Data related to demographic data, clinical status of patients and outcomes were obtained from electronic medical records and files. Cytokine values obtained from premature neonates were statistically high in terms of TLR4, IL1 and PGE2 compared to term infants. The TRL4 and IL1 values for premature infants with necrotizing enterocolitis and retinopathy of prematurity were lower compared to those without NEC and ROP. In spite of negative correlations between TAC and the other three cytokines, a statistically significant correlation was not identified. TLR4, IL1 and PGE2 were negatively correlated with weight and gestational week, contrarily TAC measurements were positively correlated with weight and gestational week. Measurements of cytokine concentrations in cord blood are among important biomarkers showing degree of inflammation and may assist in predicting neonatal complications and play an effective role in development of specific treatments.

Keywords: *Neonatal, umbilical cord blood, IL-1β, TLR4, PGE2, TAC*

Abbreviations: Necrotizing Enterocolitis (NEC), Retinopathy of Prematurity (ROP), Prostaglandin E2 (PGE2), Interleukin-1β (IL-1β), Reactive oxygen species (ROS), total antioxidant capacity (TAC), Toll-like receptor-4 (TLR4), Bronchopulmonary Dysplasia (BPD), Cord Blood Mononuclear Cells (CBMC), Tumor Necrosis Factor Alfa (TNF-α), Neonatal Intensive Care Unit (NICU), Enzyme Immunoassay (EIA), International Classification of Prematurity Retinopathy(ICROP)

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Introduction

Premature birth is an important cause of neonatal mortality and morbidity. Premature birth (<37 weeks) is a physiological process associated with negative outcomes like low birth weight (<2500 g) or very low birth weight (<1500 g) and comprises 5-10% of all births. Premature birth is linked to the maternal, fetal and placental causes. Repeated miscarriages, multiple births, placental defects, cervical and uterine anomalies, in vitro fertilization and polyhydramnios are risk factors for premature birth. Environmental factors like infection, alcohol, tobacco and low socioeconomic status are known to both increase systemic inflammation and the risk of premature birth. In order to provide a regular response to inflammation, immune cells, markers called cytokines or chemical mediators affecting other cells are released [1,2]. Cytokines released for different reasons are known to induce most premature births [2]. Contrary to a term neonate, preterm neonates have different cytokine and mediator profile levels and forms of control. These are shown as potential causes of increasing vulnerability to infections [1]. Increasing incidence of necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP) and sepsis in premature infants are thought to be associated with cytokine profiles.

One of the bioactive mediators of inflammation is prostaglandin E2 (PGE2) and effects rapidly begin within hours. The half-life is short in most biological fluids; for example, t1/2 is 5 minutes in plasma. In spite of PGE2's basic role in the inflammatory phase, it is not routinely used in clinical practice due to accelerated metabolism and natural difficulty with calculations [4].

Pro-inflammatory cytokine interleukin-1β (IL-1β) is an active pyrogen and inflammatory mediator playing a role in many early diseases. After toll-like receptor activation, IL-1β develops as a precursor protein (pro-IL-1β) and after division comprises the multiple protein inflammatory complex of caspase 1 [5]. IL-1β is the main mediator of the congenital and adaptive immune system [6]. IL-1β is basically a soluble protein created by monocytes and macrophages. A significant increase is reported in IL-1β levels in response to infection, microbial toxins, inflammatory agents, complementary products in activated lymphocytes and clotting compounds [7].

Reactive oxygen species (ROS) are highly reactive molecules that may destroy lipids, proteins, polysaccharides and DNA during cellular digestion of carbohydrates and lipids for energy production. Antioxidant defense successfully prevents the negative effects of ROS under typical physiological conditions [8]. However, immature organ systems, predisposition to infection and inflammation, extra oxygen requirements and high free iron levels make premature infants susceptible to ROS [9]. In the last trimester of pregnancy, the antioxidant enzyme systems are basically up-regulated and increasing amounts of non-enzymatic antioxidants pass the placenta in the same time period [9]. This comprises the total antioxidant capacity (TAC). The approximate contribution of antioxidants to TAC is equivalent to sulfhydryl groups in free proteins (52.9%), uric acid (33.1%), ascorbic acid (4.7%), general bilirubin (2.4%), alpha tocopherol (1.7%) and others (5.2%). Results are expressed as mmol Trolox per liter equivalent.

Toll-like receptor-4 (TLR4) is a cell surface receptor on the cell wall recognizing gram negative bacterial compounds. Premature birth is among diseases triggered by irregular activation of TLR4 to bacterial endotoxins. Diseases like neonatal sepsis, bronchopulmonary dysplasia (BPD), NEC and ROP specific to premature infants that may form as a result of premature birth do not have effective pharmacological medications [11]. The neonatal cord blood mononuclear cells (CBMC) have less tumor necrosis factor (TNF-α) and IL-1β in response to stimulation of the TLR ligand compared to adult cells; however, they release more IL-10 and IL-6 [12]. Stimulation of TLR by microbial ligands causes the necessary range of responses for inflammatory induction and adaptive immunity leading to activation of many signal pathways [12]. A variety of studies were performed with cytokines, the key agents in intrauterine inflammation and associated neonatal complications. Cytokine concentration levels in cord blood, amniotic fluid and neonatal peripheral blood may reflect the degree of inflammation and may assist in predicting neonatal conditions [13]. The aim of this study was to research the association between IL-1β, TLR4, PGE2, and TAC profiles in cord blood of term and preterm neonates with demographic features, need for admission to neonatal intensive care unit (NICU), and the neonatal complications caused by premature birth of NEC, ROP and sepsis.

Materials and Methods

Study Plan

This prospective research performed in a hospital with 17-bed tertiary NICU was completed from July 2019 to December 2020. The research included a total of 26 neonates (11 girls and 15 boys). The study

included neonates born between 24 and 42 weeks of gestation. Of these, 13 were term (>37 weeks) and 13 were preterm (<37 weeks). The research excluded patients with known or suspected congenital heart abnormalities, genetic disorders, metabolic disease and other congenital anomalies. Patients who did not require clinical blood sampling for sample collection were excluded from the study. Demographic variables, NEC, sepsis, ROP and Apgar scores were obtained from data collected. Information related to the mother was retrospectively obtained from the mother's medical history. The study was permitted by by Usak University Ethics Committee 11,07,2019/213-07 and informed consent was obtained from families. The study was performed in accordance with the Declaration of Helsinki Basil protocol 2013.

Blood Sample Collection and Cytokine measurement

Umbilical venous samples of 1 ml were obtained for preterm and term babies for IL-β, PG-E2, TLR4 and TAC serum, isolated by centrifugation for 10 minutes at 1500 rpm. Samples of serum is deposited at-80 ° C. TAC measurement of cord blood samples was done with manufacturer's kit protocol (Rel Assay Diagnostics kit; Turkey) which is based on reducing ın the samples which include antioxidants, dark blue green colored ABTS radical to colorless ABTS type. In this assay, TAS levels were colorometrically detected the change of absorbance at 660nm using microplate reader. (Thermo Fisher Scientific, Finland). The results were indicated as μmol Trolox equivalent/L (μmolTroloxeq/L) [14] .

The levels of cord blood TLR-4, PGE-2, and IL-1β (USCN Life Science, Wuhan, China) were measured by enzyme immunoassay (EIA). Absorbance was carried out on Thermo fisher Multi Sky System (Thermo Fisher Scientific, Finland). Cord blood concentrations of TLR-4, PGE2, and IL-1β were determined from a curve obtained with the standards. The package detection limits were 0.118 ng /ml and 8.43pg/ml respectively, for TLR-4 and PGE-2, and 8,43pg/mlfor IL-1β according to manufacturer's instruction

Data Processing for Patients

Neonatal data from electronic medical reports, including demographic data, clinical factors and outcomes, were reported. Apgar scores were recorded one and five minutes after birth. Patients were separated into two on the basis of APGAR scores: <7 and ≥7 [15]. All of our 6 NEC diagnosis patients were premature and 4 were evaluated as suspected necrotizing enterocolitis and 2were Conclusive medical necrotizing enterocolitis according to the modified bell criteria [16]. In 7 premature patients, the diagnosis of ROP was made according to ICROP (International Classification of Prematurity Retinopathy) as a result of regular eye exams conducted in our clinic. 4 patients Stage 1: vascular and avascular retina demarcation line, 2 patients Stage 2: back (ridge); surface swelling, and 1 patient confirmed to be Stage 3: fibrovascular extraretinal (fibrovascular) proliferation at the back [17]. Sepsis has been diagnosed in 8 patients with a positive, urine, CSF or blood culture (> 72 hours) [18]. All newborns admitted to the research center's intensive care unit underwent screening echocardiography examination within 24 hours of their admission. A systematic echocardiographic cross-sectional and doppler test was conducted with several parasternal, suprasternal, apical and subcostal orthogonal views with 6-MHz transducers (Vivid S6, GE Healthcare, UK). Six patients were diagnosed with PDA by transthoracic echocardiography.

Statistical Analysis

Descriptive statistics in the tables are given as mean and standard deviation, and median and interquartile range. As a result of the Kolmogorov-Smirnov test, the statistical distribution of cytokines values was not suitable for normal distribution in any of the groups compared. The Mann Withney U test was used both for the comparison of term and preterm and for comparisons with and without Nec, Rop and Sepsis within the preterm group. However, it was used in all of the other two group comparisons. Relationships between cytokines, week and weight were determined with the Spearman correlation coefficient. In G*Power software, For all comparisons with a statistically relevant minimum $p<0.05$, effect sizes and post-hoc power analysis were conducted for. The minimum and maximum effect sizes were calculated to be 0.673-2.41 in the study. The strength of the test was estimated at a minimum of 49.24% and a maximum of 99.9%. For statistical analysis, SPSS software for Windows version 25.0 (Statistical Package for Social Sciences Inc, Chicago, IL, USA) was used.

