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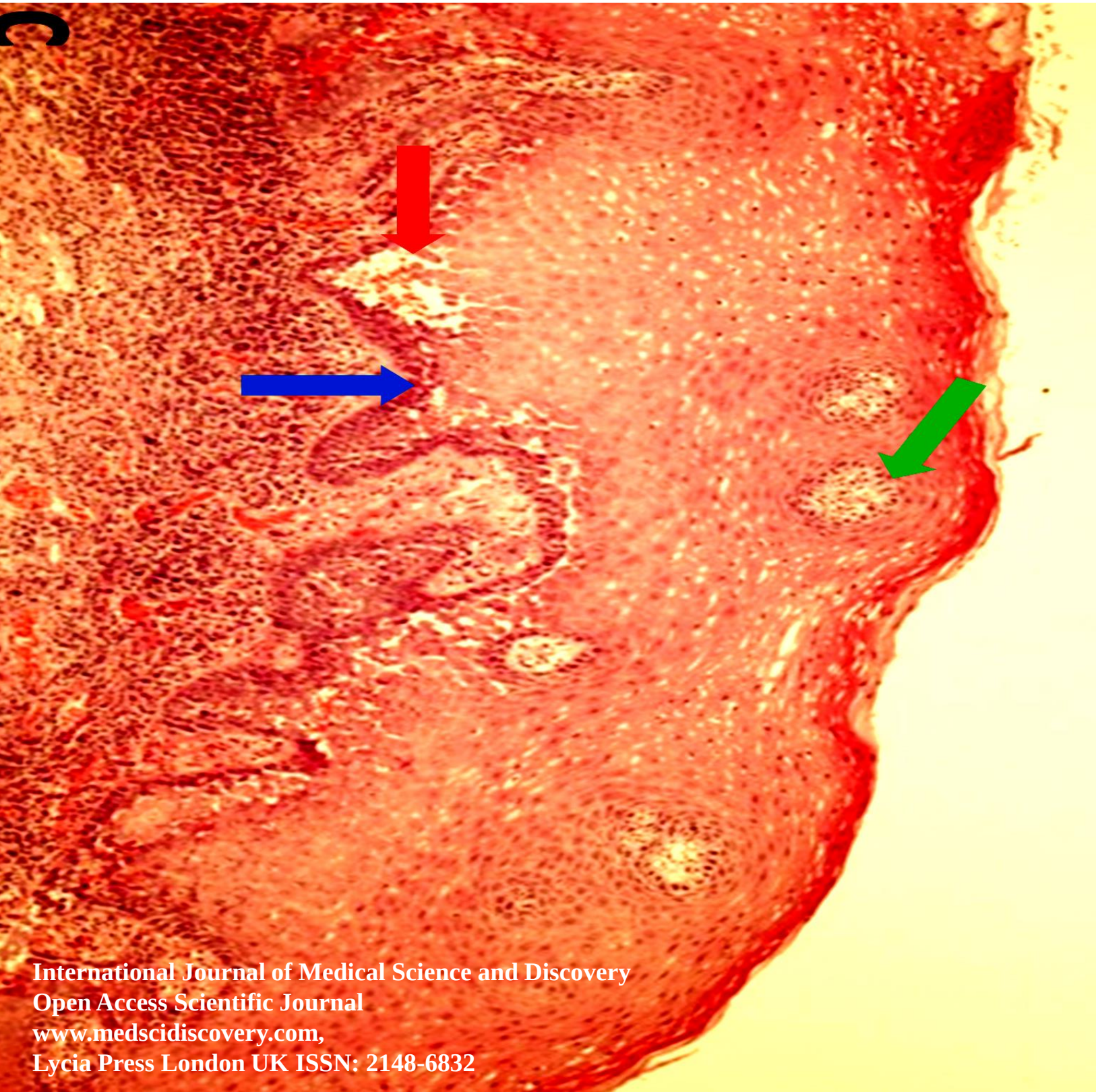

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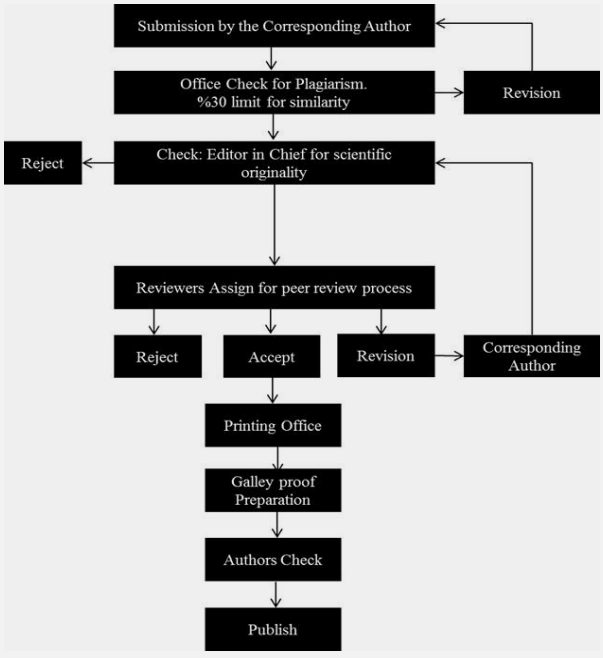

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A comparative evaluation of the effects on postoperative pain of systemic and topical forms of benzydamine hydrochloride after periodontal flap surgery: A randomized controlled clinical trial

Gülhan Kocaman[1]*

Abstract

Objective: The aim of this study was to evaluate comparatively the topical and systemic forms in the postoperative pain control periodontal flap surgery in spite of the daily dose of benzydamine hydrochloride spray form about one in twenty of the oral dose,.

Materials and Methods: In this randomized trial, the 48 systemic healthy individuals in need double-blind study with periodontal flap surgery were evaluated. Consent, demographic information and periodontal clinical parameters were obtained before surgery and periodontal flap surgery was performed with local anesthesia. The patients who underwent surgery were randomly assigned to two groups. One of the groups was prescribed tablet form of postopertive benzydamine hydrochloride and for the other was spray form as topical application. Postoperative pain was assessed by visual analog scale at 2, 6, 8, 12, 24 and 48 hours.

Results: There was no difference between systemic and topical drug groups in terms of demographic characteristics and periodontal clinical parameters. A statistically significant difference was found between 2 and 6 hours in favor of topical application. ($p < 0.05$), but there was no significant difference in pain intensity at the 8th, 12th, 24th and 48th hours.

Conclusion: Although the topical form of benzydamine hydrochloride was 1/20 lower in postoperative pain control after periodontal flap surgery, it was found to be more effective in the early period compared to the systemic form, but equally effective in the late period. We premierly recommend that topical application should be preferred primarily in the prevention of overdose and toxicity in postoperative pain control after periodontal flap operation.

Keywords: Benzydamine hydrochloride, periodontal surgery, postoperative analgesia

Introduction

The basis of successful periodontal treatment is not only the appropriate surgical technique, but also the prevention and management of postoperative complications. Pain is one of the most common symptoms after periodontal surgery. Therefore, surgeons strive for an analgesic method that provides deep analgesia and is best tolerated by the patient, thereby ensuring patient compliance.

Postoperative pain is affected by surgical site, age, sex, premedication, anesthetic agent, administration of analgesia, patient psychology and environmental factors. In addition, each analgesic method has advantages-disadvantages, the area in which it is effective and the type of pain varies. The most pain is in the first 48 hours and different combinations can be used in this period (1).

Nonsteroidal antiinflammatory drugs (NSAIDs) are often sufficient to provide effective analgesia after minor and major surgery. It can be administered in various ways including surgery, oral, parenteral, inhalation and transdermal (2,3).

Benzydamine hydrochloride (HCl) is an analgesic and NS antiinflammatory drug that can be used systemically and topically. The mechanism of antiinflammatory action of benzydamine HCl is achieved by blocking the biosynthesis of prostaglandins produced as an early response to tissue trauma by inhibition of arachidonic acid and cyclooxygenase enzyme. In addition, anti-inflammatory activity is achieved by mild inhibition of prostaglandin synthesis and strong inhibition of proinflammatory cytokines. Thus, TNF-α, IL-1β and MCP-1 (such as monocyte chemoattractant protein) cytokines can be classified as a suppressive anti-inflammatory (4). As a result of these effects, it stabilizes the cell membrane and reduces vascular permeability. resolves edema (5).

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As a result of these mechanisms, primarily antiinflammatory, as well as anti-edema, antipyretic, antitussive and muscle relaxant effects are revealed benzydamine HCl is effective in the symptomatic treatment of local acute (primary) inflammation as a result of soft tissue injury and many oral disorders such as aphthous ulcers and gingivitis (6,7).

Benzydamine HCl has gel preparations applied to the skin in soft tissues, skin and joints; dragee form in systemic doses, mouthwash form used for the treatment of inflammatory diseases of the mouth and throat region and oral spray form. It is completely and rapidly absorbed from the gastrointestinal tract. (7-9). The recommended single dose of the dragee form is benzydamine 0.7-1 mg / kg or one or two tablets. Each tablet is 50 mg.1

Benzydamine HCl Drageen contains 50 mg of active ingredient per dragee. One oral dose is 0.7-1 mg per kg. Patients are recommended to take 1 dragee on full stomach on average 3 times a day. The recommended daily dose is 150-200 mg. The course of treatment is three to five days.

Benzydamine HCl Spray contains 45 mg benzydamine HCl in 30 ml spray solution. One spray is 0.18 ml and contains 0.27 mg benzydamine HCl. Patients are advised to use an average of 4 sprayings at a time, 6 times in a day. The topical form (4 sprayings at a time: 1.08 mg; 6 times daily: 6.48 mg) is approximately one-twentht of the oral dose. Therefore, it is envisaged that there is no systemic overdose and toxicity of the spray form.

In this study, it was aimed to determine which is more effective on postoperative pain comparatively after periodontal flap surgery that benzydamine hydrochloride, can be used either systemically or topically.

Material and Methods

This study is a randomized controlled study performed in the periodontology clinic of Karabük Dental and Oral Health Hospital. The study was explained to the patients, and informed consent was obtained. The study protocol was approved by the Institutional Ethical Committee of Karabuk University, Turkey with date 08/12/2019, number 2019/54. Following the completion of Phase 1 therapy consisting of oral hygiene instructions and scaling and root planing, re-evaluation was performed after 4 weeks, after which forty-eight patients were enrolled in the study and were randomly assigned to systemic group and topical group by lottery method.

Study population

Forty patients who needed periodontal flap surgery in at least two interproximal regions on at least one side of the maxillary or mandibular arch were included in the study.

Inclusion criteria

- Patients aged between 23 and 64 years with moderate-to-severe chronic periodontitis
- Periodontal pockets >5 mm
- Systemically healthy patients fit for periodontal surgery
- Patients with good oral hygiene maintenance.
- Accepted to participate in the study,
- Has not received surgical or non-surgical periodontal treatment in the last 6 months,
- Individuals with sufficient mental health to read and understand questions

Exclusion criteria

- Patients with present or past systemic illnesses known to affect the outcomes of periodontal therapy
- Immunocompromised patients
- Patients taking medications that may interfere with periodontal therapy
- Pregnant patients
- Smokers.

Measurement of clinical parameters

The periodontal clinical parameters were evaluated to determine whether there was a clinical difference between the study groups.

Periodontal clinical parameters providing clinical evaluation of pathological changes in dental plaque deposition and periodontal soft tissues such as; Silness-Lee plaque index (PI), Lee-Silness gingival index (GI), pocket depth (CD), clinical attachment level (KAS)were used.

The PI, GI, CD, CAS were measured from 6 regions of the teeth (mesial, middle and distal regions of buccal / labial and lingual / palatinal surfaces). According to PI defined by Silness and Löe, 0: no plaque; 1: the presence of plaque to be catched by the probe; 2: the presence of visible plaque; 3: excessive plaque deposition (14).

In the evaluation of GI also defined by Löe and Silness, 0: healthy gingiva; 1: mild inflammation and discoloration, no bleeding at probing; 2: moderate inflammation, hyperemia, bleeding at probing; 3: severe inflammation, hyperemia, ulceration, edema, spontaneous bleeding have been evaluated as present (15).

The CD measurement was recorded in millimeters by recording the distance between the gingival / mucosal edge and the periodontal pocket base; The measurement of AS was made by recording the distance between the enamel-cementum and the periodontal pocket base in millimeters.

CD and AS measurements, automatic periodontal catheter (Florida Probe®, version FP 32 / 7.2.2, diameter 0.45 mm, applying standard force (15 g) and measuring with 0.1 mm accuracy, Florida Probe Corporation, Gainesville, USA). The highest score was obtained from PI, GI, CD and CAS measurements in 6 regions. All measurements were performed by a single clinician.

Surgical procedure

Periodontal flap surgery was performed under local anesthesia. After surgery, patients were prescribed analgesic and antimicobial agents. One group was prescribed tablet form (TANTUM® dragee, Santa Farma Ilac, Istanbul) for the systemic use of benzydamine hydrochloride as the analgesic and topical application of the spray form (TANTUM VERDE® spray, Santa Farma Ilac, Istanbul). The patients were randomly assigned to the groups.

Postoperative care

Postoperatively,all patients were prescribed with topical form (4 sprayings at a time, 6 times a day for 7 days) and systemic tablets (three times in a day for 5 days). The sutures were removed 1 week postoperatively. The surgical sites were gently cleansed with normal saline.

Measurement of pain intensity

Visual pain anolog scale was used to evaluate postoperative pain. Visual Analogue Scale (VAS) is the most commonly used method for the evaluation of postoperative pain severity (16). According to this assessment, the meaning of the marked points from 0 to 10

(0 points no pain, 1-4 points mild pain, 5-6 points moderate pain, and 7 points severe pain) on a 10 centimeter line was explained to the patients. Patients were asked to record the severity of pain according to VAS at 2, 6, 8, 12, 24 and 48 hours postoperatively.

Statistical analysis

All statistical analyzes were performed using SPSS 22.0 statistical program in Windows software. The normality distribution of the data was evaluated using the Shapiro Wilk test. Variable relationships between the two groups were compared by Mann Whitney U test. Significance level was calculated as $p < 0.05$.

Results

Demographic and clinical parameters of the patients included in the study is given in Table 1. Of the 24 patients receiving systemic drugs, 41.7% (10/24) were males, 58.3% (14/20) were females. furthermore, 24.2% (24/24) men receiving topical drugs were male, 70.8% (17/24). / 20) women. While the mean age of the patients in the systemic drug group was 42.04 ± 9.48, the topical group was 45.67 ± 9.43. There was no statistically significant difference between the two groups in terms of gender and mean age.

