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Morphometric Analysis of the Ameliorative Potential of Melatonin on Gentamicin-Induced Renal Corpuscle Changes in Rats

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Abstract

Gentamicin is a widely used aminoglycoside antibiotic, but its use is limited by its nephrotoxicity. Oxidative stress and inflammation, closely linked, are considered as key factors in the pathogenesis of gentamicin nephrotoxicity. Melatonin is a potent antioxidant and anti-inflammatory agent and may be used in the prevention of development of gentamicin-associated acute kidney injury. Besides proximal tubules that are the main affected structures, gentamicin also damages glomerular and interstitial compartments. Our aim was to determine the potential protective effect of melatonin on renal corpuscle changes induced by gentamicin. Twenty-four adults male Wistar rats were divided into three groups of eight rats. The G group was treated daily with gentamicin (80 mg/kg) during eight days. The GM group of rats was administered daily gentamicin (80 mg/kg) and melatonin (20 mg/kg) starting three days before and eight days simultaneously with gentamicin. The control group received 5% ethanol in Ringer solution for 11 days. Glomerular area, glomerular diameter and Bowman's space width were measured using morphometry. Thickness of glomerular basement membrane and Bowman's capsule parietal layer basement membrane were semi quantitatively determined. Gentamicin caused glomerular enlargement and hyperemia, Bowman's space expansion, and thickening of the glomerular and Bowman's capsule basement membranes. In the GM group, the glomeruli were slightly enlarged with mild thickening of the glomerular basement membrane. The results of the present study suggest that melatonin exerts protective effects on the renal corpuscle alterations induced by gentamicin.

Key words: *gentamicin, melatonin, renal corpuscle.*

Introduction

Aminoglycosides are potent, broad-spectrum antibotics used worldwide in the treatment of serious gram-negative infections (1,2). However, despite excellent activity and low resistance, their use is limited due to potentially serious dose-dependent treatment-limiting adverse effects, mainly nephrotoxicity and ototoxicity (2,3,4). Gentamicin is one of the most nephrotoxic aminoglycosides, but it is still widely used as a first and second choice in different clinical situations (3). Since gentamicin is only bacteriostatic at low concentrations, it is often necessary to use high doses (5). About 10% of the parenterally administered dose accumulates in the renal cortex (6). Oxidative stress and inflammation are the central mechanisms of gentamicin-induced nephrotoxicity. Up to 25% of treated patients develop aminoglycoside-induced nephrotoxicity despite attentive monitoring and follow-up (3,4). Thus, it is necessary to find innovative ways to prevent or reduce the development of renal morpho-functional alterations associated with gentamicin-use. Although proximal tubules are the principal site of gentamicin-induced renal cell toxicity, other structures, such as the renal corpuscles and interstitium are also affected (3,7,8).

Melatonin is a hormone produced by the pineal gland. Besides its role in the regulation of circadian rhythms, it exerts a variety of other functions such as blood pressure regulation, immunomodulation (9,10), and antioxidant and antiapoptotic effects (9). Its antioxidant effects are based on its ability to scavenge free radicals and reactive oxygen and nitrogen species and to stabilize antioxidant enzymes in different tissues. It suppresses the activity of nuclear factor kappa-B by preventing its translocation to the nucleus and binding to DNA with subsequent

decrease in the upregulation of pro-inflammatory cytokines (9,11). Additionally, it downregulates the expression of inflammation-derived inflammatory enzymes, e.g. 5-lipoxygenase. Additionally, since it inhibits the production of leukocyte adhesion molecules, it is able to reduce leukocyte migration and suppress edema formation (11). Beneficial therapeutic effects of melatonin have been reported in different diseases and disorders, e.g. cardiovascular diseases (9), certain tumors (9,11) and drug-associated toxicities (12,13).

The aim of this study was to evaluate the effect of melatonin on gentamicin induced renal corpuscle changes.

Material and Methods

Animals

Twenty-four adults male Wistar rats, weighing 200-300g, were maintained in standardized laboratory conditions with a temperature of 23 ± 2°C, and a 12-hour light-dark cycle. Both standard rat chow and water were provided ad libitum. The study was carried out at the Faculty of Medicine of the University of Sarajevo, with the approval of the local ethics committee.

Experimental protocol

The rats were randomly assigned into three groups of eight animals which all received one of the following daily intraperitoneal injections: group 1 (Control), animals that received vehicle (5% ethanol in Ringer solution) during 11 days, group 2 (G), rats that received gentamicin (80 mg/kg) during 8 days, and group 3 (GM), rats that received gentamicin (80 mg/kg) during 8 days and melatonin (20 mg/kg) 3 days before and 8 days concomitantly with gentamicin. The animals were sacrificed under ether anesthesia 24 hours after the last injection.

Qualitative histological analysis

Left kidneys were removed, fixed in 10% buffered formalin, dehydrated in graded alcohols, and embedded in paraffin. The specimens were subsequently sectioned at a thickness of 5 micrometers and stained using hematoxylin-eosin (H&E) and periodic acid - Schiff (PAS) according to standard staining protocols. The qualitative histological analysis included the cortical structures, with the accent on the renal corpuscles at the level of light microscopy.

Semiquantitative analysis

The thickness of the glomerular basement membrane and the basement membrane of the parietal layer of the Bowman's capsule were assessed in 4 grades using a modification of a previously described method (14).

Morphometric analysis

Morphometric analysis was performed using Ellipse3D software (version 2.0.8.1) and ImageJ software (version 1.8.0). Spatial calibration was performed before each analysis (7). Morphometric parameters measured during the analysis were glomerular area (μm^2), glomerular diameter (μm), and Bowman's space width (μm). In each animal at least 40 glomeruli were measured.

Statistical analysis

The data obtained from the morphometric measurements are presented as mean ± standard deviation. The comparison between groups was performed using one-way ANOVA and post-hoc Tukey test. Probability values (p) less than 0.05 were considered to be statistically significant.

Results

Qualitative histological analysis

Control group of rats

The kidney microarchitecture of the control group of rats showed no histological alterations (Figure 1 A and B).

G group of rats

In this group of animals, enlargement of glomeruli and thickening of the glomerular basement membrane were observed. The glomerular tufts showed occasionally increased lobulation, while the capillaries were dilated and hyperemic. The urinary spaces were increased. Also, the epithelium

of the parietal layer of the Bowman's capsule was sporadically taller, and its basement membrane was irregularly thickened. The glomeruli were surrounded by diffusely and severely altered proximal tubules showing cell degeneration and necrosis. The interstitium was edematous and infiltrated with mononuclear cells (Figure 1 C and D).

GM group of rats

Glomeruli were only slightly enlarged in the GM goup of rats. Thickening of the glomerular basement membrane was observed in some parts of the glomeruli. Tubular degeneration and necrosis were found to a mild to moderate extent in the proximal tubules (Figure 1 E and F).

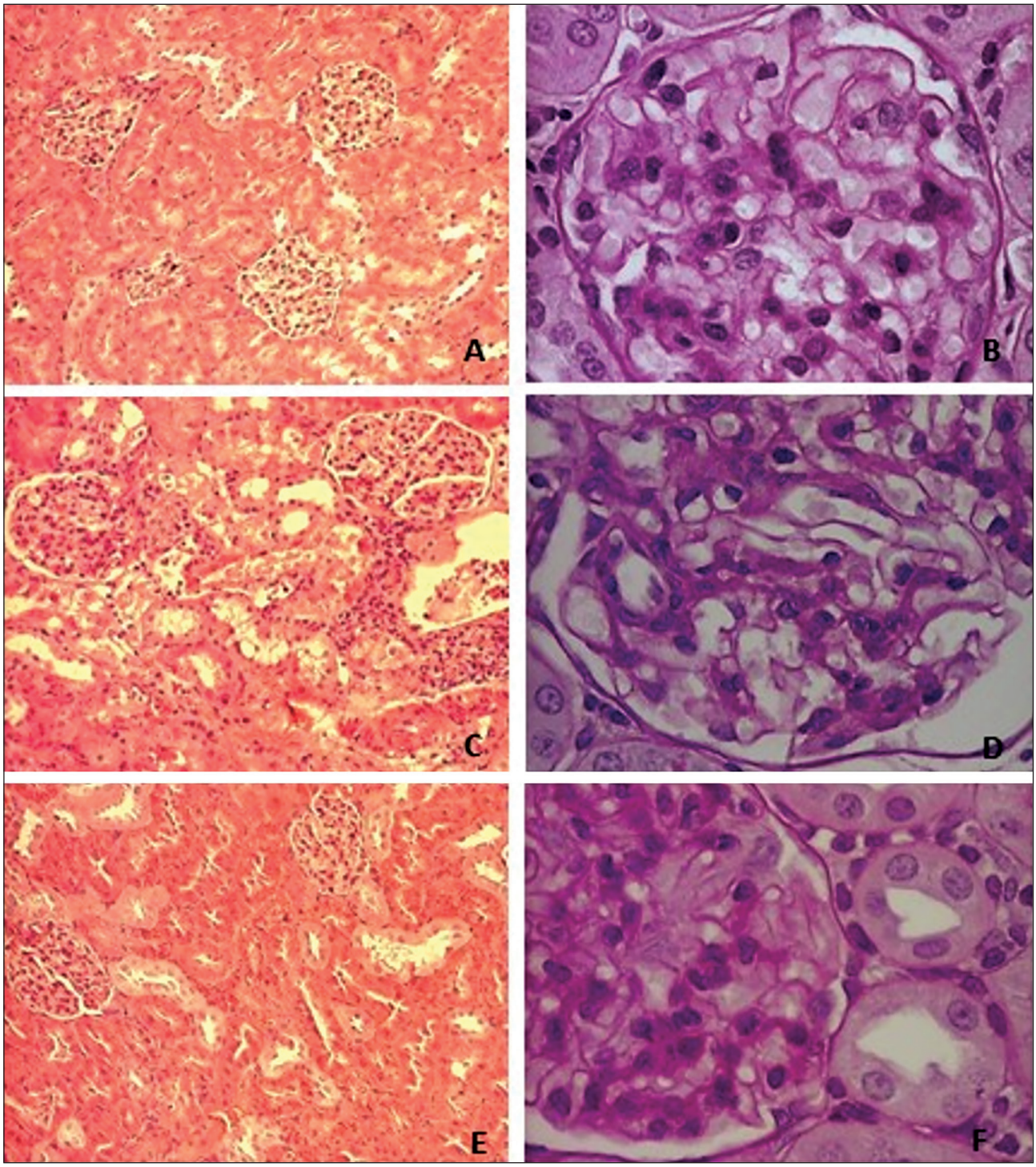

Figure 1. Histological features of the kidneys in the control and experimental groups

A) Control group, H&E, 100x; B) Control group, PAS, 400x; C) Gentamicin group, H&E, 100x; D) Gentamicin group, PAS, 400x; E) GM group, H&E, 100x; F) GM group, PAS, 400x

Semiquantitative analysis

The glomerular basement membrane was thickened in the G group of rats (62.5% of animals showed grade 2; 37.5% of animals grade 3). In the GM group, 50% of animals showed grade 2 and 50% grade 1 (Table 1).