Results

Among cytokine values, the TAC value was found to be low by a statistically significant degree in premature infants ($p<0.05$). The cytokine values obtained from premature neonates in terms of TLR4, IL1 and PGE2 were found to be statistically significantly high compared to term infants ($p<0.01$). The IL1 value

especially was four times higher in preterm neonates compared to term neonates. The descriptive statistics and statistical comparisons in terms of cytokine values of preterm and term infants are given in Table 1.

Figure 1 gives the comparison of cytokines and TAC in premature neonates in terms of those with and without NEC and ROP. Due to the low number of observations and variability, comparisons used the Mann Whitney U test. All of the investigated cytokines were not statistically significant in terms of premature neonates with/without NEC and ROP (p>0.05). The TAC and PGE2 values of those with and without NEC and ROP were very close to each other. Additionally, the TLR4 and IL1 values were found to be higher in those without NEC and ROP compared to those with these conditions. Though statistically insignificant, this difference in IL1 levels was two times more than those without these conditions.

Table 2 gives the comparisons of cytokines in preterm and term neonates in terms of sepsis, gender, NICU admission, Apgar score, type of birth, smoking and patent ductus arteriosus (PDA). The IL1 and PGE2 values of neonates with sepsis had statistically higher values compared to those without sepsis (p<0.05). In terms of gender, being a female or male infant did not appear to cause a change in cytokine values (p>0.05). In terms of need for NICU admission or not, TLR4 levels were not different (p>0.05), while neonates requiring NICU admission had statistically significant degree of elevation in IL1 and PGE2 levels, while TAC levels were significantly low (p<0.05). Apgar scores above or below 7, birth type of vaginal or cesarean, and smoking habit or not did not cause statistically significant differences in terms of cytokines (p>0.05). In the presence of PDA, only PGE2 levels were found to be high by a statistically significant degree (p<0.05).

Table 1. Comparison of cytokine levels in cord blood of term and preterm infants

	Preterm		Term		
Variables	Mean±S.D.	Median(IQR)	Mean±S.D.	Median(IQR)	p value*
TAS	0.90±0.06	0.88(0.08)	0.99±0.13	0.97(0.12)	0.026
TLR4	2.79±0.55	2.89(0.54)	2.24±0.39	2.11(0.40)	0.009
IL1	228.25±252.6	112.92(248.88)	53.77±55.52	30.39(67.52)	0.007
PGE2	1072.25±84.73	1084.37(163.13)	726.38±722.23	620.24(735.86)	0.009

*:MannWithneyU p value, S.D.:Standard deviation, IQR: interquartile range

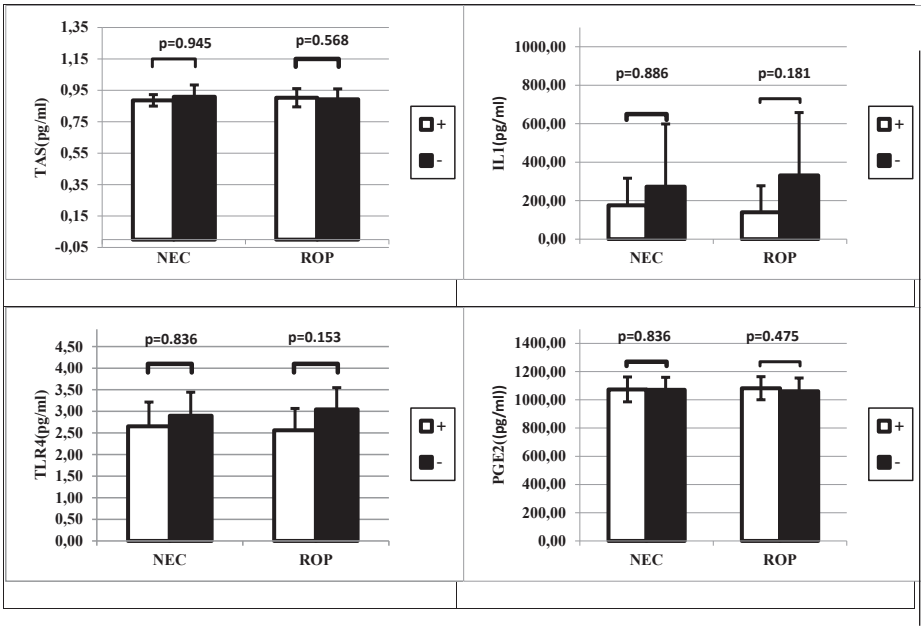

Figure 1. Comparison of cytokinins in the Premature group in terms of ROP and NEC (+:existence, - : non-existence)

Table 2. Comparison of TLR4, PGE2, IL1B and TAS values in terms of perinatal characteristics of newborns

Variables		Cytokines			
		TLR4	**IL1**	**PGE2**	**TAS**
		Median(IQR)	**Median(IQR)**	**Median(IQR)**	**Median(IQR)**
Sepsis	+	2.79(0.51)	112.92(112.76)	1015.69(163.13)	0.89(0.07)
	-	2.16(0.84)	32.68(74.42)	758.73(648.88)	0.96(0.11)
	pvalue	0.0765	**0.0165**	**0.0315**	0.1235
Gender	**Male**	2.16(0.9)	102.39(178.25)	984.47(381.85)	0.91(0.12)
	Female	2.62(0.65)	73.47(75.73)	1015.69(788.19)	0.96(0.1)
	pvalue	0.337	0.622	0.979	0.815
Need For NICU Admission	+	2.62(0.92)	112.92(288.9)	1015.69(175.22)	0.88(0.12)
	-	2.31(0.95)	32.68(65.2)	620.24(753.04)	0.97(0.08)
	pvalue	0.1435	**0.026**	**0.0365**	**0.041**
APGAR	**Down7**	2.89(1.19)	147.25(307.87)	1084.37(190.26)	0.88(0.07)
	Up7	2.33(0.85)	57.84(77.69)	990.52(651.66)	0.96(0.13)
	pvalue	0.063	0.107	0.156	0.0965
Delivery	**NSVD**	2(1.16)	30.39(339.53)	758.73(281.09)	1.1(0.49)
	C/S	2.44(0.88)	82(122.55)	1004.29(686.81)	0.91(0.1)
	pvalue	0.1995	0.2735	0.2475	0.1395
Tobacco	**Smoking**	2.98(1.35)	112.92(297.75)	1015.69(149.36)	0.9(0.11)
	Non-Smoking	2.4(0.87)	73.47(130.45)	984.47(676.17)	0.91(0.11)
	pvalue	0.446	0.316	0.399	0.399
PDA	+	2.61(1.05)	117.85(221.93)	1107.83(69.28)	0.91(0.14)
	_	2.42(0.87)	53.46(104.07)	981.45(643.36)	0.91(0.1)
	pvalue	0.165	0.081	**0.0255**	0.4755

IQR: interquartile range

Table 3. Spearman correlation matrix between cytokines, weight and weeks

	IL1	PGE2	TAS	Weight	Week
TLR4	0.565**	0.305	-0.229	-0.459*	-0.544**
IL1	1	0.554**	-0.352	-0.488*	-0.597**
PGE2		1	-0.043	-0.343	-0.402*
TAS			1	0.392*	0.495*
Weight				1	0.904**

* and ** symbols shows correlation are significant at the 0.05 and 0.01 levels respectively.

Table 3 gives the correlation coefficients and statistical significance of cytokines in correlation with weight (kilo) and week of gestation. When the correlations between cytokines and TAC levels are examined, TLR4 and IL1 had 56.5% positive correlation and IL1 and PGE2 had 55.4% positive correlation and these were statistically significant ($p<0.01$). Though there were negative correlations between TAC levels with the other three cytokines, statistically significant correlations were not present. TLR4, IL1 and PGE2 were negatively correlated with weight and week of gestation ($p<0.05$, $p<0.01$). Contrary to this, TAC levels had a positive correlation with weight and week of gestation ($p<0.05$).

Discussion

In our study, the effect or not of TLR4, PGE2, and IL-1β cytokine levels and TAC levels on early birth was investigated along with the connections between sepsis, gender, need for admission to neonatal intensive care unit, APGAR score, type of birth, smoking and PDA development with cytokine profiles. Simultaneously cytokine profiles measured in cord blood were examined for whether they could be markers for NEC, ROP and sepsis and correlations between the cytokines were compared.

Cytokines are known to play roles in placental development and birth, as much as in the immune system [2]. In our study, TLR4, IL-1β and PGE2 concentrations in cord blood of premature neonates were found to be high by a statistically significant degree compared to values in the cord blood of term infants (Table 1). A study by Huang et al. associated the correlation between cord blood levels of phagocyte mediators IL-8 and MPO and vascular mediators of PGE2 and sVCAM-1 with differences in fetal maturity with gestational age. While higher IL-8 and MPO levels were identified in preterm neonates, PGE2 levels were low; however, there was no correlation with gestational age [19]. In our study, PGE2 levels were higher in cord blood of premature neonates, while there was a negative correlation with week of pregnancy. When the physiological features of premature and term neonates and pharmacological properties of PGE2 are compared, our results are compatible with the features of premature neonates and PGE2 properties.

In our study, TLR4, IL-1β and PGE2 concentrations in the cord blood of premature neonates were found to be negatively associated with gestational age and weight (Table 4). Comparisons between groups according to gestational week by Otsubo et al. revealed the inflammatory cytokine levels of IL-6, IL-1β, IL-1ra, and IL-13 and chemokine MIP-1β levels were significantly higher in groups from 37-41 weeks and less than 32 weeks compared to the group from 32-36 weeks. In our study, a negative correlation was identified between week and IL1-β, with IL1-β levels reducing as the gestational week increased. In our study, neonates below and above 37 weeks were compared and the IL1-β level was high in the group below 37 weeks and low in the group above 37 weeks. In the study by Otsubo et al. three groups were compared, with separate assessment of the group below 32 weeks with high IL1-β and the 32-36 week group with low IL1-β. When the 32-36 week and below 32 week groups are compared, results compatible with our study emerge [20].

