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Review

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Inflammation-related cancer or cancer-related inflammation

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ABSTRACT

Inflammation is the body's defensive action against various stimuli such as physical or chemical or infectious agents. Acute inflammation and their mediators help in tissue repair and healing. If the inflammation aggravates chronically, non-resolved, dysregulated immune system, results release of various inflammatory mediators such as free radicals (ROS and RNS), cytokines, chemokines, growth factors and proteolytic enzymes produced by innate and adaptive immune cells activate transcriptional factors (NF-KB,STAT3 and HIF-1α) results in cell proliferation, angiogenesis, immunosuppression, genetic instability, invasion and metastasis. Oncogenes related to cancer activate inflammatory mediators such as chemokines and cytokines, which alters the inflammatory tumor microenvironment, promotes tumor progression. This article highlights about the role of inflammation and oncogenes activate inflammatory mediators in tumor progression.

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Keywords: Inflammation, cancer, myeloid-derived suppressor cells, inflammatory mediators, tumor associated macrophages, lymphocytes, tumor associated neutrophils, NF-KB, STAT3, HIF-1α, oncogenes, cytokines, chemokines, growth factors, COX-2

Introduction

Inflammation is the complex biological response to physical or chemical or infectious stimuli. Acute inflammatory response to tissue injury results in tissue repair by various mediators such as neutrophils, macrophages, and dendritic cells release mediators such as COX-2, ROS, TGF-β. If the inflammation is aggravated chronically, no resolving, chronic smoldering inflammation results in dysregulated immunity mediated release of cytokines, chemokines, growth factors, proteolytic enzymes by innate and adaptive immune cells. External environmental factors contribute very important roles in cancer. Single gene mutation is insufficient to transform in to neoplastic cell, instead it require four to five somatic cells genetic mutations [1, 2].

In extrinsic pathway of inflammation-related cancer, some inflammatory conditions or injury that are associated with malignancy are lichen planus, oral submucous fibrosis, gingivitis and chronic periodontitis associated oral squamous cell carcinoma, sialadenitis related salivary gland carcinoma, gastric acid associated Barrett's metaplasia and reflux

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esophagitis associated esophageal carcinoma, Sjogren's syndrome and Hashimoto's thyroiditis associated mucosa associated lymphoid tissue lymphoma, UV radiation associated skin inflammation melanoma, Silica, asbestosis, smoking associated silicosis and bronchitis associated lung carcinoma, prostatitis induced prostate carcinoma, chronic pancreatitis induced pancreatic cancer, Hepatitis B induced hepatocellular carcinoma, HPV induced cervical cancer and pharyngeal cancer. Human herpes virus 8 (HHV8) induced Kaposi's sarcoma. 20% of all cancers are associated with chronic infections, 35% of cancers are attributed to dietary factors, of which 20 percent of cancers are due to obesity, by increasing chronic inflammation promotes hepatocellular carcinoma [1-7].

Inflammatory mediators involved in tumor progression

Most of all tumors are associated with inflammatory microenvironment triggered by inflammatory response, which is protumorigenic. In intrinsic pathway of cancer-related inflammation, some oncogenes such as RAS, RET and MYC induce transcriptional program by activating signaling pathways results in remodeling of the tumor microenvironment through leucocytes and lymphocytes recruitment, expression of protumorigenic chemokines, cytokines (IL-6, IL-8, IL-1β, CCL2, CCL20) induce an angiogenic switch leading to tumor progression and immune escape by recruitment of Tregs or Th2 immunosuppressor cells [1, 8-10].

Chemokines are chemotactic cytokines that involve in positioning and migratory patterns of immune cells to the site of inflammation. Receptors of chemokines are expressed on leukocytes produced by stromal and tumor cells facilitates tumor progression. Neutrophil recruitment is mediated by CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, and CXCL8. Recruitment of macrophages, dendritic, and natural killer cells are by CCL2, CXCL12-CXCR4, CCL4, CCL5, and MCP-1.

Lymphocyte and natural killer cells recruitment by CXCL12-CXCR4, CXCL9, CXCL10,CXCL11, CCR7-CCL21, CXCL19, and CCL21 [11-13].

In initiative phase ROS, RNI and RNS free radicals produced by neutrophils, macrophages and TNF-α in tumor microenvironment cause DNA damage and genetic instability. In promotive phase growth factors (EGF, FGF, VEGF), Cytokines (TNF-α, IL-1, IL-6, IL-8, IL-10, TGF-β), proteolytic enzymes (MMP-2 and 9, UPA) produced by tumor associated neutrophils, tumor associated macrophages, mast cells and T and B lymphocytes. IL-1 induced by chemicals and TNF-α activates NF-kB key transcriptional factor and also AP-1. IL-6, IL-10, IL-22, IL-11, HGF and EGF activates STAT3 transcriptional factor for cellular proliferation, cell survival, angiogenesis, immunosuppression, invasion and metastasis in patients with oral squamous cell carcinoma, prostate, hepatocellular, lung, colorectal, gastric, bladder, ovarian, and esophageal cancers [14-22].

Damage associated molecular patterns (DAMP) and pathogen associated molecular patterns (PAMP) activated in response to Hsp70, HMGB-1, S100 calcium binding protein, IL-1α, LPS, microbes and their microbial products recognized by pattern recognition receptor (PRR) family belongs to Toll like receptor family activates cytokines induced transcriptional factors such as NF-KB, STAT3 favours tumor progression. Cytokines induced over expression of activation induced cytidine deaminase (AID) causes genomic instability in critical genes such as TP53, C-MYC and BCl-6 involved in cancers such as liver, gastric and lymphoma [5, 12, 23-25].

In hypoxic tumor microenvironment recruitment of tumor associated macrophages induce HIf-1 α acts as a transcriptional factor for IL-8, VEGF, COX-2 promotes angiogenesis and immunosuppression. MMP-2,9, UPA, prokineticin 2 (BV8) and TGF-β produced by tumor associated neutrophils (TAN) involved in tumor invasion and metastasis including oncostatin M (OSM) and HGF, which induce tumor progression. Tumor associated macrophages are abundant innate immune cells in inflammatory tumor microenvironment induce cell proliferation, angiogenesis, invasion and metastasis by producing cytokines (IL-1, IL-6, IL-8, IL-10, TNF-α, TGF-β, IL-17), chemokines (CCL17, CCL18, CCL22, CXCL8), growth factors (EGF, FGF, VEGF) and enzymes (COX-2, UpA, iNOS, MMPs, Arginase1), immunosuppressive factors (IDO, iNOS, B7-H1). B cells producing IL-10 are called as Bregs induced by STAT3 with ERK or p38 and elevated expression of PD-1. CD4 T cells expressing CD25 and FOXP3 are called Tregs, mediated by TGF-β, IL-10 and IL-4, produce IL-10, TGF-β [26]. Alternatively activated Th2 cells activates TAM (M2) phenotypic macrophages, eosinophils through cytokines and B cells, which activates phagocytes, mast and NK cells,

produce IL-10, IL-4, IL-13 and TGF-β, increased expression of arginase 1, programmed death ligand (PDL1) acts as immunosuppressive on dendritic cells, natural killer cells, T and B lymphocytes in patients with oral squamous cell carcinoma, lung, pancreatic, colorectal, breast, melanoma, esophageal, prostate, ovarian, renal cell cancer. Th1 cells activate macrophages through IFN-γ secretion and cell to cell contact [6, 11, 27-46].

B cells induced tumor progression is by activation of myeloid and mast cells, and also production of IL-10 induced immunosuppression. Mast cells are produced by bone marrow involved in innate and adaptive immunity, matured in tissue, have protumoral activity by producing TNF-α, IL-10, IL-1, IL-6 cytokines. Ability to respond to an extrinsic signals depends on surface expression of array of receptors such as TLR, NOD like receptors and FC, complement receptors, angiopoietin-1, VEGF, TGF-β, FGF-2 growth factors, release of proteases such as MMPs activated by tryptase favours degradation of extracellular matrix, angiogenesis, invasion and metastasis in patients with oral squamous cell carcinoma, colorectal, breast, bladder, lung, pancreatic, prostate, melanoma, gastric, esophageal, and ovarian cancer. Mast cells recruit eosinophils, T and B cell immune response activity and MDSC accumulation in tumor microenvironment. CD4 T and CD8 T cells mediated immunosuppression by expression of surface receptors PD-1 and CTLA-4 on its surface [47, 48].

IL-17 proinflammatory cytokine is a subtype of CD4 T cells produced by Th17 cells, expressed by tumor associated macrophages induced IL-23 procarcinogenic cytokine, mediated IL-6 and TGF-β, promotes tumor progression by activating IL-1, TNF-α, IL-6 in patients with hepatocellular carcinoma, oral squamous cell carcinoma, prostate, colorectal, esophageal, gastric cancer [1, 8, 12, 24, 49].

Myeloid derived suppressor cells (MDSC) are heterogeneous population of immature myeloid cells that are precursors of dendritic cells, macrophages and/or granulocytes derived from bone marrow is of two types granulocytic or monocytic. Myeloid-derived suppressor cells has a potent regulatory immune response and have a major role in chronic inflammation and tumor development by activation of tumor-derived mediators or cytokines such as IL-1β, IL-4, IL-6, IL-10, COX-2 and TGF-β induce expression of arginase-1, inducible nitric oxide synthase (iNOS) or ROS immunosuppressive factors. Which, can initiate apoptosis in T cells, programmed cell death and immunosuppression of effector cells such as adaptive and innate immune cells.

Expansion of myeloid-derived suppressor cells by factors such as GM-CSF, G-CSF, M-CSF, stem cell factor and VEGF. Myeloid-derived suppressor cells activates STAT3 and matrix metallo-proteases (MMPs) there by promoting angiogenesis, invasion, and cell proliferation by further activation of STAT3 induces the secretion of bFGF and VEGF. Myeloid-derived suppressor cells activate MMPs, facilitate cancer cell invasion and intravasation by disruption of endothelial cadherins, degradation of extracellular matrix, adhesion proteins or basement membrane vessels in patients with head and neck cancer, prostate, bladder, esophageal, and oral squamous cell carcinoma.

MDSC also facilitate epithelial to mesenchymal transition in cancer cells by using factors such as epidermal growth factor (EGF), hepatocyte growth factor (HGF) and TGF-β [12, 50-54].

In extrinsic pathway, external environmental factors play an important role such as tobacco, alcohol, dietary factors, viruses, chemical ingestion, induced inflammatory cells and their mediators such as cytokines, chemokines, growth factors, enzymes, released from innate and adaptive immune cells activate transcriptional factors (NF-KB, STAT-3), in majority of cancer, which is inflammation-related cancer. In intrinsic pathway of cancer-related inflammation the oncogenes-mediated activation of inflammatory mediators induced tumor progression in tumor microenvironment.

In tumor microenvironment, both intrinsic and extrinsic pathway is activated or whether intrinsic and extrinsic pathway activated individually need to be known for future diagnostic, therapeutic or prognostic purpose.

Conclusion and future prospective

Chronic inflammatory cells and their mediators have a role in tumor initiation, promotion and progression of cancer. These mediators are ROS, RNS free radicals, chemokines, cytokines, growth factors and proteolytic enzymes produced by chronic inflammatory cells in tumor microenvironment such as innate and adaptive immune cells. Oncogenes-related cancer induced activation of inflammatory mediators, promote tumor progression. Both intrinsic and extrinsic pathways are activated simultaneously or individually in tumor microenvironment need to be

known. In future, identification of inflammatory mediators will be suitable for cancer biomarkers, therapeutic strategy and prognostic purpose.

Abbreviations

HGF=hepatic growth factor, VEGF=vascular endothelial growth factor, MMP-9=matrix metallo-proteinases 9, COX2=cyclo-oxygenase 2, INOS=inducible nitric oxide synthase, ROS=reactive oxygen species, PDGF=platelet derived growth factor, EGF=epidermal growth factor, FGF=fibroblast growth factor, TNF-α=tumor necrosis factor-α, IFN-β=interferon β, IL-10=interleukin 10, TGF-β=transforming growth factor-β, CCL17=CC chemokine ligand 17, CCL18=CC chemokine ligand 18, CCL22=CC chemokine ligand 22, PGE2=prostaglandin E2, IDO=indoleamine 2,3 – dioxygenase, UPA=urokinase plasminogen activator, UPAR=urokinase plasminogen activator receptor, IL-2=interleukin 2, IL-4=interleukin 4, IL-6=interleukin 6, IFN-γ=interferon γ, COX-1=cyclo-oxygenase 1, NF-KB=neuclear factor KB, MCP-1=macrophage/Monocyte chemoattractant protein1, M-CSF=macrophage colony stimulating factor, IL-17=interleukin 17, CD4+ Th17=CD4+ T helper lymphocyte17, MDSC=myeloid-derived suppressor cells, SR-A=the class A macrophage scavenger receptor msr1, GM-CSF=granulocyte macrophage-colony stimulating factor, G-CSF=granulocyte colony stimulating factor, STAT3=signal transducer and activator of transcription 3, bFGF=basic fibroblast growth factor, MMPs=matrix metallo-proteinases, HIF-1α=hypoxia-inducible factor α, T reg cell=T regulatory cell, Th1=T helper 1, Th2=T helper 2, TAM=tumor associated macrophages

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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Original Article

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Scarf osteotomy or Mau osteotomy for correction of moderate to severe hallux valgus deformity: a prospective, randomized study

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ABSTRACT

Objective. The aim of this study was to compare the clinical and radiological results of Mau osteotomy and Scarf osteotomy with a modified McBride procedure to patients with moderate to severe hallux valgus deformity. ***Methods.*** The study included 40 feet which patients were separated into 2 groups followed up for 5 months. Scarf osteotomy was applied to 20 patients including 16 females and 4 males (Scarf group)) and a Mau osteotomy to 20 patients including 17 females and 3 males (Mau group). Radiological measurements were taken preoperative, postoperative and at the final follow-up examination of the hallux valgus angle (HVA), intermetatarsal angle (IMA), distal metatarsal articular angle (DMAA), metatarsocuneiform angle (MCA), the 1st metatarsophalangeal joint congruity, 1st metatarsal length, fibular sesamoid subluxation rate. Clinical evaluation was made according to the American Orthopaedic Foot and Ankle Society (AOFAS) and the severity of pain was assessed with the visual analog scale (VAS). ***Results.*** There was no difference between the groups in term of the mean HVA, IMA, MCA and DMAA values in preoperative and postoperative measurements. A significant improvement was determined in all the angle values in Scarf and Mau group ($p<0.001$). A significant increase in DMAA and shortening in the metatarsal length were determined in Mau group compared to Scarf group ($p<0.001$). An improvement in joint congruity was seen in the goups ($p<0.001$). There was a significant improvement in term of the AOFAS and VAS values in the groups ($p<0.001$). ***Conclusion.*** Scarf and Mau osteotomies can provide the desired level of improvement in the short-term follow-up results of moderate to severe hallux valgus deformity, taking into consideration the clinical importance that complications are not formed.