Table 1. Semi quantitatively graded glomerular basement membrane thickness on PAS-stained sections

Group	Grade 0	Grade 1	Grade 2	Grade 3
Control	8 (100%)	-	-	-
G	-	-	5 (62.5%)	3 (37.5%)
GM	-	4 (50%)	4 (50%)	-

The semiquantitative analysis of the thickness of the Bowman's capsule parietal layer basement membrane in the G group of rats showed that half of animals presented grade 2 and the other half grade 1. In the GM group only 25% of animals showed some signs of thickening (Table 2).

Table 2. Semi quantitatively graded Bowman's capsule parietal layer basement membrane thickness on PAS-stained sections

Group	Grade 0	Grade 1	Grade 2	Grade 3
Control	8 (100%)	-	-	-
G	-	4 (50%)	4 (50%)	-
GM	6 (75%)	2 (25%)	-	-

Morphometric analysis

Morphometric analysis of the renal corpuscle showed statistically significant differences between the experimental group of rats treated only with gentamicin and the control group for all observed parameters. The glomerular diameter was statistically significantly increased in the GM group of rats in comparison to the control group, but decreased in comparison to the G group. No significant differences were found between the GM and the control group for Bowman's space width and glomerular area (Table 3).

Discussion

The strong bactericidal activity of gentamicin makes it a widely used antibiotic in the treatment of gram-negative infections. However, its potentially toxic adverse effects, most commonly nephrotoxicity and ototoxicity, hinder its use (3,15). In the kidneys, gentamicin distinctively accumulates and causes damage in the proximal tubules. Nevertheless, data obtained from previous studies show that besides tubular structures, changes of glomeruli are also observed (3,7,8). Although the exact mechanisms of pathogenic action of gentamicin are not elucidated yet, oxidative stress and inflammation are considered as the main culprits (4,15). In that context, it is important to explore new possible therapeutic options to reduce renal damage. Thus, our aim was to test the protective potential of melatonin that has not only direct and indirect antioxidant, but also anti-inflammatory actions (9). It was shown that melatonin is more potent in reducing oxidative damage than other well-known antioxidants, such as vitamin E or C (16), and its protective effect has been demonstrated in different conditions (17).

We have used a well-known model and administered supratherapeutic doses of gentamicin (80 mg/kg) to induce acute kidney injury (18). Although the beneficial effects of melatonin were under observations of previous studies of gentamicin-induced nephrotoxicity (18,19), none of them was focused on determining the quantitative histological changes of the renal corpuscles, which was the goal of our morphometric analysis.

The rats treated only with gentamicin showed enlarged glomeruli with dilated and hyperemic capillaries. The morphometric analysis confirmed and strongly correlated with the results obtained by the qualitative histological analysis. Glomerular area and diameter were significantly larger in this group of animals than in the control group. Significant dilatation of the urinary spaces was also ob-

Table 3. Renal corpuscle morphometric parameters

Parameter	Control group	G group	GM group
Glomerular area (μm^2)	8597±1060	13661±2020***	10011±1987##
Glomerular diameter (μm)	102.1±7.24	131.0±11.17***	115.6±12.84*#
Bowman's space width (μm)	6.13±0.94	11.6±1.68***	7.99±2.02###

*Data are presented as mean ± SD; *P<0.05 vs. control, **p<0.01 vs. control, ***p<0.001 vs. control, #p<0.05 vs. G group, ##p<0.01 vs. G group, ###p<0.001 vs. G group*

served. The increased diameter of the glomerular tuft and the urinary space width might be the result of glomerular hyperfiltration (20), but they could also be the consequence of the morpho-functional changes of the glomerular basement membrane and the proximal tubule epithelium (21). Our semi-quantitative analysis revealed that the glomerular basement membrane was thickened in the G group of rats (grade 2 and 3). An increase in thickness was also observed for the basement membrane of the parietal layer of the Bowman's capsule (grade 1 and 2). There was an accentuated lobulation of the glomerular capillary tufts in the gentamicin group of rats. We suppose that this is a consequence of an increase in mesangial cells and/or matrix (22). Previous research has already shown that gentamicin, via intracellular calcium increase, induces proliferation of mesangial cells (23).

Also, severe alterations of the tubulointerstitial structures, surrounding the renal corpuscles, in form of degeneration and necrosis of proximal tubular cells followed by edema and mononuclear cell infiltration of the interstitium were observed. Our histological findings concerning the glomerular, tubular, and interstitial changes are mainly in accordance with those observed by other authors (3,7,24). In our study, animals injected with gentamicin and melatonin had a better-preserved kidney morphology with milder changes in comparison to the animals administered only with gentamicin. The glomeruli were slightly enlarged and the glomerular basement membrane was thickened to a lesser extent than the one in the rats treated only with gentamicin. Previous research has shown that treatment with gentamicin increases the production of reactive oxygen species (ROS) (3,15,25). Low levels of ROS exert several physiological functions, e.g. regulation of vascular tone by NO, but large amounts of ROS may also be the source of possible oxidative damage (26). Additionally, ROS are involved in inflammatory signaling pathways. Oxidative stress and inflammation form a loop of damage amplification in the pathogenesis of aminoglycoside-induced nephrotoxicity. Although the inflammatory response starts as a defense mechanism, it finally results in further progression of renal structures injury (3). The beneficial effect of melatonin might be contributed to both its antioxidant and anti-inflammatory actions. Melatonin acts as a direct ROS scavenger and increases the levels of antioxidant enzymes (9). It also dose-dependently decreases TNF-alpha and IL-beta 1 (27) that are involved in the proliferation of mesangial cells and matrix in gentamicin-induced renal injury (28).

Conclusion

Our findings show a clear nephrotoxic effect of gentamicin on the renal corpuscle structures, but also a beneficial effect of the concomitant administration of melatonin on these histological changes. The obtained results indicate that melatonin is a potentially potent substance in the prevention and treatment of renal corpuscle alterations induced by gentamicin and might be used as a supplement in patients that require high doses and/or prolonged treatment with gentamicin.

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The accessory infraorbital foramen (AIOF) - frequency, topography, size, shape and distance to the neighboring structures

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Abstract

The accessory infraorbital foramen (AIOF) is an anatomical variation associated with the infraorbital foramen (IOF) and nerve (ION). The study of the location of IOF and knowledge of its anatomical variations are important in local anaesthetic procedures such as blockage of the infraorbital nerve, in the treatment of the trigeminal neuralgia, and in maxillofacial surgeries. The aim of the present study was to analyze the anatomical and morphometric variation in shape, frequency of occurrence, direction, and position of accessory infraorbital foramen (AIOF) in relation to the neighboring structures in human dry skulls.

The IOF is an important anatomical landmark in these surgical manipulations. Because there is limited literature available on AIOF, which transmits accessory branch of the infraorbital nerve, the present study was designed. In this study, 55 human dry skulls have been used of known age and sex. With a vernier caliper the distances between the accessory infraorbital foramen (AIOF) and anterior nasal spine (ANS), frontomaxillary suture (FMS), infraorbital margin (IOM), infraorbital foramen (IOF), and zygomaticomaxillary suture (ZMS) were measured. The transverse (TD) and vertical diameter (VD) of foramen was also noted. The result of our study reveals that the presence of AIOF is more on the right side compared with the left side.

The results may provide guidance to the maxillofacial surgeons and anesthesiologists to localize accessory infraorbital foramen and so contribute to better outcome of diagnostic or therapeutic procedures.

Key words: *Accessory infraorbital foramen, skull, maxilla.*

Introduction

The infraorbital nerve is a direct extension of the maxillary division of the trigeminal nerve . It courses anteriorly through a canal within the bone of the orbital floor and provides superior alveolar nerves for the sensory innervations of the maxillary teeth. The infraorbital nerve then emerges from the infraorbital foramen and gives four branches, the inferior palpebral, the external nasal, the internal nasal and the superior labial branches for the sensory innervation to the skin of the eyelid, nose, cheek and upper lip. Infraorbital foramen is usually a single foramen but several studies have proven to have two or three foramen (1, 2, 3, 4, 5, 6, 7)

Locating the ION can be difficult and the presence of a double foramina is important when planning surgery and/or local anesthesia in the maxillofacial region. When a clinician performs ION block, nerve blocks may not provide adequate analgesia if an AION is present. It is obvious that the presence of extra branches of the nerve can result in possible iatrogenic morbidity during facial surgery, and so a surgeon should be aware of and consider this anatomic variation.

Several studies have documented the location of the AION with reference to several deep bony landmarks such as the frontomaxillary suture, zygomaticomaxillary suture, and anterior nasal spine (8,9).

The knowledge of anatomical features of IOF is essential for the dealing with maxillary region such as surgeries for fractures of zygoma and intraoral and extraoral anesthesia (10,11,12). Accessory foramina may give complications during anesthetization of the region (13). A major factor that inhibits dentists from using the infraorbital nerve block is the fear of injury to the parint s eye (14).

The presence of accessory IOF (AIOF) in the surrounding area of the infraorbital region have been reported by several authors (15,16,17).

Despite its clinical significance, very limited literature is available concerning the morphological details and the location of the AIOF in human dry skulls. Hence, the aim of this study was to elucidate the frequency, shape, dimensions, orientation, and position of AIOF in relation to the neighboring structures to provide convenience to clinical applications.

Materials and methods

A total of 55 adult dry skulls of known age and sex were collected from the Department of Anatomy, Medical faculty, University of Sarajevo and were used for anatomical and morphometric study. Both sides of the skulls were examined and the number, shape, size, and orientation of the AIOF were recorded by direct visual inspection. The shape of the AIOF was identified having an oval, semilunar, or a circular outline. The direction of opening of the accessory infraorbital canal through the anterior surface of the maxilla was recorded using a probe.

The skulls were first placed in the anatomical position before the measurement were taken. The distance of the AIOF from anterior nasal spine (ANS), frontomaxillary suture (FMS), infraorbital foramen (IOF), infraorbital margin (IOM), and from zygomaticomaxillary suture (ZMS) were measured using digital vernier calipers to the nearest 0.01 mm (Mitutoyo Corporation, Japan) The greatest transverse (TD) and vertical diameters (VD) were also noted.

Statistical analysis

The data was summarized with SPSS 21.0 using descriptive statistics of mean, standard deviation and frequency, and analysed using students t-test analysis. Level of significance was set at $p < 0.05$.