In our study, premature infants were found to have four times higher IL-1β cord blood levels compared to term infants and there was a negative correlation between IL-1β levels with gestational week. In our study, the TLR4 levels in preterm cord blood were statistically higher compared to term infants and there was a negative correlation with gestational week. A study by Robertson et al. identified a negative correlation between gestational week with TLR4, as in our study. They recommended the use of TLR4 antagonists for inhibition of fetal, placental and intraamniotic inflammatory cytokine production to prevent premature birth. The results of our study support this proposal [21]. Additionally, Shen et al. found a reduction in toll-like receptor 2 (TLR2) and TLR4 surface expression in blood monocytes of premature neonates [22]. Mathias et al. reported a significant increase in interleukin 10 (IL-10) levels in cord blood after 24-hour ex vivo TLR4 stimulation [23].

Similar studies were performed with different body fluids. A study not using cord blood found urine PGE2 levels were high in premature infants and there were higher rates of increase in the first days of life in premature infants compared to term infants [24]. A study by Yoon et al. associated the elevation in IL-1β levels in amniotic fluid, but absence in cord blood, with intrauterine infection and premature birth [25]. In our study, though statistically significant differences could not be shown between term and preterm infants for IL-1β levels in cord blood, higher levels were identified in the cord blood of preterm infants. This situation leads to the consideration that preterm birth may be associated with intrauterine infections and intrauterine infections induce premature birth. A study by Narendran et al. found higher IL-1β levels

on preterm skin (skin surface of preterm infants) compared to term, adult and vernix, similar to our study [26].

In our study, TAC values measured in cord blood were observed to be low by a statistically significant degree in premature neonates compared to term neonates ($p<0.05$). Positive correlations were found between TAC value with gestational week and weight ($p<0.05$). Huertas et al. [27] found high concentrations of hydroperoxide in the erythrocyte membranes at birth and in the first days of life of premature infants in their study. They identified that the erythrocyte membranes of premature neonates were at much lower levels and/or had lower antioxidant defense functions compared to term neonates [27]. A study by Dizdar et al. observed lower TAC levels in infants younger than 28 weeks compared to those over 28 weeks [28]; similarly, in our study, TAC levels were identified to be low in the cord blood of premature infants. Both studies show that the antioxidant defense mechanism of small infants is immature. A study of premature infants by Georgeson et al. found cord blood antioxidant enzyme activities were lower compared to term infants, similar to our study, while cord blood lipid peroxidation markers were similar in term and preterm infants [29].

In our study, statistically higher IL1 and PGE2 values were identified in patients with sepsis compared to those without sepsis ($p<0.05$) (Table 2). Siljehave et al. mentioned increases in prostaglandin E2 (PGE2) induced with proinflammatory cytokine interleukin IL-1β infection and disrupted respiration as a result of this increase. In our study, both PGE2 and IL-1β levels were increased in infants with sepsis which is compatible with the literature and this study [4].

Similar to our study, a study related to sepsis using cord blood by Santana et al. found IL-8 concentration in cord blood was the most sensitive cytokine for early neonatal sepsis [30]. Some studies identified an increase in TNF-α in cord blood with early neonatal sepsis [31]. Contrary to our study, a study by Atıcı et al. showed IL-1 concentrations significantly reduced in preterm and term neonates with sepsis [32]. Ozdemir et al. found no significant difference in serum IL-1β levels in septic neonates compared to healthy controls [31].

In our study, there was no statistical difference between cord blood TLR4 levels in neonates with and without sepsis. The study by Shen et al. showed a reduction in surface expression of TLR2 and TLR4 in blood monocytes of premature neonates and a lower response to lipopolysaccharide (LPS) stimulation compared to TNF-α and IL-8 [22]. In our study, TLR4 was negatively correlated with gestational week. In other words, compared to term infants, preterm infants were identified to have higher rates of TLR4. A study by Levy et al. stated increased TLR4 and CD14 expression with stimulation of neonatal monocyte LPS may cause flare ups of normal inflammation during severe infection [33].

In our study, neonates with PDA were found to have statistically high PGE2 cord blood levels ($p<0.05$) (Table 2). Prostaglandins, especially PGE2, play an important role in maintaining the patency of fetal PDA [34].

As a result of analyses, type of birth, in other words spontaneous vaginal birth or cesarean birth, did not cause a statistically significant difference in terms of TLR4, PGE2, IL-1β and TAC. A study by Steinborn et al. showed that TNF-α and IL-1β levels in spontaneous vaginal birth cases were much higher compared to cesarean births [35]. In our study, the reason for the lack of statistically significant difference is thought to be the small sample size. A study by Hasegawa-Nakamura et al. observed that vaginal birth can induce TLR4 expression on monocytes and that lower receptor levels were seen in infants born by cesarean section [36]. Molloy et al. reported that in cesarean neonates, neonatal neutrophils had higher TLR4 expression compared to neonates born by the vaginal route [37].

When neonates in our study are assessed in terms of NICU admission requirements, there was no statistically significant difference in TLR4 levels ($p>0.05$). Statistically significant elevations in IL-1β and PGE2 and statistically significant fall in TAC values were identified in neonates requiring admission to hospital ($p<0.05$) (Table 2). Dizdar et al. [28] analyzed the association between TAC and total oxidative stress (TOS) levels of infants admitted to the NICU and healthy infants and similarly found low TAC levels were associated with longer duration of respiratory support and hospitalization [28].

In our study, the TAC levels and PGE2 values of premature infants with and without NEC and ROP were observed to be very close. However, TLR4 and IL2 values were higher in patients without NEC and without ROP. Though statistically insignificant, this difference was two times higher for IL-1β (Figure 1). Goepfert et al. showed increased IL-6 levels in umbilical blood samples and increased NEC risk in premature infants [38]. Satar et al. identified that

premature birth and NEC were associated with IL-8 in cord blood [39]. Yazji et al. showed disrupted neonatal intestinal perfusion in the NEC pathogenesis with TLR4 activation in endothelium. In experimental NEC induced in rats deficient in TLR4, mucosa inflammation and intestinal necrosis were reduced [40]. In our study, the basic reason for the lack of significant difference is the small sample size. We think developing this study with larger sample groups will identify a significant difference.

Conclusion

Preterm infants were found to have higher IL-1β values, especially, along with TLR4 and PGE2 levels compared to term infants. Among preterm infants, those with ROP and NEC were found to have higher IL-1β values, by two times, and TLR4 values. It is considered that if samples are taken from cord blood and studied before the development of NEC and ROP, IL-1β and TLR4 antagonists can be administered with the threat of early birth and both premature birth and NEC and ROP development may be prevented. This is supported by literature information (21). Additionally, design of studies administering IL1 and TLR4 antagonists in the early stages of NEC and ROP development in larger sample groups will form an important stage for the transition to treatment.

IL1 and PGE2 levels were higher in septic neonates. Additionally, infants admitted to the NICU were identified to have higher IL1 and PGE2 levels. The use of IL1 antagonists for sepsis treatment may be promising and cheering.

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Conflict of interest

The authors have notified that no competing interests conflict and published at the stage of preparation of this manuscript.

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ORIGINAL ARTICLE

Evaluate the compliance of perioperative practices of the patients with the enhanced recovery after surgery protocols

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Abstract

The Enhanced Recovery after Surgery (ERAS) protocol is a multimodal and evidence-based medical practice developed to define the concept of perioperative interventions to improve postoperative outcomes. The protocol consists of a number of elements implemented in the pre-, intra - and post-operative periods. This study aimed to evaluate the compliance of perioperative practices with the ERAS protocols in patients undergoing surgical intervention. In this descriptive and prospective study, 405 patients who underwent surgery in the General Surgery Clinic of a University Hospital created a sample of the study. In the study, where no intervention was made to the patients included in the study, the compliance of routine perioperative practices in the clinic offered to patients undergoing surgery to the protocol was evaluated using the questionnaire prepared in this direction. Procedures such as, in the preoperative period, providing verbal information to all the patients and giving antibiotic prophylaxis to 98.5% of the patients, in the intraoperative period, preferring the smallest possible surgical incision, and, in the postoperative period, using the paracetamol (99.5%) as the first choice for analgesia were compatible with the ERAS protocols. Procedures such as, in the preoperative period, not providing oral carbohydrate to any of the patients and keeping the fasting period longer period (10.91 ± 4.79 hours), in the intraoperative period, preferring anesthetic agents that are effective for a long time, and not perform the necessary practices to ensure normothermia in any of the patients, and, in the postoperative period, not starting the oral nutrition early and using urinary catheterization for 87.7% of the patients were not compatible with the ERAS protocols. As a result of the research, it was determined that the routine perioperative applications in the clinic did not sufficiently comply with the ERAS protocol.

Keywords: *Enhanced recovery after surgery, perioperative process*

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Introduction

The Enhanced Recovery after Surgery (ERAS) protocol is a multimodal and evidence-based medical practice developed to define the concept of perioperative interventions to improve postoperative outcomes [1]. The protocol consists of a number of elements implemented in the pre-, intra - and post-operative periods [2].

ERAS Protocol implemented since the 1990s provides benefits such as oral food intake facilitation and acceleration, minimizing the duration of hospital stay and reduction of complications, early mobilization, accelerating the return to daily activities after discharge [3]. A recently published meta-analysis study emphasizes that by applying ERAS protocols in major surgeries, the duration of hospital stay is shortened by 2-3 days and the incidence of complications is reduced by 30-50% [1].