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Keywords: Hallux valgus, Scarf osteotomy, Mau osteotomy

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Introduction

No consensus has yet been reached on the treatment for hallux valgus and more than 130 surgical techniques have been reported [1-6]. Although successful results have been reported with a distal soft tissue procedure in the adults with mild and moderate level hallux valgus, recurrence of hallux valgus deformity has been reported in up to 11% of patients. In moderate level deformities unsuccessful results have been reported from the distal soft tissue procedure [6-11]. The distal soft tissue procedures are important in stabilizing the joint biomechanics in the surgery of incompatible joints. These soft tissue procedure cannot be seen only as a supplementary surgical procedure in cases where the bony procedure needs additional correction, but rather is an indispensable procedure to restore the physiological situation and function of the first [12]. In patients with moderate to severe hallux valgus, to bring the intermetatarsal angle (IMA) within normal physiological limits, several metatarsal osteotomy techniques together with the distal soft tissue procedure have been described [6, 13, 14]. According to the area where it is applied, distal, diaphyseal and proximal osteotomies are applied.

As Chevron [15], Mitchell [16] and Wilson [17] distal osteotomies are generally less invasive, the recovery time of patients is shorter. Unwanted outcomes may also be observed such as insufficient correction, recurrence, avascular necrosis in the metatarsal head when applied together with the distal soft tissue procedure, shortening in the metatarsal neck in Wilson osteotomy and elevation in the metatarsal head in the Mitchell osteotomy, and these osteotomies are often used in the treatment of mild and moderate level deformities [18, 19-21]. Proximal metatarsal osteotomies are defined in several types as open wedge, closed wedge, crescentic and Chevron osteotomies [6, 22-24]. Proximal osteotomies may worsen the deformity in hallux valgus deformities compatible with a high preoperative distal metatarsal articular angle (DMAA) [25-27]. Of the metatarsal diaphyseal osteotomies, the Scarf, Mau and Ludloff are the most frequently used types.

To the best of our knowledge, there is no study in literature that has compared the clinical and radiological results of Scarf and Mau osteotomies. Therefore, the aim of this prospective, randomized study was to compare the clinical and radiological results of Scarf and Mau osteotomies applied together with a modified McBride procedure in patients with moderate to severe hallux valgus deformity.

Methods

Approval for the study was granted by the Local Ethics Committee. Patients who had a diagnosis of moderate to severe hallux valgus deformity according to Mann and Coughlin classification were taken into study [6]. There was no evidence of degenerative arthritis, the pain did not respond to conservative treatment and was over 18 years of age. Informed consent was obtained from all patients. Patients were excluded from the study if they had metatarsocuneiform laxity, had previously undergone a surgical intervention or had a history of diabetes mellitus, peripheral vascular disease, peripheral neuropathy, pes planus or inflammatory disease. A total of 40 feet of 40 patients met the study inclusion and exclusion criteria and they were randomly separated into 2 groups for surgery. All the patients were prospectively followed up postoperatively for at least 5 months.

Randomization was applied with the sealed envelope method for each patient indicating either the Scarf osteotomy together with the modified McBride procedure or the Mau osteotomy together with the modified McBride procedure. The details of the operation to be applied were explained to the patients. The patient with bilateral hallux valgus underwent a different operation on each foot at a 3-month interval. The Scarf group comprised 20 patients including 16 females and 4 males with a mean age of 41.25 ± 13 years. The Mau group comprised 20 patients including 17 females and 3 males with a mean age of 40.63 ± 15 years. The hallux valgus angle (HVA) and IMA were measured preoperatively and at 3rd week and 5th months postoperatively. All the other radiological parameters were measured and the clinical evaluations were made preoperatively and at 5th month postoperatively. The preoperative and postoperative physical examinations, and the objective and subjective measurements were undertaken by an experienced orthopaedic resident who was not involved in the study.

For the subjective evaluations, the American Orthopaedic Foot and Ankle Society (AOFAS) hallux Metatarsophalangeal-Interphalangeal (MTP-IP) Evaluation Score (AOFAS-MTPIP) [28], a Visual Analog Scale (VAS) [29], and the Subjective Foot

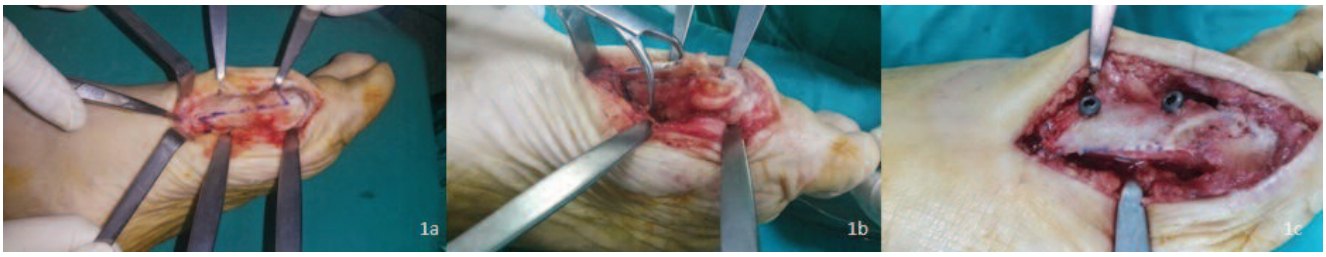

Figure 1. Scarf osteotomy planning (1a). 1st metatarsal osteotomy and fixation with mini-cannulated screw with the method described by Coetzee and Rippstein [33] (1b and 1c)

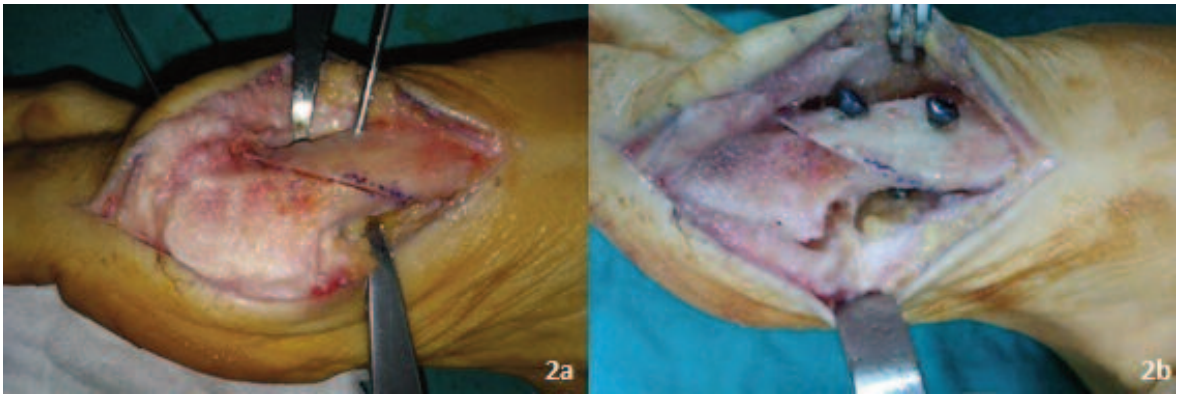

Figure 2. First metatarsal osteotomy with the Easley method [34] in cases applied with Mau osteotomy (1a) fixation with mini-cannulated screw (2b)

Evaluation Form (SFEF),as described by Haapaniemi *et al.* [30], were used. During the preoperative and follow-up examinations, standing anterior posterior and lateral radiographs were taken of all patients. For the objective evaluations, the HVA, IMA, DMAA, 1st metatarsal length [31], MTC [32], 1st metatarsophalangeal joint congruity were measured and the fibular sesamoid subluxation rate was calculated by considering the distance of the sesamoid from the metatarsal long axis [6]. All the radiological measurements were made using the Picture Archiving Communication Systems (PACS) Winsoft program on the hospital computer system.

Surgical Technique

Osteotomy was applied to the 1st metatarsal with the method described by Coetzee and Rippstein [33] in the cases applied with Scarf osteotomy (Figure 1) and with the method described by Easley *et al.* [34] in the cases applied with Mau osteotomy (Figure 2). Sutures were removed at 2nd week postoperatively and at the 3rd week the splint was removed and a hallux valgus night splint was applied. Partial weight-bearing was permitted as tolerated until union was observed.

Statistical Analysis

As the variables did not show conformity to normal distribution, comparison was made with non-parametric methods. In the comparisons between groups, the Mann Whitney U-test and the Kruskal Wallis test were used, for dependent groups the Wilcoxon test and for categorical variables, the Chi-square and Fisher tests. A value of $p<0.05$ was accepted as statistically significant.

Results

No statistically significant difference was determined between the groups in respect of the preoperative demographic characteristics (Table 1). In the Scarf group, at the final follow-up, an increase of mean 43.5 points was seen in the AOFAS criteria and a decrease of mean 3.8 points in the VAS score. A statistically significant difference was determined in the AOFAS and VAS values at the 5th month postoperatively compared to the preoperative values ($p < 0.001$, $p < 0.001$; respectively). In the Scarf group a statistically significant decrease was seen in all the measured angle values compared to preoperative values ($p < 0.001$) and the metatarsal length was seen to have shortened but to a non-significant level

Table 1. A comparison of the preoperative clinical and radiological findings of the Scarf and Mau osteotomy groups.

	Scarf group (n = 20)	Mau group (n = 20)	*p* value
Age (year)	41 ± 13 (24-63)	41 ± 15 (19-68)	0.890
HVA (º)	37.90 ± 8.2 (25-60)	35.95 ± 8.8 (23-60)	0.470
IMA (º)	16.25 ± 2.4 (13-21)	16.95 ± 3.0 (14-25)	0.460
MCA (º)	27.55 ± 4.8 (19-38)	26.35 ± 4.1 (17-34)	0.400
DMAA (º)	14.95 ± 7.8 (3-35)	12.70 ± 4.4 (3-20)	0.270
MTL (mm)	57.90 ± 4.8 (50-69)	59.20 ± 5.4 (50-70)	0.430
AOFAS score	33.50 ± 15.7 (5-60)	35.75 ± 18.3 (5-78)	0.680
VAS	6.45 ± 1.8 (3-9)	7.30 ± 1.4 (3-9)	0.200

Data are shown as mean ± standard deviation (range; min-max). HVA = Hallux valgus angle, IMA = 1-2 intermetatarsal angle, MCA = Metatarsocuneiform angle, DMJA = Distal metatarsal articular angle, MTL. Metatarsal length, AOFAS = American orthopaedic foot and ankle society, VAS = Visuel analog scale

(*p*=0.892).

In the Mau group, at the final follow-up, an increase of mean 36.1 points was seen in the AOFAS criteria and a decrease of mean 4.5 points in the VAS score. A statistically significant difference was determined in the AOFAS and VAS values at the 5th month postoperatively compared to the preoperative values ($p < 0.001$, $p < 0.001$; respectively). Compared to the Scarf group, a significant increase was seen in the DMAA in the Mau group ($p < 0.001$), a significant shortening in the metatarsal length ($p < 0.001$) and a significant decrease in the other angles ($p < 0.001$) (Table 2.) The preoperative and postoperative 5th month radiological values of the Scarf group and the Mau group are shown in (Figures 3 and 4).