Result

Among the 55 skulls (110 sides) the frequency of AIOF is observed as 11.8% (13/110), of which 69.2% (9/13) were present on right side, 7.7% (1/13) were on the left side, and 23.1% (3/13) were located bilaterally. Location of AIOF with respect to IOF when evaluated showed that 89.3% of them were superomedial and 10.7% were just medial to IOF.

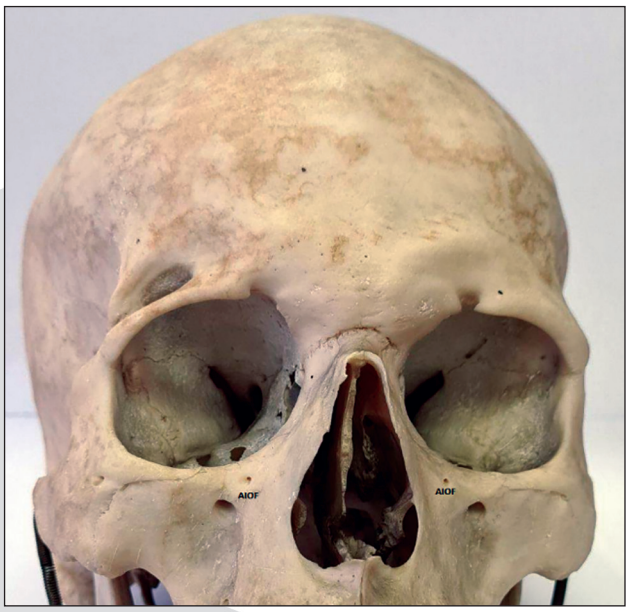

Figure 1. Superomedial location of accessory infraorbital foramen (AIOF) on right and left side of skull

When the assessment of shape of foramen was done, it was observed that 47.6% were oval (of which 42% were located on the right side and 44% on the left), 23.2% were circular (of which 52% were on the right and 40% were on the left) and the rest 29.2% were semilunar (of which 46% were on the right and 10% were on the left) (Table 1).

Table 1. Shape of the accessory infraorbital foramen (AIOF) on the right and left sides of the crania (%)

Shape	Right%	Left%
Oval	42	44
Circular	52	46
Semilunar	6	10

The direction of foramen was highly variable, 31% were directed downward, 14.3% were directed backward, 8% were upward, 14.3% were directed medially, 18% of foramen were directed backward and downward, and 14.4% were upward and backward.

Measurements of distance between AIOF to anatomical landmarks (Figure 2) and transverse and vertical diameter of foramen are summarized in Table 2.

Table 2. Distances from AIOF to anatomical landmarks

Dimensions	Mean±SD (mm)		P value	Median		Range	
	Rt	Lt		Rt	Lt	Rt	Lt
AIOF - ANS	26.41 ±1.35	27.64±2.53	0.57	27.63	27.84	19.84-30.54	25.52-29.86
AIOF - FMS	26.36±4.13	23.23±3.52	0.24	26.59	21.64	22.60-32.61	18.86-26.72
AIOF - IOM	5.15±1.59	5.68±3.50	0.18	5.44	5.77	1.89-6.32	3.25-8.93
AIOF - IOF	10.06±4.57	10.89±2.67	0.27	11.11	11.48	2.61-14.37	7.91-13.60
AIOF - ZMS	23.7±5.49	27.11±5.64	0.36	25.53	25.05	13.04-29.92	21.47-33.96
TD of AIOF	2.35±1.03	3.82±1.26	0.33	2.53	3.62	1.28-4.01	1.77-4.58
VD of AIOF	2.22±0.8	2.35±0.47	0.69	2.51	2.55	1.04-3.51	1.23-3.27

ANS - anterior nasal spine, FMS - frontomaxillary suture, IOF - infraorbital foramen, IOM- infraorbital margin, ZMS - zygomaticomaxillary suture, TD- transversal diameter, VD- vertical diameter, Rt-right, Lt-left

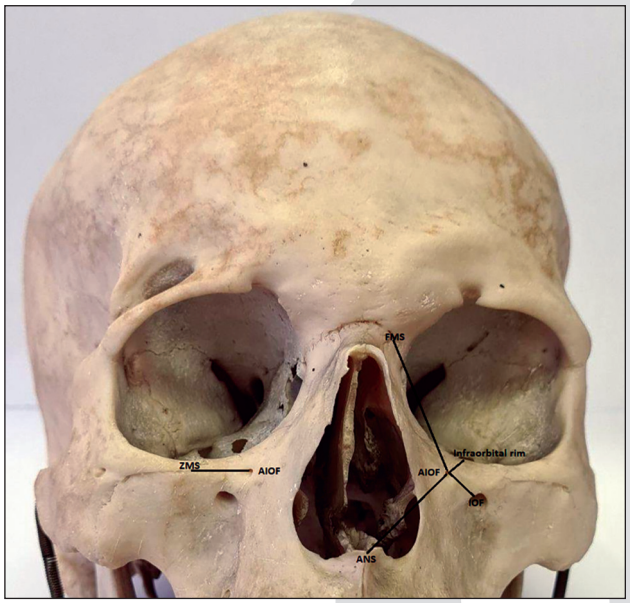

Figure 2. Distance between AIOF to anatomical landmarks

Discussion

Reviewing the literature suggests mixed results as to frequency of occurrence of accessory infraorbital foramen (9, 18). The highest frequencies approaching 40% were reported in the South Chinese and in the Micronesian samples. In western Europe, German samples showed the highest frequency (32%), (6). Recent studies performed in skulls and cadaver heads have documented much lower frequencies of AIOF ranging between 1.3% and 20% (9, 18, 19, 20).

In a previous study, AIOF was found in 11.8%, of which 69.2% were present on right side, 7.7% were on the left side, and 23.1% were located bilaterally. Bressan et al. reported a higher incidence of AIOF on the left, and Rai et al. on the right (5, 9).

Only two studies have evaluated the size of AIOF and/or the distances from AIOF to the surrounding landmarks, and studies correlating the morphologic and morphometric data of AIOF with those of IOF are lacking (5,9).

The location of the accessory infraorbital foramen (AIOF) has been reported with higher frequency to be either superomedial or medial to the infraorbital foramen and less frequently inferomedial (9, 22).

Saylam et al. reported the localization of AIOF as 79.6% superomedial to IOF, which was similar to a study documented by Boopathi et al. (15, 17). Whereas Tezer et al, in their study, found that 93.3% of AIOF were located superomedial to IOF and 6.7% were inferomedial (8). We found a similar result as that of Tezer et al, showing 89.3% of them placed superomedial and 10.7% inferomedial to IOF (8).

The shape of the AIOF as reported by Tezer et al. was round in 53.3%, and oval in 46.7% (8). According to Gour et al, most AIOF were round (23). In our study, 47.6% were oval, 23.2% were circular and the rest 29,2% were semilunar.

Despite its clinical significance, very limited literature is available concerning the morphological details and the location of the AIOF in cadaveric dry skulls. Hence, the aim of this study was to elucidate the frequency, shape, dimensions, orientation, and position of AIOF in relation to the IOF and surrounding landmarks to provide convenience to clinical applications.

The present study provides a great deal of information on the detailed morphometry and position of the AIOF in dry cadaveric skulls.

For precise localization of foramen, distance from AIOF to ANS, to FMS, to IOF, to IOM, and to ZMS was taken into consideration in our study.

Measurements showed that the AIOF is located at a greater distance from the above anatomical landmarks on the left than on the right except for the distance of the AIOF from the frontomaxillary suture (FMS) where a greater distance was recorded on the right.

Our study also showed that the mean (SD) transverse and vertical diameter of foramen was higher on the left side when compared with that on the right side.

Conclusion

Knowledge about the anatomical and morphometric characteristics of the frequency, location, shape, direction, distances, and diameter 5 of AIOF may have important implications in blocking the accessory branch of the infraorbital nerve for surgical and local anesthetic planning. Hence, awareness of location of AIOF is very essential to surgeons and anesthetists for various diagnostic and therapeutic oral and maxillofacial surgical procedures.

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Characteristics of primary tumor, age, and gender in relapse of superficial bladder cancer

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Abstract

Introduction: Approximately 70% of patients with superficial bladder cancer develop relapses. Risk factors of relapse are sex and age of the patients, and the characteristics of the primary tumor (grade, stage, number of tumors and tumor localization). Aims are to prove that the characteristics of the primary tumor: number, localization and tumor grade with age and gender of the patient have an impact on the time of the first relapse.

Subjects and methods: This study includes 77 patients that were treated in the Department of Urology of the University Clinical Centre of Sarajevo. It is a cross-sectional, clinical study based on data from the history of the patient's disease treated in this clinic during the past four years. It was used the regression model created in PASW Statistics 18 software with backward linear regression method.

Results: There are differences ($p<0.05$) between gender, age, grade and the localization of the tumor in relation with the time of the first relapse. Relapse approximately occurs 2 years earlier in patients with high grade tumors, 5 years earlier in patients with cardiovascular comorbidity, and approximately 4 months earlier in patients with multiple primary tumors.

Conclusions: Older age, male gender, multiplicity of tumor, high grade and localization of the primary tumor together with cardiovascular comorbidities significantly influence the earlier occurrence of the first relapse.

Key words: *relapse, bladder cancer, risk factors.*

Introduction

About 90% of bladder cancers are cancers of the transitional epithelium (urothelium), or the so-called transitional cell carcinoma (TCC), while squamous cell carcinoma is much less prevalent, accounting for about 5% of all tumors, and the rarest adenocarcinoma with prevalence of only 2%. More than 70% of patients with TCC have a tumor limited to the mucosa and submucosa, the so-called superficial or, as defined in the recent literature, „Non-Muscle Invasive Bladder cancer – NIMBC", which specifies the nature of the tumor. (1) The term superficial bladder cancer includes a heterogeneous group of tumors that involves: only the mucosa (Ta), squamous tumors limited to the epithelium (Tis), and superficially invasive carcinomas that penetrate the lamina propria or submucosa (T1). (2) As many as 70% of patients diagnosed with superficial carcinoma develop relapses, while 10-30% progresses to muscle invasive cancer. Most relapses occur over a period of up to 5 years. (3) The most common symptom of bladder cancer is painless intermittent hematuria that occurs in 85% of patients.