According to Table 1, the mean PI value in the periodontal clinical parameters of the patients included in the study was 0.46 ±, 059mm, while in the systemic drug group and 0.50 ± 0.51mm in the topical drug group. The mean GI value was 0.67 ± 0.70, while in the systemic drug group and 0.46 ±, 059 in the topical drug group. The mean CD value was 6.30 ± 1.08, while in the systemic drug group and 6.46 ± 1.18 in the topical drug group. The mean value of CAS was 4.71 ± 0.73, while in the systemic drug group and 5.52 ± 1.32 in the topical drug group. The mean values of PI, GI, CD and CAS were not statistically significant ($p > 0.05$).

Table 2 shows the distribution of the pain intensity of the patients in the topical and systemic groups according to the results of the time and scoring.

According to hours of pain intensity scores of the topical and systemic groups of benzydamine hydrochloride postoperatively results with Mann-Whitney U test are given in Table 3. When both groups were compared; The mean pain severity at the 2nd and 6th hours were lower in the topical group than the systemic group and the difference was statistically significant ($p < 0.05$). on the other hand, 8, 12, 24, 48. there was no statistically significant difference in pain sensation scores at postoperative hours ($p > 0.05$).

Table 1. Comparison of periodontal clinical parameters of study groups

Parameters	Groups	n(F/M)	Mean ± standard deviation	p
Sex	**Topical**	24(14/10)		
	Systemic	24(17/7)		
Age	**Topical**	24	45.67±9.43	.364
	Systemic	24	42.04±9.48	
PI	**Topical**	24	0.50±0.51	.670
	Systemic	24	0,46±,059	
GI	**Topical**	24	1.80±4.15	.101
	Systemic	24	0.67±0.70	
PD	**Topical**	24	6.46±1.18	.690
	Systemic	24	6.30±1.08	
CAL	**Topical**	24	5.52±1.32	.890
	Systemic	24	4.71±0.73	

Table 2. Table of distribution of pain intensity of study groups

Postop hours	Groups	Pain severity values on VAS											n
		0	1	2	3	4	5	6	7	8	9	10	
2nd hour	Topical	9	4	6	0	1	2	1	1	0	0	0	24
	Systemic	5	2	2	8	2	0	1	0	2	0	2	24
6th hour	Topical	11	6	0	1	3	0	1	0	2	0	0	24
	Systemic	5	2	5	4	2	1	1	0	0	2	2	24
8th hour	Topical	14	3	1	1	2	1	0	1	1	0	0	24
	Systemic	5	5	7	2	2	2	0	1	0	0	0	24
12th hour	Topical	15	2	4	1	1	0	1	0	0	0	0	24
	Systemic	8	6	6	0	1	2	0	1	0	0	0	24
24th hour	Topical	15	5	3	0	0	0	1	0	0	0	0	24
	Systemic	12	6	2	1	2	0	1	0	0	0	0	24
48th hour	Topical	17	2	3	2	0	0	0	0	0	0	0	24
	Systemic	15	3	3	2	0	1	0	0	0	0	0	24

Table 3. Comparison of the mean pain intensity of the study groups according to hours with Mann-Whitney U test table

Postop hours	Groups	n	Mean pain intensity ± Standard deviation	P
2nd hour	Topical	24	1.80±2.11	**.040**
	Systemic	24	3.33±3.03	
6th hour	Topical	24	1.79±2.55	**.035**
	Systemic	24	3.38±3.23	
8th hour	Topical	24	1.50±2.40	.055
	Systemic	24	2.08±1.84	
12th hour	Topical	24	0.70±1.57	.101
	Systemic	24	1.63±1.88	
24th hour	Topical	24	0.96±1.33	.324
	Systemic	24	1.17±1.76	
48th hour	Topical	24	0.58±1.02	.538
	Systemic	24	0.83±1.34	

Discussion

In this study, we aimed to compare the effect of local and systemic use of benzydamine HCl on postoperative pain after periodontal flap surgery. Benzydamine hydrochloride, a molecule whose analgesic effect is proven in many studies, topical and systemic forms were used. Subjects were divided into two groups. Comparison of clinical characteristics of both groups with periodontal clinical parameters, postoperative pain was assessed by visual pain scale.

In the study results, when the periodontal clinical parameters were compared before surgery, there was no difference between the groups and the groups had similar characteristics (Table 1 for p> 0.05).

Benzydamine HCl was found to be effective in postoperative pain control after periodontal flap surgery, when topically used form and systemic effective tablet form compared to the effectiveness of pain, it was found to be more effective in the postoperative 2nd and 6th hours, ie in the early postoperative period. They were equally effective on postoperative pain in both forms at 8th, 12th, 24th, 48th hours, ie in the late postoperative period (Table 3 for p <0.05).

Postoperative pain not only causes stress on the patient, but also prolongs the recovery period of the disease. Therefore, postoperative pain control is a subject that is continuously studied. Many agents have been used for postoperative pain control. Most of them have limited clinical use due to their potential serious side effects. The agent used for postoperative pain control in the clinic; It is expected to be effective, effect in a short time, not have side effects and be inexpensive (13,14).

Benzydamine hydrochloride is a nonsteroidal antiinflammatory drug that is antiinflammatory, local anesthetic, antipyretic, analgesic effect and can be used systemically and topically (15-18). Peeva et al. according to the results of their study, the use of local benzyadmin is effective in reducing local inflammation and pain by reducing especially prostaglandin and cytokine activity, in the postoperative period. and its postoperative use was recommended (17).

In their study of Cigerim and Eroglu, the analgesic-anti-inflammatory effect used after extraction of the patient's lower third molar was compared and it was shown that benzydamine hydrochloride had a similar effect with

diclofenac potassium and could be used as a non-steroidal anti-inflammatory analgesic drug (16). In a study by Peeva et al. reported that local benzydamine HCl used in tissue trauma after surgery in oral soft and bone tissues is effective in reducing postoperative pain and local inflammation (17). However, in the study of Goswami, stated that oral use of benzydamine hydrochloride does not reduce pain and is insufficient to alleviate pain in on pain after mandibular third molar extraction (18). In our study, in all patients using benzydamine HCl, 81.3% at the 2nd and 6th hours, 87.5% at the 8th hour and at the 12th hour, 91.7% of the patients had mild pain (pain level (1-4 points mild pain, 5-6 points moderate pain). There was no statistical difference between the two forms in achieving mild pain. As a result of this study, we can say that benzydamine HCl is highly effective in relieving postoperative pain after periodontal flap operation.

In postoperative care after periodontal flap surgery, antibiotic, analgesic and antimicrobial agents are needed. Benzydamine hydrochloride is effective in reducing pain and inflammation after surgical procedures in dentistry due to its antiinflammatory and analgesic effect at low doses and it has been reported to have some degree of antibacterial and antifungal activity (7).

The importance of rational drug use is spreading all over the world. In this context, it described as medicines appropriate to the clinical needs of patients, doses that meet personal requirements, for a sufficient period of time, use them with minimum cost to themselves and the society" (19-22). For this reason, medicines in sufficient quantities and in suitable dosage forms at any time should be preferred. In the literature, after periodontal flap surgery, benzydamine HCl has been reported that the capacity of condensation in inflamed tissues is good and potential systemic side effects are limited (20). In a study published in Allergy Journal, benzydamine HCl is a tolerable NSAID and has been demonstrated to be tolerable, and is a viable alternative in patients who are adversely affected by other NSAIDs (23).

In our study, we aimed to provide antiinflammatory, analgesic and antibacterial effects after periodontal surgery, as well as to reduce the number of drugs used and the daily dose taken. In the study results, benzydamine HCl is an effective agent on pain after periodontal flap surgery. Although the daily dose of topical spray form was 1/20, it was found to be more effective on early postoperative pain and equally effective on late pain.

Conclusion

In conclusion, the results of this study both topical and tablet form of benzydamine HCl are effective in reducing postoperative pain. In postoperative administration, the spray form provides better pain control than the tablet form. In the light of these data, topical form of benzydamine HCl may be a better alternative for pain after periodontal flap surgery.

Conflict of interest statement: The authors declare that there is no actual or potential conflict of interest.

Author's contiributions: GK; Design of research, data collection and Patient examinations, **GK;** preparation of article and revisions

Ethical issues: Author declare, originality and ethical approval of research. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

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Effect of serum vitamin D levels on weight loss in obese patients doing aerobic exercises: A retrospective study

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Abstract

Objective: This study evaluates the effect of serum vitamin D (Vit D) levels on weight loss in obese patients during an aerobic exercise program.

Material and Methods: The study included 88 participants with body mass index (BMI) ≥25 kg/m2. A serum level of 25(OH)D3 >30 ng/ml was accepted as normal, 20–29 ng/ml as insufficient and <20 ng/ml as deficient. The obese patients were classified into three groups based on a serum level of 25(OH)D3. All participants enrolled on an eight-week aerobic exercise program. The BMI, body fat percentage (BF%) and body fat mass (BFM) of the participants were measured before and after aerobic exercise.

Results: No statistically significant differences were identified between the groups in the first and last measured BMI, BF% and BFM values ($p>0.05$). The differences between the first and last measured weights, BMI, BF% and BFM were statistically significant within the groups ($p<0.05$).

Conclusion: Aerobic exercise can lead to weight loss in obese patients, although the level of serum Vit D has no effect on weight loss in obese patients engaged in aerobic exercise.

Keywords: Aerobic exercise, obesity, vitamin D

Introduction

Obesity is a serious and growing health problem that is caused by an extreme increase in the amount of fat tissue in the body. A BMI ⩾25 kg/m2 is defined as overweight, while a BMI ⩾30 kg/m2 is defined as obese (1,2).

Vit D is a fat soluble hormone that plays a role in several physiological activities, such as calcium homeostasis and musculoskeletal system health (3,4). Vit D deficiency is today considered a significant global health issue (5). Other than its effect on the musculoskeletal system, Vit D also plays a role in the synthesis and secretion of insulin, and regulates calcium entry into the pancreatic beta-cells. There is evidence that active Vit D modulates intracellular ionized calcium signaling in adipocytes. Besides, Vit D also plays a role in the regulation of glucose transporter 4 (GLUT-4) expression and stimulates the translocation of GLUT-4. In Vit D deficiency, this mechanism is impaired, leading to elevated fasting plasma insulin levels, reduced hepatic and peripheral insulin sensitivity, and significantly decreased peripheral glucose utilization in the obese.

It is thus believed that Vit D plays a role in the pathogenesis of obesity (6,7), although studies analyzing the link between obesity and serum Vit D levels have produced conflicting results. While some studies have reported lower Vit D levels in the obese than those of normal weight, there are other studies reporting similar serum Vit D levels between the obese and those of normal weight (8–10). Literature contains studies assessing Vit D levels in the obese. There are also studies reporting a positive impact of Vit D replacement on weight loss in obese patients (11).

In previous clinical trials investigating the effect of Vit D on weight loss, Vit D replacement was administered to obese individuals with Vit D deficiency. Different from literature, the present study examines the effect of the serum Vit D levels on weight loss in obese and overweight individuals engaged in an aerobic exercise program without Vit D supplement.

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Materials and Method

This retrospective study included 88 individuals who applied to the obesity rehabilitation unit of the Physical Medicine and Rehabilitation clinic between June 2016 and June 2019 with a BMI ⩾25 kg/m2, and who completed the rehabilitation program. Those who discontinued the aerobic exercise program, those who joined the aerobic exercise program within the last one year, and those who underwent Vit D replacement therapy within the last 3 months and who started to diet prior to the study were excluded from the study.

Obese patients were divided into three groups based on the serum levels of Vit D. A serum level of 25(OH)D3 <20 ng/ml was accepted as deficient (Group 1), 20–29 ng/ml as insufficient (Group 2) and >30 ng/ml as normal (Group 3) (12).

Sociodemographic and laboratory data of all participants were recorded. All of the participants were weighed using the same digital scale, and their heights were measured using a stadiometer (F. Bosch Medizintechnik, Germany) while barefoot, head straight and eyes looking forward, before starting and after completing the eight-week aerobic exercise program.

Waist circumference was measured naked using a standard measuring tape at the level of the iliac bone and umbilicus. BFM and BF% were measured using a bioelectrical impedance analyzer (Tanita TBF 300, Japan) after an 8-hour fasting period. Body mass index was calculated using the formula; BMI = weight (kg)/height (m2).

All of the participants were administered a cardiopulmonary exercise test using an ergospirometry device (CareFusion MasterScreen CPX 7402, Germany). Maximal oxygen consumption (VO_2max) and metabolic equivalent (MET) values were calculated. Exercise programs were created to achieve 70–75% of the maximum heart rate, considering also the age and gender of the individual patients. A treadmill (Profitness 3000, Taiwan) was used for the aerobic exercise. The duration of exercise was planned as 40–50 minutes, including 5 minutes for warm-up and cool-down.

The intensity of exercise was determined according to the heart rate, oxygen saturation (SPO_2) and Borg rating of the perceived exertion values measured during the exercise.

All participants were prescribed a low-calorie diet. During the time of data recording, the same physician, nurse, physiotherapy technician and dietician were on duty in the obesity rehabilitation unit.

The serum levels of vitamin 25(OH)D3 were measured in the venous blood via an electrochemiluminescent method (Roche Cobas e601, Germany) in the biochemistry laboratory of our hospital.

Approval for the study was obtained from the Clinical Trials Ethics Committee of our university, and the study was conducted in accordance with the Declaration of Helsinki.

Statistical analysis: Data obtained in the study were analyzed statistically using the IBM SPSS Statistics version 22.0 software (IBM Corp., Armonk, NY, USA). Conformity of the data to normal distribution was analyzed using the Kolmogorov-Smirnov test. Student's t test and post hoc ANOVA test were applied when the parametric test assumptions were met. A Mann-Whitney U test and post hoc Kruskal-Wallis test were used when the parametric test assumptions could not be met, and a chi-square test was used to evaluate the categorical data. Data were expressed as number and percentage or as mean/median ± standard deviation values. A value of $p<0.05$ was considered statistically significant.