In the Mau group, a significant shortening in the metatarsal length and increase in DMAA were seen at the final follow-up examination ($p < 0.001$, $p < 0.001$; respectively). In the Scarf group, a statistically significant increase was determined in the 5th month

Table 2. A comparison of the preoperative, postoperative 3th week and 5th month clinical and radiological findings of the Scarf and Mau osteotomy groups.

	n	Scarf group	*p* value	n	Mau group	*p* value
HVA (º)[a]	20	37.9 ± 8.2 (25-60)	**a-b** (< 0.001)	20	35.9 ± 8.8 (23-60)	**a-b** (< 0.001)
HVA (º)[b]	20	16.8 ± 5.7 (8-30)	**a-c** (< 0.001)	20	15.3 ± 5.6 (8-25)	**a-c** (< 0.001)
HVA(º)[c]	20	23 ± 8.6 (9-45)	**b-c** (< 0.001)	20	17.1 ± 5.2 (10-27)	**b-c** (0.199)
IMA (º)[a]	20	16.25 ± 2.4 (13-21)	**a-b** (< 0.001)	20	16.9 ± 3.0 (14-25)	**a-b** (< 0.001)
IMA (º)[b]	20	7.05 ± 2.4 (3-12)	**a-c** (< 0.001)	20	8.2 ± 2.4 (5-13)	**a-c** (< 0.001)
IMA (º)[c]	20	8.16 ± 2.1 (5-13)	**b-c** (0.003)	20	9.2 ± 2.9 (3-15)	**b-c** (0.230)
MCA (º)[a]	20	27.55 ± 4.8 (19-38)		20	26.3 ± 4.1 (17-34)	
MCA (º)[b]	20	20.95 ± 6.3 (8-33)	**a-b** (< 0.001)	20	22.0 ± 4.6 (15-30)	**a-b** (< 0.001)
DMAA (º)[a]	20	14.95 ± 7.8 (3-35)		20	12.7 ± 4.4 (3-20)	
DMAA (º)[b]	20	9.58 ± 5.8 (1-19)	**a-b**(0.003)	20	16.0 ±4.0 (1-19)	**a-b** (< 0.001)
MTL (mm)[a]	20	57.90 ± 4.8 (50-69)		20	59.2 ± 5.4 (50-70)	
MTL mm)[b]	20	57.58 ± 4.6 (49-67)	**a-b** (0.892)	20	51.6 ± 6.3 (40-67)	**a-b** (< 0.001)
AOFAS[a]	20	33.50 ± 15.7 (5-60)		20	35.7 ±18.3 (5-78)	
AOFAS[b]	20	77.00 ± 13.4 (50-95)	**a-b (**< 0.001)	20	71.8 ± 9.1 (52-83)	**a-b** (< 0.001)
VAS[a]	20	6.45 ± 1.8 (3-9)		20	7.3 ±1.4 (4-10)	
VAS [b]	20	2.63 ± 1.4 (6-14)	**a-b** (< 0.001)	20	2.8 ± 1.4 (7-13)	**a-b**(< 0.001)
AOFAS[d]	13	49.1 ± 15.6		11	37 ± 19.1	
AOFAS[e]	7	29.6 ± 20	**d-e** (0.034)	9	37.5 ± 20.2	**d-e** (0.957)
VAS[d]	13	4.4 ± 2		11	4.4 ± 1.8	
VAS[e]	7	2 ± 3.1	**d-e** (0.057)	9	4.5 ± 1	**d-e** (0.952)

Data are shown as mean ± standard deviation (range; min-max). HVA = Hallux valgus angle, IMA = 1-2 intermetatarsal angle, MCA = Metatarsocuneiform angle, DMJA = Distal metatarsal articular angle, MTL. Metatarsal length, AOFAS = American orthopaedic foot and ankle society, VAS = Visuel analog scale, n = number of patient, [a] preoperative values, [b] postoperative 3th week values, [c] postoperative 5th month values, [d] Patients under 45 years of age (subgroup A), [e] Patients over 45 years (subgroup B)

Table 3. Results of the SFEF showing distribution from satisfaction to dissatisfaction. *

Point	Scarf group	Mau group
6	7	
7	2	2
8	5	10
9		1
10	3	4
11		
12	3	3

SFEF = Subjective foot evaluation form. *The scores indicate the distribution between them as completely satisfied (6 points) and completely dissatisfied (18 points)

postoperative HVA and IMA values compared to the postoperative 3rd week values ($p < 0.00$, $p = 0.003$; respectively) (Table 2).

The results of the SFEF at the 5th month final follow-up examination of the Scarf group and the Mau group are shown in Table 3.

To evaluate the effect of patient age on the clinical results, the patients were separated categorically into two subgroups as those aged 45 years and younger in group A and those aged over 45 years in group B. This approach was previously used by Fuhrmann *et al.* [35]. It was investigated whether or not there was a difference in the preoperative and 5th month postoperative AOFAS and VAS values between the A and B groups of the Scarf and Mau groups. While the mean AOFAS values of the Scarf group A increased by 49.1 points, Group B increased by 29.6 points. The difference between the A and B groups was determined to be statistically significant ($p = 0.034$). The mean VAS points decreased by 4.46 points in group A and by 2.00 points in group B, with no significant difference determined between the groups ($p = 0.057$).

The mean AOFAS values of the Mau group A increased by 37 points and group B increased by 37.5 points, with no significant difference determined between the groups ($p = 0.950$). The mean VAS points decreased by 4.4 points in group A and by 4.5 points in group B, with no significant difference determined between the groups ($p = 0.950$) (Table 2).

The congruity of the base of the proximal phalanx with the 1st MTP joint was calculated with 2 lines drawn taking the basis of the estimated cartilage surface. In the Scarf group, preoperatively 17 (85%)

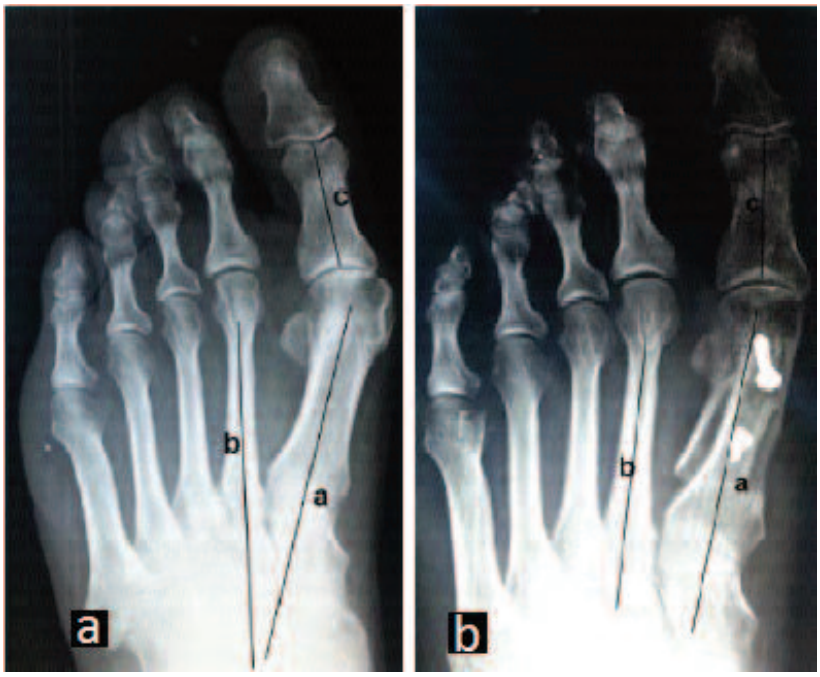

Figure 3. Scarf osteotomy. Preoperative radiograph of the foot of a 41-year old female patient with HVA 30º and IMA 16º (a). In the same patient, at postoperative 5 months, a decrease of HVA 11º and IMA 5º can be seen (b). HVA = Hallux valgus angle (HVA), IMA = Intermetatarsal angle

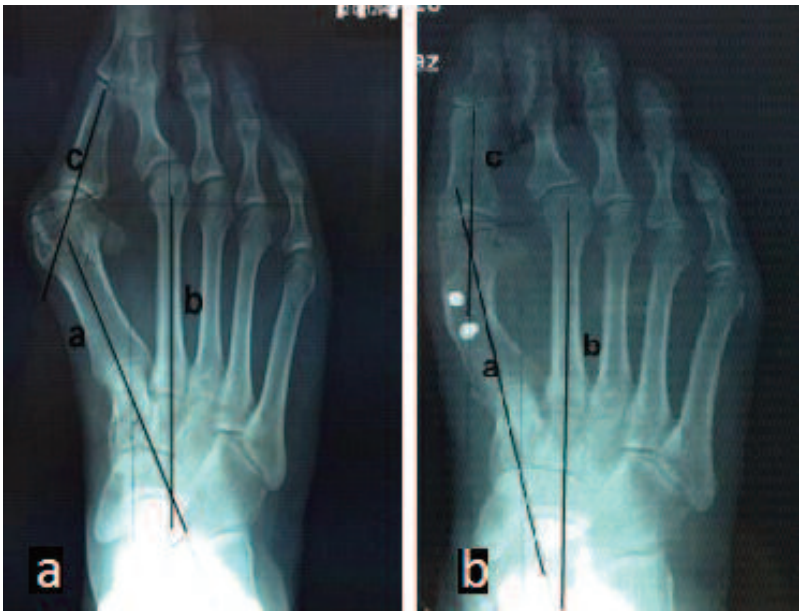

Figure 4. Mau osteotomy. Preoperative radiograph of the foot of a 41-year-old female patient with HVA 48º and IMA 25º (a) . In the same patient, at postoperative 5 months, a decrease of HVA 15º and IMA 13º can be seen (b). HVA = Hallux valgus angle (HVA), IMA = Intermetatarsal angle

feet were seen to be incongruous and 3 feet had joint congruity and postoperatively, a significant improvement was seen in 16 feet ($p < 0.001$). In the Mau group, preoperatively 18 (90%) feet were seen to be incongruous and 2 feet had joint congruity and postoperatively, a significant improvement was seen in 16 feet ($p < 0.001$). No difference was determined between the groups in respect of joint congruity ($p = 1.00$).

The fibular sesamoid subluxation rate in the Scarf group was determined as E1, in 2 patients and E2 in 18 (90%) patients preoperatively and this changed to E0 in 6 patients, E1 in 5 patients and E2 in 9 patients at the final follow-up examination. In the Mau group, 3 patients were determined as E1, 17 (85%) patients as E2 preoperatively and these changed to E0 in 4 patients, E1 in 6 patients and E2 in 10 patients at the final follow-up examination. No difference was determined between the groups in respect of fibular sesamoid subluxation rate ($p = 1.00$).

Complications such as recurrence, delayed union, 1st metatarsal elevation, insufficient correction, superficial infection, arthritis, and deep vein thrombosis were observed in 5 patients of the Scarf group and in 11 patients of the Mau group. In the Scarf group, 4 patients were admitted for a second operation to remove the screws due to skin discomfort after sufficient union in the osteotomy line was seen on radiographs taken postoperatively. In the Mau group, screws were removed from 2 patients after union was seen.

Discussion

This is the first study to have made a prospective randomized comparison of Scarf and Mau osteotomies. The results of the study showed that clinically and radiologically, similar improvements were provided in the early stage by Scarf and Mau osteotomies applied to moderate to severe hallux valgus cases. In the Scarf osteotomy, an increase which was not clinically important was determined in the HVA and IMA. In the Mau osteotomy, an increase was determined in the DMAA and the metatarsal length shortening. However, there was no change in the metatarsal length in the Scarf osteotomy, this allows the prevention of metatarsal elevation and provides balanced fixation [33, 36, 37]. In a study where Scarf osteotomy was applied to 178 feet, the mid-term retrospective results of mean 44.9-month showed that although the final follow-up mean AOFAS points were very good, excellent alignment of the 1st row was determined in only 55% of the feet. Unsatisfactory clinical results were reported to have been obtained in feet with HVA > 30° and with degenerative changes in the 1st MTP joint.

In addition, the radiological evaluation criteria

(HVA, IMA, hallux valgus interphalangeus, MTP joint congruity, arthritic findings in the 1st MTP joint) at the final follow-up examination were found to have deteriorated compared to postoperative 3th month [35]. In another prospective study which reported the mid-term results of Scarf osteotomy applied to 31 feet of 22 patients, a significant improvement was determined at the end of 12 months in the AOFAS points, and the HVA and IMA measurements. At the 5th year, a significant reduction in pain points was determined compared to the preoperative period, 90.9% of patients were satisfied with the intervention of Scarf osteotomy, the mid-term results were excellent and the method was determined to be reliable and repeatable [38].

In a study by Adam *et al.* [39], Scarf osteotomy was associated with 94% satisfactory results. They reported that complications were recurrence in 2 patients, metatarsal collapse in 3, and the need for an additional osteotomy (Akin osteotomy) in 4. In another study, Scarf and Akin osteotomies were applied to 36 feet of 35 patients, a significant improvement was determined in the AOFAS points and radiological measurements at the end of 6th month compared to the preoperative period and there was no difference in the first and 2nd metatarsal lengths in the sagittal plane. Scarf and Akin osteotomies together was recommended as a method that could be safely applied to cases with IMA ≤ 20°. The authors considered that by adding the Akin procedure to Scarf osteotomy, regardless of hallux valgus interphalangeus, the deformity could be more effectively corrected [40].

In the current study, the Akin procedure was not added to the Scarf osteotomy as there were no cases with hallux valgus interphalangeus deformity. In the 20 patients with Scarf osteotomy, we showed that the HVA, IMA and MTP joint congruity improved to an excellent degree at the end of 5th month compared to the preoperative period. In our study there was a significant increase in the AOFAS points and a significant decrease in the VAS points. When the good results obtained in the patients applied Scarf osteotomy are taken into consideration, this method can be recommended for application to cases with moderate to severe hallux valgus deformity.

During the follow-up period of some metatarsal osteotomies, including Scarf osteotomy, there may be a deterioration in the radiological criteria and there are some studies that have reported metatarsal shortening of mean 2-3.2 mm in patients applied Scarf osteotomy [35-38]. In the current study, an increase was seen in HVA and IMA without creating any clinical difference at the end of 5th month in cases applied Scarf osteotomy and a mean shortening of 0.3 mm was determined in the metatarsal length. This shortening in the metatarsal length did not create any clinical problem. Recurrence was seen in 2 patients with IMA ≥11° but as there was no problem with the patient satisfaction, no additional intervention was made. As the reason for recurrence could not be explained with the results obtained in the current study, there can be considered to be a need for further studies of more extensive series.

In a study which published the short-term objective results of Mau osteotomy, sufficient correction was obtained in the HVA and IMA, and it was emphasized that this was a method which could be safely applied in the surgical treatment of moderate to severe hallux valgus cases [13]. In the same study it was reported that revision surgery was required for recurrence in 3 cases, dorsal cortical non-union in 8 cases, insufficient correction in 5 cases and fracture during the follow-up period in 1 case [13]. In another study, the 4-month results of 24 cases applied Mau osteotomy and 10 cases applied proximal crescentic osteotomy were compared and it has been reported an significant improvement by both surgical methods. A higher rate of non-union in the osteotomy line and metatarsal elevation was reported in the cases applied proximal crescentic osteotomy and a mean shortening of 2 mm in the metatarsal length was reported in the cases applied Mau osteotomy [31].