Bladder cancer is the most common malignant disease of the urinary tract, affecting about 400,000 people worldwide each year. (4) The incidence of bladder cancer in Europe and the United States is 20 per 100,000, with 5 deaths per 100,000 each year. (5) In men, it is the fourth most common type, after prostate, lung and colorectal cancer with an incidence rate of 6.8% of all cancers, while in women it is in ninth place in frequency with a share of 2.4% of all cancers. (6)

Bladder cancer rarely occurs before the age of fifty, and about 80% of patients are aged 50-80 years. (7) Due to the frequent relapse of the disease and the need for control examinations, cytology and cystoscopy, bladder cancer is a disease for which a lot of money is allocated in Western countries. (8)

It is one of the first cancers for which is proven, that its occurrence is under the major impact of environmental factors. (9) Women more often attribute symptoms to a urinary tract infection and consult a urologist less often, which contributes to later diagnosis of bladder cancer and thus poorer prognosis. (10) The lower incidence of cancer in women is explained by lower exposure of women to chemical carcinogens originating from industry and tobacco. (11-13) Women who have undergone radiotherapy for ovarian cancer or cervical cancer have a 2-4 times higher risk of developing bladder cancer compared to women who underwent surgery only. The risk also increases if patients underwent chemotherapy. Similar results have been reported in men treated with radiotherapy for prostate cancer. (14)

In a study of 7410 patients diagnosed with a high-grade tumor over a 10-year period, relapses occurred in almost ¾ patients during the follow-up period. (15) Grade, not tumor stage, is responsible for progression and relapse because it has been proven that high-grade tumors have a higher rate of relapse and progression, regardless of whether it is stage Ta or T1. It is known that relapse of tumors located in the lower third of the bladder, more precisely around the vesico-urethral orifice, the area of the trigonum and the area of the prostatic urethra, occurs earlier.

Persons with vascular diseases have a 19% higher risk of developing bladder cancer. According to a study conducted on 6172 patients followed over a 5.5 years period, there is a high association between vascular diseases and bladder cancer. These results demonstrate the importance of monitoring individuals with cardiovascular diseases, with the goal of reducing the risk of relapse of bladder cancer. (16)

Today, the classification of tumors according to the degree of differentiation into low (G1) and high grade (G2 and G3) tumors, or tumors of low and high malignant potential, is accepted, regardless of the wall invasion depth. Superficial carcinoma includes the Ta, Tis and T1 stages of the tumor, but it is important to note that these are three biologically different entities, with different malignant potential. Members of the AUA (American Urological Association) are of the opinion that the term superficial cancer is insufficiently precise, and that the tumor should necessarily be described by the stage (Ta, Tis, T1) and grade (G1-3) of the tumor.

Ta tumors make up 70% of all superficial cancers, and are among the tumors of low malignant potential. Recent studies shows that due to the high relapse rate, it is necessary to monitor patients for at least 10 years from the diagnosis of the primary tumor. (17) T1 tumor penetrates the lamina propria and occurs in about 20% of cases of superficial cancer. These tumors have a generally worse prognosis compared to Ta tumors. Relapses occur in 80% of cases, and progress in 50% of cases in the first three years after the diagnosis. This is a high-grade tumor and occurs in about 10% of cases. (6)

The period until the first relapse is shorter in the elderly and males. Evaluation of the number of tumors, localization and degree of cell anaplasia, is necessary when assessing the risk of tumor relapse or tumor progression to invasive.

The aims are to determine how the characteristics of the primary tumor: tumor number, location, stage, and tumor grade affect the time of superficial bladder cancer relapse. Also, to determine that age and gender are risk factors for relapse of superficial cancer and that they affect the length of time until the occurrence of the first relapse, and examine the impact of cardiovascular disease on the occurrence of relapse of bladder cancer.

Patients and methods

Patients

The study included 77 patients diagnosed with relapse of superficial bladder cancer of both genders, of which, 57 male and 20 female patients, aged 30-85 years. All patients were hospitalized at the Clinic of Urology, University Clinical Centre Sarajevo, the past four years. The study involved 77 patients diagnosed with relapse of transitional cell carcinoma who have given their informed consent.

Criteria for inclusion of patients in the study were:

- Patients older than 18 years.
- Pathohistologically confirmed relapse of superficial bladder cancer.
- Pathohistologically confirmed TCC

Criteria for exclusion of the patients from the study are:

- Primary superficial bladder cancer.
- Patients under 18 years of age.

- Invasive bladder cancer.
- Bladder adenocarcinoma.
- Squamous cell carcinoma.

Methods

A cross-sectional study of an analytical type was performed. Data were collected through medical records of the patients hospitalized at the Clinic of Urology, University Clinical Centre Sarajevo.

Diagnoses of relapse of superficial bladder cancer were made on the basis of anamnestic data (occurrence of blood in urine, which may be accompanied by dysuric problems), on the basis of medical documentation, on the existence of a previous bladder tumor, and on the basis of pathohistological findings obtained by transurethral resection (TUR) of the suspicious lesion.

This study explores the influence of the most important factors for the occurrence of bladder cancer relapse: age, gender, number of primary tumors (solitary or multiple), stage, degree of cell anaplasia (tumor grade), tumor localization, cardiovascular comorbidities, and time of first relapse.

Statistical analysis

The regression model was created in *PASW statistics 18 software*. The linear regression procedure, the *backward* method (Howell, 2013), was chosen. The dependent variable is the time to occurrence of the first relapse of bladder tumor and is expressed in years.

Results

The study included a total of 77 patients with a diagnosis of superficial bladder cancer relapse, who were surgically treated on at the Clinic of Urology, University Clinical Centre Sarajevo. Of the total number of patients included in this study, 57 (74%) were male and 20 (26%) were female.

Of the total number of patients included in the study, 7 (9%) are in the age group of 30 to 50 years, 14 or 18% of patients were aged 51 to 60 years and 26 patients or 34% aged 61 to 70 years and from 71 to 80 years, while the smallest number of patients is older than 81 years - a total of 5% or 4 patients out of a total of 77 respondents.

The period until the occurrence of the first relapse is longer in women than in men. On average, relapse in men occurs 5 months earlier than in women. The mean time to the occurrence of the first relapse in men averaged 3 years, and in women 3.4 years ($p<0.05$).

Relapse of the primary tumor occurs earliest in the oldest patients. In patients diagnosed with a primary tumor before the age of 50, the first relapse occurs in 15 years. In patients older than 50 years, the period until the appearance of the first relapse is shortened several times. Namely, in the age group from 51 to 60 years, the mean time that elapses until the first relapse is 2.7 years, while in patients from 61 to 70 years it is shortened to 2 years. Slightly earlier, on average in 1 year and 10 months relapse occurs in patients in the age group from 71 to 80 years, while in those older than 80 years the time of the first tumor relapse is less than one year and averages to 11 months ($p <0. 05$). (Table 1.)

Table 1. Time of the first relapse in relation to the patient's age

Patients age (years)	No. of patients	Time to first relapse (years)	
		Mean	Std. deviation
From 30 to 50	7	15.0	14.9
From 51 to 60	14	2.7	2.9
From 61 to 70	26	2.0	2.2
From 71 to 80	26	1.8	1.6
More than 80	4	0.9	0.8

Of the total number of patients included in the study, 41 (53.2%) had Ta stage tumor, 31 (40.2%) T1 stage and 5 of them (6.5%) Tis. The earliest relapse occurs in patients diagnosed with cancer in situ. On average, these patients had relapse in about 1.6 years. The mean of relapse time in patients with Ta - papillary tumors is 2 years, while in patients with T1 stage of the tumor this period is the longest and averages to 4.8 years, $p<0.001$ (Table 2).

Table 2. First relapse occurrence and the tumor stage

Tumor stage	No. of patients	Time to first relapse (years)			
		Mean	Std. deviation	Min	Max
Ta	41	2.0	1.9	0.3	7
T1	31	4.8	9.0	0.8	41
Tis	5	1.6	1.1	0.5	3

Of the 77 patients included in the study, 54 (70%) had a low-grade tumor, while 23 (30%) had a high-grade tumor. In patients with high-grade tumors, relapse occurs earlier. The mean of relapse was 3.7 years for patients with low grade tumors, while it amounted to 1.7 years for patients with high grade tumors ($p < 0.05$).

The first relapse occurs earlier in patients with multiple primary tumors. A total of 51 (66.2%) patients had multiple primary tumors, and the mean of time to relapse in these patients was 3 years. In patients with solitary primary tumor, of which there were a total of 26 (33.8%), relapse occurs on average after 3.3 years.

Patients with lower tumor localization in the bladder develop relapses earlier compared to those in whom the tumor are localized in the upper third of the bladder. For a total of 12 (15.6%) patients, the exact location of the tumor in the bladder is unknown. In 36 (46.6%) patients, the tumor was located in the upper third, and the mean of the time to first relapse was 3.7 years. 29 (37.7%) of a total of 77 patients had a tumor located in the lower two thirds of the bladder, and the mean time to the occurrence of the first relapse was 2.8 years ($p<0.01$). (Table 3)

Table 3. First relapse occurrence and the tumor localization

Tumor localization	No. of patients	Time to first relapse (years)			
		Mean	Std. deviation	Min	Max
Upper part	36	3.7	7.4	0.8	41
Lower part	29	2.8	5.1	0.2	28
Unknown	12	2.0	2.5	0.3	7

A total of 49 (64%) patients diagnosed with bladder tumor relapse had another diagnosis related to the cardiovascular system. The mean time to occurrence of the first relapse in these patients is 2.5 years and is shorter than in patients in whom cardiovascular comorbidity is not present. The mean time to occurrence of the first relapse in the remaining 28 (36%) patients was 4.2 years. (Table 4)

The tumor grade has a statistically significant effect on the time before the occurrence of the first relapse. On average, in patients diagnosed with high-grade tumors, the first relapse occurs 1.7 years earlier than in patients diagnosed with low-grade tumors. This comparison is based on the assumption that patients do not differ from each other with respect to other predictors from the model, or other predictors are kept constant ($p<0.05$).

If the tumor is diagnosed at a relatively early age, then the time to occurrence of the first relapse is shorter for men than for women, if the other predictors in the model are kept constant. On the other hand, if the tumor is diagnosed at an older age, the situation is reversed and tumor relapse occurs earlier in women than in men ($p<0.01$). (Figure 1)

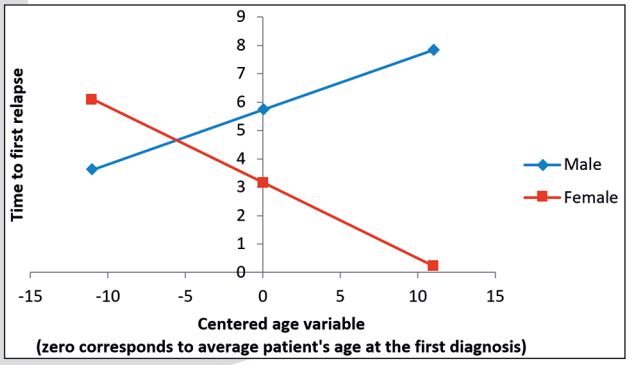

Figure 1. The influence of gender on the time of the first relapse depending on the patient's age at the time of diagnosis

In other words, in patients in whom the tumor is diagnosed in the lower part and in whom cardiovascular comorbidity is present, relapse occurs much earlier than in patients in whom the tumor is diagnosed in the same part without comorbidity. In the case of patients with the above-mentioned localization, the association with the dependent variable looks significantly different ($p<0.01$). (Figure 2)

Table 4. First relapse occurrence and the cardiovascular comorbidity

Cardiovascular comorbidity	No. of patients	Time to first relapse (years)			
		Mean	Std. deviation	Min	Max
Absent	28	4.2	8.3	0.8	41
Present	49	2.5	4.3	0.2	28

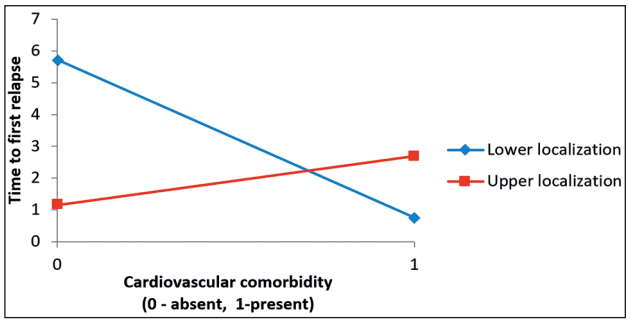

Figure 2. Influence of cardiovascular comorbidity on the time of the first relapse depending on the tumor localization

By applying the backward method in PASW 18 software, a regression model was finally obtained which is presented in Table 5. Comment: Model: $F(10)=12.43$, $p<0.001$; $R^2=0.653$. Regression coefficients: *p<0.05, **p<0.01, ***p<0.001.