Results

A total of 88 participants were included in the study, comprising 70 (79.5%) females and 18 (20.5%) males. The vitamin D levels and demographic data of the groups are presented in Table 1. No statistically significant difference was noted between the first and last measured BMI, BFM and BF% values between the groups ($p>0.05$) (Table 2). The difference between the first and last measured BMI, BFM and BF% values was statistically significant within the groups ($p<0.05$) (Table 3). No statistically significant correlation was found between Vit D levels and waist circumference ($p>0.05$).

Tablo 1. Vitamin D levels and demographic data of the groups

	Group 1 (n=19)	Group 2 (n=44)	Group 3 (n=25)	p
Vit D levels (ng/mL)	11.7 ± 4.2	23.7 ± 2.3	44.2 ± 19.4	<0.0001
Age (years)	49 ± 9.5	51.4 ± 11.5	50 ± 8.7	0.73
Gender (Female/Male)	13/6	33/11	24/1	0.42

*p<0.05, Results were given as mean/median ± standard deviation; n: Number of patients

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Table 2. The first and last measured BMI, BF% and BFM values between the groups

	Group 1 (n=19)	Group 2 (n=44)	Group 3 (n=25)		
Weight 1* (kg)	96.46 ± 16.23	90.20 ± 16.29	86.99 ± 16.74	p=0.167	p=0.351[a] p=0.146[b] p=0.715[c]
Weight 2 (kg)**	93.21 ± 16.26	86.88 ± 15.65	84.15 ± 15.40	p=0.163	p=0.312[a] p=0.147[b] p=0.767[c]
BMI 1*	36.81 ± 6.51	35.13 ± 7.15	34.65 ± 6.68	p=0.564	p=0.650[a] p=0.560[b] p=0.958[c]
BMI 2**	35.50 ± 6.25	33.72 ± 6.91	33.67 ± 6.31	p=0.580	p=0.593[a] p=0.637[b] p=0.999[c]
BF 1* (%)	41.52 ± 7.00	40.22 ± 7.82	41.67 ± 7.01	p=0.680	p=0.799[a] p=0.998[b] p=0.715[c]
BF 2 (%)**	39.17 ± 8.01	38.10 ± 8.09	40.66 ± 7.05	p=0.427	p=0.872[a] p=0.805[b] p=0.394[c]
BFM 1* (kg)	41.03 ± 12.27	37.05 ± 12.92	37.27 ± 11.74	p=0.484	p=0.478[a] p=0.585[b] p=0.997[c]
BFM 2 (kg)**	37.25 ± 11.78	33.84 ± 12.24	35.35 ± 11.38	p=0.575	p=0.553[a] p=0.860[b] p=0.868[c]

p<0.05; Results were given as mean/median ± standard deviation; BMI: Body Mass Index; BF: Body Fat; BFM: Body Fat Mass; n: Number of patients; a Comparison between Group 1 and Group 2; b Comparison between Group 1 and Group 3; c Comparison between Group 2 and Group 3; 1: Before aerobic exercise; 2**: After aerobic exercise

Table 3. The difference in the first and last measured BMI, BF% and BFM values within the groups

	Group 1 n=19)	p	Group 2 (n=44)	p	Group 3 (n=25)	p
Weight 1*- Weight 2**	3.25 ± 2.16	<0.001*	3.32 ± 1.89	<0.001*	2.84 ± 2.15	<0.001*
BMI 1*-BMI 2**	1.31 ± 1.31	<0.001*	1.41 ± 1.13	<0.001*	0.98 ± 1.30	0.001*
BF 1*-BF 2**	2.35 ± 1.92	<0.001*	2.11 ± 2.64	<0.001*	1.01 ± 1.76	0.008*
BFM 1*-BFM2**	3.77 ± 3.17	<0.001*	3.20 ± 2.73	<0.001*	1.91 ± 2.09	<0.001*

p<0.05; Results were given as mean/median ± standard deviation; BMI: Body Mass Index; BF: Body Fat; BFM: Body Fat Mass; n: Number of patients; 1: Before aerobic exercise; 2**: After aerobic exercise

Discussion

This study has evaluated the effect of serum Vit D level on weight loss in obese and overweight patients enrolled in an aerobic exercise program. A significant decrease was noted in weight loss, BMI, BFM and BF% after undertaking aerobic exercise in all three groups. That said, serum Vit D levels were found to make no additional contribution to weight loss, BMI, BFM or BF% in obese patients undertaking aerobic exercise.

Vit D is a fat-soluble steroid hormone, the most important known effect of which is on the calcium metabolism and bone mineralization (13). There have been several studies suggesting a link between Vit D deficiency and many chronic diseases (14). In particular, Vit D deficiency is reported to be a risk factor for cardiovascular disease and diabetes, similar to obesity (15). The prevalence of obesity worldwide is high, and it is considered to be an epidemic by the World Health Organization (16).

There has been a significant increase in the last decade in the number of studies investigating the link between Vit D and obesity (11). The study by Walsh et al. identified lower serum levels of Vit D in the obese than in healthy individuals (17). Likewise, another study reported Vit D deficiency to be more common in the obese than in the healthy population (18). It has also been reported that Vit D level and BMI are negatively correlated (19,20). Although the mechanism underlying the link between Vit D and obesity has yet to be fully clarified, there have been studies identifying Vit D deficiency as a likely cause of obesity (21,22). Additionally, literature contains studies suggesting that obese patients with Vit D deficiency can lose weight when administered with Vit D supplements (23–25). A recent study showed that Vit D supplement given to obese women had a positive effect on weight loss (26). Likewise, a recent study by Perticone et al. demonstrated positive

effects of Vit D supplement on weight loss in obese patients (27). The present study, different from previous research, evaluated the impact of existing serum Vit D levels on weight loss without any intervention in obese patients undergoing aerobic exercises. In the present study, it was demonstrated that serum level of vitamin D had no impact on weight loss in obese patients engaged in aerobic exercises. The findings of the present study seem to be in conflict with those of previous studies evaluating the link between Vit D and obesity; although we believe that aerobic exercise has an important effect on weight loss, and may have masked the impact of Vit D in our study. These conflicting findings may also have resulted from the Vit D measurement method, lifestyle and cultural differences, and geographical condition-related changes.

The present study has a number of strengths. Existing literature contains no studies evaluating the link between serum Vit D levels and weight loss together with aerobic exercise in obese patients. Furthermore, the present study did not intervene in the existing serum levels of Vit D in obese patients.

We are well aware that this study has certain limitations, being limited by its retrospective design and its lack of a separate Vit D supplement group; the low number of patients in the low and normal Vit D groups; the lack of re-assessment of Vit D levels at the end of aerobic exercise; and the lack of a long-term follow-up of the patients after aerobic exercises.

Conclusion

Aerobic exercise has an effect on weight loss in obese patients, while serum Vit D levels make no additional contribution to weight loss in obese patients engaged in aerobic exercise. That said, any deficiencies in this regard should be addressed in individuals with low levels of Vit D, since a relationship has been established between Vit D and numerous diseases. Further, more extensive clinical studies are needed to evaluate the association between obesity and Vit D on a physiological and genetic base.

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How is NLR and PLR affected in Type 2 diabetes mellitus compared to healthy population?

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Abstract

Objective: Diabetes Mellitus (DM); has become an important public health problem in Turkey and in the world. In this study, we aimed to investigate the effect of neutrophil / lymphocyte ratio and platelet / lymphocyte ratio in diabetic patients compared to healthy population in terms of cost effectiveness.

Material and Methods: A control group consisting of 82 diabetics and 85 healthy individuals who applied to the internal medicine outpatient clinic between January 2019 and November 2019 were included in the study. The patients were divided into two groups as those with diabetes and healthy individuals. Files were scanned retrospectively and hemoglobin, mean platelet volume (MPV), glycosylated hemoglobin (HbA1c), hematocrit counts (hct), neutrophil and lymphocyte counts, and neutrophil-lymphocyte ratio (NLR), platelet count (plt), platelet lymphocyte ratio (NLR) PLR) has been recorded.

Results: We retrospectively compared the demographic and laboratory parameters of the healthy group and the diabetic patients (82 patients and 85 healthy). The mean age of the diabetic group was 55.9 years, while the mean age of the healthy group was 37.5. Mean NLR was 2.4 and 2.1 in diabetic and healthy groups, respectively. NLR value was higher in diabetic group compared to healthy group and there was no statistically significant difference ($p = 0.07$). MPV values in diabetic group and healthy group were 8.53 and 8.51, respectively, and there was no significant relationship between them ($p = 0.81$). PLR value was 145.9 and 146.7 in diabetic group and healthy group, respectively, and we did not find any significant relationship ($p = 0.97$).

Discussion: As a result; In our study, when we evaluated the diabetic group within the diabetic group and the healthy group, we could not find a statistically significant relationship between the groups in terms of hematological parameters.

Keywords: Diabetes mellitus, neutrophil, lymphocyte, Ratio

Introduction

Diabetes Mellitus (DM) is a systemic chronic metabolic disease with chronic hyperglycemia.

It is characterized by disorders of carbohydrate, protein and fat metabolism resulting from partial or total deficiency of insulin and / or insulin resistance (1).

Neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR) and platelet indices are easy, inexpensive and accessible rates calculated from whole blood count and have been shown to be associated with many medical conditions and pathologies(2-4).

There are studies showing a correlation between metabolic and endocrinological diseases and this index and rates(5,6).

Inflammatory processes play a key role in chronic diseases, including cardiovascular disease, cancer, chronic kidney disease and diabetes mellitus (7).

Studies have shown that neutrophil / lymphocyte (N / L) ratio. inflammation is a systemic indicator.In addition, N / L ratio has been shown to be an important predictor of short and long term cardiovascular mortality and prognosis in cancer patients. (8,9).

The aim of our study was to evaluate the feasibility of routine hemogram examination in diabetic patients between diabetic patients and healthy group and diabetic patients according to HbA1c levels.

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Material and Methods

Ethical approval of this study was obtained from Fırat University Scientific Research Projects Coordination Unit. Data; Elazığ City Hospital was established based on the data obtained from retrospective files of patients who applied to the internal medicine outpatient clinic and clinic between January 2019 and November 2019.

The study included 82 patients with Type 2 diabetes and a control group of 85 healthy subjects. Patients were divided into two groups as diabetes mellitus and healthy subjects. The diabetic group consisted of patients aged 30-78 years who applied to the internal medicine outpatient clinic due to diabetes mellitus. Patients with a different chronic disease (coronary artery disease, hematological diseases, malignancy, severe liver disease, severe renal failure),and smoking DM patients were not included in the study. Files were scanned retrospectively.

Hemoglobin, mean platelet volume (MPV), glycosylated hemoglobin (HbA1c), hematocrit numbers (hct), neutrophil and lymphocyte count and rate (NLR), platelet count (plt), platelet lymphocyte ratio information were obtained from the file records.

Statistical analysis: All statistical analyzes were done with a computer package (SSPS-22) program. While evaluating the study data, in addition to the descriptive statistical methods [Average (), Standard deviation (SD)], Student's t was used in the parametric tests that showed normal distribution in the comparison of quantitative data, and one-way ANOVA in group comparisons.

The Wilcoxon paired sample test, which is the significance test of the difference between the two partners, was used to compare the qualitative data and the Chi-Square test. The results were evaluated in the 95% confidence interval and the significance level was p <0.05.

Results

Table 1 shows the comparison of demographic and laboratory parameters between diabetic and healthy groups. The mean age of the diabetic group was 55.9 years, while the mean age of the healthy group was 37.5 years. Mean NLR was 2.4 and 2.1 in diabetic and healthy groups, respectively. There was no significant difference in NLR between the two groups (p = 0.07). MPV values in diabetic group and healthy group were 8.53 and 8.51, respectively, and the relationship was not statistically significant (p = 0.81). PLR value was 145.9 and 146.7 in diabetic group and healthy group, respectively, and the relationship was not significant (p = 0.94).

Table 2 shows the relationship between MPV, NLR, PLR in patients diagnosed with diabetes based on HbA1c level.We divided diabetic patients with HbA1c level 10 and above (n = 39) and below 10 (43) into two groups.

The NLR value was found to be 2.6 in the high HbA1c group, while the HbA1c value was 2.2 in the group below 10 and there was no statistically significant relationship (p = 0.18).

The PLR value was 140.4 and 150.8, respectively, and there was no statistically significant relationship. We did not find any statistically significant relationship (p = 0.58).

Table 1: Demographic and Laboratory Data of Diabetic and Healthy Individuals

	Groups	N	Median	Standart Deviasyon	p value
Age	control	85	37,5	11	<0.001
	patient	82	55,9	12,9	
HbA1c	control	85	5,6	0,2	<0.001
	patient	82	9,5	2,2	
Hematocrit	control	85	41,1	5,6	0,54
	patient	82	41,7	6,8	
Thrombosit	control	85	264070	55506	0,54
	patient	82	269853	68379	
Neutrofil	control	85	4146	1513	0,13
	patient	82	4539	1852	
Lymphocytes	control	85	1984	452	0,10
	patient	82	2191	1080	
MPV	control	85	8,5	0,9	0,81
	patient	82	8,5	0,7	
NLR	kontrol	85	2,1	0,8	0,07
	patient	82	2,4	1,2	
PLR	control	85	146,7	59,4	0,94
	patient	82	145,9	85,6	
Monocytes	control	85	392	94	<0.001
	patient	82	463	144	

Table 2: Relationship between MPV, NLR, PLR in diabetic patients according to HbA1c level

	Groups	N	Median	Standart Deviasyon	p value
Age	HbA1c>10	39	54.3	10.2	0,27
	HbA1c<10	43	57.4	14.8	
HbA1c	HbA1c>10	39	11.4	1.2	<0.001
	HbA1c<10	43	7.7	1.1	
Hematocrit	HbA1c>10	39	42.9	6.8	0,12
	HbA1c<10	43	40.6	6,7	
Thrombosit	HbA1c>10	39	281846	71030	0,13
	HbA1c<10	43	258976	64791	
Neutrofil	HbA1c>10	39	5101	2103	<0,05
	HbA1c<10	43	4030	1435	
Lymphocytes	HbA1c>10	39	2394	1416	0,10
	HbA1c<10	43	2007	602	
MPV	HbA1c>10	39	8,4	0,7	0,06
	HbA1c<10	43	8,7	0,7	
NLR	HbA1c>10	39	2,6	1.3	0,18
	HbA1c<10	43	2,2	1,1	
PLR	HbA1c>10	39	140.4	62.4	0,58
	HbA1c<10	43	150.8	102.8	
Monocytes	HbA1c>10	39	447	128	0.36
	HbA1c<10	43	477	158	

Discussion

Neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) are inexpensive and easily accessible parameters calculated from whole blood count. It has been shown to be associated with many medical conditions and pathologies (2-4). There have been reports of a correlation between metabolic and endocrinological diseases and this index and rates in studies (5,6). In a study, elevation of NLR levels and the presence of this elevation in sedimentation in elderly osteoporosis showed that inflammation may play an important role in bone remodeling (10). In our study, the mean NLR value in the diabetic and healthy group was 2.4 and 2.1, respectively. There was no significant difference in NLR between the two groups. In many epidemiological studies, chronic inflammation has been shown to play an effective role in the pathogenesis of chronic diseases such as metabolic syndrome, hypertension and diabetes (11,12).