ERAS protocols have begun to be discussed and widely used following the remarkable and promising results of studies conducted in many countries [4]. However, in a survey study conducted with a large number of surgeons from different centers during the transition of the protocol into practice, it was found that innovations, although based on evidence, were not easily accepted [5]. In another similar study, it was reported that the implementation of the ERAS protocol was perceived positively, while the most important factors that prevent the implementation were lack of manpower, poor communication and cooperation, and resilience to change [6]. The foundation of the ERAS Society Turkey in 2017 and the organization of the first ERAS Congress in Ankara in May 2018 are important indicators that the ERAS protocol is becoming increasingly common in Turkey [1]. However, according to studies conducted in Turkey, it seems that doctors and nurses' knowledge of the ERAS protocols and practices is limited at insufficient levels [7], and all the recommendations of ERAS are not implemented as a whole, and doctors and nurses find it difficult to implement it despite increasing awareness [8]. The study results with a high level of evidence report that ERAS protocols are in the best interest of the patient. But the results of the study, which examined the awareness, knowledge, and practices of health professionals for ERAS protocols, suggest the question of what level of adequacy of protocol implementation transfer is.

This study was conducted to evaluate the compliance of perioperative practices used on patients admitted in the General Surgery clinic with ERAS protocols.

Materials and Methods

Ethical considerations

In order to carry out the study, ethics committee approval was obtained from the Clinical Research Ethics Committee, Afyon Kocatepe University (approval number 2016/3-34), and written permission was obtained from the related institution and informed consent from the patients participating.

Type of the study

This study is a descriptive type of research planned to assess the compliance of perioperative applications of patients in surgical clinics with the ERAS protocol and its impact on patient outcomes. The research which was performed as a single-centered was conducted in the General Surgery Clinic of Afyon Kocatepe University Hospital between November 2016 and January 2017.

Participants

This descriptive and prospective study was conducted in the General Surgery Clinic of a university hospital located in the city of Afyonkarahisar between November 2016 and January 2017. The universe of the study consisted of 473 patients who were treated for surgery at the general surgery clinic at the time of the study. 17 patients who had emergency operations performed, 12 patients whose extubation was over 24 hours, 2 patients who were foreign nationals and could not be communicated, 9 patients who did not agree to participate in the study, and 28 patients whose data could not be obtained completely, were excluded from the study. The study was completed with a total of 405 patients who received perioperative patient care in the clinic, who were conscious and agreed to participate in the research (Figure 1).

Data Collection

"The Patient Information Form", "Patient Monitoring Form" and "ERAS Protocol Compliance Form" were used as data collection tools (Table 1).

Data analysis

Analysis of the study data was completed by using SPSS version 20.0 (Armonk, NY: IBM Corp) package program. Descriptive statistics of continuous variables were shown with mean, standard deviation, minimum and maximum values, while descriptive statistics of categorical variables were shown with frequency and percentage. The Skewness-Kurtosis values and Shapiro-Wilk test were used to assess whether the

data were normally distributed.

Results

The average age of the patients was 49.68 ± 15.50, 51.9% were women, 43.7% were high school graduates, and 51.1% were not working anywhere. A total of 70.6% of patients did not have any chronic disease, 30.9% have been smoking, and 56.3% never had previous surgery for any reason. A total of 33.3% of the patients included in the study had hepatopancreatobiliary, 14.1% had a hernia, 10.9% had stomach-esophagus, 10.9% had other, 9.4% had breast, 8.4% had rectum, 6.9% had intestine and 6.2% had colon surgery.

Distribution of which the patients' perioperative process compliance with ERAS protocol is presented in Table 2. When the ERAS protocol compliance of preoperative period was examined; all the patients were informed about their diseases, surgery and the process of the surgery during the preoperative stages, 37% of them had mechanical bowel cleansing, none of the patients were given carbohydrates orally, and applied premedication, 88.9% of them were not applied to thromboembolism prophylaxis, 98.5% of them had prophylactic antibiotics applied 30-45 min before, all patients were forced to fasting after midnight, and the average fasting period was found to be 10.91 ± 4.79 hours. During the intraoperative period, 44.4% of patients were used drain, 73.8% were administered antiemetic drugs, none of the patients had any application to provide normothermia (blankets, IV warm liquids, hot air systems, etc.), while long-acting anesthetics were preferred in 95.1% of patients, and the smallest possible incision was performed in all patients. In the postoperative period, 29.4% of patients had an NG catheter and 87.7% had

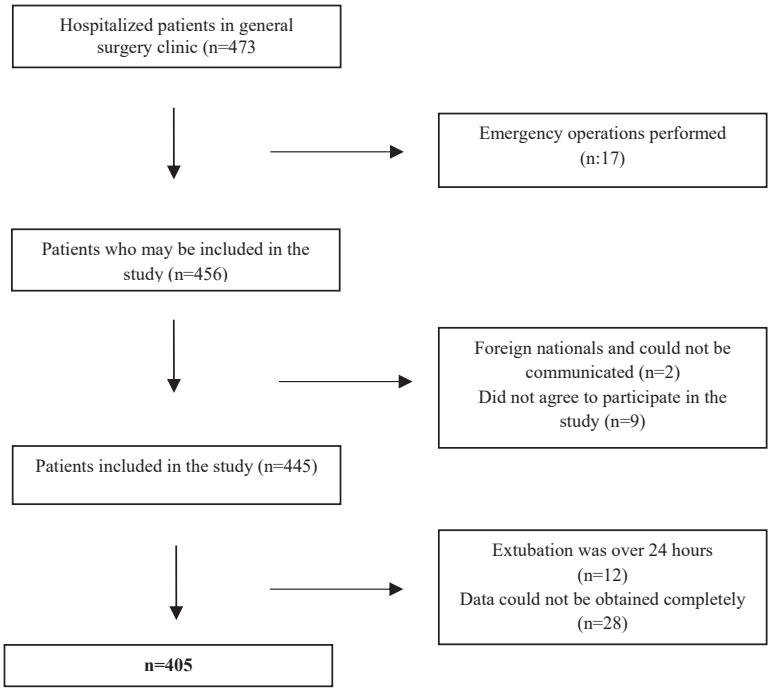

Figure 1. Study flow chart

Table 1. Data Collection Tools

Tools	Features
The Patient Information Form	10-item questionnaire prepared by the researchers after a review of the relevant literature
Patient Monitoring Form	Includes perioperative vital signs, surgical information (such as surgery entry/ exit time, intubation time, duration of surgery), hemogram-biochemistry - coagulation parameters, blood gas parameters, and Visual Analog Scale pain scale. Patients were asked to put a vertical mark on the 10 cm straight line. Other information was obtained from the patient file.
ERAS Protocol Compliance Form	Consists of 3 sections and 20 articles in which perioperative applications on which the ERAS protocol is based are evaluated. The information required to complete this form was obtained from the patients' files

Table 2. Perioperative processes and their distribution according to compliance with the ERAS protocols (n=405)

Period	Items		Yes		No	
			n	%	n	%
Preoperative Period	Preoperative information		405	100	-	-
	Preoperative mechanical intestine cleansing		150	37	355	63
	Preoperative oral carbohydrate intake		-	-	405	100
	Preoperative assessment of general situation		399	98.5	6	1.5
	Premedication		-	-	405	100
	Thromboembolic prophylaxis		45	11.1	366	88.9
	Prophylactic antibiotic use		399	98.5	6	1.5
	Fasting after midnight		405	100	-	-
	Solid foods 6 hours before surgery, liquid foods 2 hours before surgery		-	-	405	100
	Preoperative fasting time (hour) (Mean ± SD)		10.91 ± 4.79			
Intra-operative Period	Drain use		180	44.4	225	55.6
	Antiemetic use		299	73.8	106	26.2
	Maintaining normothermia		-	-	405	100
	Anesthesia procedure	Short-acting anesthetics	20	4.9		
		Long-acting anesthetics	385	95.1		
	Surgical incision	Transverse	-	-		
		Longitudinal	-	-		
		The smallest possible	405	100		
		Large enough to enable ease-of-work	-	-		
Postoperative Period	NG intubation		119	29.4	286	70.6
	Urinary catheterization		355	87.7	50	12.3
	Analgesics Administration	Epidural anesthesia + paracetamol	1	0.2		
		Paracetamol + narcotic	403	99.5		
		NSIA	1	0.2		
	Start to take liquid foods at 2. hour		-	-	405	100
	Start to take solid foods at 4. hour		-	-	405	100
	Mean duration before starting liquid food intake after surgery ((hour) Mean ± SD		9.38 ± 6.63			
	Mean duration before starting solid food intake after surgery (hour) (Mean ± SD)		15.06 ± 11.50			
	Mobilization time (hour) (Mean ± SD)		8.00 ± 2.46			
	Discharge (day) (Mean ± SD)		6.15 ± 4.51			

a urinary catheter inserted, 99.5% of patients had paracetamol and narcotic analgesics applied for pain control. While the liquid intake on the second hour and solid food on the fourth hour was not started for any of the patients. The mean time to start liquid foods was 9.38 ± 6.63 hours and the mean time to start solid foods was 15.06 ± 11.50 hours. Patients were mobilized after a mean of 8.00 ± 2.46 hours, and the mean discharge times were 6.15 ± 4.51 days.

Discussion

The ERAS protocol introduces important innovations that move beyond classical surgical and anesthesia practices and can be characterized as radical. These innovations, which suggest changes regarding the entire journey of a patient that starts before the surgery and ends at home, were used since the 1990s. They provide benefits such as facilitating and accelerating oral food intake, reducing hospital stay time and complications, providing early mobilization, and accelerating the return to daily life activities after discharge [2,3].