Table 5. Characteristics of the final regression model

Factor	B (SE)	β
Constant	5.73 (1.23)	
Tumor grade*	-2.72 (1.18)	-0.21
Gender*	-2.56 (1.10)	-0.19
Cardiovascular comorbidity***	-4.98 (1.33)	-0.40
Age (at the time first diagnosis)*	0.19 (0.09)	0.35
Tumor localization**	-4.58 (1.72)	-0.37
Tumor stage***	4.48 (1.04)	0.38
Age x Gender***	-0.46 (0.10)	-0.48
Age x Cardiovascular comorbidity*	-0.23 (0.09)	-0.26
Age x Tumor stage***	0.47 (0.09)	0.66
Cardiovascular comorbidity x Tumor localization**	6.55 (2.02)	0.48

Based on the fact that $F(10)=12.428$ ($p<0,001$), we can conclude that the obtained model allows statistically significantly more accurate prediction of the time after which the first tumor relapse will occur in subjects, compared to the situation when we would try to make predictions with empirically obtained mean values of the time that elapses before the occurrence of relapse. From the data that $R=0.808$, or that $R^2=0.653$, it follows that the predictors from the obtained model enable the explanation of 65.3% of the variance of the dependent variable. In addition, we can conclude that the correlation coefficient between the predicted and actual values of the dependent variable (the time that elapses before the first relapse) is extremely high, because the coefficient of multiple correlation is 0.808.

Discussion

In this study, an analysis of case histories of 77 patients diagnosed with relapse of superficial bladder cancer, who were treated at the Clinic of Urology of the Clinical Center of the University of Sarajevo was performed. For all patients included in the study, data on age and gender were taken, as well as on the stage and degree of the tumor according to the pathohistological finding, and on the location and number of tumors according to the surgical finding. Data on the presence of cardiovascular diseases in all patients included in the study were also taken from the medical documentation.

Out of a total of 77 of patients, 74% or almost three times more are male patients. According to the American National Cancer Institute, bladder cancer is 3 times more common in men, which corresponds to our findings. (18) On the other hand, study shows that this ratio is as much as 4: 1 in favor of men. (4) The more common disease in men than in women is explained by the fact that they are less exposed to chemical carcinogens originating from industry and tobacco. On the other hand, poorer tumor prognosis in women is attributed to anatomical, hormonal, environmental, and social factors. (19) Our analysis showed that in women the first relapse occurs on average 6 months earlier.

However, the statistical significance of gender as a risk factor for the occurrence of the first relapse increases if it is moderated by an age variable. Our analysis showed that men who were diagnosed with superficial bladder cancer at a relatively early age relapsed earlier than women of the same age. On the other hand, women will develop relapse earlier than men if the diagnosis of the tumor is made at a slightly older age. This condition can be partly explained by the fact that women at a younger age have a protective effect of estrogen on the cardiovascular system, and this study showed that the first relapse occurs almost five years earlier in patients with cardiovascular comorbidity.

A study conducted by Palow et al. on 146 patients diagnosed with T1G3 superficial cancer showed that female gender and the presence of in situ carcinoma (CIS) in the prostatic urethra were the only prognostic factors for relapse, progression, and mortality. About 45% of the total number of patients developed a relapse, and the associ-

ation between the female gender and the presence of CIS in the prostatic urethra was statistically high p≤0.001. (20)

The largest number of our patients was aged 60 to 80 years, or in total 68%. The smallest number of patients is older than 80 years, only 5%. The average age of the patients was 69 years, the youngest patient was 34 and the oldest 83 years. A study by Howlader et al. proved that bladder cancer occurs in the elderly with an average age of occurrence of 73 years, which is similar to our results, and that the age at which cancer occurs depends on gender and ethnicity. (21)

Our study has shown that if the diagnosis is made at a younger age, the longer it takes for the first relapse to occur. That is, in patients in at the age group up to 50 years, on average, 15 years pass before the first relapse occurs, while in patients older than 80 years, this period is less than one year. There is a very pronounced difference in the time to the occurrence of the first relapse in patients younger than 50 years compared to other age groups. A clinical study of Nomikos and associates on patients younger than 40 years, during a six-year follow-up period, showed that the highest percentage of patients have a low-grade Ta and T1 stage. (22)

The largest number of patients had the tumor in Ta stage (53.2%), slightly less the T1 stage (40.2%) and the smallest number of patients included in our study were with the tumor in situ - Tis (6.5%). Studies show that papillary Ta stage of the tumor is present in 70% of cases, T1 stage of the tumor in 20% of cases, and Tis in 10% of cases. (6) However, it should be borne in mind that 77 patients were included in our study explains such deviations. Also, a large number of patients with T1 stage can be one of the indicators of poor quality of the health system and the patient's care for their own health. Namely, due to socio-economic circumstances, patients often neglect their health, which affects late diagnosis, earlier progression, more frequent relapses and, in general, a worse prognosis. This study showed that the first relapse occurs first in cancer in situ by an average of one year, then in stage Ta by 1.9 years, while the latest relapse occurs in stage T1.

A study by Larsson et al. on 508 patients diagnosed with bladder cancer, who were followed for 5 years, showed that 62% of all patients diagnosed with Ta and T1 tumors developed relapse within 5 years, with the first relapse occurring earlier in patients with T1 tumors. In 32% of patients with T1 stage, progression to a muscle invasive tumor occurs. The survival rate during the five-year follow-up period was 78%. (23,24) Our research, unlike the study of Larsson et al., showed that the first relapse occurs at the latest in T1 tumors, which in turn may be due to sample size or the fact that in our country people occur quite late doctor, which is a consequence of the socio-economic situation, and the lack of health education.

A study by Sylvester et al showed that the median survival time in patients with superficial bladder cancer was 10 years. However, it is important to emphasize that there are large differences in tumor behavior in patients with Ta, T1, and Tis stage tumors, although all of these categories are grouped together as superficial bladder cancer. The authors of this study have the opinion that it is necessary to change the name "superficial" because there are large differences in the risk of relapse, disease progression, and thus the overall prognosis. (25,26)

Patients with high grade tumors have a higher risk of relapse compared to patients with low grade tumors regardless of whether it is a Ta or T1 stage of the tumor. (27) About 30% of patients included in our study have high grade cancer and, in these patients, the first relapse occurred in 1.7 years, which according to the results obtained 2 years earlier compared to 70% of patients with low grade tumor.

Sylvester and colleagues developed a special scoring system that predicts patient risk for relapse (0-17 points) and disease progression (0-23 points). The study was performed on 2596 patients who were included in seven EORTC (European Organization for Research and Treatment of Cancer) clinical trials. The number and size of tumors together with the existence of previous relapses have been shown to be the main predictors of relapse. According to this scoring system, the EAU (European Association of Urology) divided all patients into three groups: low, medium and high risk of relapse. The low-risk group includes patients with solitary tumors, TaG1 tumors, and less than 3 cm in diameter. The high-risk group consists of patients with multiple primary T1G3 tumors, and CIS, and the rest

belong to the group at medium risk. (25,28,29) Further analysis showed that the probability of relapse in the first year is 15-61%, and a period of 5 years ranging from 31-78%. The lowest relapse rate was in low-risk patients (15%), followed by medium-risk patients (31%), while according to the scoring system, the highest relapse rate was in high-risk patients at 61%. (30) Other studies show a higher rate relapses occur in high-risk patients, up to 90% in the first two years after TUR. (31)

What is common to almost all studies are the fact that high-risk individuals have an almost equal chance of relapse and progression to a muscle invasive tumor, while medium-risk individuals have a much higher chance of relapse compared to progression. (28,29) The frequency of relapse is related to the number of primary tumors, the occurrence of relapse during the first 3 months after the first TUR and the number of previous relapses. These three parameters are the main criteria for inclusion of patients in the group with a high risk of relapse, regardless of the therapy used. (32,33) In solitary tumors, the probability of relapse is in the range of 18-60%, while for multiple tumors that interval of 40-80%. (34)

Multivariate analysis in which the leading prognostic factors of relapse were included showed that the number of tumors is the most important prognostic factor of tumor relapse, while the stage and grade of the tumor are more specific predictors of progression to a muscle invasive tumor. (25,24) Study of Rodriguez et al. in 1529 patients diagnosed with primary superficial bladder cancer showed that multiple primary tumors with a diameter greater than 3cm were the main predictor of relapse and tumor progression, while the stage of the tumor had no effect on further evaluation of the disease. On the other hand, the CIS is a predictor of relapse, progression, and overall mortality, and a high tumor grade is the most important predictor of progression and mortality. (35)

If the patient's primary tumor is localized in the lower third of the bladder (trigonum, right and left urethral orifice, bladder neck area and prostatic urethra), the first relapse occurred much earlier if the patient had a cardiovascular disease at the same time, acute myocardial infarction, hypertension, varicose veins, aortic aneurysm/abdominal aneurysm, etc.).