Cross-sectional and prospective studies have shown a positive relationship between Type 2 DM and its complications and CRP, IL-6 and white cell count (13).

In the study of Onalan and et al(14) on 100 diabetic patients and 100 healthy controls, NLR and PLR values were found to be higher in diabetic group compared to healthy group and statistically significant.

In addition, it was found that NLR value increased significantly in diabetic retinopathy and diabetic nephropathy group compared to non-diabetic nephropathy group.

In a study evaluating the relationship between gestational diabetes and mean platelet volume (MPV), MPV value was found to be significantly higher in gestational diabetics than in control.

In addition, the researchers found a correlation between MPV and insulin resistance index (HOMA-IR) (15).

Some studies showed a significant correlation between MPV and neuropathy. However, Hekimsoy et al.'s study with 145 diabetic and 100 nondiabetic individuals found no significant statistical difference (16, 17). Similarly, in our study, we did not find any significant difference between the diabetic group and the healthy group in terms of MPV value. Increased NLR was found to be a poor predictor of prognosis in patients undergoing cardiovascular intervention.

In some studies, increasing NLR values have been shown to be parallel with the increase in mortality rates (16,17). For example, in a study evaluating the effect of smoking, NLR, PLR and platelet indices were found higher in smokers and were also associated with NLR and platelet smoking intensity (18). Therefore, these factors should be taken into consideration when studying NLR, PLR and other indices.

In our study, when we compared diabetic group and healthy population, we found differences in NLR, PLR and MPV values, but there was no statistically significant relationship. When we compared the diabetic group according to HbA1c value, we did not find any statistically significant relationship. Different and similar results from previous studies may be due to some limitations of our study.

The lack of homogeneous distribution of cross-sectional patients in terms of age, sex, oral antidiabetic drugs and body mass index are the deficiencies of our study.

Conclusion

As a result; In our study, when we compared the diabetic group and the healthy group and the diabetic group according to the HbA1c value, we found differences in some hematological parameters, although not statistically significant.

We found that hematocrit, MPV, NLR, PLR values found in a simple laboratory test such as hemogram are cost-effective parameters for demonstrating hyperglycemia. Further comprehensive research is needed to conclude concordance and lack of concordance between the studies and our studies.

Conflict of interest statement: The authors declare that there is no actual or potential conflict of interest.

Author's contiributions: YD; Design of research, data collection and Patient examinations, preparation of article and revisions

Ethical issues: Author declare, originality and ethical approval of research. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

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Hemispheric lateralization of depression and attention deficit

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Abstract

Objective: There is a complex interaction among to the ischemic cerebrovascular diseases, cognition and depression. The aim of present study is to investigate the relationship between lesion side and depression and attention deficit in patients with Middle Cerebral Artery (MCA) infarction.

Methods: This study was conducted on 41 patients with right and left MCA infarction. Beck Depression Inventory (BDI) was used for determination of depression severity of patients and Montreal Cognitive Assessment (MoCA) scoring was used for evaluation of cognitive status. Attention sub-test of MoCA score was also examined.

Results: 20 patients had right MCS. The mean age of the patients was 72.21 years. 51.2% of the patients were male. BDI mean score was found to be 11.25 in patients with right MCA infarction and 16.9 in patients with left MCA infarction (p:0.04). The total MoCA scores between two groups were similar (right/left MCA infarction: 20.8/21.3). It was seen to be lower attention sub-score in patients with right hemisphere effects compared to patients with left hemispheric lesion (3.1/5.9; p:0.00).

Conclusion: According to our findings, it is understood that attention of patients with right MCA infarction is more affected and patients with left MCA infarction is more depressed. In future studies, depression and attention affects which are at risk of developing after MCA infarctions should be evaluated in detail and should be put emphasis to rehabilitation of these areas.

Key words: Cerebrovascular disorder, Cognitive Impairment, Depression, Attention Deficit

Introduction

Stroke is one of the most common neurological diseases which make life difficult in many ways. Although post-stroke depression and cognitive impairments are often seen, they can be poorly understood and not treated enough (1). Indistinguishability between cognitive findings which generated basing on post-stroke ischemic cerebral damage and depressive findings increase the diagnostic difficulties. In addition to this, in some studies which are aimed to reveal the mechanism of the formation of the disease, it was mentioned the relationship between infarct localization and depression and it was observed to be more common depression in left frontal and right posterior lesions (2, 3). Also, some in some studies, it was reported a relationship between depression severity and the proximity of the lesion to the left frontal region (4).

In the literature, it is stated a common post-stroke depression especially in patients with left hemispheric effects (1, 3). However, the recognition and treatment of depression post-stroke is fewer. In addition to depression, stroke is also a risk factor for general cognitive functions deterioration.

As a matter of fact, it is reported cognitive inefficiency is developed in about one third of the patients with stroke and the affected cognitive area is associated with lesion localization as well (5). In recent studies, it has been showed that ischemic cerebral disorders are related with depressive symptoms and cognitive functions deficits (1,5). Also, in some studies, it has been reported the emergence of neuropsychological symptoms and the affection of sub parameters of cognitive functions are at different levels according to the effected brain regions by ischemic Cerebrovascular Accident (CVA) (1).

The relationship between cognitive inefficiency and depression after stroke is still being investigated. There are different results among the studies (4, 6). In addition, there are very few studies in the literature that evaluate post-stroke depression and the affected level of cognitive functions as comprehensively. Therefore, in this study, it is aimed to investigate the relationship between cognitive function parameters and depression of patients with ischemic CVA based on right and left hemispheric Middle Cerebral Artery (MCA) infarction.

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Material and Methods

This study was conducted on patients with right and left MCA infarction who were over the age of 18 years. Patients who underwent cognitive status and depression evaluation in the post-stroke third month checks were determined as a sample group. Patients who were diagnosed depression and/or dementia and being used medical treatment because of these diagnoses before the stroke, had malignity history and had B12 deficiencies were excluded the study. Patients who had dysmnesia and emotional dysregulation were also excluded from the study.

This study was approved by the Local Ethic Committee (Protocol No: 2019/003-002). According to the inclusion and exclusion criteria, 20 patients with right MCA infarction and 21 patients with left MCA infarction were included in the study. Montreal Cognitive Assessment (MoCA) Scala and Beck Depression Inventory (BDI) were performed each patient. Attention sub-test of MoCA score was also recorded.

Statistical Analysis: In the analysis of statistical data, mean ± standard deviation was used for continuous variables. Discrete variables were expressed as numbers and percentage, median, minimum and maximum values. In the comparative analysis of categorical variables, Chi-square test was performed. For the analysis of continuous data, firstly, normality distribution was investigated with Kolmogrov Smirnov. Parametric tests were used for normally distributed data and non-parametric tests were used for non-normally distributed data. Student's t test was performed to compare the differences between the dependent samples and Paired Sample T Test was used for dependent variable. The differences between groups reliability range was taken 95% and $p<0.05$ was considered as statistically significant. SPSS 18.0 package program was used for statistical analysis(7).

Results

The number of patients with MCA in this study was 41.The mean age of the patients was 72.21 ± 5.71 years. 51.2% of the patients were male. 20 patients had right MCA infarction and 21 patients had left MCA infarction. Patients with right and left MCA infarction were similar in terms of total years of education (8.4/7.7) (Table 1).

There were no statistically significant differences between patients with right and left MCA infarction in terms of MoCA test results at third month checks after stroke. However, when attention sub-scores were evaluated, it was seen to be lower scores in patients with right MCA infarction (3.15 / 5.09, p:0.00). The results of BDI scores were showed higher scores in patients with left MCA infarction compared to patients with right MCA infarction and it was statistically significant (11.25 / 16.90, p:0.04) (Table 2).

Discussion

In this study, it was investigated the results of depression and cognitive functions parameters in patients with after ischemic CVA based on right and left hemispheric MCA infarction. For this reason, three-month follow-up results of patients were evaluated as retrospectively. Our findings showed statistically similar MoCA scores in the ischemic CVA which affected the both hemispheres due to the MCA infarction. When the sub-parameters of MoCA test towards to evaluation of cognitive functions were examined, attention was more deteriorated in patients who had right hemispheric lesion compared to patients with left hemispheric lesion.

In a way that overlaps with our findings Lee and Pyun (2014) reported more cognitive dysfunction and especially increasing attention deficit in patients who had right hemispheric lesion compared to patients with left hemispheric lesion. They obtained their data from 36 patients with right hemispheric lesion and 32 patients with left hemispheric lesion (8).

Likewise, in the systematic review study which was conducted by Umorova (2017), it was highlighted an emergence of cognitive impairment and attention deficit in post-stroke patients who had right hemispheric lesion as well (9). Qazaz et al (2014) reported a cognitive impairment in patients with right hemispheric lesion. Also, they indicated the more memory dysfunction development in patients with right hemispheric lesion unlike to our findings (10).

Table 1: Demographic properties an characteristics of Patients

	Right MCA N:20	Left MCA N:21
Age [years], mean (SD)	73.1(5.9)	71.3(5.4)
Male gender [%]	50	52.3
Education [years], mean (SD)	8.4 (3.6)	7.7 (4.4)

Table 2: MoCA and BDI Scores of Patients

	Right MCA N:20	Left MCA N:21	P Value
MoCA, mean (SD)	20.8 (3.67)	21.3 (3.83)	0.65
Attention sub-score, mean (SD)	3.15 (1.3)	5.09 (1.17)	0.00
BDI, mean (SD)	11.25 (7.36)	16.90 (9.98)	0.04

Distinctly from literature and our results, in a cohort study made by Zhao et al (2018), it was found left angular gyrus, left basal ganglia structures and the white matter around the left basal ganglia as strategic structures for global cognitive impairment after stroke. In this study, authors aimed to determine strategic brain regions for post-stroke cognitive impairment by applying multivariate lesion-symptom mapping in a large cohort of 410 acute ischemic stroke patients. They used the Montreal Cognitive Assessment at three to six months after stroke for assessing the global cognitive functioning and cognitive domains (memory, language, attention, executive and visuospatial function). In their study, the relation between infarct location and cognition was assessed in multivariate analyses at the voxel-level and the level of regions of interest using support vector regression (11).

In our study it was found that depression is more common in the left hemispheric lesions related with MCA infarction than right hemispheric lesions. Indeed, in one study which was conducted by Rashid et al (2017), it was reported that depression was more common in patients with left hemispheric lesion after stroke (12). Also, in one meta-analysis study which was made by Robinson and Jorge (2016), it was indicated that post-stroke depression was mostly originated by left hemisphere lesions (13). Unlike to our findings Agrill and Dehlin (2013) stated that the prevalence of depression was 46% in patients with post-stroke in a prevalence study of 93 patients, and they found no significant relationship between right and left hemisphere lesions and depression (14). It is considered that the reason of differences between the findings may be arise from the features of sample groups.

In studies, cognitive dysfunctions related with ischemic CVA and neuropsychological influences were found at different levels (13, 14). Evaluation time, criteria and technics are not homogeneous for cognitive and psychiatric evaluations. In recent studies have focused on the side of the lesion and the importance of localization in disorders of cognitive functions related with ischemic CVA and psychological pathologies and tried to develop treatment strategies for ischemic lesions.

Conclusion

At the result of our study, depression and cognitive parameters effects that emerged after ischemic CVA were found to be associated with the side of ischemic lesion and localization. At the endpoint of the study, at the 3rd month evaluations after ischemic CVA, attention was significantly impaired in cognitive function parameters in right hemisphere lesions and depression was more common in left hemisphere lesions. It is thought that prospective, randomized, double-blind and long-term studies involving large numbers of patients are needed to be understand entirely the effects of lesions region associated with ischemic CVA on psychopathologies and cognitive functions.

Conflict of interest statement: The authors declare that there is no actual or potential conflict of interest.

Author's contributions: YD; Design of research, data collection and Patient examinations, preparation of article and revisions

Ethical issues: Author declare, originality and ethical approval of research. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits. Approval was received for the study from the Ethics Committee of Liv Hospital Ankara (2019/003-002).

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Survival analysis and factors affecting survival in patients with pancreatic cancer

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Abstract

Objective: The study aims to investigate the effects of clinicopathological characteristics and laboratory data at the time of diagnosis and of the administered treatments on survival in patients with pancreatic cancer.

Material and Methods: In this retrospective cohort study, we included the patients who presented to the Medical Oncology Outpatient Clinic of Isparta Süleyman Demirel University Medical Faculty Hospital and were diagnosed with pancreatic cancer between January 1, 2010 and December 31, 2017.

Results: A total of 124 patients were examined. The median survival time was 6.97 (%95 CI:4.663-9.270) months, and the 5-year survival rate was 8%. The survival time was shorter in patients diagnosed with adenocarcinoma (HR: 5.350), history of alcohol use (HR: 2.195), an Eastern Cooperative Oncology Group (ECOG) performance score of >2 (HR:2.763), Ca 19-9 value >400 (HR:1.790). Stages 2, 3 and 4 posed 2.034, 3.175 and 6.023 times higher risk of death than stage 1, respectively. Considering the adjuvant chemotherapy group as reference, risk of death was 1.250 times higher for those who received palliative chemotherapy and 2.314 times higher for those who did not receive chemotherapy.

Conclusion: In conclusion, history of alcohol use, Ca 19-9 level, ECOG performance status, disease stage, histopathological subtype of the disease, and whether the patient received chemotherapy or radiotherapy affect survival in patients with pancreatic cancer.

Key words: Cancer, Pancreatic Cancer, Survival, Prognostic Factors

Introduction

The incidence and mortality rates of cancer are rapidly increasing throughout the world, making it an important public health concern. Cancer is the cause of death in 1 of 6 deaths (1); it is estimated to be responsible for 10 million deaths in 2020 (2).