Having the patients to fast the night before surgery induces insulin resistance in the perioperative process negatively affects the nitrogen balance, and reduces the quality of life of patients [1]. In order to avoid these metabolic disadvantages in patients undergoing surgery, the European Society of Anesthesiology recommends that patients should stop taking solid foods 6 hours before surgery and liquid foods 2 hours before surgery [9]. Contrary to recommendations it is reported in the literature that patients still continue to be forced to fast for a longer time [10]. It is recommended that the patients should be given

800 ml of carbohydrate drinks until midnight before surgery and 400 ml 2-3 hours before surgery [1]. In studies, patients whose fasting period was shortened by carbohydrate-containing liquids had better insulin and inflammatory parameters, fewer indicators of malnutrition (handgrip strength, etc.), and shorter hospitalization period [11,12]. It was observed in this study that all the patients were made to fast after midnight, none of the patients were given oral carbohydrates therefore the protocol recommended by ERAS was not followed at all. In this study, it was found that the mean fasting time of patients was 10.91±4.79 hours (solid and liquid food intake was stopped at the same time). This may be related to two factors: the patients being inadequately informed by the healthcare professionals, who evaluated the patient last, about how to fast and the duration of fasting in accordance with the protocols, and the socio-cultural levels of the community where the study carried out.

The purpose of premedication is to reduce the stress response and anxiety caused by surgery. In recent studies, there have been no evidence-based results that premedication reduces anxiety [13]. Therefore, unnecessary premedication should be avoided [1]. In this study, it was found that none of the patients undergoing surgery were applied premedication (anxiolytic or sedative agent) during the preoperative period, which shows compliance with ERAS protocols.

It has been recommended that thromboembolic therapy be initiated in the preoperative period [1] and that prophylaxis is continued after discharge in order to reduce/eliminate the risk of deep vein thrombosis and pulmonary embolism, which causes serious complications in the postoperative period [14]. In this study, 11.1% of the patients were detected to be given antithromboembolic medications in the preoperative period.

Antibiotic prophylaxis is recommended in the preoperative period to prevent and reduce wound site/surgical area infections that may develop in the Post-operative period [15]. In this study, antibiotic prophylaxis was given to 98.5% of the patients, who underwent surgery, in the preoperative period. Third-generation cephalosporin antibiotics, administered 30-45 min before surgical incision, were preferred for antibiotic prophylaxis. In studies examining this issue, it has been reported that the rate of infection development at the surgical site was lower and the duration of hospital stay was shorter in patients undergoing antibiotic prophylaxis [16].

Although there is no definite recommendation about the shape of the incisions in the ERAS protocols, it is reported that the smallest possible incision should be used [1]. In a systematic review investigating the effects of incisions in abdominal surgery on patients, it was reported that the need for narcotic analgesics was lower in patients with transverse incisions while the deterioration of pulmonary function was high in patients with longitudinal incisions [17]. In this study, it was determined that there was no standard choice of incision, therefore the incisions were made according to the surgical interventions, and the smallest possible incisions were made.

Maintaining preoperative normothermia is quite important. Warming the patients during the perioperative period has been reported to be effective in reducing postoperative pain, wound infection, and tremor [18]. In this study, it was detected that the methods for maintaining normothermia were not applied to the patients (blanket, IV fluid, heater, etc.). In the intraoperative period, the mean body temperature of the patients was 35.42±0.33 °c (n=38), while 36.03±0.20 °C in the postoperative period.

Drains placed in the intraoperative period are traditionally used to ensure postoperative fluid accumulation and drainage of fluid that will occur with a possible anastomosis leakage. But drain creates a physical barrier in the patient, can prevent the mobilization of the patient, and makes pain control difficult [7]. It has also been shown that the use of drains has no effect on anastomosis leakage [19]. For this reason, routine use of drains should be avoided, if it is used, the drains used should be removed as soon as possible [1]. In this study, 44.4% of patients had drains placed in during the intraoperative period.

In this study, it was determined that the rate of patients who had a nasogastric catheter (NG) was 29.4% and that the NG catheter was removed after an average of 2.30 ± 1.79 days in the postoperative period. In patients undergoing colon surgery, it was reported that with the use of ERAS protocols, the patients used NG decreased from 88.3% to 9.6% and the NG removal time was 2.5 days on average [20]. These results show similarities to our study.

The ERAS protocol argues that liquid food on the 2nd hour and solid food intake on the 4th hour of the post-operative period should be encouraged for the patients [1]. Studies conducted in different countries indicate that the earlier oral feeding starts for the patients the shorter the time of the first defecation and the duration of hospital stay is [21,22], not the presence of anastomosis leakage and abscess and the patient

satisfaction was high [23]. In laparoscopic colorectal resection surgery, in addition to preoperative oral carbohydrate administration in accordance with ERAs recommendations, patients, who switched to post-operative oral nutrition early had faster recovery of their postoperative clinical functions, decrease in recovery time and decrease in-hospital stay [24]. In this study, none of the patients have been begun the liquid food on the 2nd hour and solid food intake on the 4th hour of the post-operative period. It was determined that the mean start time of liquid food intake was 9.38±6.63 hours, and the mean start time of solid food intake was 15.06±11.50 hours.

Early mobilization of patients is recommended in the postoperative period [1]. Pain control should also be provided for adequate mobilization [25]. It was detected in studies examining the relationship between the postoperative mobilization and pulmonary complications that patients not mobilized early enough had a higher incidence rate of pulmonary complications, patients with pulmonary complications had extended hospital stay [26], and 58% of the patients were managed to be mobilized later [27]. In this study, the mean mobilization time of the postoperative period was determined to be 8.00±2.46 hours.

Conclusion

Findings obtained from this study examining how much ERAS protocols, which include evidence-based applications, reflect on the clinic show that, none of the patients were given oral carbohydrates and the fasting was kept for a long time. It also indicated that necessary applications were not used to maintain the normothermia for the patients, early oral feeding not started, drains and urinary catheterization was still being used at high percentages. This study offers important results in that it shows that the compliance of routine clinical perioperative practices with the ERAS protocol is not sufficient. The rate of compliance could be increased by raising healthcare professionals' awareness by providing them with better training on the ERAS protocols, supporting their participation in the training, and providing individualized ERAS-compliant care from the point of admission till discharge to patients undergoing surgical operations which use a multi-disciplines.

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Conflict of interest

There are no conflicts of interest for the authorship and/or publication of this article.

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ORIGINAL ARTICLE

Evaluation of metabolic factors affecting the presence of hepatosteatosis and the effect of insulin like growth factor-1 level in overweight and obese children

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Abstract

Although previous studies related to non-alcoholic fatty liver disease (NAFLD) in childhood were predominantly ALT and uric acid level, the number of studies that have been handled in terms of insulin like growth factor-1 (IGF-1) level or IGF-1 standard deviation score (SDS) is limited. In this study, all factors that may affect NAFLD, including IGF-1 level and IGF-1 SDS, were evaluated in two groups of children who were not statistically different from each other in terms of age, gender, weight, height, body mass index and puberty. This study was a cross-sectional study. 36 children with evidence of fatty liver disease on ultrasound imaging and 38 children without it were included in the study. Anthropometric data, laboratory measurements and radiological results of all participants were evaluated. All factors that could affect NAFLD were evaluated by binary logistic regression analysis. Weight, weight SDS, body mass index (BMI) SDS, homeostasis model assessment of insulin resistance (HOMA-IR), AST, ALT, GGT, uric acid, triglyceride, HDL-cholesterol, IGF-1, IGF-1 SDS were evaluated in this model to predict NAFLD. In the statistical model, the percentage of predicting those with NAFLD, that is, the sensitivity, was 88.9%, while the detection rate of those without NAFLD, that is, the specificity, was 94.7%. IGF-1 level was found to be significantly lower in the group with NAFLD (p: 0.04), but there was no significant difference between the groups in terms of IGF-1 SDS (p: 0.10). There are conflicting results in studies examining the relationship between IGF-1 SDS and NAFLD. This may be due to ethnicity, regional differences, kit-specific laboratory reference ranges, or method of measurement. Laboratory measurements including appropriate parameters with a detailed physical examination can be used to predict the presence of NAFLD without the need for radiological examination.

Keywords: *Children, insulin like growth factor-1, non-alcholic fatty liver disease, overweight*

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Introduction

The liver is an important organ that plays a key role in glucose and lipid metabolism in the body. In addition, many proteins that are used for important functions in the body (including IGF-1) are also produced in the liver. The most common chronic liver disease in childhood is NAFLD [1]. Non-alcoholic fatty liver disease is a chronic disease that occurs with abnormal levels of triglyceride accumulation in the liver in an individual who does not consume a significant amount of alcohol. Although obesity is the most important risk factor; overweight, hypertension, insulin resistance, dyslipidemia, and other pre-atherogenic conditions have been associated with NAFLD [2-4]. Reports of study results on NAFLD prevalence in childhood are variable. The frequency varies depending on the differences in the methods used for detection. There are differences in terms of noninvasive methods (ultrasound, magnetic resonance imaging) and liver biopsy, which is seen as the gold standard in diagnosis. Reported prevalence rates range from 1.7-85% [2,5]. Because liver biopsy is a risky method, ultrasonographic imaging has become a more common method. In addition, many studies have been conducted to predict NAFLD with some parameters thought to be associated with NAFLD. Body mass index (BMI), liver function tests (ALT, AST), uric acid and HOMA-IR calculated by measuring glucose and insulin levels and IGF-1 levels are some of them [6-10]. Therefore, our primary aim in this study is to examine the relationship between IGF-1 level and IGF-1 SDS and NAFLD in overweight or obese children, and to evaluate the relationship between biochemical and hormonal parameters to predict NAFLD.