Carr and Boyd [41] stated that shortening in the length of the 1st metatarsal of up to mean 7 mm was not clinically significant but a greater of amount of shortening could cause transfer metatarsalgia. In severe hallux valgus cases, while a high IMA is corrected in Mau osteotomy, as the DMAA could be impaired, corrective distal metatarsal closed wedge osteotomy may be necessary [42]. In our study, in the 20 cases underwent Mau osteotomy because of moderate to severe hallux valgus deformity, there was a significant improvement radiologically at the end of 5th month compared to the preoperative period. Clinically, an increase was seen in the AOFAS points and a decrease in the VAS points. A clinically non-significant shortening was seen in the metatarsal length and an increase in DMAA. No transfer metatarsalgia was observed in any patient. The shortness in the metatarsal length in the Mau osteotomy compared to the preoperative period could

have been due to the relatively lower intrinsic resistance of the distal part of osteotomy to shear forces, compared to Scarf osteotomy, but this cannot be explained with the findings obtained in this study and therefore it is recommended that further biomechanical experiments and clinical studies are made on this subject. Provided that shortening of the metatarsal length and impairment of DMAA are kept in mind, the results obtained in this study suggest that Mau osteotomy can be applied in cases of moderate to severe hallux valgus.

In biomechanical studies, distal Chevron and proximal crescentic osteotomy and Scarf osteotomy have been compared and the Scarf osteotomy has been determined to be two-fold more stable [34, 37, 43, 44]. In another biomechanical study made using plastic bone models, Mau, Ludloff and crescentic osteotomies were compared and it was reported that both Mau and Ludloff osteotomies were more resistant in fatigue tests [45]. In the same study, it was determined that Scarf, closed wedge, Mau and Ludloff osteotomies were more balanced than proximal Chevron and crescentic osteotomies. By comparing 6 different 1st metatarsal diaphyseal osteotomies in cadavers, with the exception of Ludloff, the Mau osteotomy was determined to be the most rigid osteotomy and stronger than the other diaphyseal osteotomies [46]. Consistent with all these studies, Unal *et al* [47] reached the conclusion that Mau osteotomy was the most stable shaft osteotomy. Taking all these bimechanical findings into account, both Scarf and Mau osteotomies allow early mobilization as they provide stability in the osteotomy line in the surgical treatment of hallux valgus deformity [42]. In the current study, early mobilization was encouraged in all patients and no problems were determined related to early weight-bearing. Therefore, in patients with moderate to severe hallux valgus treated with Scarf and Mau osteotomies, early weight-bearing can be applied.

In a study applied Scarf osteotomy by Fuhrmann *et al.* [35], patients were separated into 2 groups aged 50 years and younger and over 50 years. There was seen to be no difference between the groups in respect of mean preoperative and postoperative AOFAS and VAS groups. In the current study patients were evaluated in 2 age groups as older and younger than 45 years. In the cases applied Scarf osteotomy, a significant increase in AOFAS points was determined in patients aged ≤ 45 years and a non-statistically significant decrease in VAS points. In the Scarf osteotomy cases aged > 45 years and in the Mau osteotomy cases of both age groups, there was no difference in the clinical and radiological improvements. These findings suggest that better clinical results may be obtained with Scarf osteotomy in patients aged ≤ 45 years.

Recurrent hallux valgus, hallux varus, metatarsal elevation, delayed union, superficial infection, transfer metarsalgia, arthritis, and insufficient surgical correction are accepted as the most frequently seen complications in diaphyseal osteotomies [18, 35, 48-52]. In Scarf osteotomy, if the distal and proximal osteotomy fragments come to rest in the diaphyseal rather than the metaphyseal area, rotation in the metatarsal head, reduction in metatarsal height and elevation may occur because of impaction [6, 39]. Smith *et al.* [53] stated a perioperative complication rate of 6% in Scarf osteotomy. In a mid-term retrospective evaluation at mean 44.9 months after Scarf osteotomy in 178 cases, recurrence was seen in 24% and a moderate level of joint incongruity in the MTP joint in 19%. In the same study, development of hallux varus was reported in 1.6%, transfer metatarsalgia in 9 patients, arthritis in 13, metarsal fracture in 5 and reoperation in 12 patients at the final follow-up examinations. In the patients with metatarsal fracture, tomography imaging showed the reason to be metatarsal collapse [39]. In a series of 20 cases applied Scarf osteotomy, Coetzee and Rippstein [33] reported high complication rates at 6 months with metatarsal collapse in 7 feet (35%), delayed union in 5%, poor rotational union in 30%, fracture in the proximal metatarsal in 10%, infection in 5% and recurrence in 25%. In a study by Hyer et al. [31] of 24 Mau osteotomies, complications such as infection, non-union, recurrence, metatarsal elevation, insufficient correction and transfer metatarsalgia were reported to have developed.

In the current study, complications developed in 5 patients applied Scarf osteotomy and in 11 patients applied Mau osteotomy. These complications were recurrence in 7 cases, metatarsal elevation in 6 cases, superficial infection in 3, arthritis in 1, insufficient correction in 7, delayed union in 4 and deep vein thrombosis in 1. In the patient who developed thromboemboli, recovery was seen with medical treatment. A second operation to remove the screws was necessary in 2 patients in the Scarf osteotomy group. When the radiographs were examined retrospectively, the screw lengths were seen to be normal postoperatively, but at the final follow-up

examination, the screws were determind to have migrated outwards from the dorsal and plantar cortices. It was thought that this could have been due to metatarsal collapse, which is the most frequently seen complication of Scarf osteotomy. When the complications of the two osteotomies applied in this study were compared, the complication rate of the Mau osteotomy was higher but no clinical difference was determined between the two techniques.

The most important advantage of this study was that it was prospective and randomised and therefore the scientific evidence is of a high level. Other advantages are that it was conducted at a single centre, all operations were performed by a single surgeon and there was no loss of data due to patients withdrawing from follow-up.

The Limitation of the Study

Limitations of the study could be said to be the low number of cases and the relatively short follow-up period. The long-term results of a greater number of cases operated on by the same surgeon would make a greater contribution to literature.

Conclusions

In conclusion, the short-term results obtained in this study were observed to be satisfactory. When it is considered that no complications of clinical importance are created, the Scarf and Mau osteotomies can be recommended for use together with the modified McBride procedure in patients with moderate to severe hallux valgus deformity that have no degenerative changes in the MTP joint.

Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The effectiveness of soft and semi-rigid cervical collars on acute cervical radiculopathy

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ABSTRACT

Objective. Cervical radiculopathy is one of the common causes of the neck pain. Medical devices in the form of cervical collars are frequently recommended in acute cervical radiculopathy. We aim to investigate and compare the effect of soft and semi-rigid cervical collars on neck pain, disability and daily life activities in the patients with acute cervical radiculopathy. ***Methods.*** We designed a prospective, single-blind, randomized controlled study. This study was conducted on 101 patients who were diagnosed with clinical features of radiculopathy and imaging showing cervical disc herniation. Visual Analog Scale (VAS), Neck Disability Index (NDI) and SF-36 were applied to the subjects. Evaluation of the patients was done before the treatment and 2 weeks and 6 weeks after the start of the treatment. Patients were divided into three groups according to the computer-generated randomization table: Soft cervical collar, semi-rigid cervical collar and control group. The patients in collar groups were asked to wear the collars for 8 hours during the day for the first 2 weeks. ***Results.*** Comparison of the soft cervical collar group with the control group showed significantly better improvement in the former in VAS and NDI scores at week 2 and 6 ($p < 0.05$), in SF-36 pain perception subunit at week 2 ($p < 0.05$), and in SF-36 physical component score at week 6 ($p < 0.05$). Comparison of the semi-rigid cervical collar group with the control showed significantly better improvement in the former for NDI scores and SF-36 pain perception subunit at week 2 and 6 ($p < 0.05$). ***Conclusions.*** The results of our study have indicated that the use of soft and semi-rigid cervical collars was more effective than conservative treatment in treatment of neck pain and disability in acute cervical radiculopathy in the short term. Soft cervical collars were also found to be more effective for pain management than semi-rigid cervical collars.

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Introduction

The incidence of neck problems has steadily increased as a result of the burden of the modern lifestyles on the musculoskeletal system [1, 2]. As people rapidly became accustomed to spending long hours at their computers, smartphones, and other devices in a disadvantageous posture, not only in the workplace but practically everywhere, neck pain has become a frequently recurring complaint which may cause substantial disability and socio-economic problems in the society [1-3]. It is predicted that approximately one-third of adults'experience neck pain within one year [2-4]. Cervical radiculopathy is one of common causes of neck pain. Radiculopathy is the result of mechanical pressure on the nerve root exerted by disc protrusion, spondylotic spurring or a combination thereof, and the ensuing inflammatory response [5, 6]. Conservative treatment of acute cervical radiculopathy is primarily focused on reduction of pain and improvement of function and quality of life. The standard therapeutic regimen used in patients with acute cervical radiculopathy comprise medical treatment (non-steroidal anti-inflammatory drugs [NSAIDs], myorelaxants), patient education (posture, behavior, and ergonomics training), home-exercise program (stretching, posture, mobilization, functional and proprioceptive exercises), physiotherapy (TENS, hotpack, theurapeutic ultrasound, etc,.) and orthoses (cervical collar) [6-10].

Medical devices in the form of cervical collars are frequently recommended in acute cervical radiculopathy [11, 12]. Although debate on the precise mechanism of action of cervical collars continues, there is consensus on their positive effect on treatment of these patients by limiting cervical range of motion and neck muscle activity, providing kinesthetic feedback, and increasing proprioception. Soft cervical collars are exothermic, psychologically reassuring, and effective as a kinesthetic reminder to restrict cervical range of motion; yet they can not provide structural support [11, 12]. Reports have estimated that soft cervical collars may decrease full, active cervical range of motion (ROM) by only 10-25%. Rigid cervical collars are made of plastic material and have been suggested as an effective tool to markedly restrict the ROM. However, multiple studies have shown that the latter type of orthoses fail to completely eliminate motion and may indeed allow up to 50% of full, active ROM in most cases [12, 13].

Despite the popularity of cervical collars, there are very few randomized controlled studies assessing their efficacy in acute cervical radiculopathy [12]. To our knowledge, the comparative effectiveness of soft cervical collars versus semi-rigid cervical collars (Nelson) has not been previously investigated. The aim of this study is to investigate and compare the effect of soft and semi-rigid cervical collars on neck pain, disability and daily life activities in the patients with acute cervical radiculopathy.

Methods

We designed a prospective, single-blind, randomized controlled trial in patients with cervical radiculopathy. This study was conducted on 101 patients who were diagnosed with cervical radiculopathy by the Department of Physical Medicine and Rehabilitation. Before the study, patients filled out a consent form. Local Ethical Committee approval was obtained for the study.

Inclusion criteria for the study were: Age of 18-65 years, neck pain on a Visual Analog Scale (VAS) of 4 or more (radicular arm pain), diagnosis of cervical radiculopathy evident clinically by physician and confirmed with magnetic resonance imaging. Exclusion criteria were: Previous surgical operation on the cervical spine, another systemic, neurological or psychiatric problem, rheumatic and infectious disease, current malignancy, motor deficit in the upper extremity, previous treatment with cervical collar, and neck and arm pain that lasted for longer than 12 weeks.

Treatment protocol

Patients were allowed to take NSAIDs (etodolak 600 mg) at a stable dose throughout the study whenever necessary. The patients were instructed to do the home exercises comprising cervical isometric, cervical mobilization (ROM), and shoulder protraction and retraction exercises. They performed the exercises twice with 10 repetitions at each session in the morning and the evening everyday for 6 weeks. They were advised to avoid holding their neck in prolonged flexion or extension during daily activities and to use a suitable pillow during sleep. Monitoring of home exercises and education of the patients were performed by the same physician in the research team.

Patients were divided into three groups according to the random table. Group 1: Soft cervical collars (anatomic cut of the soft sponge collar) (Figures 1A

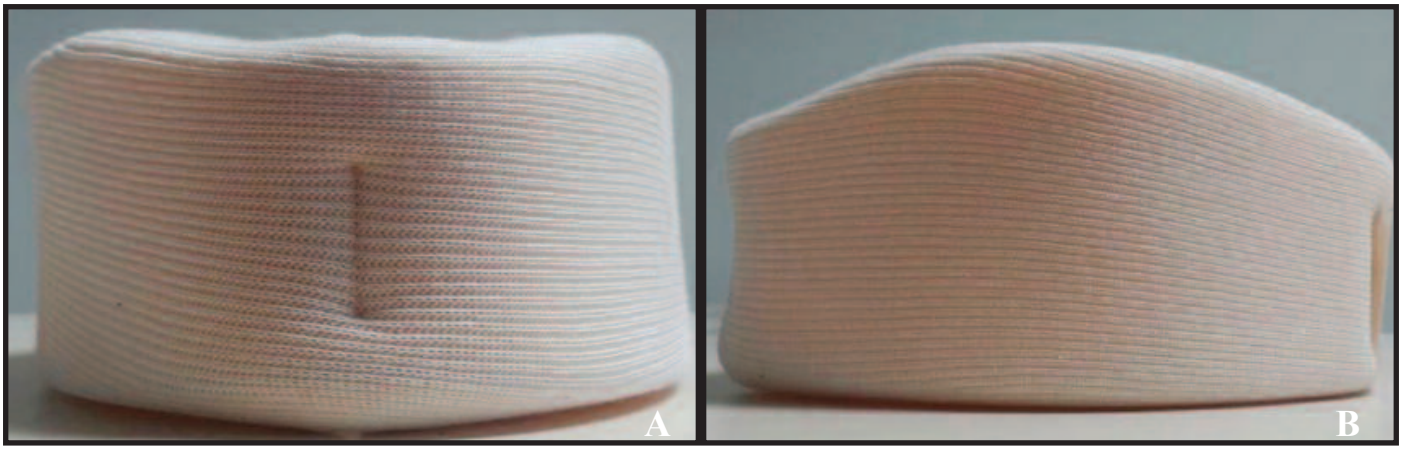

Figure 1. Soft cervical collars (A and B).

and 1B) plus exercise (n = 34); Group 2: Semi-rigid cervical collars (Nelson type plastozote, anatomically designed collar, manufactured from plastazote foam material) (Figures 2A and 2B) plus exercise (n = 33); and Group 3: Control; only exercise (n = 34).