Globally, pancreatic cancer is the 11th most prevalent cancer with 338,000 new cases diagnosed each year, and with more than 334,000 deaths, it is the 7th leading cause of cancer-related deaths. The incidence of pancreatic cancer is increasing by 0.5%–1% each year. The lifetime risk of pancreatic cancer is about 1.6%. Pancreatic cancer has the worst survival rate among all cancers, with a 5-year survival rate of 3% in 1975 and approximately 8.2% today. It is the third leading cause of cancer-related deaths in the USA with more than 53,000 patients diagnosed and more than 43,000 deaths each year. It is estimated to be the 2nd leading cause of cancer-related deaths by 2030. Pancreatic cancer is more common in patients at an advanced age, especially those aged 65–74 years, and it is more prevalent in males than females (3).

According to the 2015 cancer statistics in Turkey, the incidence of pancreatic cancer is 5.6 per 100,000 for men and 3.3 per 100,000 for women (4).

Patients with pancreatic cancer usually present with epigastric pain and jaundice or weight loss without jaundice (3). Approximately 60%, 15%, and 5% tumors are localized in the head, body, and tail of the pancreas, respectively, whereas the remaining 20% are diffuse within the pancreas (5). Smoking, history of diabetes, high body mass index, excessive alcohol use, family history of pancreatic cancer are some important risk factors (6). Only 10%–20% patients present with resectable pancreatic cancer (3).

Thus, we investigated the effects of clinicopathological characteristics and laboratory data at the time of diagnosis and of the treatments administered during follow-up on survival in patients with pancreatic cancer. The results of the study help in appropriate patient management.

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Material and Methods

The study was conducted between 2018 and 2019. Ethics Committee of the Isparta Süleyman Demirel University Medical Faculty approved the study (Approval no: 213, dated December 13, 2018).

In this retrospective cohort study, we included the patients who presented to the Medical Oncology Outpatient Clinic of Isparta Süleyman Demirel University and were diagnosed with pancreatic cancer between January 1, 2010 and December 31, 2017. A total of 124 patients were included. Patient information was obtained from the archive files and information system of the hospital. Patient deaths were updated after verifying the same with the system on December 20, 2018. Mean follow-up time and survival time were calculated. Survival time was defined as the duration of time (months) until death for deceased patients and as the duration of time (months) since the diagnosis for living patients.

We recorded the patients' gender, age at diagnosis, presence of abdominal pain and jaundice as presenting symptoms, history of weight loss of >10% in the last 6 months, personal–family medical histories, Eastern Cooperative Oncology Group (ECOG) performance scores, CA 19-9 and CEA levels, treatment history, latest follow-up date, and time of death, if the patient was deceased. The presence of diabetes was particularly investigated in pancreatic cancer cases. A cutoff value of 400 for Ca19-9 level was used in the analyses (7); this value corresponded to the 66th percentile for Ca 19-9. The performance scoring used by the ECOG was employed to identify the performance status of the patients (8).

Data such as tumor localization, TNM stage, site of metastasis (if any), date of pathological diagnosis, and histopathological subtype were obtained from the patient files. In terms of tumor localization, pancreatic cancer was classified as cancer localized in the head, body, and tail and diffused cancer within the pancreas. Because non-adenocarcinoma cases were limited, they were combined with other adenocarcinomas cases for evaluation. AJCC Version 8 TNM staging system was used for staging (9).

Patients who presented to the Oncology Outpatient Clinic of Süleyman Demirel University Hospital and were histopathologically diagnosed with pancreatic cancer between 2010 and 2017 were included.

The data was evaluated using descriptive statistics (number, percentage, mean, median, and standard deviation), Kaplan–Meier analysis, and Cox regression analysis using a statistical software package. Significant variables and variables that were not found to be significant with p values below 0.250 in univariate analyses were used in Cox regression analysis. $P<0.05$ was considered statistically significant.

Results

Overall 124 patients diagnosed with pancreatic cancer between 2010 and 2017 were examined. The mean age of the patients at diagnosis was 62.8 ± 11.6 years, 56.5% (n = 70) patients aged ⩾60 years at diagnosis, and 64.5% (n = 80) patients were male. Patients with a history of smoking constituted 36.3% (n = 45) of the group, and 6.5% (n = 8) were alcohol users. At admission, 71.8%, 27.4%, 29.1%, and 35.5% (n = 89, 34, 36, and 44) patients stated that they had abdominal pain, jaundice, weight loss in the last 6 months, and a history of diabetes, respectively (Table 1).

Table 1. Demographic and clinical data of patients

		n(%)	Median survival time±SE	p
Age	(Mean ± SD)	62.8±11.6		
	< 60	54 (% 43.5)	9.73±1.67	0.015
	≥ 60	70 (% 56.5)	5.20±0.91	
Gender	Female	44 (% 35.5)	9.73±3.08	0.063
	Male	80 (% 64.5)	6.57±1.23	
Smoking history	Absent	79 (% 63.7)	6.97±1.53	0.793
	Present	45 (% 36.3)		
	< 40 py	30 (% 24.2)	6.93±3.40	
	≥ 40 py	15 (% 12.1)	8.80±2.02	
Alchol history	Present	8 (% 6.5)	4.53±1.79	0.174
	Absent	116 (% 93.5)	7.70±1.22	
Abdominal pain	Present	89 (% 71.8)	6.30±1.29	0.134
	Absent	35 (% 28.2)	10.07±2.94	
Jaundice	Present	34 (% 27.4)	8.80±2.84	0.322
	Absent	90 (% 72.6)	6.40±1.53	
Weight loss (6 months)	Absent	88 (% 70.9)	8.60±1.49	0.584
	Present	36 (% 29.1)		
	< %10	24 (% 19.4)	5.50±1.51	
	≥ %10	12 (% 9.7)	6.30±3.35	
Comorbidities	Diabetes Mellitus	44 (% 35.5)	5.50±0.98	0.189
	Other comorbidities	24 (% 19.4)	7.83±2.45	
	Absent	56 (% 45.1)	9.23±1.66	
Total		124 (100.0)	6.97±1.18 (median±SE) 15.93±2.09 (mean±SE)	

P: log rank (mantel-cox

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The distribution of histopathological diagnosis was as follows: 92.8%, 4.8%, 1.6%, and 0.8% (n = 115, 6, 2, and 1) of adenocarcinomas, neuroendocrine tumors, acinar cell carcinomas, and sarcomatoid carcinoma, respectively. Because non-adenocarcinoma cases were limited, they were combined with other adenocarcinoma cases for evaluation. Cancer stage at diagnosis was recorded. AJCC Version 8 TNM staging system was used for staging. A total of 4, 12, 40, and 68 (3.2%, 9.7%, 32.3%, and 54.8%) patients had stage 1, 2, 3, and 4 cancer, respectively (Figure 1). Furthermore, 46 (67.6%) patients with stage 4 cancer had single organ metastasis, whereas 22 (32.3%) had multiple metastases. The tumor was localized in the head, body, and tail in 66.9%, 14.5%, and 13.8% patients, respectively, whereas 4.8% had diffuse cancer within the pancreas. In addition, performance status according to the ECOG performance scale was >2 in 31 (25.0%) patients (Figure 2).

CEA values were not available in the file or in the system for 31 (25.0%) patients, whereas 51 (41.1%) had CEA values above 4. Moreover, Ca 19-9 values were not available in the file or in the system for 23 (18.6%) patients, whereas 35 (28.2%) had Ca 19-9 values above 400.

Mean follow-up time was 9.7 ± 13.9 (min: 0.0; max: 81.7) months. Treatments administered during follow-up were as follows: 57, 40, and 17 (46.0%, 32.3%, and 13.7%) patients underwent surgery, radical surgery, and palliative surgery, respectively. Additionally, 67 (54.0%) received systemic chemotherapy; of these, 24 (19.3%) received adjuvant therapy, 43 (34.7%) received palliative treatment, and 2 who received adjuvant therapy were also administered neoadjuvant therapy (Table 2).

Table 2: Clinical-laboratory-pathology data and treatment details at the time of diagnosis of patients

		n(%)	Median survival time±SE	p
ECOG	≤ 2	93 (% 75.0)	10.57±1.25	<0.001
	> 2	31 (% 25.0)	2.80±0.41	
CEA	≤ 4	42 (% 33.9)	11.33±1.65	0.005[1]
	> 4	51 (% 41.1)	4.53±1.07	
	Unknown	31 (% 25.0)	6.30±1.61	
Ca 19-9	≤ 400	66 (% 53.2)	9.40±1.64	0.001[2]
	> 400	35 (% 28.2)	3.90±0.48	
	Unknown	23 (% 18.6)	7.83±1.97	
Stage	1	4 (% 3.2)	35.67±14.31	<0.001[3]
	2	12 (% 9.7)	19.80±6.44	
	3	40 (% 32.3)	10.57±1.27	
	4	68 (% 54.8)	4.00±0.40	
Number of metastases	Single	46 (% 67.7)	4.53±1.11	0.780
	Multiple (≥ 2)	22 (% 32.3)	3.77±0.27	
Histopathological subtype*	Adenocarcinoma	115 (% 92.8)	12.96±1.78**	<0.001
	Other subtype*	9 (%7.2)	53.53±11.17	
Tumor localization (pancreas)	Head	83 (% 66.9)	7.70±1.52	0.510
	Corpus	18 (% 14.5)	7.83±2.23	
	Tail	17 (% 13.8)	6.40±3.77	
	Common	6 (% 4.8)	4.40±2.51	
Operation	Present	57 (% 46.0)		
	Radical	40 (% 32.3)	16.93±1.79	<0.001[4]
	Paliative	17 (% 13.7)	6.40±2.68	
	Absent	67 (% 54.0)	4.43±0.53	
Chemotherapy	Present	67 (% 54.0)		
	Adjuvant	24 (% 19.3)	15.67±1.84	0.001[5]
	Paliative	43 (% 34.7)	6.40±1.22	
	Absent	57 (% 46.0)	4.77±1.04	
Radiotherapy	Present	14 (% 11.3)		
	Adjuvant	12 (% 9.7)	42.18±9.39**	0.004[6]
	Paliative	2 (% 1.6)	9.58±1.75	
	Absent	110 (% 88.7)	12.85±1.84	
Chemoradyotherapy	Present	7 (% 5.6)	6.93±1.88	0.490
	Absent	117 (% 94.4)	7.70±1.22	
	Total	124 (100.0)	6.97±1.18 (median±SE) 15.93±2.09 (mean±SE)	

*Neuroendocrine tumor; 6(% 4,8), Acinar cell carcinoma; 2 (% 1,6),Spindle cell carcinoma; 1 (% 0,8)

**calculate mean 1 : The difference is due to CEA ⩽ 4 ones. 2 : The difference is between Ca19-9 ⩽400 and >400.

3 :lineer4 : The difference stems from the group undergoing radical operation.

5 : The difference arises from the group receiving adjuvant chemotherapy.

6 : The difference arises from the group receiving adjuvant radiotherapy.

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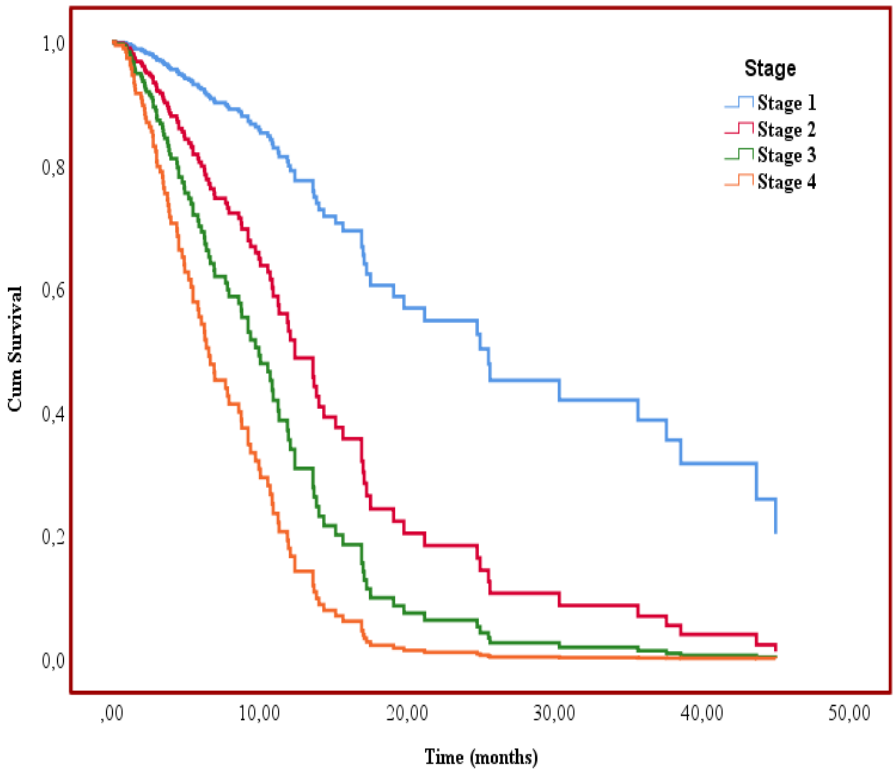

Figure 1. Survival curves according to stages

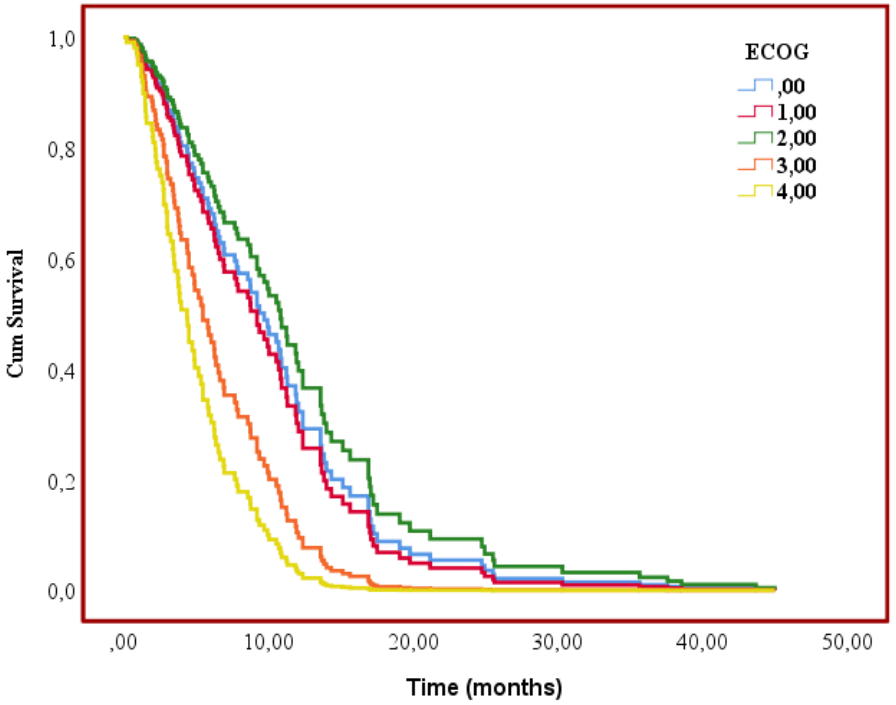

Figure 2. Survival curves according to ECOG performance status

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Univariate Survival Analysis

The median survival was 6.97 (%95 CI:4.663-9.270) months, and the 5-year survival rate was 8%. Mean survival time was 12.96 ± 1.78 months for patients with adenocarcinoma and 53.53 ± 11.17 months for those with non-adenocarcinoma. This difference was statistically significant ($p < 0.001$). Median survival time for those aged ⩾60 years at diagnosis was significantly shorter than that for patients aged <60 years at diagnosis ($p = 0.015$). Gender, history of smoking and alcohol use, symptoms at presentation, and presence of chronic diseases did not significantly affect survival. Patients with an ECOG performance score of >2, CEA values above 4, and Ca 19-9 values above 400 had significantly short median survival time ($p < 0.001$, $p = 0.005$, and $p = 0.001$, respectively). Survival time significantly decreased with advancing stage of the disease ($p < 0.001$). Tumor localization or the presence of single metastasis or multiple metastases did not significantly affect survival time. Patients who underwent radical surgery, received adjuvant chemotherapy, or radiotherapy had significantly long median survival time ($p< 0.001$, $p= 0.001$, and $p= 0.004$, respectively). Chemoradiotherapy had no significant effect on survival (Table 3).