A study by Mungan et al. on 340 male patients diagnosed with superficial bladder cancer showed that the number of tumors was an independent predictor of the development of superficial TCC of the prostatic urethra. Their analysis showed that in patients with multiple tumors, the risk is 16 times higher than in other patients. Due to the risk of developing cancer of the prostatic part of the urethra, additional monitoring of these patients is necessary. (36)

Cardiovascular comorbidity is present in 64% of patients included in our study, and their first relapse occurs on average 5 years earlier than in patients with no personal history of CVD. However, cardiovascular comorbidity has been shown in our study to be an extremely important risk factor for relapse and in combination with tumor localization. According to a study by Van Kruijsdijk et al. conducted on 6172 patients followed for 5.5 years, there is a high association between vascular disease and bladder cancer. (16)

All factors including tumor size, multifocality, in situ cancer presence, tumor localization, and tumor presence in the prostatic urethra are in fact risk factors proven in population studies, however neither factor alone determines further tumor behavior or overall patient prognosis. (37) A study by Göğüş et al. showed that the relapse rate of 40-80% after TUR of primary tumor is a major problem in the management of patients with bladder cancer. (38) The investigated prognostic factors - stage, grade, number of tumors, existence of CIS and tumor size have been proven to influence the occurrence of relapse, especially in combination with older age. (39)

When it comes to the regression model obtained in this study, it is generally true that the nature of the association of a large number of factors (cardiovascular comorbidity, gender, tumor stage) with the time of first relapse ultimately depends on the age at which the first tumor diagnosis was made. If we take the standardized regression coefficient as a measure of the strength of the effects obtained, we note that the three strongest risk factors are: age at diagnosis of primary tumor in combination with tumor stage, cardiovascular comorbidity in combination with tumor localization and age at diagnosis in combination with patient gender.

Limitations of this study are relatively small sample of patients, as well as their follow-up period.

Conclusions

At an earlier age, the time to relapse is significantly longer, compared to patients diagnosed with cancer at older age.

At an earlier age, relapse occurs earlier in men, while in older age the time to occurrence of the first relapse is shorter in women.

In patients with tumor localization in the lower third of the bladder who have a cardiovascular disease, relapse occurs earlier than in patients in whom cardiovascular comorbidity is not present.

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Presence and microbiological composition of dental plaque in children with acute limfoblastic leukemia (ALL)

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Abstract

Introduction: Leukemias are systemic malignant diseases of hematopoietic stem cells. Plaque is a soft, sticky layer of bacteria on the surface of a tooth. It consists of viruses, bacteria, food debris and dead cells. ***Respondents:*** The study included children aged 0-15 years who have ALL. ***Results:*** Quantitative composition and qualitative representation of microorganisms in plaque depends on: age, oral hygiene, saliva properties, periodontal condition, plaque maturation, use of antibiotics and some other drugs. ***Conclusion:*** Good oral hygiene is a basic prerequisite for reducing the frequency and intensity of radiation and / or chemotherapy complications.

Key words: *plaque, microorganisms, children, leukemia, ALL.*

Introduction

97% of childhood leukemias are acute leukemias. Modern treatment of childhood leukemias includes the combined use of cytostatics (treatment protocols), radiotherapy and bone marrow transplantation (1,2,3).

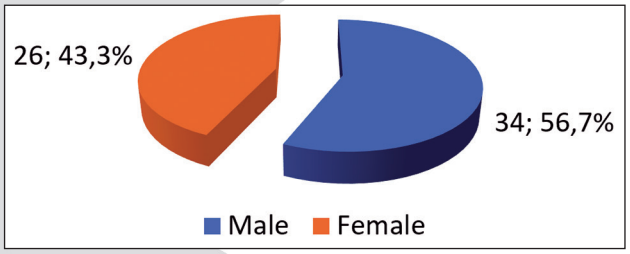
Plaq is a sticky layer that accumulates on the teeth after consuming food or drink. Bacteria in plaque multiply and pretend debris into acid, which causes the decay of enamel, tartar, caries and periodontitis (4,5). If teeth are not brushed regularly and adequately, plaque is seen as a whitish layer on the teeth along the very edge of the gums (6).

About 30 species of microorganisms have been found and described in the oral cavity so far. They form a permanent and normal oral flora. The composition of the normal oral flora includes: cocci, bacilli, fungi, filamentous and spiral forms of bacteria, fungi, protozoa and viruses (7,8,9).

Respondents, materials and methods

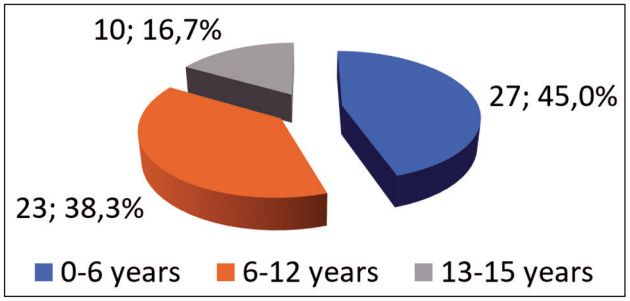
The study included 60 children, aged 0 to 15, who were treated at the Clinic of Pediatrics, Department of Hematooncology in Sarajevo (10). The results are presented in graphs by measures of central tendency (arithmetic mean, standard error, range of values) and by absolute and relative number of cases. Clinical examination has also determined the level of oral hygiene maintenance using the plaque index according to Silness and Loe (1964) (11,12,13).

Statistical processing and presentation of results



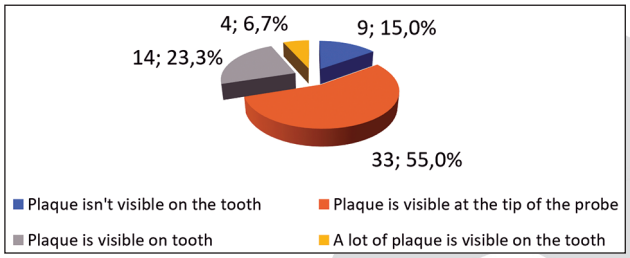
Graph 1. Gender structure of respondents

In this study, we had more boys than girls. A review of the gender structure shows that in the total sample (N = 60) boys are more represented in 34 or 56.7% of cases than girls in 26 or 43.3% of cases.



Graph 2. Age structure of respondents

The mean age in the total sample was 8.02 ± 0.57 years and ranged from 1-15 years. According to the defined age groups, the largest number of respondents was aged 0-6 years (27 or 45%), followed by the most common respondents aged 6-12 years (23 or 38.3%), and the smallest number of respondents aged 13-15 years / 10 or 16.7%).



Graph 3. Presence of plaque on teeth

Plaque was visible at the tip of the probe in most subjects (33 or 55%), in 14 or 23% of subjects plaque was visible on the tooth, in 9 or 15% there was no visible plaque on the tooth, and in 4 or 6.7% many plaques were noticeable. There was a statistically significant difference, but no correlation in the sense that the presence of plaque increases with age.

Discussion

The amount and number of bacteria in plaque are directly related to each individual's risk of periodontal disease and caries. Some of the changes can be so invasive that they significantly complicate or slow down treatment and can lead to discontinuation of treatment for malignant diseases (14, 15, 16).

Plaque was visible at the tip of the probe in most subjects (33 or 55%), in 14 or 23% of subjects plaque was visible on the tooth, in 9 or 15% there was no visible plaque on the tooth, and in 4 or 6.7% many plaques were noticeable. There was a statistically significant difference, but no correlation in the sense that the presence of plaque increases with age.

These data can be compared with a study called Dental Health in Children with cancer by JE Clarkson and OB Eden. The same was done in the Department of Pediatric Oncology at Manchester Children's Hospital. The study also studied 60 children receiving oncology therapy. Visible plaque was observed in 20 children or 33%. Which, compared to our study, shows that plaque is more present in our children, in our children it is 55%, and in children in the children's hospital in Manchester 33% (17,18,19).

The comparison of age by sex shows statistically significant differences ($p < 0.05$) in the sense that boys were mostly aged 6-12 years (87%) and girls aged 0-6 years (63%).

The study found that boys have slightly more plaque than girls. The boys had visible plaque on their teeth and a lot of plaque on their teeth, while most of the girls had plaque on top of the probe.

Quantitative composition and qualitative representation of microorganisms in plaque depends on: age, oral hygiene, saliva properties, periodontal condition, plaque maturation, use of antibiotics and some other drugs (20,21).

The composition of microorganisms differs in three phases:

Phase 1 (0-2 days) gram positive cocci and gram positive bacilli appear. Ito Streptococcus mutans (50%) and Neisseria (12%) Streptococcus salivarius (only 1%).

Phase 2 (2-4 days) occurrence of anaerobic forms of bacilli (fusiform) gram negative bacilli melaninogenicus), filamentous bacteria, gram negative cocci.

Phase 3 (4-9 days) appearance of a large number of spiral forms of Fusobacterium, Actinomyces, Vibrioni and Veilonellae, which are strictly anaerobic.

After the seventh day, the dental plaque fully matures. Percentage filamentous bacteria increases, while the number of streptococci decreases (2, 23, 24).

Conclusion

Plaque side effects vary from child to child, and so do treatments. Therapeutic agents, such as antibiotics, can significantly affect the composition of the bacterial flora of dental plaque (25). They lead to a reduction in the number of microorganisms that are sensitive to these drugs, but also to the reproduction of species that are resistant to them.

Good oral hygiene is a basic prerequisite for reducing the frequency and intensity of radiation and / or chemotherapy complications. Therefore,

all patients should undergo dental treatment before starting radiation and / or chemotherapy and approach therapy with a completely healthy oral cavity, which would significantly improve the quality of life of these patients.

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Nursing Care According to the Model of Daily Living Activities of an Individual Diagnosed with Breast Cancer: A Case Report

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Abstract

Introduction: It is aimed to apply nursing care according to Roper Logan Tierney Activities of Daily Living Model of a woman with breast cancer hospitalized general surgery service.

Case Presentation: Diagnoses such as acute pain, nausea, diarrhea, malnutrition, activity intolerance, changes in oral mucosa, deterioration in sleep patterns, fatigue, deterioration in body image, social isolation, changes in family processes, risk of infection were made and nursing interventions were applied for these diagnoses.

Practical Implication: It has been determined that the Model is a useful model in determining problems of breast cancer patients, making necessary plans and meeting their needs.

Key words: *activities of daily living, patient care plan, breast cancer, nursing care.*

1. Introduction

Cancer is a disease that initially manifests itself with uncontrolled cell growth and proliferation in different parts of the body, then metastasizes to spread over large areas and causes multiple organ failures (Akyolcu et al., 2019; Aslan & Olgun, 2017; Public Health Institution of Turkey, 2016). Among the reasons why cancer is an important health problem in terms of morbidity and mortality rates; it is seen frequently in the world and in our country, causes death, is seen in all age groups, and affects the individual and his family negatively by making the individual in need of care (Aslan & Aslan, 2019; Ehsani et al., 2016; Greenlee at al., 2017). Breast cancer, which represents one of the most important health problems of the world population, is the name given to malignant tumors caused by epithelial cells forming the breast (Coleman, 2017[a]; Coleman, C, 2017[b]; Fahad Ullah, 2019). Breast cancer is a type of cancer that consists of cells that have the potential to proliferate uncontrollably and metastasize to surrounding tissues (American Cancer Society, 2018; Parker et al., 2020; Taşkin, 2021; Ursavaş & Karayurt, 2015).