The patients in groups 1 and 2 were asked to wear the collars for 8 hours during the day for the first 2 weeks, then reduce the collar time by one hour every other day for the next 2 weeks, and finally quit the collar at the end of the fourth week. Evaluation of the patients in all 3 groups was done by the same physician before the treatment and 2 weeks and 6 weeks after the start of the treatment who was blind to the study.

Main Outcome Measures

Visual analog scale (VAS): Pain intensity was assessed by the patient in a 10 cm horizontal line numbered from 0 to 10. The meaning of the numbers from 0 to 10 was explained to the patients as 0 = no pain, 5 = moderate pain, and 10 = unbearablepain. Patients were asked to rate their pain by choosing the best representing numerical value on the line [14].

Neck Disability Index (NDI): NDI is a self-report questionnaire used to determine how neck pain affects a patient's daily life and to assess the self-rated disability of patients with neck pain. NDI has a total of 10 sections each of which has six possible answers. Each item is scored from 0 (no disability) to 5 (complete disability). The total score ranges from 0 (no disability) to 50 (total disability), or, in percentage terms, between 0 and 100. Disability increases with increasing score. Items of the scale are: 'intensity of pain', 'personal care', 'lifting', 'reading', 'headaches', 'concentration', 'work', 'driving', 'sleeping' and 'recreation'. The Turkish version of this index was used in this study [15-17].

Short Form-36 (SF-36): SF-36 scale designed by Ware *et al.* [18, 19] evaluates the effects of the disease on quality of life. The scale is not specific to any disease or treatment group. It consists of 36 items and includes eight health concepts: pain, physical function, vitality/ energy, social function, disabilities caused by mental health, vitality/ energy, social function, disabilities caused byphysical problems (physical role) and emotional problems (emotional role), and general

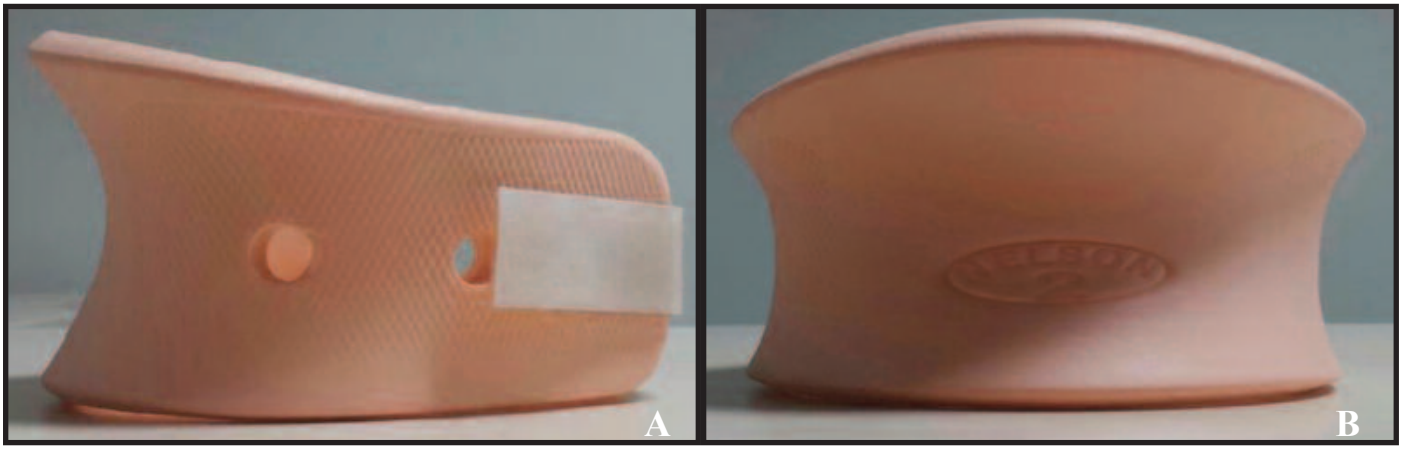

Figure 2. Semi-rigid cervical collars (A and B)

health. Questions were coded for each health concept. Score distribution was determined between 0 (worst) and 100 (best). The Turkish version of the survey was used in the study [20].

Statistical Analysis

Data analysis was performed by using IBM SPSS 22.0 statistical software package. The chi-square test and Fisher's exact test were used for comparison of categorical variables. Normal distribution of the data was assessed by the Shapiro-Wilk test. Wilcoxon Signed Rank test was used for comparison within groups and Kruskall-Wallis test was used to compare more than two independent groups. The Mann-Whitney U test was used to compare meaningful outcome variables. The values of $p < 0.05$ were accepted as significant.

Results

Two patients from soft cervical collar group, 7 patients from semi-rigid cervical collar group, and 5 patients from the control group failed to complete the study. Two patients from soft collar group and 5 patients from semi-rigid group reported discomfort such as hot flashes, skin erythema, and irritation as the reason to quit while the others abandoned the study without an excuse. The study was completed with the remaining 85 patients (30 patients from group 1, 26 patients from group 2, and 29 patients from group 3). The flow diagram of the study is presented in Figure 3.

There was no statistically significant difference between the three groups in demographic data, initial

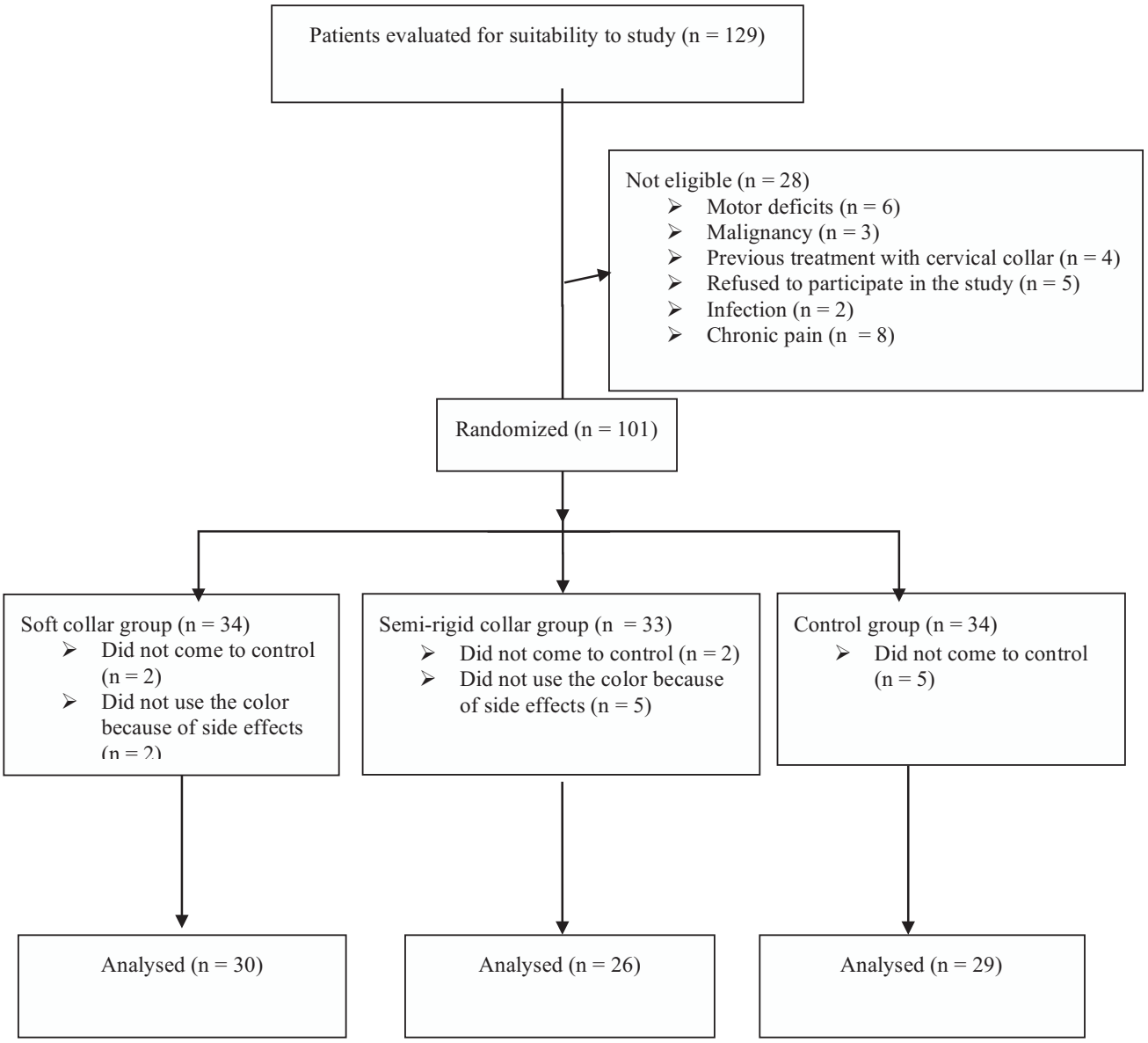

Figure 3. Study flow diagram.

VAS, NDI, and SF-36 subscores ($p > 0.05$) (Table 1). In soft cervical collar group, statistically significant improvement was found in all evaluation parameters at week 2 and week 6 ($p < 0.05$) (Table 2). In semi-rigid cervical collar group, there was statistically significant difference in all parameters at week 2 and week 6 ($p < 0.05$) except for SF-36 general health and mental health subunits ($p > 0.05$) (Table 2). In the control group, there was statistically significant improvement in all parameters at week 6 and in all but SF-36 general health and mental health subunits at week 2 ($p < 0.05$) (Table 2).

Comparison of the soft cervical collar group with the control group showed significantly better improvement in the former in VAS and NDI scores at week 2 ($p = 0.010$ and $p = 0.002$; respectively) and week 6 ($p < 0.001$ and $p = 0.002$; respectively), in SF-36 pain perception subunit at week 2 ($p = 0.003$), and in SF-36 physical component score at week 6 ($p = 0.013$) (Table 3).

Comparison of the semi-rigid cervical collar group with the control showed significantly better improvement in the former for NDI scores ($p = 0.003$, $p = 0.027$; respectively) and SF-36 pain perception subunit ($p = 0.030$, $p < 0.001$; respectively) at week 2 and 6 (Table 3).

Comparison of the two collar groups showed significantly better improvement in the soft collar group in VAS and SF-36 physical component scores at week 6 ($p = 0.023$, $p = 0,038$, respectively) but no significant difference between the groups for other parameters ($p > 0.05$) (Table 3).

Discussion

Cervical radiculopathy is among the leading causes of neck pain, which is one of the most prevalent and costly health problems encountered in the industrialized societies [21]. Cervical radiculopathy can usually be treated without surgery [10, 21]. The epidemiologic study by Radhakrishnan *et al.* [22] showed that at 14-year follow up, nearly 90% of patients with cervical radiculopathy were either asymptomatic or only mildly symptomatic.

A brief period of immobilization of the neck is a standard approach following the onset of symptoms of cervical discopathy [6, 12, 21, 23]. A cervical collar is usually sufficient to provide adequate immobilization required to reduce motion and nerve root irritation. Such collars do not completely eliminate motion and indeed may allow an active cervical ROM of up to 50% ofnormal in the semi-rigid and up to 75 to 90% of the normal in the soft collar type [11].

The results of our study showed that both soft and semi-rigid collars were effective in reducing pain and disability caused by acute cervical radiculopathy. While both soft and semi-rigid collars have been recommended frequently in management of these patients, there are in fact, few randomized, controlled studies evaluating the use of cervical collars in treatment of acute cervical radiculopathy. It should also be noted that cervical collars have only been used supplementary to the other conservative treatment modalities in the majority of the reported studies. Saal

Table1. Comparison of the demographic characteristics of the patients and pre-treatment evaluation parameters

		Group 1 (n=30)	Group 2 (n=26)	Group 3 (n=29)	*p* value
Age (year)		41 (25-57)	40 (25-61)	46 (25-62)	0.149
Gender	Female	23 (76.7%)	14 (53.8%)	18 (62,1%)	0.195
	Male	7 (23.3%)	12 (46.2%)	11 (37.9%)	
VAS		8.26 (6-10)	8.30 (6-10)	7.72 (5-10)	0.131
BMI		25.71 (19.10-36.20)	25.07 (19.10-35.16)	26.34 (21.80-35.16)	0.477
NDI		66 (33-80)	64 (30-86)	55 (22-86)	0.136
SF-36 Physical function		46.70 (29.90-57.10)	46.70 (29.90-57.10)	48.80 (29.90-57.10)	0.724
SF-36 Physical role		35.00 (28.00-56.20)	35.00 (28.00-56.20)	42.10 (28.00-56.20)	0.188
SF-36 Pain		32.80 (22.00-43.10)	29.30 (25.10-41.80)	33.20 (24.20-4650)	0.578
SF-36 General health		39.90 (24.20-57.90)	48.05 (21.90-57.90)	43.90 (21.90-60.30)	0.413
SF-36 Energy-vitality		39.60 (15.00-63.30)	39.60 (30.10-63.30)	44.30 (34.90-60.90)	0.538
SF-36 Social function		35.40 (19.10-46.30)	35.40 (24.60-40.90)	35.40 (24.60-51.70)	0.295
SF-36 Emotional role		34.30 (23.70-100)	34.30 (23.70-55.30)	44.80 (23.70-55.30)	0.324
SF-36 Mental health		34.30 (11.80-55.00)	36.80 (11.80-59.50)	36.80 (20.90-59.50)	0.528
SF-36 Physical component score		39.20 (28.10-49.30)	40.70 (24.30-52.10)	41.00 (24.00-52.70)	0.480
SF-36 Mental component score		36.80 (19.90-51.90)	37.35 (19.90-52.30)	38.20(26.60-54.80)	0.608

Data are shown as median (min–max) or number (%). VAS = Visual analog scale, NDI = Neck disability index, BMI = Body mass index, SF-36 = Short form-36. Chi-square and Fisher's exact test and Kruskal-Wallis test was used.