Multivariate Survival Analysis

History of alcohol use (HR: 2.195; 95%CI: 1.036–4.649), an ECOG performance score of >2 (2.763, 95%CI: 1.569–4.866), and Ca 19-9 value over 400 (1.790, 95%CI: 1.134–2.824) were the factors that led to short survival time. Stages 2, 3 and 4 posed 2.034 (95%CI: 0.429–9.643), 3.175 (95%CI: 0.727–13.863), and 6.023 (95%CI: 1.333–27.222) times higher risk of death than stage 1, respectively. In terms of the histopathological subtypes, survival time was shorter for patients with adenocarcinoma (HR: 5.350, 95%CI: 1.775–16.120) than that for patients with other subtypes. Considering the adjuvant chemotherapy group as reference, risk of death was 1.250 (95%CI: 0.684–2.285) times higher for those who received palliative chemotherapy and 2.314 (95%CI: 1.252–4.277) times higher for those who did not receive chemotherapy.

Considering the adjuvant radiotherapy group as reference, risk of death was 1.282 (95%CI: 0.234–7.036) times higher for those who received palliative radiotherapy and 3.506 (95%CI: 1.421–8.651) times higher for those who did not receive radiotherapy (Table 3).

Table 3. Multivariate analysis of overall survival (Cox regression-backward-LR).

	Covariates	Multivariate survival analysis	
		Hazard Ratio (95% CI)	P-value
Alchol History	Absent	1	
	Present	2.195 (1.036-4.649)	**0.040**
ECOG	ECOG 1-2	1	
	ECOG 3-4	2.763 (1.569-4.866)	**<0.001**
Ca 19-9	Ca 19-9 ≤ 400	1	
	Ca 19-9 > 400	1.790 (1.134-2.824)	**0.012**
Stage	Stage 1	1	
	Stage 2	2.034 (0.429-9.643)	0.371
	Stage 3	3.175 (0.727-13.863)	0.124
	Stage 4	6.023 (1.333-27.222)	**0.020**
Histopathological subtype	Other subtype	1	
	Adenocarcinoma	5.350 (1.775-16.120)	**0.003**
Chemotherapy	Adjuvant	1	
	Paliative	1.250 (0.684-2.285)	0.469
	Absent	2.314 (1.252-4.277)	**0.007**
Radiotherapy	Adjuvant	1	
	Paliative	1.282 (0.234-7.036)	0.775
	Absent	3.506 (1.421-8.651)	**0.006**

Discussion

According to 2001–2010 data from Surveillance, Epidemiology and End Results, median survival time for pancreatic cancer is 7 months (10). Similarly, the median survival time was 6.97 ± 1.18 months in the present study. History of alcohol use, Ca 19-9 level, ECOG performance status, disease stage, histopathological subtype of the disease, and whether the patient received chemotherapy or radiotherapy were found to affect survival in patients with pancreatic cancer.

Furthermore, 90% pancreatic cancers are exocrine pancreatic ductal adenocarcinomas (11), and 92.8% patients in our study group had adenocarcinoma. Studies that involve ductal adenocarcinoma cases constitute a considerable part of the pancreatic cancer literature. In the present study, survival times were shorter in patients with adenocarcinoma (HR: 5.350; 95%CI: 1.775–16.120) than in those with other subtypes. The mean survival time was 12.96 ± 1.78 for patients with adenocarcinoma and 53.3 ± 11.17 in the other group.

Because neuroendocrine tumors were also included in the present study, the mean survival time was higher in this group. In a study by Nitschke et al. including exocrine pancreatic cancer cases and comparing ductal adenocarcinoma and other exocrine pancreatic cancers, the risk of death from ductal adenocarcinoma was 2.519-fold high (12).

In the present study, risk of death was 2.195 (95%CI: 1.036–4.649) times higher in patients with a history of alcohol use. Although there are no consistent results regarding the relationship between alcohol use and pancreatic cancer, there are several large-scale studies demonstrating that heavy drinking increases the risk of pancreatic cancer (13,14). Although 6.5% of our patients had a history of alcohol use, there was no information regarding the amount of alcohol consumption in these patients.

Moreover, the patients with ECOG performance scores of >2 had lower survival rates and 2.763-fold (95%CI: 1.569–4.866) increased risk of death. Other studies have shown that ECOG performance status is an important determinant of survival in pancreatic cancer patients, and increased performance score leads to shorter survival (15–17).

In the present study, another prognostic factor was the disease stage. Stage 4 posed 6.023 (95%CI: 1.333–27.222) times higher risk of death than stage 1. A study by Malwinder et al. showed that stage 3 and 4 increased the risk of death by 3.8- and 5.7-fold, respectively, compared to stage 1 (17). Pancreatic cancers have the worst survival rates among all cancers, and one of the most important reasons for this is the fact that most of the patients are already at an advanced stage at diagnosis. Stage 4 patients constituted 54.8% of our study group.

Although the Ca19-9 biomarker cannot be used for the early diagnosis of pancreatic cancer, it is the most commonly used marker to monitor the therapeutic progress (18). Elevated Ca 19-9 values were among the factors that decreased survival time in the present study.

Patients who received adjuvant chemotherapy or radiotherapy had significantly high survival, which is also supported by other studies (19,20). Considering that only 10%–20% patients have resectable pancreatic cancer at diagnosis, radiotherapy and chemotherapy have an important role in the treatment of pancreatic cancers.

Conclusion

In conclusion, the median survival time in pancreatic cancer was found to be 6.97 months. Furthermore, history of alcohol use, Ca 19-9 level, ECOG performance status, disease stage and histopathological subtype of the disease, and whether the patient received chemotherapy or radiotherapy are the factors that affect survival. Knowing the survival rate and the factors affecting survival rate for a cancer will guide physicians in patient management as well as I predicting the prognosis of the disease.

Conflict of interest statement: The authors declare that there is no actual or potential conflict of interest.

Author's contributions: ÖÖ, SDY, HNE, İE, MK; Design of research, data collection and Patient examinations, **ÖÖ;** preparation of article and revisions

Ethical issues: Author declare, originality and ethical approval of research. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits. Approval was received for the study from the Ethics Committee of Liv Hospital Ankara (2019/003-002).

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Hypothyroidism prevalence in pregnant women according to age groups

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Abstract

Objective: Investigation of the thyroid function test (fT3, fT4 and TSH) results and the prevalence of overt/subclinical hypothyroidism according to age groups in patients who had applied to our hospital and diagnosed with pregnancy.

Material and Methods: Two thousand nine hundred and thirty-six women diagnosed with pregnancy for the first time upon seeing the fetal heartbeats with ultrasonography between January 2015 and December 2018, were included in our study. Patients were divided into 5 age groups, namely, the age groups of ≤18 years of age, 19-25 years, 26-35 years, 36-45 years and >45 years of age. The fT3, fT4 and TSH levels were statistically compared between all the patients and age groups.

Results: Two thousand nine hundred and thirty-six pregnant women were included in the study. The mean fT3 value was found as 3.180±0.519 (pg/mL), fT4 value as 1.051±0.258 (ng/dl) and TSH value was found as 2.000±1.595 (mIU/mL) in all the population. The mean fT3, fT4 and TSH values were not statically different among the age groups (p=0.06, p=0.08 and p=0.829, respectively). No statistically significant differences were found among all the age groups as regards hyperthyroidism, euthyroidism, subclinical hypothyroidism and overt hypothyroidism (p=0.200).

Conclusion: Consistently with the previous studies in our country, the prevalence of subclinical hypothyroidism was found as high as 22.7% in our study. We think that scanning for hypothyroidism must be performed in the pregnancy period without discriminating between risk groups in our country, which is located in the iodine deficiency region. However, considering the different age groups, we believe that TSH levels must be measured with the same apprehensiveness for each age group since no statistically significant differences are found between age groups.

Keywords: Pregnancy, Subclinical hypothyroidism, TSH

Introduction

Thyroid hormone is an essential hormone for normal pregnancy physiology. Moreover, it is a critical factor for fetal development. The reason for the increase in thyroxine binding globulin (TGB) and β-HCG levels is the decrease in fT3 (free triiodothyronine), fT4 (free thyroxine) and TSH (Thyroid Stimulating Hormone) levels (1). Due to these physiological changes in thyroid hormone levels observed during the gestation period, it becomes imperative to determine reference intervals for this period. The American Thyroid Association (ATA) has demonstrated thyroid hormone values specified for pregnancy in its published guidelines (2). TSH value must be 2.5 mIU/L or lower during the first trimester of pregnancy, and 3.0 mIU/L or lower during the second and third trimesters. However, the physiologic lower limits, have been determined as 0.1 mIU/L for the first trimester, 0.2 mIU/L for the second trimester, and 0.3 mIU/L for the third trimester.

The frequency of hypothyroidism during pregnancy is 0.3 to 0.5% for overt hypothyroidism, and 2 to 3% for subclinical hypothyroidism (3). Functional disorders of the thyroid especially within the first half of the pregnancy have been associated with increased abortus risk, retardation of intrauterine development, hypertensive disorders, preterm labor and also lower IQ in the newborn (4).

Overt hyperthyroidism is defined as the low fT4 levels together with low levels of TSH. However, subclinical hyperthyroidism is the condition of normal fT4 levels together with low levels of TSH. Hyperthyroidism during pregnancy is a much rare condition as compared to hypothyroidism with a prevalence of about 0.2% (5). An untreated hyperthyroidism during pregnancy has been associated with perinatal complications such as

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preeclampsia, preterm labor, fetal loss and hyperemesis gravidarum (6, 7).

Diagnosis and treatment of functional thyroid disorders in pregnancy in time will allow the prevention of potential maternal and fetal complications. In recent years, the number of adolescent pregnancies has increased with the increasing refugee population in our country. In addition, pregnancies with advanced maternal ages have increased with the frequent use of assisted reproductive techniques. Therefore, we thought that it would be appropriate to evaluate thyroid function tests according to different age groups. In this study, we aimed at evaluating the TSH, fT4 and fT3 levels determined during the first trimester mainly based on different age groups, and to investigate the prevalence of thyroid function disorders during pregnancy.

Material and Methods

This study was planned as a retrospective study in Ankara, University of Health Sciences, Gülhane Education and Research Hospital, Gynecology and Obstetrics Clinic. Approval of the Ethics Committee was obtained for the study (Date:18/12/2018, Decision No:18/327). The study was conducted in accordance with the Helsinki Declaration.

Two thousand nine hundred and thirty-six women who had applied to our hospital between January 2015 and December 2018, diagnosed with pregnancy for the first time upon seeing the fetal heartbeats with ultrasonography and routine pregnancy tests were carried out in the Gynecology and Obstetrics Clinic of our Hospital were included in our study. Patients' data were accessed through the data processing system of our Hospital (Fonet Data Processing Systems). Ages at admission and fT3, fT4 and TSH levels of patients were recorded.

fT3, fT4 and TSH hormone tests were run in the Biochemistry Laboratory of our Hospital using the 10-cc blood samples harvested from the antecubital vein at admission. In these tests, TSH hormone levels were determined using the two-side immune-enzymatic assay (sandwich) method, fT4 hormone was determined using the two-step enzyme immunoassay method, and fT3 hormone was determined using the competitive binding immune-enzymatic assay method with Beckman Coulter DXI-600 immunoassay analyzer (Beckman Coulter, Inc., CA, USA).

According to ATA recommendations, the patients with singleton pregnancy, no history of thyroid pathology or autoimmune disease, no goiters and no use of medicines affecting the thyroid hormone levels were included the study. The exclusion criteria determined as twin pregnancies, women who used thyroid interfering medication before pregnancy or during pregnancy, women who had pre-existing thyroid disease.

With the purpose of comparing the thyroid function tests of patients included in the study between the age groups, patients were divided into 5 groups as <18 years of age, 18-25 years of age, 26-35 years of age, 36-45 years of age and >45 years of age. Levels of fT3, fT4 and TSH were compared among the entire group of patients and among the age groups. According to the World Health Organization (WHO), the adolescent pregnancy period is between 10-18 years old (8); pregnancies at ages older than 35 years are described advanced maternal age (9) and pregnancies at ages older than 45 years are described very advanced maternal age groups (10).