Chemotherapy drugs, which prevent cancer cells from multiplying, can also affect living cells in the body and cause some side effects that are difficult to prevent. Due to the side effects of chemotherapy, women are affected physically, psychologically, socially and spiritually. Anorexia, cachexia, taste changes, hair loss, skin reactions, nausea-vomiting, oral mucositis, fatigue, weakness and dyspnea are among the physical problems that women frequently encounter (Gudenkauf & Ehlers, 2017; İzci et al., 2016; McFarland et al., 2018; Ursavaş & Karayurt, 2017). Among the social problems faced by women, there are deterioration in family functions, social isolation, stigma, married couples experiencing marital problems, difficulty in finding suitable clothes, and changes in family roles and responsibilities. The spiritual problems faced by women include not accepting the disease, bargaining and denial. In addition to these, it is stated that women experience various psychological problems such as anxiety, depression, sleep disorders, anger, uncertainty about the future, hopelessness, suicidal thoughts, decreased self-esteem, deterioration of body image, fear of losing female characteristics, and sexual dysfunction (Corey et al., 2020; Harbeck & Gnant, 2017; Jankowska-Polańska at al., 2020; Park et al., 2020; Tsaras et al., 2018).

The degree and incidence of these side effects vary depending on the type of chemotherapy administered, the mode of administration, doses, duration and intervals of treatment, the patient's age, general condition, presence of chronic disease, and the level of meeting their needs (İzci

et al., 2016; Wöckel et al., 2018). Breast cancer, which is common among women all over the world, draws attention in terms of mental and psychosocial aspects among cancer types due to the fear and anxiety of being cancer, as well as the loss of the breast, which appears as a symbol of femininity and sexuality, provides nourishment for the baby, expresses love and motherhood feelings. type has been. Especially since it is a disease that evokes death, the individual needs more care than other diseases (Chan et al., 2020; Farge et al., 2019; Lanta et al., 2019). Models used in the delivery of nursing care make it easier for caregiver nurses to provide more planned care. While these models create a common approach in the delivery of planned care for patients, they provide the systematic collection of data and provide nursing care with holistic, humanistic and holistic content (Ackley at al., 2019; Karadağ et al., 2020).

The use of the Individualized Activities of Daily Living Model is an important practice in preventing, reducing and solving problems related to daily living activities in individuals with breast cancer (Karadağ et al., 2020; Roper et al., 2018; Torre et al., 2017). The model developed by Roper, Logan and Tierney in 1970 aims to recognize the individual as a whole, to identify and solve the problems experienced by the individual, and to provide holistic care to the individual (Bilgiç et al., 2017; Roper et al., 2018; Torre et al., 2017). Model; It consists of 12 sub-titles, including providing and maintaining a safe environment, communication, respiration, nutrition, excretion, individual hygiene and clothing, body temperature control, movement, work and entertainment, expressing sexuality, sleep, and death (Karadağ et al., 2020; Roper et al., 2018; Torre et al., 2017). Considering the sub-dimensions of the activities of daily living model, it was thought that the case with breast cancer had difficulty in performing daily living activities at home due to mastectomy and chemotherapy and was at risk for complications in the recovery process. In this article, to diagnose the patient with breast cancer within the framework of Roper, Logan, Tierney Activities of Daily Living Model and to create an evidence-based nursing care plan for the patient with NANDA (North America Nursing Diagnosis Association) nursing diagnoses, NIC (Nursing Intervention Classification), NOC (Nursing Outcomes Classification) classification. intended.

2. Case presentation

A 42-year-old patient named N. B. was admitted to the hospital with complaints of a mass in the right breast, nipple retraction, fatigue, weakness, and joint pains that had woken him up at night for the past month. As a result of the tests performed at the hospital, the patient was diagnosed with breast cancer, a mastectomy was performed on her right breast, and chemotherapy treatment was started. The patient, who stated that she was very sorry to have her breast removed, states that she no longer sees herself as a woman. Nausea, vomiting, change in taste in the mouth, ulcerations in the mouth and weight loss occurred in the patient whose chemotherapy treatment was still ongoing. While the patient was 70 kg before receiving chemotherapy, it decreased to 60 kg after chemotherapy treatment. The patient also has pallor, shortness of breath, and dyspnea with mild movement. The patient verbally expresses that his joints continue to ache and expresses his discomfort from the pain by frowning and grimacing with his body language. E.B. He stated that there was no change in his urinary excretion, he emptied urine 3 times a day, but now he has watery stools 4 times a day, while he normally goes out once a day for bowel evacuation. As she received chemotherapy, the patient's hair began to fall out. The patient thinks that his hair is coming in locks and that one day he will not have any hair, and he thinks that he will have a very ugly appearance. The patient, who has 3 children, stated that there were disruptions in the care of his children as long as he was in the hospital. While he is in the hospital, his mother takes care of the children.

It was decided to carry out the nursing care of the patient in line with the Roper Logan Tierney Activities of Daily Living Model.

3. Discussion

Nursing care of the case was presented in line with the titles in the Roper Logan Tierney Activities of Daily Living Model.

3.1. Ensuring and Maintaining a Safe Environment

Data on vital activity: "Acute Pain" associated with cancer, which is detected by the presence of pain symptoms such as joint pain that awakens sleep at night, frowning, groaning, grimacing, and the patient marking the number 8 on the pain assessment scale.

Nursing Diagnosis: Acute Pain

Purpose: To enable the patient to verbally express that his pain is gone and to be able to perform daily life activities without pain.

Expected Patient Outcomes: The patient does not have joint pain, sleeps without getting up at night without pain, and pain intensity is reduced to at least 4

Interventions: The patient's pain and vital signs were evaluated and recorded. The extremities were supported with a pillow by giving the appropriate position. Activities of daily living that increase and decrease pain were determined by interviewing the patient. Methods of distraction such as massage and listening to music were used. Analgesic treatment was planned and applied in accordance with the physician's request.

Evaluation: The patient stated that the severity of pain decreased from 8 to 4.

Data on vital activity: Decreased platelet count due to immunosuppressive chemotherapy treatment (platelet value 40000)

Nursing Diagnosis: Risk of Trauma due to immunosuppressive medical treatment

Purpose: To learn the bleeding symptoms and to recognize them early

Expected Patient Results: The platelet value is within normal limits (between 150,000 and 400,000) in the blood and the patient does not show symptoms such as petechiae and widespread bruising on his body.

Interventions: Early bleeding symptoms were observed and these symptoms were taught to the patient. From the laboratory findings, the platelet value was checked. Vital signs were followed up frequently. The patient was informed about the practices that may cause trauma (using a soft toothbrush, using a razor instead of a razor during shaving, avoiding hard nose cleaning, proper diet practice to avoid constipation). Invasive interventions were avoided unless necessary.

Evaluation: The platelet value increased to 30000. Despite the reduction, the risk of bleeding and trauma continues.

Data on vital activity: hospitalization of the patient, invasive procedures, and reduction of leukocyte count from bone marrow cells of chemotherapy treatment

Nursing Diagnosis: Risk of Infection due to bone marrow suppression by chemotherapy

Purpose: To prevent the patient from having nosocomial infections during hospitalization, to show that the patient and family know the risk factors related to infections and apply appropriate precautions to prevent infections.

Expected Patient Outcomes: Leukocyte values are within the normal range (4000-10000 µL) in the blood and no signs of infection are fever

Interventions: All systems were evaluated for signs and symptoms of infection. The patient was isolated in a private room. Visitors are restricted. The importance of hand washing was explained to the staff and visitors. Aseptic technique was used in invasive procedures by applying appropriate isolation techniques. Laboratory and vital signs were evaluated at regular intervals. Oral hygiene and daily skin care were applied in cooperation with the patient. Risk factors for infection were taught to the patient.

Evaluation: The leukocyte value was found to be 5,500 µL in the blood and is within the normal range.

3.2. Communication

Data on vital activity: "Social Isolation" associated with hair loss and pale appearance, change in physical appearance and having a chronic disease.

Nursing Diagnosis: Social isolation

Purpose: To enable the patient to express his/her acceptance of his/her current social situation, to define and implement interaction attitudes that will enable him/her to socialize, to express his/her desire to get rid of isolation, to determine the strengths he/she has and the existence of social support resources.

Expected Patient Outcomes: The patient states that although his hair is shed, he is not very ugly and he accepts that hair loss is a side effect of treatment.

Interventions: Relevant risk factors were identified and controlled (for example, if she has lost hair, she can wear a wig). Methods that will enable the patient to socialize were chosen together. Environments and opportunities for socialization were created. The patient's social support was activated. The patient was treated in a supportive manner while caring.

Evaluation: The patient stated that changes in his physical appearance emerged as side effects of the disease and treatment.

3.3. Respiratory

Data on vital activity: No respiratory problems, respiratory rate 16/min.

3.4. Nutrition

Data on vital activity: "Nausea" associated with chemotherapy treatment, as manifested by gastric complaints and removal of gastric contents.

Nursing Diagnosis: Nausea

Purpose: To enable the patient to express that his/her nausea has decreased and to learn the foods and beverages that increase nausea.

Expected Patient Outcomes: The patient's symptoms of nausea and stomach complaints are reduced.

Interventions: The patient was advised to eat frequently, in small amounts, slowly, to avoid very hot/cold, fibrous, fatty, spicy foods, and caffeine. Care was taken to avoid bad odors and appearances in the environment where he ate. The patient was allowed to lie in the semifawler position after the meal and then slowly change his position. He was told not to lie flat on his back for at least two hours after a meal.

Evaluation: Nausea continues as a side effect of chemotherapy as chemotherapy treatment continues. However, the feeling of nausea was reduced by interventions made before the feeding time.

Data on vital activity: "Under-Bodily Nutrition" associated with immunosuppressive medical treatment as manifested by loss of appetite and weight reduction (from 70 kg to 60 kg).

Nursing Diagnosis: Nutrition less than body requirement

Purpose: To ensure that the patient is of normal weight, has normal laboratory values, and has no signs of malnutrition.

Expected Patient Outcomes: Increased appetite and body mass index between 18-24.

Interventions: It was ensured that he was fed with sufficient calories by talking to the dietitian and observing his daily food intake. Daily weight monitoring was done. The patient was fed at small and frequent intervals throughout the day, and he was allowed to choose what he wanted from the appropriate foods. Antiemetic was given before, during and after chemotherapy according to the doctor's order. Oral care was given to the patient before meals, and the patient was kept away from the smell of the place where the meal was made.

Evaluation: Since chemotherapy treatment continues, loss of appetite and weight loss continue as side effects of chemotherapy.

3.5. Excretion

Data on vital activity: "Diarrhea" associated with irritation of the gastrointestinal tract from chemotherapy, as manifested by a feeling of watery defecation and defecation 4 times a day

Nursing Diagnosis: Diarrhea

Purpose: To ensure that the patient has stool with normal frequency and consistency, proper hygiene, perianal care and hand washing.