Table 2. Comparison of VAS, NDI and SF-36 subunit values of the groups at 2nd and 6th week.

		W2	W6	(W0-W2) *p* value	(W0-W6) *p* value
VAS	Grup 1 (n = 30)	4.46 ± 1.19	3.40 ± 1.37	< 0.001	< 0.001
	Grup 2 (n = 26)	4.84 ± 1.68	4.15 ± 1.68	< 0.001	< 0.001
	Grup 3 (n = 29)	4.79 ± 1.34	3.89 ± 1.51	< 0.001	< 0.001
NDI	Grup 1 (n = 30)	28.00 (18-49)	24.50 (17-48)	< 0.001	< 0.001
	Grup 2 (n = 26)	34.50 (14-55)	31.00 (14-52)	< 0.001	< 0.001
	Grup 3 (n = 29)	36.00 (14-55)	30.00 (14-52)	< 0.001	< 0.001
SF-36 Physical function	Grup 1 (n = 30)	52.90 (34.10-57.10)	55.00 (44.60-57.10)	< 0.001	< 0.001
	Grup 2 (n = 26)	52.90 (34.10-57.10)	53.95 (42.50-57.10)	< 0.001	< 0.001
	Grup 3 (n = 29)	52.90 (40.40-57.10)	57.10 (42.50-57.10)	0.021	< 0.001
SF-36 Physical role	Grup 1 (n = 30)	49.20 (28.0-56.20)	56.20 (42.10-56.20)	< 0.001	0.020
	Grup 2 (n = 26)	49.20 (35-56.20)	56.20 (42.10-56.20)	< 0.001	< 0.001
	Grup 3 (n = 29)	49.20 (28-56.20)	56.20 (42.10-56.20)	< 0.001	0.017
SF-36 Pain	Grup 1 (n = 30)	44.35 (29.30-55.90)	46.50 (37.50-55.90)	< 0.001	< 0.001
	Grup 2 (n = 26)	42.20 (29.30-55.90)	46.50 (33.20-55.90)	< 0.001	< 0.001
	Grup 3 (n = 29)	42.20 (29.30-55.90)	46.50 (33.20-62.70)	< 0.001	< 0.001
SF-36 General health	Grup 1(n = 30)	42.40 (24.20-57.90)	43.90 (24.20-57.90)	0.003	< 0.001
	Grup 2 (n = 26)	45.05 (24.20-57.90)	45.05 (24.20-57.90)	0.937	0.916
	Grup 3 (n = 29)	41.90 (25.10-60.30)	43.90 (25.10-60.30)	0.218	0.012
SF-36 Energy-vitality	Grup 1 (n = 30)	45.50 (34.90-63.30)	46.70 (34.90-63.30)	0.003	< 0.001
	Grup 2 (n = 26)	44.35 (34.90-63.30)	44.35 (34.90-63.30)	0.021	0.012
	Grup 3 (n = 29)	46.70 (37.20-60.90)	49.10 (37.20-63.30)	0.004	0.002
SF-36 Social function	Grup 1 (n = 30)	40.90 (35.40-51.70)	46.30 (35.40-57.10)	< 0.001	< 0.001
	Grup 2 (n= 26)	40.90 (30.0-46.30)	46.30 (35.40-57.10)	< 0.001	< 0.001
	Grup 3 (n = 29)	40.90 (30.0-57.10)	46.30 (35.40-57.10)	0.002	< 0.001
SF-36 Emotional role	Grup 1 (n =3 0)	44.80 (34.30-55,30)	55.30 (44.80-55.30)	0.010	0.001
	Grup 2 (n = 26)	44.80 (23.70-55,30)	55.30 (34.30-55.30)	0.002	< 0.001
	Grup 3 (n = 29)	44.80 (23.70-55.30)	44.80 (34.30-55.30)	0.017	0.004
SF-36 Mental health	Grup 1 (n = 30)	36.80 (14.10-55.0)	41.35 (16.40-55.00)	0.017	0.004
	Grup 2 (n = 26)	39.10 (14.10-59.50)	40.25 (16.40-59.50)	0.094	0.062
	Grup 3 (n = 29)	39.10 (20.90-55.0)	43.60 (20.90-55.00)	0.453	0.012
SF-36 Physical component score	Grup 1 (n = 30)	46.20 (33.80-55.40)	50.20 (42.80-57.90)	< 0.001	< 0.001
	Grup 2 (n = 26)	47.50 (33.70-54.10)	48.30 (35.50-56.70)	< 0.001	< 0.001
	Grup 3 (n = 29)	46.10 (33.70-56.60)	50.80 (35.50-58.20)	< 0.001	< 0.001
SF-36 Mental component score	Grup 1 (n = 30)	41.75 (26.70-54.50)	41.80 (32.60-54.00)	< 0.001	< 0.001
	Grup 2 (n = 26)	41.95 (26.70-54.50)	44.00 (30.60-54.00)	0.003	< 0.001
	Grup 3 (n = 29)	41.20 (26.70-53.30)	45.60 (30.60-52.90)	0.031	< 0.001

Data are shown as median (min–max). W0 = Week 0, W2 = Week 2, W6 = Week 6, VAS = Visual analog scale, NDI = Neck disability index, SF-36 = Short form-36. The Wilcoxon signed rank test was used for intra-group comparisons.

et al. [24] employed in 26 patients with cervical disc hernia hard cervical collar in addition to traction, ice, NSAID, exercise, and oral steroid and epidural injection when necessary and reported good to excellent recovery in 83% of the patients. However, since they did not attempt to delineate the specific role of either modality in the favorable outcome, it is not possible to infer the definitive impact of the collar in that study. In another study where either surgery, physiotherapy, or collar were used in 3 separate groups

Table 3. Comparison of the difference scores between the groups

		Group 1 n = 30	Group 2 n = 26	Group 3 n = 29	*p value*
VAS	W2-W0	-3.80 (-6.00--1.00)	-3.46 (-6.00--1.00)	-2.93 (-6.00--1.00)	0.029
	W6-W0	-4.86 (-6.00--3.00)	-4.15 (-6.00--2.00)	-3.82(-6.00--2.00)	< 0.001
NDI	W2-W0	-29.13 (-48--8)	-27.50 (-46--10)	-18.27 (-36--2)	0.002
	W6-W0	-34.10 (-51--9)	-30.46 (-51--12)	-23.58 (-37--1)	0.005
SF-36 Physical function	W2-W0	6.39 (0-14.70)	4.98 (-12.50-14.70)	4.15 (-12.50-25.10)	0.499
	W6-W0	3.54 (0-10.50)	2.34 (0-10.50)	3.52 (-0-14.60)	0.183
SF-36 Physical role	W2-W0	9.17 (-7.0-28.20)	8.96 (-14.10-21.20)	8.32 (-5.60-28.20)	0.784
	W6-W0	6.59 (-7.0-28.20)	4.07 (-7.10-7.10)	2.92 (-7.10-28.20)	0.133
SF 36 pain	W2-W0	11.28 (3.90-18.00)	10.44 (0-18)	6.36 (-12.50-17.60)	0.010
	W6-W0	2.98 (-5.10-14.10)	1.17 (-5.10-9.00)	6.47 (-4.70-26.60)	0.004
SF 36 General health	W2-W0	2.60 (-2.30-16.90)	-0.98 (-24.30-11.70)	2,00 (-10.30-22)	0.185
	W6-W0	2.78 (-2.30-11.80)	-0.86 (-24.30-11.70)	3.16 (-7.00-24.30)	0.064
SF-36 Energy-vitality	W2-W0	3.84 (-18.10-34.10)	1.82 (-9.50-14.20)	2.69 (-9.50-14.10)	0.646
	W6-W0	4.95 (-16.60-31.70)	2.10 (-9.50-14.20)	5.23 (-9.50-14.20)	0.163
SF 36 Social function	W2-W0	6.91 (-5.40-16.30)	6.88 (0-10.90)	5.61 (-10.90-21.70)	0.787
	W6-W0	10.71 (-2.10-21.80)	11.06 (5.40-21.70)	10.86 (-5.40-27.10)	0.978
SF 36 Emotional role	W2-W0	4.73 (-55.20-31.60)	10.11 (-21.80-31.60)	5.07 (-10.60-31.60)	0.090
	W6-W0	9.63 (-55.20-31.60)	14.16 (-10.50-31.60)	9.43 (0-31.60)	0.202
SF 36 Mental health	W2-W0	2.86 (-2.30-25.00)	1.48 (-9.10-25.00)	0.47 (-15.90-11.30)	0.941
	W6-W0	3.96 (-4.50-24.70)	1.73 (-9.10-25.00)	3.84 (-15.90-13.70)	0.226
SF-36 Physical component score	W2-W0	8.15 (-0.90-16.80)	6.4 (-10.40-14.00)	6.21 (-16.50-29.60)	0.110
	W6-W0	12.14 (0.90-21.90)	8.45 (-8.90-16.80)	9.87 (0.40-33.60)	0.027
SF-36 Mental component score	W2-W0	3.64 (-2.80-9.80)	3.90 (-10.20-15)	1.82 (-11.40-15)	0.113
	W6-W0	5.22 (-4.60-14.40)	5.74 (-5.70-14.40)	5.32 (-4.60-14.10)	0.849

Pairwise comparisons

		Group 1-Group2	Group 1-Group 3	Group 2-Group 3
VAS	W2-W0 (*p* value)	0.354	0.010	0.090
	W6-W0 (*p* value)	0.023	< 0.001	0.257
NDI	W2-W0 (*p* value)	0.633	0.002	0.003
	W6-W0 (*p* value)	0.226	0.002	0.027
Sf 36 pain	W2-W0 (*p* value)	0.602	0.003	0.030
	W6-W0 (*p* value)	0.120	0.056	< 0.001
SF-36 Physical component score	W6-W0 (*p* value)	0.038	0.013	0.667

Data are shown as median (min–max). W0 = Week 0, W2 = Week 2, W6 = Week 6, VAS = Visual analog scale, NDI = Neck disability index, SF-36 = Short form-36. Kruskal-Wallis and Mann-Whitney U test was used for intra-group comparisons.

of patients who were symptomatic for more than 3 months with a diagnosis of cervical radiculopathy confirmed by MRI, Perrson *et al.* [25] found no difference between the groups at the end of 12 months according to the evaluation criteria of pain, function, and mood assessed by VAS, Sickness Impact Profile, and Mood Adjective Checklist, respectively. While the results of that study have a clear implication for the role of the isolated collar application, it does not provide information as to what type of collar was more effective since a combination of a shoulder-resting rigid collar and a soft collar was used. We used soft and semi-rigid collars but no rigid collar and only for 2 weeks versus 3 months in acute versus chronic cervical radiculopathy patients.

Kuijper *et al.* [26] compared effectiveness of physical therapy accompanied by home exercise (PT), cervical collars (semi-rigid), and wait-and-see strategy in alleviating symptoms of acute cervical radiculopathy. They found significant improvement in

the parameters of NDI in the collar group compared to the group where wait and see policy was employed. Although both the cervical collar group and PT groups had significantly less pain at week 3 and 6, all three groups showed equal improvement at the end of the study. They concluded that cervical collar was at least as effective as PT in treatment of cervical radiculopathy, yet its cost was much lower than that of the latter. In our study, we used both soft and semi-rigid cervical collars to assess and compare their effectiveness and limited the duration of application to 4 weeks to avoid counterproductive effects of prolonged immobilization of the neck. The results of our study indicated significantly better pain relief and SF-36 physical component score with the soft collar compared to the semi-rigid collar whereas both collar types were found to be more effective than the control group.

Semi-rigid collars have usually been suggested as a more convenient type since they cause less limitation of ROM than rigid collars. It has been shown by electro goniometric measurements that the extent of limitation of flexion/extension, lateral bending, and rotation was 27.1%, 26.1% and 29.3%; respectively, with soft collar, and 53.7%, 34.9%, and 59.2%; respectively, with rigid collar. However, no significant difference between two collar types was detected in the limitation of a series of 15 daily life activities in the same study. In other words, electro goniometric limitation did not directly translate into limitation of daily life activities. As an explanation for these findings, the authors suggested the role of both collars as proprioceptive guides allowing patients to regulate their own cervical motion based on their level of comfort [13]. We believe the improvement for all parameters observed in the soft collar group in our study supports the above explanation that kinesthetic feedback plays a more important role in the recovery than physical limitation.

Although cervical collar application has been shown to be effective in the treatment of radiculopathy in several studies [23, 25, 26, 29], the literature is still lacking in objective data and a standard protocol as to the ideal collar wearing time. The lack of such data precludes any correlation between collar wearing time and clinical outcomes obtained in various studies in which these times seem to have been rather arbitrarily used. It is a well-known fact that collar application for longer periods may have a negative effect on the symptoms by creating weakness in the cervical muscles [27]. Atrophy-related secondary damage due to immobilization in closed plaster casts has been detected in muscle, bone, capsular, and tendinous tissue. Animal experiments have shown that structural changes can be detected in healthy muscle tissue after immobilization for a period of as short as 1 week [27]. While it is reasonable to assume that the magnitude of this problem would be the least with soft collars which allow a substantial range of motion, it should also be remembered that physiologic mechanisms developed for avoiding from pain regardless of the degree of immobilization may also cause muscular changes [28]. To avoid the latter effect, we designed collar wearing time as only 8 hours in the first 2 weeks, gradually decreased it during the next 2 weeks, and discontinued the collar at the end of the fourth week. The wearing time in our study is obviously much shorter than in several studies where it varied between 6 weeks and 3 months. We also added home exercises in the treatment protocol as a supplementary precaution against muscular atrophy. Since we observed significant improvement in most parameters in all groups in our study, we think our treatment protocol has been effective in mitigating atrophy-related muscular damage.