Materials and Methods

Subjects

The study was approved by the clinical research ethics committee of Afyonkarahisar Health Sciences University, where the patients were examined, with the number of 2011-KAEK-2, 2021/7. This retrospective cross-sectional study was carried out on overweight and obese children who were followed up in Afyonkarahisar Health Sciences University Pediatric Endocrinology Outpatient Clinic. A total of 74 patients with and without evidence of hepatosteatosis in ultrasonography examined between August 2020 and April 2021 were included in the study. Inclusion criteria in the study were body mass index above 1 standard deviation score according to age and gender according to CDC growth references and being between 6 and 19 years of age. The exclusion criteria from the study were; 1) use of drugs and alcohol that could affect blood pressure, liver, glucose and lipid metabolism in the last 3 months; 2) conditions causing secondary obesity (i.e. hypothyroidism, Cushing's disease), monogenic, syndromic or hypothalamic obesity; 3) primary and secondary liver diseases, including hepatitis B and hepatitis C. When cases with body mass index standard deviation score above +1 SD were divided into two groups according to the presence of NAFLD in ultrasonography; 36 cases were NAFLD patients and 38 cases were as controls. Anthropometric examinations, laboratory measurements and abdominal ultrasonography evaluation by an experienced pediatric radiologist were performed from all participants. Written informed consent was obtained from all participants and their accompanying parents. The research ethical principles were carried out in accordance with the Declaration of Helsinki.

Liver ultrasonography

The presence of hepatosteatosis in ultrasonographic imaging was predicted according to the presence of either diffuse increase in liver echogenicity, increased liver echogenicity compared to kidneys, and decreased visual visualization in the intrahepatic vessels or diaphragm. Ultrasonographic examination was performed by the same operator in all participants after 12 hours of fasting. Ultrasonic scanning of the liver was performed using a high quality abdominal and superficial tissue transducer in the range of 7.5-13.5 MHz, and liver imaging was performed with Canon Medical Systems USA, Inc.

Anthropometric measurements

As anthropometric examinations; weight, height, body mass index and standard deviation scores were calculated using a comprehensive online calculation program (www.childmetrics.org) [11]. It was evaluated according to CDC's age and gender specific references. Physical examination and evaluation of puberty of all patients were performed. According to Tanner staging, the absence of breast development in girls and testicular volume less than 4 ml in boys were considered prepubertal period. The onset of breast development in girls and a testicular volume of 4 ml or more in boys were considered to be puberty or postpubertal, regardless of the presence or absence of pubic hair growth. Blood pressures of all children in the study and control group were within normal ranges according to age and gender.

Laboratory measurements

Blood samples were obtained for biochemical and hormonal measurements in the early morning after 8 hours of overnight fasting. Liver function tests, lipid status and uric acid were measured using an automated biochemical analyser (Cobas 8000 c502-c702 and Cobas 6000 c501-e601, Roche Diagnostics, Mannheim, Germany). Plasma glycosylated hemoglobin A1c (HbA1c), insulin, cortisol, TSH, free T4 and insulin-like growth factor-1 (IGF-1) were measured by electrochemiluminescence immunological method (ECLIA) on the Cobas 8000 e602 analyzer (Roche Diagnostics, Mannheim, Germany). Glucose was measured by hexokinase method and insulin was measured by ECLIA. The HOMA-IR method [glucose (mmol/L) X insulin (mIU/mL) / 22.5] was used to assess insulin resistance [12]. IGF-1 SDS was calculated according to age and gender specific reference data [13].

Statistical analysis

SPSS version 24.0 (IBM Corporation, Armonk, NY, USA) software program was used for all statistical analyzes. Mean and standard deviation values of numerical variables were calculated. Categorical variables were shown as frequency and percentage. Shapiro Wilk test was used to evaluate the normal distribution of variables. In addition, the data with kurtosis and skewness values within the range of -2, +2 were accepted as showing normal distribution. When comparing the means of two independent variables, Student's T test was used if the data showed a normal distribution, and the Mann Whitney U test was used if it did not comply with the normal distribution. Chi-square analysis was used to compare categorical variables. Pearson and spearman correlation analyzes were used to evaluate the degree and direction of the relationship between variables. Binary logistic regression analysis was used to evaluate the effect of independent variables to predict the presence of fatty liver in ultrasonography. A p value of <0.05 was considered statistically significant.

Results

The study was conducted in children aged 6-19 years with a body mass index standard deviation score of 1 SD or above. Participants were divided into two groups consisting of 36 individuals with hepatosteatosis on ultrasonography and 38 controls without radiological findings. Age, anthropometric and laboratory measurements of both groups were summarized in Table 1.

When the groups were compared according to gender, 14 (38.9%) of the NAFLD cases were girls, 22 (61.1%) of them were boys, while 23 (60.5%) of the non-NAFLD cases were girls and 15 (39.5%) of them were boys. When the groups were compared according to the puberty stages, 8 (22.2%) children with NAFLD were in the prepubertal period, 28 (77.8%) children were in the pubertal or postpubertal period, while 6 (15.8%) children without NAFLD were in the prepubertal period, 32 (84.2%) children were in puberty or postpubertal period. There were no significant difference between groups according to gender and puberty status, respectively (p: 0.06; p= 0.48). There was no statistically significant difference between the groups in age, gender, puberty status, weight, height, BMI and BMI SDS ($p<0.05$). Therefore, the parameters planned to be investigated in terms of metabolism could be compared in two groups similar to each other in these aspects. The linear relationship of independent variables that can affect NAFLD is shown in detail in Table 2.

Independent variables affecting NAFLD were evaluated by binary logistic regression analysis. The outputs of the model are presented in Table 3 (3a, 3b, 3c, 3d).

A statistically significant difference was found in individuals with NAFLD in terms of IGF-1 levels. IGF-1 was found to be lower in individuals with NAFLD. However, there was no statistically significant difference between the groups in terms of IGF-1 SDS.

Table 1. Clinical and laboratory parameters of the participants.

Parameter	NAFLD (n=36)	Non-NAFLD (n=38)	p value
Age (months)	148±27	149±33	0.82
Weight (kg)	80.9±19.9	75.8±18.7	0.26
Height (cm)	158±9.2	157±13.9	0.72
BMI (kg/m^2)	31.9±5	30.1±4	0.09
Weight SDS	2.53±0.59	2.28±0.41	**0.04***
Height SDS	1.03±1	0.83±1.07	0.41
BMI SDS	2.28±0.36	2.16±0.25	0.11
FPG (mg/dL)	93.3±6.5	91,7±7.9	0.35
Insulin (mIU/mL)	34.7±15.8	23.4±8.3	**<0.001***
HOMA-IR	8±3.7	5.2±2	**<0.001***
HbA1c (%)	5.4±0.3	5.1±0.2	**0.01***
AST (U/L)	26 (22-39)	21 (16-24)	**<0.001*** (Ω)
ALT (U/L) (U/L)	34 (23-53)	17 (12-25)	**<0.001*** (Ω)
GGT (U/L)	22 (14-35)	14 (11-20)	**0.001*** (Ω)
Uric acid (mg/dL)	5.5±1.1	4.9±1	**0.02***
TSH (mIU/mL)	3±1.2	2.3±1	**0.01***
Free-T4 (ng/dL)	1.25±0.16	1.29±0.14	0.31
Triglyceride (mg/dL)	128±53	117±48	0.34
Total cholesterol (mg/dL)	150 (133-177)	143 (137-173)	0.82 (Ω)
LDL-C (mg/dL)	107 (87-122)	97 (83-123)	0,74 (Ω)
HDL-C (mg/dL)	41±7	45±8	**0.02***
Cortisol (ug/L)	12.6±5.2	13±5	0.74
IGF-1 (ng/mL)	227±99	285±133	**0.04***
IGF-1 SDS	-0.20±0.82	0.14±1	0.10

* p value < 0.05 The data were presented as mean and standard deviation if they were suitable for normal distribution, and as median and interquartile ranges (Q1-Q3) if not. Data with normal distribution evaluated with Student's T test, Ω symbol used if evaluated with Mann Whitney U test.

Abbreviations: NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; SDS, standard deviation score; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; HbA1c, glycosylated haemoglobin A1c; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl-transferase; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; IGF-1, insulin like growth factor-1.

Table 2. Linear relationship of factors affecting NAFLD.

Parameter	p value	r
Age (months)	0.82	-0.02
Sex	0.06	0.21
Weight (kg)	0.25	0.13
Height (cm)	0.72	0.04
BMI (kg/m2)	0.09	0.19
Weight SDS	**0.04**	0.23
Height SDS	0.41	0.09
BMI SDS	0.11	0.18
Pubery status	0.48	-0.08
FPG (mg/dL)	0.36	0.10
Insulin (mIU/mL)	**<0.001**	0.41
HOMA-IR	**<0.001**	0.41
HbA1c (%)	**0.01**	0.29
AST (U/L)	**<0.001**	0.42*
ALT (U/L)	**<0.001**	0.58*
GGT (U/L)	**0.001**	0.39*
Uric acid (mg/dL)	**0.02**	0.26
TSH (mIU/mL)	**0.01**	0.27
Free-T4 (ng/dL)	0.31	-0.11
Triglyceride (mg/dL)	0.34	0.11
Total cholesterol (mg/dL)	0.82	-0.02*
LDL-C (mg/dL)	0.74	0.03*
HDL-C (mg/dL)	**0.02**	-0.27
Cortisol (ug/L)	0.74	-0.03
IGF-1 (ng/mL)	0.04	-0.23
IGF-1 SDS	0.10	-0.18

Pearson correlation analysis was used to examine the relationship of the variables. * symbol used if spearman corelation analysis was used. Abbreviations: NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; SDS, standard deviation score; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; HbA1c, glycosylated haemoglobin A1c; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl-transferase; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; IGF-1, insulin like growth factor-1.

Table 3. Effect of weight, weight SDS, BMI SDS, HOMA-IR, HbA1c, AST, ALT, GGT, uric acid, triglyceride, HDL cholesterol, IGF-1 and IGF1 SDS to predict the presence of NAFLD.

3a. Significance of the model coefficients.