Furthermore, all the above-mentioned age groups were compared with each other as regards hyperthyroidism, euthyroidism, subclinical hypothyroidism and overt hyperthyroidism. TSH range between 0.1 and 2.5 mIU/L was accepted as euthyroidism based on the American Thyroid Association (ATA) guidelines and Turkish Endocrinology and Metabolism Association Guidelines. Pregnant women with TSH levels in the range between 2.5 and 10 mIU/L and fT4 levels in the range of 0.61-1.2 mIU/L, which is the reference range used in our Hospital, were accepted as subclinical hypothyroidism. Patients with TSH levels >10 mIU/L or fT4 levels >1.2 mIU/L were accepted as overt hypothyroidism.

Data were analyzed using the IBM SPSS V23. The one-way variant analysis was used to compare the mean T3, T4 and TSH values based on age groups. Chi-square test was used to analyze the status of TSH levels under 2.5 and over 2.5 according to age groups. Results of the analysis were presented as the mean values and standard deviation for quantitative data, and as frequency (percentage) for categoric data. The level of significance was accepted as $p<0.05$.

Results

Two thousand nine hundred and thirty-six pregnant women were included in the study. The mean age of the pregnant women was 29.09±5.97 (min:13, max:52). The mean fT3 value was 3.180±0.519 (pg/mL), fT4 value was 1.051±0.258 (ng/dl) and TSH value was 2.000±1.595 (mIU/mL) for the entire group. Also, the mean values of fT3, fT4 and TSH were determined for all the age groups. (Table 1, Figure 1)

The mean fT3 value did not differ among the age groups ($p=0.06$). The mean fT3 value in the age group of 45 years of age or older was found lower than the values in age groups of 18 years or younger and the age group between 19 and 25 years of age ($p<0.05$). The mean fT4 values also did not differ among the age groups ($p=0.08$). The mean TSH values did not differ based on age groups ($p=0.829$) (Table 1).

Considering patients diagnosed with subclinical hypothyroidism; when fT4 is within the normal range (0.61-1.2 mIU/L), the rate of the pregnant women with TSH value between 2.5-10.0 mIU/L for the different age groups were; 17.5% for 18 years old or younger (n= 57), 22.4% for those in the age range of 19 and 25 years (n= 829), 22.6% for those in the age range of 26 and 35 years (n= 1596), 24% for those in the age range of 36-44 years (n= 420) and 23.5% for those 45 years of age or older (n= 34); respectively. (Table 2, Figure 2)

Considering patients diagnosed with overt hypothyroidism the rate of the pregnant women with TSH values were >10 (mIU/L) for the different age groups were; 1.75% for 18 years old or younger (n= 57), 2.5% of those in the age range of 19 and 25 years (n= 829), 1.82% of those in the

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age range of 26 and 35 years (n= 1596), 2.1% of those in the age range of 36-44 years (n= 420). (Table 2, Figure 2)

The rate of the pregnant women who has normal TSH values (between 0.1-2.5 mIU/L) called as euthyroidism, in different groups were; 78.9% for 18 years old or younger ages (n= 57), 72.5% for the age range of 19 and 25 years (n= 829), 72.1% for the age range of 26 and 35 years (n= 1596), 71.9% for the age range of 36-44 years (n= 420), 73.5% for 45 years of age or older (n= 34). (Table 2)

Upon evaluation based on TSH levels, it was seen that TSH values were <0.1 mIU/L in 1.75% in the pregnant women 18 years old or younger (n= 57), in 2.5% of those in the age range of 19 and 25 years (n= 829), in 1.82% of those in the age range of 26 and 35 years (n=1596), 2.1% of those in the age range of 36-44 years (n= 420) (hyperthyroidism). (Table 2, Figure 2)

No statistically significant differences were found in all the age groups as regards hyperthyroidism, euthyroidism, subclinical hypothyroidism and overt hypothyroidism. (p=0.200).

Table 1. Comparison of fT3, fT4 and TSH values according to age groups

Age Groups (year)	Age (average ±SD)	T3 (pg/ml)	T4 (ng/dl)	TSH (mIU/l)
≤18 (n=57)	17,3±1,1	3,28±0,529[b]	1,12±0,232[ab]	1,92±1,164
19-25 (n=829)	23,02±1,2	3,29±0,531[b]	1,06±0,252[ab]	2,05±1,438
26-35 (n=1596)	29,85±2,8	3,16±0,495[ab]	1,04±0,262[a]	1,98±1,765
36-44 (n=420)	38,35±2,11	3,06±0,547[ab]	1,07±0,263[ab]	1,97±1,270
≥45 (n=34)	47,7±2,1	2,92±0,384[a]	1,16±0,157[b]	1,84±0,930
Total (n=2936)	29,09±5.97	3,18±0,519	1,05±0,258	2,00±1,595
p*	.	0,06	0,08	0,829

*One Way ANOVA, a-b: There is no difference between age groups with the same letter

Table 2. Comparison of TSH values according to age groups

Age Groups (year)	Hyperthyroidism [α]	Euthyroidism[β]	Subclinical hypothyroidism[¥]	Overt hypothyroidism [µ]	p*
≤18 (n=57)	1 (1,75 %)	45 (78,9%)	10 (17,5%)	1 (1,75%)	
19-25 (n=829)	21 (2,5%)	601 (72,5%)	186 (22,4 %)	21 (2,5%)	
26-35 (n=1596)	29 (1,82%)	1151 (72,1%)	361 (22,6%)	55 (3,4%)	0,200
36-44 (n=420)	9 (2,1%)	302 (71,9%)	101 (24%)	8 (1,9%)	
≥45 (n=34)	-	25 (73,5%)	8 (23,5%)	1 (2,9%)	
Total (n=2936)	60 (2%)	2124 (72,3%)	666 (22,7%)	86 (2,9%)	

[α]: TSH <0,1 (mIU/L, [β]: TSH (0,1- 2,5 (mIU/L)), [¥]: TSH is in the range of 2.5-10 (mIU / L) and fT4 values are within normal limits according to our hospital reference values (0.61-1.2 ng / dl), [µ] TSH> 10 (mIU / L) or fT4 values below the hospital reference values <0.61, *Chi Square test

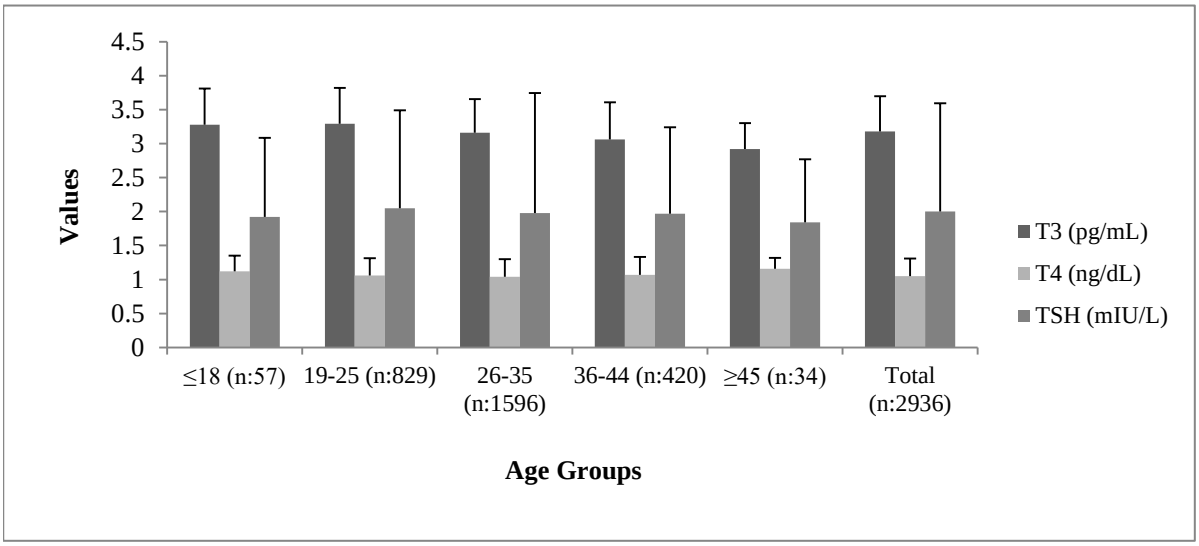

Figure 1. fT3, fT4 and TSH values according to age groups

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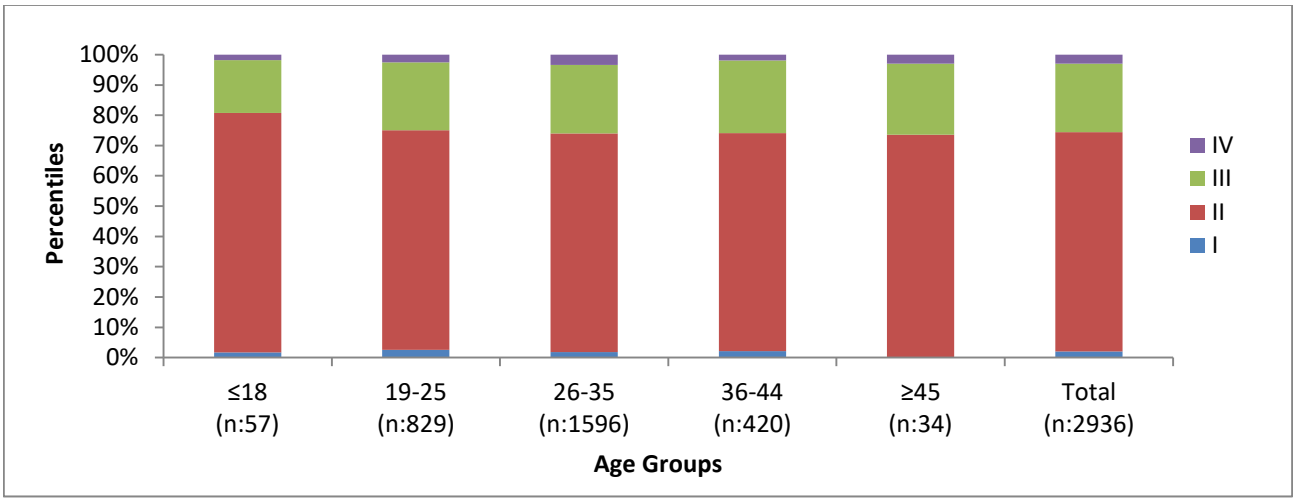

Figure2. Distribution of clinical conditions due to Thyroid values by age groups.
I: Hyperthyroidism, II:Euthyroidism, III:Subclinical hypothyroidism, IV:Overt hypothyroidism

Discussion

In our study, the prevalence of subclinical hypothyroidism in patients admitted to our hospital, which is a tertiary center and diagnosed with pregnancy, was found as high as 22.7%. However, no statistically significant differences were found among the age groups. Thyroid pathologies are the second most common endocrine disease in women of reproductive age, following gestational diabetes mellitus. (5). Fetal and placental development in pregnancy (especially in early pregnancies) are related to maternal thyroid hormones (11). The fetal thyroid gland synthesizes thyroid hormone only after the second half of pregnancy, and therefore, maternal thyroid hormone levels play a critical role in the early periods (12). Even if the signs of thyroid diseases are overt, physiologic changes of pregnancy can mask such signs.

In the current literature, untreated thyroid disorders have been associated with increased maternal and fetal complications from the preconception period till the postpartum period (13). However, Ong et al. did not find any association between functional thyroid disorders and increased complications of pregnancy in the first trimester (14). In addition to overt thyroid disorders, neurodevelopmental outcomes were also investigated in infants born from pregnant women following the administration of subclinical hypothyroidism treatment. In the study of Casey et al, there was no IQ difference between the babies of the pregnant women who were diagnosed and treated with subclinical hypothyroidism and followed up without treatment (15). However, treatment is recommended for subclinical hypothyroidism (5). Since neurocognitive improvement following the treatment of subclinical hypothyroidism has not been clinically proven and also subclinical hypothyroidism incidence is about 2%, American College of Obstetricians and Gynecologists (ACOG) does not recommend routine thyroid scanning during pregnancy (16). However, routine scanning appears more rational based on subclinical hypothyroidism prevalence found as 22.7% and overt hypothyroidism prevalence as 2.9% and considering the conditions of our country, which is a region of iodine deficiency.

The pregnant women are diagnosed as overt hypothyroidism if the TSH values specific for the trimester are increased (TSH >2.5 mIU/ml for the first trimester) and fT4 levels are decreased. In cases where TSH level is >10 mIU/ml, overt hypothyroidism diagnosis is made without regarding the T4 levels. In the patients included in our study, the prevalence of overt hypothyroidism was found as 2.9%. In the study of Güzel et al., overt hypothyroidism prevalence was found as 10.18% (18). However, the number of patients in this study was meager compared to our study. Iodine deficiency is a common condition in our country. Compared to developed countries, we think that the reason for the higher frequency of hypothyroidism in our country is iodine deficiency (19).

In subclinical hypothyroidism cases TSH levels are in the range of 2.5-10 mIU/ml, and fT4 levels are normal. In the patients included in our study, subclinical hypothyroidism prevalence was found at 22.7%. In our country, this rate was found as 15.6% in the study of Güzel et al., and 16.38% in the study of Seven et al. (17, 18). The prevalence of subclinical hypothyroidism in the USA has been reported as 2-2.3% (20). Hypothyroidism prevalence as high as 21.5% had been shown in India previously (6). In the study of Li and colleagues in China, subclinical hypothyroidism prevalence was found as 27.8% (21). Although it has been suggested that the proportional differences in our country are related to the iodine intake varying according to the areas that studies are carried out in, it is also seen that subclinical hypothyroidism prevalence is high consistently with other Asian countries. Together with this, such variable proportions and prevalence found very high depending on the cutoff value for TSH as 2.5 mIU/ml indicates that population-specific values should be determined (22, 23).

In hyperthyroidism cases, TSH levels are <0.1 mIU/ml. In the patients included in our study, hyperthyroidism prevalence was found at 2%. This rate was found as 5.38% in the study of Güzel et al., and 2.47% in the study of Seven et al. in our country (17, 18). We think that the differences in these studies conducted in the same country are caused by regional differences (19).

In a study investigating the relationship between age and thyroid functions, it was found that serum TSH levels increased with the increasing age; however, there are no changes in fT4 levels, and there were no age-dependent increases in thyroid diseases (24). However, in another study investigating the changes in TSH with age, it was shown similarly with the above that TSH levels increased with age; however, taking the TSH >2.5 level as the basis in the advanced age group can lead to erroneous hypothyroidism diagnoses (25).