The Limitations of the Study

This is not a double-blind study, and this is one of the shortcomings of the study. It is not possible for patients who wear cervical collar to be blind study. The doctors who treat the patients and who evaluate the clinical conditions are different, which has reduced this shortcoming a little. One of the other limitations of this study is that NSAID is given to this patients. NSAIDs relieve pain and reduce inflammation on acute radiculopathy. The significant improvement observed in the control group at the end of 6th week in our study can be attributed to the fact that it was not a no-intervention group but the patients were given both NSAID and exercise due to ethical and methodological reasons. All our patients had substantial neck and arm pain due to the radiculopathy and it would have been unethical to deprive the patients in the control group of active treatment. Since neither collars nor exercise was enough to alleviate the pain in the acute setting, we decided to give a stable dose of NSAID to all patients despite our awareness that NSAID would make a substantial contribution to recovery via its anti-inflammatory effect on the compressed nerve root and the surrounding tissue. However, significant superiority of the results in both collar groups compared to the control group is

supportive of the specific contribution of collar application to improvement. Kuijiper *et al.* [26] allowed the patients to receive paracetamol, NSAID, or even opioid during the study, but did not employ a standard drug protocol and requested the patients to keep a diary of their drug intake. In other studies, mentioned above, no details regarding such medication have been reported by the authors.

Conclusions

The results of our study have indicated that the use of soft and semi-rigid cervical collars given in addition to home exercise program and NSAID was more effective than exercise plus NSAID without collar application in treatment of neck pain and disability in acute cervical radiculopathyin the short term. Soft collars were also found to be more effective for pain management than semi-rigid collars. In the light of the results of our study, we suggest soft collars as an effective, less expensive, and more comfortable orthotic device choice in treatment of acute cervical radiculopathy and disability. However, it should also be noted that there is still need for more studies that would focus on optimizing collar wearing time and delineating specific effects of various collar types with longer follow-up periods.

Authorship declaration

All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Are total thyroidectomy and loboisthmectomy effective and safe in benign thyroid diseases? An analysis of 420 patients

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ABSTRACT

Objectives. Ideal thyroid surgery is still a debated issue due to preoperative pathology and varying rates of postoperative incidental carcinoma and complications. In our clinic loboisthmectomy and bilateral total thyroidectomy are the treatment of choice in benign nodular thyroid diseases. The objective of this study was to analyse effectiveness and safety of bilateral total thyroidectomy and loboisthmectomy for treating benign thyroid diseases. ***Methods.*** Patient charts of the subjects that have undergone thyroid surgery due to benign thyroid diseases between 2009-2015 were evaluated retrospectively. We extracted data including number of patients, type of surgery, preoperative and postoperative pathologies and postoperative complications from departments medical records. ***Results.*** Four hundred and twenty patients including 98 (23.3%) male and 322 (76.7%) females aged between 14-80 years (mean; 47.3 ± 12.5) were included into the study. Bilateral total thyroidectomy was performed in 348 (82.9%) patients and loboisthmectomy was performed in 72 (17.1%). Mean duration of follow-up was 41 (range: 15-70) months. Incidental thyroid carcinoma rate was 24.5% (n = 103) in postoperative pathological examination. Temporary and permanent hypocalcemia was seen in 53 (15.2%) patients and 8 (2.3%), respectively. Permanent and transient recurrent laryngeal nerve palsy rate were 2.6% and 2.1%, respectively. Postoperative hematoma was observed in 7 (1.7%) patients. ***Conclusions.*** Incidental thyroid carcinoma is frequent in patients who had surgical operation for benign thyroid diseases. When revision surgeries and additional complications due to revision surgery in the remaining cases are kept in mind, bilateral total thyroidectomy or loboisthmectomy at the minimum can be considered as the ideal surgical approach for benign thyroid diseases.

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Keywords: Benign thyroid disease, multinodular goiter, thyroid surgery, papillary thyroid microcarcinoma, hypoparathyroidism

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Introduction

The main determinant in surgical treatment of thyroid disease is the findings of thyroid Fine Needle Aspiration Biopsy (FNAB) as well as subjective symptoms and suspicious ultrasonography (USG) results. FNAB findings were classified into 6 groups in 2008 by National Cancer Institute (NCI) according to Bethesda cytopathology as non-diagnostic and unsatisfactory, benign, atypia of undetermined significance or follicular lesion of undetermined significance, follicular neoplasm or suspicious for a follicular neoplasm, suspicious for malignancy and malignant [1].

The current preferred surgical approaches in benign thyroid diseases are bilateral subtotal thyroidectomy, Dunhill procedure (hemithyroidectomy and subtotal resection of the other side), loboisthmectomy (LI) (hemi-thyroidectomy and isthmectomy) and bilateral total thyroidectomy (BTT) [2, 3]. Ideal thyroid surgery is still a debated issue due to preoperative pathology and varying rates of postoperative incidental carcinoma [4, 5] and complications [2, 6-8].

In our clinic LI is the treatment of choice in benign nodular thyroid diseases involving one thyroid lobe but sparing the other lobe; however, BTT is the treatment of choice in benign multinodular goitre. The objective of this study was to analyse effectiveness and safety of total thyroidectomy and LI operations performed in our clinic in the light of literature data.

Methods

The study was approved by the Clinical Research Ethics Committee (No: 2016/184). Patient charts of the subjects that had undergone thyroid surgery due to benign thyroid diseases between 2009-2015 were evaluated retrospectively. Results of FNABs were classified according to Bethesda thyroid cytopathology system published in 2009 [9]. Patients with preoperative FNAB findings such as suspicion of malignancy or established malignant cytology, history of radiotherapy targeting neck region, history of familial thyroid carcinoma, patients with Graves' disease, who underwent complementary thyroidectomy, had pre-operative hypocalcemia or vocal cord paralysis and patients who also had parathyroid surgery because of co-existing parathyroid nodule were excluded from the study.

In patients with total thyroidectomy, calcium levels were measured at postoperative 6, 24 and 48 hours. If two consecutive measurements were lower than 8 mg/dl or if the patients have symptoms such as numbness, contractions or Chvostek or Trousseau signs, they were considered hypocalcemic [7]. Ongoing requirement of calcium and vitamin D supplementation after 1 year or having PTH level < 10 pg/ml were considered as permanent hypoparathyroidism [3]. If postoperative recurrent laryngeal nerve palsy (RLNP) improved within one year, it was considered transient, while those lasting more than one year were considered permanent [10]. We extracted data including number of patients, type of surgery, preoperative and postoperative pathology results and postoperative complications from the medical records of our department.

Statistical Analysis

Data are shown as the mean ± the standard deviation of the mean or number (percent) when necessary.

Results

Four hundred and twenty patients aged between 14-80 years (mean: 47.3 ± 12.5) were included in the study. Ninety-eight patients (23.3%) were male and 322 (76.7%) were females. Preoperative pathology was classified according to Bethesda thyroid cytopathology system (Table 1). BTT was performed in 348 (82.9%) patients and LI was performed in 72 (17.1%) patients. Mean duration of follow-up was 41 (range; 15-70) months.

Postoperative pathological examination of surgical specimen was done (Table 2). Malignant pathology rate was 24.5% (n = 103) in postoperative pathological examinations (Table 3). In 41 (80.4%) patients with malignant pathology, additional surgery was not required since BTT was done previously.

However, during follow-up period, revision surgery was performed in 3 (0.9%) patients who had undergone BTT due to recurrent disease. In 10 (19.6%) patients who had undergone LI, complementary total thyroidectomy was done since malignancy was detected. However, in 9 patients with papillary microcarcinoma no additional surgery was performed. Postoperative complications are shown in Table 4. Transient hypocalcemia occured in 53 (15.2%) the patients, when permanent hypocalcemia occurred in 8 (2.3%). There was no hypocalcemia in

Tablo 1. Preoperative Bethesda thyroid cytopathology

	BTT (n = 348)	LI (n = 72)	Total (n = 420)
Benign Cytology	195	41	236 (56.2%)
Follicular Neoplasia or Suspicion of Follicular Neoplasia	78	11	89 (21.2%)
Non-diagnostic Cytology	51	15	66 (15.7%)
Atypia of undetermined significance or follicular lesion of undetermined significance	24	5	29 (6.9%)

Data are show as number or number (percent). BTT = bilateral total thyroidectomy, LI = loboisthmectomy

Tablo 2. Distribution of postoperatve final histopathologic results

Pathology	BTT (n = 348)	LI (n = 72)	Total (n = 420)
Adenomatous Hyperplasia	225	38	263 (62.6%)
Papillary Microcarcinoma	43	9	52 (12.4%)
Papillary Thyroid Carcinoma	38	8	46 (11%)
Follicular Adenoma	28	14	42 (10%)
Hashimoto Thyroiditis	8	0	8 (1.9%)
Subacute Thyroiditis	3	0	3 (0.7%)
Follicular Carcinoma	2	1	3 (0.7%)
Medullary Carcinoma	1	1	2 (0.5%)
Riedel Thyroiditis	0	1	1 (0.2)

Data are show as number or number (percent). BTT = bilateral total thyroidectomy, LI = loboisthmectomy

Tablo 3. Histological classification of patients with incidental thyroid carcinoma

Pathology	BTT (n = 84/348)	LI (n = 19/72)	Total (n =103/420, 24.5%)
Papillary Microcarcinoma	43	9	52 (12.4%)
Papillary Thyroid Carcinoma	38	8	46 (10.9%)
Follicular Carcinoma	2	1	3 (0.7%)
Medullary Carcinoma	1	1	2 (0.5%)

Data are show as number or number (percent). BTT = bilateral total thyroidectomy, LI = loboisthmectomy

patients who had undergone LI. Permanent RLNP rate was 2.6% and transient RLNP rate was 2.1%. Permanent bilateral RLNP was found in one (0.3%) patient. When unilateral permanent RLNP was dominant at right side, unilateral transient RLNP was dominant at left side. Postoperative hematoma was observed in 7 (1.7%) patients.

Discussion

Incidental thyroid carcinoma was detected in 24.5% of patients who had undergone surgery due to benign thyroid disease. In the literature, incidental carcinoma rates were reported as 8.6-27.4% [11-14]. These rates may stem from insufficient FNAP. High specificity and sensitivity rates of FNAB are reported in the literature [15]. However, since FNAP is usually performed after a suspicious or dominant nodule was found on USG examination, foci of cancer at other locations may be missed. In addition, presence of multiple nodules in benign thyroid diseases poses a difficulty for sampling from every single nodule [5]. Furthermore, it is reported that FNAB is not adequate

Tablo 4. Postoperative complication rates of bilateral total thyroidectomy and loboisthmectomy

	BTT (n = 348)	LI (n = 72)	Total (n = 420)
Hypocalcemia	61		61 (17.5%)
Transient	53	0	53 (15.2%)
Permanent	8	0	8 (2.3%)
Permanent RLNP	10	1	11 (2.6%)
Right	8	1	9 (2.2%)
Left	1	0	1 (0.2%)
Bilateral	1	0	1 (0.2%)
Transient RLNP	8	1	9 (2.1%)
Right	1	0	1 (0.2%)
Left	6	1	7 (1.7%)
Bilateral	1	0	1 (0.2%)
Hematoma	6	1	7 (1.7%)

Data are show as number or number (percent). BTT = bilateral total thyroidectomy, LI = loboisthmectomy, RLNP = recurrent laryngeal nerve palsy

for revealing capsule invasion that is a pre-requisite for follicular neoplasia diagnosis [16].

In our study, we have performed BTT in 80.4% of patients who had incidental carcinoma except papillary microcarcinoma detected postoperatively. So, the second operation was not required. Over half of the incidental cancers were papillary microcarcinoma. Miccoli *et al.* [5] have reported that 58.6% of incidental carcinoma cases were papillary microcarcinoma. There is no consensus in the follow-up of incidentally detected papillary microcarcinoma cases in the literature. Some authors recommend only follow-up, the others recommend complementary thyroidectomy along with ipsilateral central neck dissection and radioactive iodine therapy [17]. However, unilateral LI is strongly recommended for differentiated carcinomas, if the cancer is less then 1 cm in diameter, unifocal and there is no lymph-node involvement [18].

Only 9 patients who had undergone LI and had papillary microcarcinoma have been followed up in our study and no recurrence requiring surgery was observed, but on the other hand 17.6% of patients who had LI have also undergone complementary thyroidectomy for cancers other than papillary microcarcinoma.

Complications have a strong impact on surgical treatment choices in benign thyroid diseases. The main postoperative complication associated with thyroidectomy is hypocalcemia which is a consequence of hypoparathyroidism. In the literature, the rates of transient hypocalcemia and permanent hypocalcemia have been reported in a wide range of frequencies, which are 0.9-45% and 0-24.2%, respectively [19-21]. In our study the rate of transient hypocalcemia was 15.2% and permanent hypocalcemia was 2.3% that are accepted reasonable in the literature.

Another complication that effects quality of life negatively is RLNP. The rate of transient RLNP is reported as 0.5-13.6% and permanent RLNP as 0-5.9% [6, 22-24]. In our study, the rate of transient RLNP was 2.1% and permanent RLNP was 2.6% in concordance with in the literature. Life-threatening bilateral RLNP developed in 2 (0.47%) patients. However, no additional surgery was needed in both patients. Similar rates were reported in the literature [25]. A meticulous capsular dissection and proceeding to surgery after finding the nerve is recommended to prevent RLN injury [10]. We use a similar technique in our clinic. It was shown that using intraoperative nerve monitor does not prevent RLNP; however, it was stated that it can be used as an adjunctive tool in difficult cases [10].

Hematoma, which is a serious complication requiring reoperation, has a frequency of 1-2.1% in the early postoperative period and has been found as 1.7% in our study [26, 27].