		Chi square	df	Sig.
Step 1	Step	51.530	13	.000
	Block	51.530	13	.000
	Model	51.530	13	.000

Model coefficients are significant. Independent variables contribute to estimating the dependent variable.

3b. The degree of relationship between variables.

	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	51.002	.502	.669

Independent variables with dependent variable in logistic regression model the degree of the relationship between 50.2% according to Cox-Snell and 66.9% according to Nagelkerke.

3c. Classification chart of the model.

	Observed		Predicted		
			NAFLD		Percentage correct
			No	Yes	
Step 1	NAFLD	No	36	2	94.7
		Yes	4	32	88.9
		Overall percentage			91.9

As seen from the table, 94.7% of those without NAFLD and 88.9% of those with NAFLD were correctly estimated. In general, 91.9% of it was correctly estimated.

3d. Variables of the model.

		B	Sig.	Exp (B)
Step 1	Weight	-.027	.471	.973
	Weight SDS	2.326	.259	10.241
	BMI SDS	-2.038	.510	.130
	HOMA-IR	.430	.062	1.538
	HbA1c	1.032	.470	2.806
	AST	-.053	.580	.949
	ALT	.111	.110	1.117
	GGT	-.029	.710	.972
	Uric acid	.791	.079	2.206
	Triglyceride	-.001	.943	.999
	HDL cholesterol	-.129	.038	.879
	IGF-1	-.005	.510	.995
	IGF-1 SDS	-.280	.679	.756
	Constant	-5.564	.506	.004

Factors thought to be effective in NAFLD estimation were analyzed. Weight SDS, HOMA-IR, HbA1c, ALT, uric acid variables were found to be more effective.

Discussion

In this study, the relationship between NAFLD and metabolic parameters previously reported to be associated with NAFLD, including IGF-1 level and IGF-1 SDS, has been the subject of investigation. In our study, we found a positive significant correlation with NAFLD and weight SDS, AST, ALT, GGT, insulin, HOMA-IR, HbA1c, uric acid and TSH levels, and a negative significant correlation with HDL cholesterol and IGF-1 levels. There was no significant relationship with IGF-1 SDS.

Evidence-based data and long-term follow-up results suggest that NAFLD in childhood is associated with increased cardiovascular disease and mortality in adulthood [14]. Many previous studies have shown the relationship between insulin resistance and NAFLD [15,16]. The incidence of insulin resistance was found to be 95% in NAFLD cases proven by biopsy in children [17]. Insulin resistance plays an important role in hepatocyte damage and hepatosteatosis. Dietary fat, free fatty acids increased by endogenous lipolysis lead to oxidative stress and hepatic triglyceride accumulation. Detecting insulin resistance with a hyperinsulinemic euglycemic clamp gives more reliable results. However, this technique is expensive and not applicable in daily practice. For this reason, HOMA-IR was used as a simple technique. A very strong relationship was found between metabolic syndrome and NAFLD in a study conducted with overweight and obese children [18]. In another study, abdominal obesity, insulin resistance, type 2 diabetes and dyslipidemia were also closely related to NAFLD(3). As in our study, ultrasound imaging has been the preferred method to detect NAFLD in most studies, since it is a non-invasive and easily applicable technique [19,20].

In a study evaluating obesity and NAFLD, obesity accompanied NAFLD in one fourth of the girls and one third of the boys [21]. In previous studies examining the relationship between uric acid level and NAFLD, it was found that hyperuricemia was associated with NAFLD, and the degree of fatty liver and lobular inflammation and hyperuricemia were found to be associated with NAFLD cases proven by liver biopsy [22-24]. In some experimental studies, an increase in triglyceride level was observed with uric acid incubation with hepatocyte cells. Potential effective mechanisms and possible hypotheses were interpreted as mitochondrial stress, endoplasmic reticulum stress, increase in inflammatory response and hepatic steatosis [25,26].

In this study, while IGF-1 level was found to be low in overweight and obese children with NAFLD, there was no significant difference in IGF-1 SDS levels compared to non-NAFLD controls. It has been reported in experimental studies that fatty liver after high-calorie total parenteral nutrition is caused by a decrease in IGF-1 mRNA levels in the liver [27]. Insulin resistance causes down-regulation of IGF-1 level by acting through hepatic growth hormone (GH) receptors. IGF-1 is a polypeptide that has antioxidant and anti-inflammatory effects [7,28,29]. In one study, IGF-1 level was found to be negatively correlated with hepatic steatosis, but when IGF-1 was evaluated in terms of SDS, this degree of correlation was significantly decreased [30]. In some studies in adults, IGF-1 deficiency has also been used to evaluate tissue level progression in non-alcoholic steatohepatitis (NASH). In Japan, the use of growth hormone therapy in NASH cases has been approved in adults. There were no indications for the use of such treatment in children worldwide. Participants were divided into 3 subgroups according to the result of IGF-1 SDS level as below -1 SDS, between -1 SDS +1 SDS and above +1 SDS. There was no statistically significant difference in IGF-1 SDS levels between the groups with and without NAFLD ($p= 0.50$).

In our study, we found a close relationship between HbA1c level and NAFLD. When we look at previous studies, it is known that the relationship of NAFLD in cases where the HbA1c level is more than 5.7%, but in one study, NAFLD was reported with a rate of 29.8% in the groups where the HbA1c level was found to be less than 5.7%. Therefore, it has been stated that the HbA1c level being in the upper limit of normal may also be associated with NAFLD [31]. In some studies conducted with adults, it has been stated that HbA1c also plays a key role in the development of NAFLD in patients without diabetes mellitus and was an independent risk factor [32,33]. When we divided the groups into 3 subgroups according to the HbA1c level as below 5.3%, between 5.3% and 5.7% and above 5.7%; We found that the HbA1c level was above 5.7% in 88.9% of the NAFLD cases, and HbA1c level was above 5.3% in 42.9% of the NAFLD cases.

Our study had some limitations. The first was that the number of children in our sample was not large enough. Secondly, although age, gender and puberty status were similar in both groups in terms of evaluating IGF-1 level, reference ranges used in the evaluation of IGF-1 levels differed according to each country, ethnicity and measurement method. In addition, basal or stimulated levels of growth hormone in patients and

insulin-like growth factor binding proteins (such as IGFBP-3 level) were not evaluated. Therefore, we may not have found a significant difference between the group with NAFLD and the group without NAFLD in terms of IGF-1 SDS levels in our study. There is a need for new studies evaluating basal and stimulated GH levels in larger cohorts of NAFLD cases. Meta-analyzes using standard reference ranges and similar measurement methods to evaluate the IGF-1 level in NAFLD cases will also be enlightening.

Conclusion

Evaluation of biochemical and hormonal parameters together is as valuable as radiological diagnosis in NAFLD cases. In the clinical follow-up of the patients, the effectiveness of the treatment can be evaluated by monitoring these parameters and observing their changes. In our study, we wanted to show that HbA1c and IGF-1 levels can yield important results, as well as markers such as ALT, uric acid, and HOMA-IR, which are known to be closely related to NAFLD in previous studies. In order to make sharp and clear comments about the relationship between IGF-1 SDS and NAFLD, more studies with larger groups and standard measurement methods are needed.

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Conflict of interest

The authors declare that they have no conflict of interest.

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REVIEW

The concept of nursing and compassion during COVID-19

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Abstract

This article was designed to draw attention to the importance of the compassionate approach in the recovery of individuals during the pandemic, and the development of compassionate behavior. It contributes to the learning of the positive and negative behaviors of the members of the profession and the candidates in their approach to sick individuals. The uncertainty, isolation and loneliness experienced by infected individuals during the COVID-19 highlighted the sense of compassion and compassionate approach. With compassionate approach and supporting the process with evidence, nurses will reveal the impact on patient care and contribution to professional practice.

Keywords: *Pandemic, COVID-19, compassion, nursing*

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Introduction

The COVID-19, which has impacted the whole world, is a disease that affects the respiratory system and many other systems and can be fatal. As the severity of the disease increases in infected individuals, the symptoms become more serious, and severe shortness of breath and hypoxia are often observed with many symptoms [1,2]. The presence of symptoms in infected individuals, the daily media coverage of the process and course of the pandemic with up-to-date data, and the deaths that were witnessed have been increasing the concerns and anxiety. The process of the pandemic is an important problem for the infected individuals, their families and healthcare professionals. In these periods of strict isolation, infected individuals need healthcare professionals who understand them psychosocially and attention where compassionate behavior is prominent [3,4]. The concept of compassion, the essence and fundamental value of nursing, and compassionate behaviors are becoming more important with the nursing profession during the COVID-19 pandemic [5,6].

The concept of compassion

A sense of compassion is an innate human emotion. Compassion is defined as the transition from an approach that is centered on self-love and respect to a conception that distributes respect and love to the whole being and appreciates this [7]. The concept of compassion is intertwined with the concepts of empathy, sympathy, altruism [8], pity, kindness and goodness, and are used interchangeably or with close meanings. The concept of compassion is stated to include all of these concepts used and is an emotion above all these concepts [9].

Compassion, according to The Turkish Language Association, is defined as "sadness and pity due to the bad situation faced by one person or another being" [10]. Another definition of compassion is "a feeling of deep sympathy and sadness for someone who has experienced pain or a misfortune, along with a desire to remove the suffering and its causes" [11]. In the Encyclopedia of Islam, it is used as a verb in the sense of "to show pity, to show kindness", and as a noun in the sense of "feeling of pity, kindness and grace which is done with this feeling" [12].

The German Philosopher Schopenhauer defined the concept of compassion as one of the three fundamental forces that exist in human beings. According to Schopenhauer, these fundamental forces are egoism, malice and compassion. Compassion is emphasized to be the feeling at the root of human love which allows people to treat well without benefit and prevents injustice [13]. The concept of compassion has taken its place in psychology as a subject of late since it has been considered within or with close meanings of the concepts of self-renunciation/selflessness, intimacy and prosocial behavior (positive social behavior) and difficult to measure [14].