However, this age-dependent change is especially marked in 50 years of age and afterward, and this corresponds to the end of the reproductive period. In our study, when we compared the different age groups of pregnant women with each other, no statistically significant differences were seen in mean TSH values (p=0.829). No statistically significant differences were found in the comparison of various age groups as regards subclinical hypothyroidism and overt hypothyroidism (p=0.200).

The most important limitation of our study is that it reflects the thyroid function test results in pregnant women coming from a particular area. More comprehensive results can be obtained through analyses carried out on data from different areas.

Conclusion

Subclinical hypothyroidism prevalence was high as 22.7% in our study like in previous studies carried out in our country. We think that hypothyroidism scanning must be performed in the pregnancy period without discriminating between risk groups in our country, which is located in the iodine deficiency region. However, considering the different age groups, no statistically significant differences are found between age groups. We believe that TSH levels must be measured with the same apprehensiveness for each age group.

Conflict of interest statement: The authors declare that there is no actual or potential conflict of interest.

Author's contributions: BÇ*, BÇ, ÖŞK, CŞ, REP, KEK; Design of research, data collection and Patient examinations, **BÇ*;** preparation of article and revisions

Ethical issues: Author declare, originality and ethical approval of research. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

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Circumcision requirement in children with phimosis: immediately or elective?

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Abstract

Objective: Phimosis is define as unretractable prepuce and has two different clinical presentation; pathological (PaP) and physiological. Physiological phimosis (PhP) is a common condition in children that does not require treatment. In our study, we aimed to determine the actual requirement for circumcision in patients with phimosis who were recommended circumcision.

Material and Methods: Children who were offered circumcision due to phimosis between July 2019 and January 2020 and applied to the pediatric surgery and pediatric urology outpatient clinic were included in the study. They were evaluated in terms of referring physicians, genital examination findings and requirement for circumcision.

Results: Between the study dates, 199 patients applied for circumcision due to phimosis. 126 patients are under one year old, 73 patients are over one year old. PhP was present in 194 of the patients and PaP in 5 of them. While PaP is not detected in patients under one year of age, there are 5 patients with PaP over one year of age (2%). There was no requirement for urgent circumcision in any of the patients. Genital examination revealed incidentally undescended testicle in 3 patients and hydrocele in 12 children.

Conclusion: Male genital system examination and pathological findings are not well known by physicians. We think that there is a need for detailed training for physicians regarding PhP and childhood testicle pathologies.

Key words: Physiological phimosis, male circumcision, children

Introduction

Phimosis is a condition in which the prepuce cannot be retracted over the glans penis (1). Prepuce, which is attached to the epithelium of glans penis in the antenatal period, start to detach itself in the 24th antenatal week (2,3). This adhesion and detachment processes also continues through the newborn period. This adhesion is observed in 96% of newborns (3). The slow separation of the two epithelia is completed in 90% of children around the age of 3 with the erection of the penis and with the help of a physiological layer called smegma that is shed from prepuce and the epithelium of glans penis (2,3). Phimosis in infants, which is a completely physiological condition, may be perceived as an obstructive condition and misinterpreted as an indication for emergency circumcision. It is important to distinguish physiological phimosis (PhP), which is most commonly seen in this period, from pathological phimosis (PaP). The distal part of the prepuce is fibrotic during the retraction of the prepuce in PaP, whereas there is no fibrotic tissue in PhP (4).

Circumcision is a surgical procedure. There is an ongoing debate with regards to the circumcision performed in newborns and during the phallic period spanning the ages of three to six years where sexual development takes place. Meatal stenosis and cosmetic problems are the complications that may arise following circumcision in this period. These complications lead to recurrent surgical interventions. Therefore, establishing actual indications for circumcision are important in terms of preventing complications in this period. Additionally, suggesting a surgical intervention for a physiological condition proves stressful for the family. Identifying children with a need for emergency circumcision is important due to these two factors.

This study aims to determine the actual requirement for circumcision in children recommended emergency circumcision due to phimosis during normal follow-up examinations.

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Material and Methods

The study included children with the diagnosis of phimosis who were referred to the pediatric surgery and pediatric urology outpatient clinic between July 2019 and January 2020 for emergency circumcision and excluded children whose examination revealed anatomical problems in the penis.

The records of the children has been reviewed in terms of the type of the application to the hospital (voluntarily or referred by a physician), physical examination findings (penile and testicular evaluation, findings related to other organ systems) and indications for circumcision. The patients who were referred with a pre-diagnosis of urinary tract infection (UTI) and phimosis have been evaluated by urine culture and urinary system ultrasound.

Results

Between the dates of the study, 199 patients applied to the outpatient clinic for circumcision due to phimosis. One hundred twenty six patients were younger than 1 year of age while 73 patients were older than 1 year of age. The mean age of the children was 10,02 months (27 days-4 years).

Twenty seven of these children were brought to the clinic by their families and acquaintances, 98 were referred by their family physicians and 74 were referred by their pediatricians for emergency circumcision due to phimosis.

One hundred ninety four patients had PhP while 5 had PaP (Figure 1 and 2). While PaP was not detected in patients under the age of 1 year, 5 patients were diagnosed with PaP in the group of the patients over 1 year of age (2%). Five children with PaP have been recommended to apply steroid-containing pomade (0.05% betamethasone 2x1) after sitting in a sit bath for 15 minutes. None of these patients required emergency circumcision. One patient with PaP has been elective circumcised as he did not respond to medical treatment.

Genital examination revealed scrotal pathology in 15 (7,5%) patients, incidentally. The identified pathologies were non-palpable testicle in one child and an undescended testicle located in inguinal canal in 2 children. These 3 patients have been operated due to the indication of the undescended testicle. 12 children showed hydrocele and were monitored closely. No surgery was required due to hydrocele during their follow-up period.

Smegma was defined as infection in 25 children and as calcification in 17 children, and the prepuce was retracted for cleaning in 15 children before they were referred to us. Following the diagnosis of balanitis, these children have been treated with sit bath and antibiotic pomade application.

No patient showed problems related to urine output and urine volume. Two patients reported urinary accumulation underneath the circumcised skin accompanied by ballooning. The children who complained of ballooning had PhP. There were no scars. Children with ballooning have been evaluated by urine analysis, urine culture and urinary system ultrasound. Urine analysis and ultrasound results came out normal. Five children with PhP were referred to us with a pre-diagnosis of UTI. Three children who were diagnosed with urinary tract infection during the urine analysis and had findings such as bacteria and leukocyturia have been evaluated by urine culture and urinary system US. None of these children showed bacterial growth in urine culture. No pathological findings related to urinary system have been found in any of the children, which ruled out pre-diagnosis of UTI.

The families of the patients with PhP have been informed about phimosis and smegma. No additional treatments have been administered.

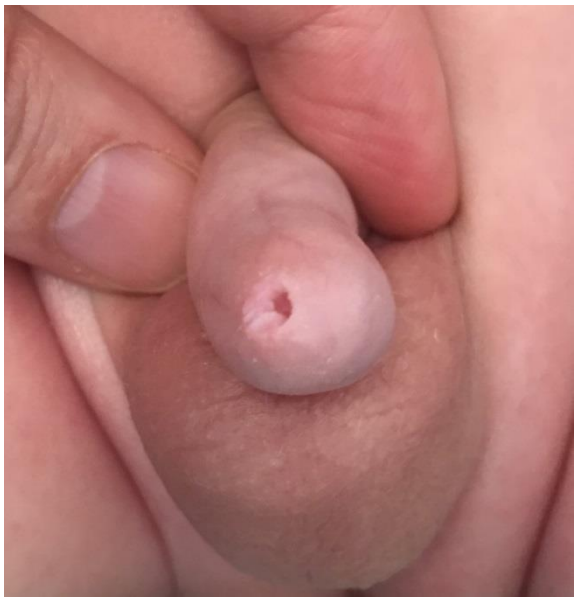

Figure 1: Physiologic Phimosis: distal part of the prepuce is healthy without fibrosis

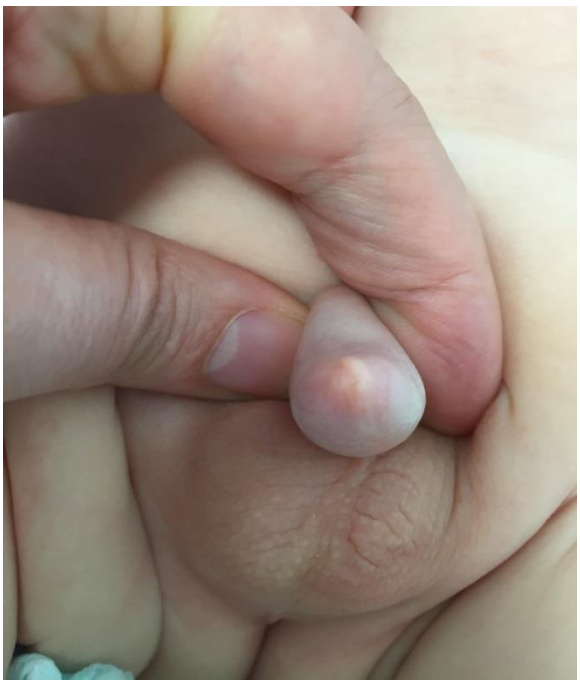

Figure 2: Pathological phimosis: distal part of the prepuce is fibrotic

Discussion

The separation of the prepuce and glans penis, which is seen in early antenatal period, continues after birth. This separation occurs only in 4% of infants in the newborn period and in 90% of them by the time they reach 3 years of age. (3). And phimosis can be seen at an approximate rate of 1% in the adolescence period (5).

PhP refers to the condition where the prepuce shows no scar tissues and cannot be retracted however can be opened like a flower if pulled by force (6). Prepuce may not always open like a flower in the case of PhP. Inability to retract the skin or the absence of scarring is sufficient to establish its diagnosis. In PhP, the distal part of the foreskin is healthy and the narrowed part is proximal to the prepuce. This is different from the PaP, which shows a white and fibrotic distal part when retracted gently and has a conical shape (4). In PaP, the preputial opening when the prepuce is retracted has a fibrotic structure. It is important to distinguish between these two types of phimosis, since the physiological one requires no interventions, while surgical intervention may be required for pathological phimosis. This distinction is not always drawn by the family physicians or pediatricians during the first examination of the children, hence circumcision is recommended to the children with phimosis and they are referred to the pediatric surgery or pediatric urology outpatient clinics.

This causes concern in parents due to the requirement for emergency circumcision. In addition, misinformation may lead to many children being circumcised under inadequate conditions and when it is not medically required. In our study, none of the 126 patients who were referred to us for circumcision under one year of age have been found to be requirement of emergency circumcision. Examination of these children revealed PhP. Sixty eight of the patients with phimosis over 1 year of age who were referred to us for circumcision have been reported to be PhP and 5 have been reported to be PaP. Five patients with PaP have been treated with sit bath and steroid pomade. In the study by Golubovic et al.(7), 19 of 20 children with pathological phimosis treated with steroids recovered. However, only 4 of 20 children treated with petroleum jelly recovered (7). Therefore, 0.05% betamethasone twice daily for 4 weeks was recommended for the medical treatment of PaP (7,8,9). In our study, recovery has been observed in 4 of 5 children with PaP. Only one child required circumcision as almost the whole prepuce was fibrotic, and glans penis and penile skin were oedematous. PaP incidence is 0.4 per 1000 men per year. This is much less common than PhP, which is commonly seen in young children and decreases with age (10). Based on this incidence, it is seen that the number of patients who are referred with the diagnosis of phimosis is very high. In our study, when full genital examination was performed, scrotal pathology revealed in 15(7,5%) patients, incidentally. Three. patients had undescended testicles and 12 patients had hydrocele. Patients with undescended testicle underwent surgery, patients with hydrocele didn't need to surgery. A gentle retraction of the skin is important for diagnosis in phimosis examination. Especially in children younger than one year of age, forcible retraction of the prepuce may result in fissures and bleeding of the prepuce, and these may turn into scarring and pathological phimosis later on (1). Therefore, retraction should not be performed in infants with PhP. This is sometimes a traditional behaviour and sometimes a wrong practice applied by physicians. This process is sometimes applied in a very traumatizing manner in order to remove the smegma. Smegma is misdiagnosed for an infection or calcification by physicians during an attempt for cleaning, who then recommend circumcision. The glands in the prepuce and glans penis produce secretions that help moisturize and defend against infections. Lysozyme in these secretions acts against harmful microorganisms (11,12). Smegma is seen when these secretions from the glans and prepuce accumulate in the epithelium. These are also known as prepuce pearls (1). Smegma, which is a completely physiological accumulation, is misinterpreted during physiological phimosis and traumatizing procedures are applied to remove it. Traumatizing procedures lead to fissures, haemorrhage, and scarring in the recovery period and also result in pathological phimosis.

Smegma was previously defined as infection in 25 children and calcification in 17 children in our study, and 15 prepuces were retracted for cleaning before patients were referred to our outpatient clinic for circumcision. Such an attempt to treat a physiological condition may cause infection and PaP, followed by an unnecessarily painful intervention for the child. In our study, patients who had developed balanitis and oedema due to the retraction of the prepuce did not develop PaP after sit bath and antibiotic pomade treatment. In addition, among the patients with phimosis, urinary tract infection could not be confirmed in any of the patients referred to us with UTI. None of these patients required circumcision.

In the study by Babu et al.(13), post-void residues of patients with PhP who developed ballooning underneath prepuce and of patients with physiological phimosis who did not develop ballooning were evaluated by uroflowmetry and ultrasonography, and no differences were found between them. As a result of this study, it can be said that there is no require for emergency circumcision based on urinary system findings in ballooning accompanying PhP. Similarly, in our study, urinary analyses and urinary ultrasounds of 2 patients who developed ballooning were normal. Emergency circumcision indication was not considered.

Interventions to smegma and PhP, which is a completely physiological condition, and circumcision recommendations suggest that there is a misinformation both within the society and amongst family physicians and pediatricians. Additionally, testicular pathologies not previously detected reveal inadequacies in full genital examination practices.

Conclusion

PhP is a physiological condition that does not require circumcision. Physicians do not have a very good command of male genital system examinations and pathological findings. In-service trainings can be organized for physicians on PhP and childhood testicular pathologies.

Conflict of interest statement: The authors declare that there is no actual or potential conflict of interest.

Author's contributions: SS, EAK; Design of research, data collection and Patient examinations, and Surger **SS*;** preparation of article and revisions

Ethical issues: All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standarts.

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