Expected Patient Outcomes: The patient does not have a continuous feeling of defecation, decreased defecation frequency, and stool of normal consistency (1 time per day).

Interventions: The daily amount, characteristics, and frequency of diarrhea were observed and recorded. The foods that cause diarrhea were avoided and the appropriate diet was arranged. Bowel sounds were listened and recorded. The importance of fluid intake was explained to the patient, and if necessary, IV fluid support was provided in accordance with the doctor's request. From the laboratory findings, especially the electrolyte values were monitored. Skin integrity was ensured, perianal area was kept clean and emollients were recommended to be applied. The patient was informed about appropriate hygienic rules (such as toilet cleaning and hand washing).

Evaluation: As a result of the treatments and nursing practices, the patient's diarrhea resolved

and he started to have regular stools (1 time per day).

3.6. Individual Cleaning and Hygiene

Data on vital activity: "Change in Oral Mucous Membranes" associated with the effect of Chemotherapy on the gastrointestinal tract, as manifested by ulceration in the mouth and altered taste.

Nursing Diagnosis: Change in Oral Mucous Membrane

Purpose: To heal the ulceration of the mucous membrane of the patient and to ensure painless eating.

Expected Patient Outcomes: Healing of the patient's ulcerations in the mouth area and resolution of the taste disturbances.

Interventions: Oral mucosal status of the patient was evaluated, oral care was performed with 5% Sodium Bicarbonate according to the doctor's request to prevent fungal infections, and the patient was educated on this subject. The quality of the materials to be used in oral care was decided in cooperation with the doctor according to the oral-mucous membrane of the patient. The patient was informed about keeping away from hot, sour, spicy and acidic foods and fed with soft foods. Fluid intake was supported as tolerated.

Evaluation: As a result of oral care, healing was observed in ulcerations in his mouth.

3.7. Body Temperature Control

Data on vital activity: Body temperature 36.3°C.

3.8. Movement

Data on vital activity: "Activity Intolerance" associated with leukemia and anemia, as manifested by fatigue, pallor, shortness of breath, dyspnea with mild activity

Nursing Diagnosis: Activity Intolerance

Purpose: To enable the patient to perform activities of daily living without being disturbed.

Expected Patient Outcomes: Being able to move without pain, dyspnea and fatigue, the patient states that he/she sleeps and rests adequately, shows that he/she tolerates increased activity, and maintains adequate nutrition without feeling dyspnea and fatigue.

Interventions: Activities that are important were determined by the patient. The patient was encouraged about the activities that he could do and were able to do. The importance of movement was discussed with the patient, and criteria for assessing movement tolerance (vital signs, distance, duration, pain control and strength) were determined. Vital signs of the patient were evaluated before and after the activity. Range of motion (ROM) exercises were taught to the patient and he was allowed to do them. Rest periods were created according to the patient's daily schedule. The patient's activity intolerance was increased by taking more breaks or helping out by doing slower and shorter activities.

Evaluation: Dyspnea that increases with movement continues.

3.9. Work and Fun

Data on life activity: "Change in Family Processes" associated with the disease and the uncertainty of the future, detected by the patient's family caring for their children.

Nursing Diagnosis: Change in Family Processes

Purpose: To enable the patient to express his/her feelings comfortably to the nurse or other people, to ensure that family members participate in the care, and to maintain the functionality of the support system that will provide common decisions for each member.

Expected Patient Outcomes: It is the patient's statement that he has the power to take care of his children.

Interventions: The patient and family were assisted to assess the situation. Those at risk were encouraged to have a realistic perspective on the family by giving accurate and complete information about the situations to be gained or lost, by answering the questions. The family was assisted and informed about the preferences/possibilities to be aware of their roles at home, to set priorities to maintain family integrity, and to reduce stress. The family was directed to social institutions in need of the help that could be provided. Family members were encouraged to participate as much as possible in the patient's care. As time passed, the family was encouraged to become capable of tak-

ing care of the sick person. Family members were assisted to realistically change expectations of the sick member. While the disease was continuing, family members were informed beforehand about the symptoms of anxiety, depression and addiction, which are part of the disease process.

Evaluation: Since the patient's treatment at the hospital continues, he cannot take care of his children.

3.10. Expressing sexuality

Data on vital activity: "Body Image Deterioration" associated with chemotherapy treatment, which was found by the patient's hair loss and thinking that his hair would be very ugly when all of his hair fell out.

Nursing Diagnosis: Distortion in body image

Purpose: To enable the patient to verbally express an increase in body image feelings and to evaluate himself realistically without distorting it.

Expected Patient Outcomes: *The person states that he/she is not very ugly despite his/her hair loss and he/she accepts that hair loss is a side effect related to treatment.

Interventions: The patient was encouraged to express his feelings, especially his feelings, thoughts and feelings about his own outlook, and to ask questions about his health problem, treatment, prognosis, and progress. His misconceptions and concepts about his own care and his caregivers were clarified. The patient and the patient's family were supported to ensure adaptation. Visits by peers and significant others were encouraged and the patient expressed how important they were to them. The meaning of the loss for the individual and their relatives, and the individual's reactions to the loss were evaluated. Being aware of the reactions of his relatives to the loss, the patient was allowed to express his feelings. He was taught the social resources he could refer to when necessary (for example, mental health centers)

Evaluation: Hair loss continues due to chemotherapy treatment.

3.11. Sleep and Rest

Data on vital activity: Frequent waking at night due to joint pain, dark circles under the eyes, decreased metabolic energy production, increased cell destruction, medical treatment that suppresses the immune system, pain-related "Disruption in Sleeping Pattern"

Nursing Diagnosis: Sleep Disturbance

Purpose: To reduce the symptoms of insomnia, to ensure that the patient has enough energy to continue activities of daily living and is rested by sleeping more.

Expected Patient Outcomes: Sleeping at night without pain and without waking up, no dark circles under the eyes, and no daytime sleepiness.

Interventions: Relevant individual, environmental and therapeutic risk factors were controlled. The sleep patterns and habits of the individual were determined and the stimuli in the environment were tried to be reduced (light, noise, etc.). In line with the habits of the individual, measures (warm milk, relaxation techniques, listening to music, etc.) were taken to facilitate drug-free sleep. Since the patient could not sleep due to joint pain, the doctor was talked to and appropriate analgesics were administered.

Evaluation: The doctor started to administer analgesic treatment for joint pain. After the analgesic treatment was applied to the patient, the patient stated that he slept more comfortably.

Data on vital activity: "Fatigue" associated with chemotherapy treatment, decreased metabolic energy production, as manifested by fatigue and difficulty in performing activities of daily living.

Nursing Diagnosis: Fatigue

Purpose: To enable the individual to express that he or she has taken control of the situation.

Expected Patient Outcomes: The patient does not have fatigue while performing activities of daily living.

Interventions: By trying to identify the causes of fatigue, priorities were set for daily and weekly activities. The patient was allowed to express the effects of fatigue on his life. The individual was helped to recognize their strengths and abilities. In a 24-hour period, the individual was taught to record the level of fatigue every hour. Fatigue was assessed using an appropriate scale (eg, Rohen fatigue scale-0: not tired, 10: complete burnout). Jobs that the individual can do and leave to others have been identified. Planning was made to carry out important applications during high energy hours.

Evaluation: The patient stated that the symptoms of fatigue continued due to the side effects of chemotherapy.

3.12. Death

Data on life activity: He stated that he did not have any fear of death.

4. Implications for nursing practice

It was determined that the use of the Individualized Activities of Daily Living Model in determining the possible problems that the individual with breast cancer experienced and may experience after mastectomy, which was considered as a case report, and in solving these problems, is an important model in gaining independence and preventing possible complications. With the use of this model, problems such as diarrhea, changes in the oral mucous membrane, deterioration in sleep patterns, deterioration in body image, social isolation were eliminated, and acute pain and nausea were reduced. It was observed that the problems of fatigue, changes in family processes, activity intolerance, undernutrition, infection and trauma risk still continued.

The use of the Daily Living Activities Model in nursing care provides great convenience to determine the existing problems in the patient, to plan the nursing care for these problems, to implement and evaluate the interventions. In addition, achieving positive results with a systematic approach helps to create holistic, humanistic and holistic care for the patient. As a result; It has been found that the Roper, Logan, Tierney Activities of Daily Living Model are useful in breast cancer cases. It is recommended to use this model in other cases as well.

Limitations

The patient was hospitalized for 30 days in the clinic. Since the follow-up of the patient was done on the days of clinical practice, the patient was followed up for 16 days. The fact that the patient could not be followed up in the clinic every day was considered as a limitation of the study.

Ethical statement and consent

This study was conducted following the guidelines of the Helsinki Declaration 1975 and ethical review boards' rules and regulations. Besides, the case was presented anonymously and informed consent was obtained in respect to publishing the case report along. A copy of the written consent is available for review by the Editor-in-Chief of the journal.

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Abstract

In this paper the instructions for preparing camera ready paper for the Journal are given. The recommended, but not limited text processor is Microsoft Word. Insert an abstract of 50-100 words, giving a brief account of the most relevant aspects of the paper. It is recommended to use up to 5 key words.

Key words: Camera ready paper, Journal.

Introduction

In order to effect high quality of Papers, the authors are requested to follow instructions given in this sample paper. Regular length of the papers is 5 to 12 pages. Articles must be proofread by an expert native speaker of English language. Can't be accepted articles with grammatical and spelling errors.

Instructions for the authors

Times New Roman 12 points font should be used for normal text. Manuscript have to be prepared in a two column separated by 5 mm. The margins for A4 (210×297 mm2) paper are given in Table 1.

Table 1. Page layout description

Paper size	A4
Top margin	20 mm
Bottom margin	20 mm
Left margin	20 mm
Right margin	18 mm
Column Spacing	5 mm

Regular paper may be divided in a number of sections. Section titles (including references and acknowledgement) should be typed using 12 pt fonts with **bold** option. For numbering use Times New Roman number. Sections can be split in subsection, which should be typed 12 pt *Italic* option. Figures should be one column wide. If it is impossible to place figure in one column, two column wide figures is allowed. Each figure must have a caption under the figure. Figures must be a resolution of 300 DPI, saved in TIFF format, width 10 cm min. For the figure captions 12 pt *Italic* font should be used. (1)

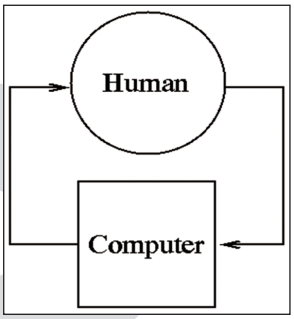

Figure 1. Text here

Conclusion

Be brief and give most important conclusion from your paper. Do not use equations and figures here.

Acknowledgements (If any)

These and the Reference headings are in bold but have no numbers.

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