A sense of compassion is very important for sick individuals. The reason for this is, besides the technical care of the patients, they express that they need more compassionate attitudes and behaviors from the individuals who provide the service and care to them [15]. The concept of compassion is an important core value of the nursing profession, both because it has a significant impact on the quality of care and it is an indispensable element of patient-centered care [9].

Nursing and compassion

Nursing is the profession spending the longest time with patients whose health deteriorates and needs help, and witnesses the most vulnerable and special processes of patients. In these periods, nurses form the basis of nursing care with a humane approach and compassionate behavior [16]. Positive effects of showing interest in reducing the stress levels of individuals in nursing care, and communicating well emotionally and psychologically on clinical outcomes have been supported by the literature [8]. In the research conducted by The Royal College psychiatrists on the innate sense of compassion and compassionate approach in humans, the observation of compassionate behavior in terms of nurses and health workers is based on the following itemsThe characteristics of the nurse, which includes the innate sense of compassion in humans, were listed as three items by The Royal College psychiatrists;

1) Characteristics that must be possessed in terms of awareness:

• Awareness about the patient and his / her history, noticing the problems of the patients, listening carefully, taking the needs of the patients into account

• Awareness of emotions that will affect the compassionate approach of the nurse (for example busyness, anger, pressure to complete tasks, limited time).

2) Characteristics that must be possessed in terms of emotional response:

• A sense of warmth, affection, attachment

• Openness to being affected by the situation in the patient's mind: Being able to empathize with the patient as a separate individual

• Being able to overcome difficulty instead of avoiding or ignoring it,

• Not to judge, not to use accusatory terms, not to see the patient at the bottom hierarchically, to consider people as individuals, not as objects or part of their duties

3) Features that must be possessed in terms of responding to the needs of others:

• Being respectful and open to cooperation, communicating concerns accurately

• Being able to use a language reflecting a compassionate attitude (for example: not to manipulate patients by using their position, to administer the treatment after explaining it to the patients)

• Trying to alleviate the suffering of individuals in a sincere, polite and generous way.

• The nurse should balance organizational and occupational requirements with individual needs. The nurse should be in every detail of the patient's health care in effective treatment [7,17].

Being able to recognize the difficult situations that individuals are in, listening, smiling, tapping, answering the questions of individuals, performing painful procedures gently, having awareness of situations that cause stress are actions that include a sense of compassion and increase the quality of care [18]. In a study, the role of courtesy and kindness in care in oncology patients was investigated [19]. Five roles of kindness have been identified in individuals, deep listening, empathy, generous behavior, timely care, and support of family members. These behaviors have been concluded to be more important than questioning the treatment process. The positive effects of compassionate behaviors on recovery are supported by the studies in the literature. This once again reveals the importance of nursing and compassion in the COVID-19 process [19-21].

Nursing and compassion during COVID-19 pandemic

In the COVID-19 pandemic, when infected individuals need to be admitted to receive health care, their treatment and follow-ups are performed in their rooms alone without any family members accompanying them. Visit restrictions during the pandemic, limitations on the communication of patients with their family members, and the uncertainty caused by the disease increase the stress levels in the process of coping with the disease. In this period, it is stated that if the isolation, uncertainty, fear and anxiety of individuals diagnosed with COVID-19 are not identified and managed correctly, the process may be physiologically and psychologically destructive [22]. The compassionate approach shown during the pandemic has been expressed as the key to meeting the needs of patients [23].

Nurses once again demonstrate the importance of compassionate behavior in the nursing profession by providing psychosocial support as well as medical treatment to sick individuals during the pandemic they perform with dedication [22]. In the management of the COVID-19 pandemic, they displayed the artistic dimension of the profession by giving the necessary attention and support not only to the patients also to their families and relatives. The family members couldn't hold their hands or hug them while their relatives were passing away. In this period, the compassionate approach of nurses has been the solution that will help patients both recover and not feel lonely with the bond established between them [24].

In a qualitative study conducted with a group of nurses providing care for COVID-19 patients, it is stated that humanistic care based on mutual understanding between nurse and patient is stated to be necessary [25]. It has been mentioned that it is necessary for healthcare professionals to have effective empathy and compassion to provide these patients with the most appropriate care. Nurses have stated that compassionate care would increase the spiritual vitality of the patient, and considering the importance of the issue, it should be addressed in family-centered care as well as physical care to ensure holistic care for these patients. Nurses have stated that a compassionate approach can help COVID-19 patients to get on with their lives [22,25].

In a study conducted during the pandemic, positive emotions in patients have been shown to be revealed with the approach of nurses with empathy, compassion and altruistic feelings towards patients [26]. There are health professionals who stated experiencing a high level of compassion satisfaction in this period. The basis of compassion satisfaction has been stated to be an empathetic, selfless, voluntary, benevolent relationship with individuals and their families and kind behaviors showing that they understand them

[6]. Nurses can bring out positive emotions in patients with a compassionate approach and provide effective nursing care by experiencing compassion satisfaction [27]. Compassion satisfaction is also necessary and important in the quality of patient care [21].

Conclusion

Staying in isolation which the COVID-19 patients needed to cope with the disease during the pandemic, staying away from family members and the uncertainty created by the pandemic is known to adversely affect the psychological and physical health of the individuals. As can be seen from studies conducted on patients, the compassionate approach and behavior of nurses facilitates the treatment process of individuals and positively affects their physical and psychological health. With the COVID-19 outbreak, the importance of compassion and compassionate behavior and its place in inpatient care has once again been revealed. Nurses involved in the management of the pandemic can be given the opportunity to share their experiences in the in-service training of health institutions and the content of the course in schools. This can support the development of the nursing profession by contributing to the development of a sense of compassion. In this way, it contributes to the learning of the positive and negative behaviors of the members of the profession and the candidates in their approach to sick individuals.

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Conflict of interest

The authors have no conflicts of interest declared.

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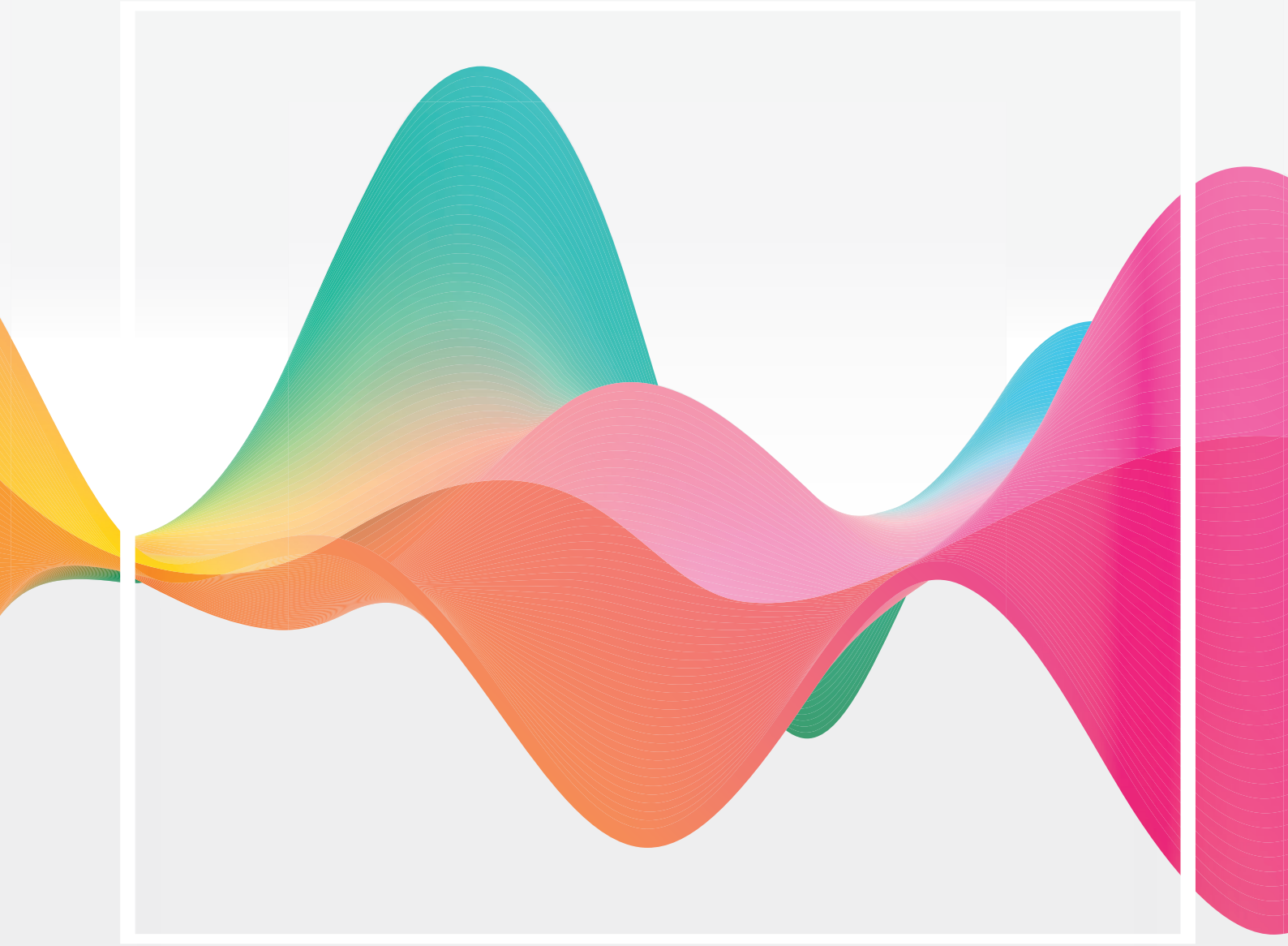

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