Recurrent disease was reported as 0.5-14% in the long-term follow-up in patients operated due to benign multinodular goitre and the rates were higher particularly in patients who had undergone subtotal thyroidectomy or Dunhill procedure [2, 28]. In surgeries other than total thyroidectomy for benign thyroid diseases, it has been shown that preserved tissue was pathologic in 62% of the cases [29]. In this

study, we performed revision surgery in 3 (0.7%) patients' due to recurrent disease during 41 months of follow-up. There was no recurrence requiring surgery in patients who underwent LI. The high rate of pathology in the preserved tissue, high rate of incidental carcinoma and increased complications following revision surgery may lead to the decision that ideal minimum surgery is LI as primary surgical treatment. It has been reported that postoperative complications increases after revision surgeries [8, 30, 31]. However, complication risk of complementary surgery is same as primary surgery in LI since there is no intervention to contralateral lobe in the first operation [20]. Further studies are needed in order to differentiate patients with incidental carcinoma in the preoperative period.

Conclusions

Incidental thyroid carcinoma is frequent in patients who had surgical operation for benign thyroid diseases. More than half of the incidental carcinomas are papillary microcarcinoma. When revision surgeries and additional complications due to revision surgery for remaining cancers are kept in mind, bilateral total thyroidectomy or LI at the minimum can be considered as the ideal surgical approach in the surgical treatment of benign thyroid diseases.

Conflict of interest

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Author contributions

Concept –HD, ÖY; Design –HD, BH, ÖY; Supervision –HD, ÖY; Resources and materials –HD, BH, AVS; Data collection and processing –HD, BH, AVS; Analysis interpretation and literature search –HD, BH; Writing manuscript –HD, BH; Critical review –ÖY, BH.

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The relation between the serum anti-Mullerian hormone levels and follicle count in polycystic ovary syndrome

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ABSTRACT

Objectives. Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders, affecting up to 10% of reproductive-age women. Anti-Mullerian hormone (AMH) is a member of the transforming growth factor β family and has an inhibitory effect on primordial follicle recruitment in the ovary. The study aimed to investigate the importance of serum AMH levels in the different phenotypes of PCOS and find the optimal cut-off level of AMH in PCOS patients. ***Methods.*** This was a prospective clinical trial in which diagnoses of 50 PCOS patients based on Rotterdam revised criteria were compared to 50 normo-ovulatory cases. Additionally, the PCOS group was divided into 2 subgroups based on 2 or 3 Rotterdam criteria and compared to 50 normo-ovulatory cases. ***Results.*** When compared with the control group, the AMH levels of the PCOS group were significantly higher than those of the control group (6.81 ± 2.8 ng/ml vs. 3.22 ± 2.2 ng/ml, $p < 0.001$). In the subgroup analysis, the AMH levels of Group 1 and Group 2 were significantly higher than those of the control group ($p < 0.001$). The AMH cut-off value of 4.1 ng/ml was found to distinguish healthy women from PCOS patients, with 84% sensitivity and 80% specificity. ***Conclusions.*** Subgroup analyses showed higher levels of AMH in the severe PCOS group, but the difference was not statistically significant. More studies are suggested for researching the different PCOS subgroups to detect optimal AMH thresholds.

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Keywords: anti-Mullerian hormone, ovarian follicles, polycystic ovary syndrome, ultrasonography

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders, affecting up to 10% of reproductive-age women [1]. Its prevalence varies according to the definition used and according to the reference population [2]. PCOS is responsible for many of the cases of hyperandrogenism and/or oligoanovulation.

In the last two decades, three different descriptions have been prepared for the diagnosis of PCOS. The most widely used 1990 National Institutes of Health (NIH) criteria include clinical and/or biochemical hyperandrogenism and chronic anovulation [3]. The

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2004 Rotterdam criteria suggest that PCOS should be diagnosed by two of the following three criteria: oligoanovulation, clinical or biochemical hyperandrogenism, and polycystic ovaries on ultrasound [4]. The most recent Androgen Excess and PCOS Society (AE-PCOS Society) criteria recommend that PCOS should be defined as clinical or biochemical hyperandrogenism associated with ovulatory dysfunction in the form of oligoanovulation or polycystic ovaries [5]. All three sets of criteria emphasize the exclusion of other related disorders before making a diagnosis of PCOS.

Anti-Mullerian hormone (AMH) is a product of the granulosa cells of growing follicles [6-9] and may regulate their growth and development by exerting a paracrine negative feedback effect on the recruitment of precursor (primordial) follicles [7, 10]. AMH also inhibits the sensitivity of follicles to follicle-stimulating hormone (FSH) [10, 11]. AMH levels are increased in PCOS in proportion to its clinical severity, as reflected by their number of diagnostic features [12] and the antral follicle count [8, 13]. Considerable evidence has been put forward that this increased AMH level results from the stimulatory effect of androgens on early follicular growth [11]. Besides, blood AMH levels were shown by cluster analysis to be associated with androgen levels and so have been proposed as a diagnostic marker for ovarian hyperandrogenism [14]. AMH levels are also raised in ovulatory women with a polycystic ovary [15]. There is debate about whether this increase indicates ovarian hyperandrogenism or rather indicates an enlarged oocyte pool (increased "ovarian reserve"). In the meta-analysis conducted by Pepe et al. [16], an AMH cutoff value of 4.7 ng/ml was determined to distinguish healthy women from PCOS patients. Additionally, AMH shows different PCOS phenotypes of varied severity [12, 13, 17, 18]. Koninger et al. [19] compared the diagnostic potency of AMH with sonographic views of ovaries, ovarian volume, testosterone, androstenedione, luteinizing hormone (LH), and the LH/FSH ratio for the purpose of establishing the age-dependency of AMH.

The aim of the present study was to evaluate serum AMH levels in PCOS subgroups and to compare serum AMH levels with ovarian ultrasound features and determine the optimal cut-off level of AMH in PCOS patients.

Methods

This was a prospective clinical trial in which diagnoses of 50 PCOS patients based on Rotterdam revised criteria were compared to 50 normo-ovulatory cases. Additionally, PCOS group was divided in to 2 subgroups with inclusion of 2 or 3 Rotterdam criteria and compared to 50 normo-ovulatory cases. Thus, Group 1 involved patients with oligomenorrhea and polycystic ovarian morphology and was defined as the mild PCOS group, and Group 2 involved patients with oligomenorrhea, hyperandrogenism, and polycystic ovarian morphology, and it was defined as the severe PCOS group. The study was approved by the institutional review board of University, and all patients gave their informed consent before inclusion in this study. The study was conducted between November 2012 and May 2013. Participants were recruited from the obstetrics and gynecology polyclinics of University Medical School. Patients aged 18-35 years were taken in to the study. Weight and height were measured, and BMI was calculated as weight (kg)/height (m2). During the medical examination, patients were specifically asked about their menstrual history. Oligomenorrhea was defined as an average cycle length of more than 35 days and included women with frank amenorrhea. Clinical hyperandrogenism was defined by the presence of hirsutism (a modified Ferriman-Gallwey score over 8) and/or acne located in more than two areas as previously reported [20]. Blood samples from all the participants were collected on day 3 of the menstrual bleeding between 8:00 and 9:00 a.m. after an overnight fast. The blood samples were transferred to a central laboratory the same morning; following centrifugation at 4°C for 20 min at 3000 rpm, the serum samples were transferred into polypropylene tubes and stored at -80°C until final analysis. The patients' serum levels of FSH, LH, estradiol (E2), thyroid-stimulating hormone (TSH), prolactin, total testosterone, dihydroepiandrosteronesulphate (DHEAS), and 17-hydroxyprogesterone (17-OHP) were measured by immunoassays as described previously [20]. Serum AMH levels were assessed using the enzyme-linked immunosorbent assay human AMH ELISA kit provided by Sunred Biological Technology (China). In addition, on the third day of the cycle, the antral follicle count was performed with a General Electric Alfa Logic 3 ultrasound system with a 5 mHz transvaginal transducer by the same

physician. In virgin patients, a transabdominal transducer was used. After determination of the longest medial axis of the ovary, the length and thickness were measured and the ovarian volume was calculated as described previously [21]. For each ovary, the total number of all visible follicles smaller than 10 mm in diameter was counted by slow and continuous scanning of the entire ovary, from one margin to the other in a longitudinal cross-section. For the ovarian volume and the follicle number, the data used for statistical analysis were the mean of recorded values for the left and right ovaries. We excluded from the analysis patients with a history of ovarian surgery.

Statistical Analysis

The sample size calculation was based on mean AMH levels. Mean AMH levels were found to be 6.86 ± 3.13 and 2.70 ± 1.67 in each group of 30, for a total of 60 patients in a pilot study. Calculated with GPower 3.1 (http://www.gpower.hhu.de/), a power of 80% with alpha = 0.05 was calculated when comparing the two-means using Student t-test with a total sample size of 12. We extended the study until completion of the 50 patients in each group, with the aim of making subgroup analyses. SPSS v.15.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Numbers and percentages were used to express the categorical variables. Continuous variables were represented with mean and standard deviation. When the variables showed normal distribution, independent samples t-test was performed for the age, FSH and AMH. The Shapiro wilktest was used to compare the mean levels of AMH. In the case of histograms, the nonparametric Mann-Whitney U-test and Kruskal-Wallis test were used to evaluate the variables that did not fit a normal distribution. AMH levels were compared among PCOS groups using ANOVA test and subgroups analysis were performed. Correlation analysis was used to determine whether there was a statistically significant association between continuous variables and Spearman's correlation coefficient was computed. Receiver operating characteristic (ROC) curves were used to analyze the accuracy of AMH levels in predicting PCOS. According to this method, the following criteria should be met for the best test: sensitivity = 100%; false negativity = 0 (1-Specificity = 0); the area under the curve (AUC) = 1; and diagnostic value of AUC (p-value) < 0.05. The Youden index, which uses the point with the highest sensitivity and specificity on the ROC curve, was used to determine the cutoff values. p values < 0.05 were considered statistically significant.

Results

Between November 7, 2012 and May 2013, a total of 100 volunteers aged 18-35 years agreed to participate in the study. As shown in Table 1, when compared with the control group, weight was significantly higher in the PCOS group (p = 0.004). The body mass indexes (BMIs) of the PCOS group were higher than in the control group (p < 0.001). The waist circumferences of PCOS group were significantly higher than those of the control group (p = 0.002). Results of the Ferriman-Gallwey scoring were significantly higher than those in the control group (p < 0.001) (Table 1). FSH, E2, and TSH levels were similar in all groups, but LH levels were higher in the PCOS group (p < 0.001) (Table 2).

The AMH levels of the PCOS group (6.81 ± 2.8 ng/ml) were higher than those of the control group (3.22 ± 2.2 ng/ml), and this was statistically significant (p < 0.001).

In the subgroup analysis, the AMH levels of Group 1 (Mild PCOS Group = Polycystic Ovary + oligo/amenorrhea) and Group 2 (Severe PCOS = Polycystic Ovary + oligo/amenorrhea + hyperandrogenism) were significantly higher than

Table 1. Demographic data in PCOS and control groups.

	PCOS (n=50)	Control (n=50)	*p*
Age (years)	26.2 ± 4.89	29.56 ± 4.92	< 0.001
Weight (kg)	67.4 (48-99)	61.1 (49-80) [a]	0.004
Length (m)	1.62 (1.53-1.75)	1.63 (1.56-1.74)	0.08
BMI (kg/m^2)	25.7 (18-36)	23.9 (18-95) [a]	< 0.001
Waist circumference (cm)	80.5 (62-114)	73.7 (62-114) [a]	0.002
Ferriman-Gallwey score	10.34 (2-23)	3(0-5) [a]	< 0.001

Data are shown mean ± standart deviation or mean (range). BMI = body mass index, PCOS = polycystic ovary syndrome. p values were determined by non-parametric Mann-Whitney U test

Table 2. Serum AMH levels and hormonal and metabolic data in PCOS and control groups.

	PCOS	Control	*p*
AMH (ng/ml)	6.81 ± 2.8	3.22 ± 2.2	< 0.001
FSH (mIU/ml)	5.01 ± 1.43	4.62 ±1.81	0.054
LH (mIU/ml)	10.64 (2.80-33)	4.80 (2.1-32)	< 0.001
E2 (pg/ml)	61.74 (25-219)	54.9 (22-173)	0.242
PRL (mIU/ml)	16.07 (1.9-29)	14.2 (6-25)	0.08
TSH (mIU/ml)	1.56 (0.2-5.0)	1.72 (0.56-3.2)	0.075
DHEAS (mg/dl)	263 (96-450)	195 (56-310)	0.056
17-OHP (ng/ml)	0.90 (0.3-1.5)	0.61 (0.01-1.4)	0.965

Data are shown mean ± standart deviation or mean (range). PCOS = polycystic ovary syndrome, AMH = anti-Mullerian hormone, FSH = follicle-stimulating hormone, LH = luteinizing hormone, E2 = estradiol, PRL = prolactin, TSH = thyroid-stimulating hormone, DHEAS = dihydroepiandrosteronesulphate, 17-OHP = 17-hydroxyprogesterone. *p* values were determined by the Shapiro wilk test.

those of the control group (6.68 ± 2.8, 6.88 ± 2.9, and 3.22 ± 2.2 ng/ml, respectively; $p < 0.001$). The AMH levels of Group 2 were higher than those of Group 1, but this wasn't statistically significant ($p = 1.0$).

The AUC was calculated for AMH levels. According to the ROC curves, the estimated AUC for AMH levels was 0.88 for detecting PCOS in patients ($p < 0.001$). We found an AMH cut-off value of 4.1 ng/ml to distinguish healthy women from PCOS patients, with 84% sensitivity and 80% specificity (Figure 1).

There was no relation between AMH levels and ovarian stromal thickness ($p = 0.866$) or ovarian volume ($p = 0.797$). A positive correlation was found between follicle numbers and AMH levels ($p < 0.001$) (Table 3).

Discussion

AMH has an important role in folliculogenesis. Increased serum levels of AMH have been defined in patients with PCOS [8]. The highest expression of AMH is found in preantral and small antral follicles

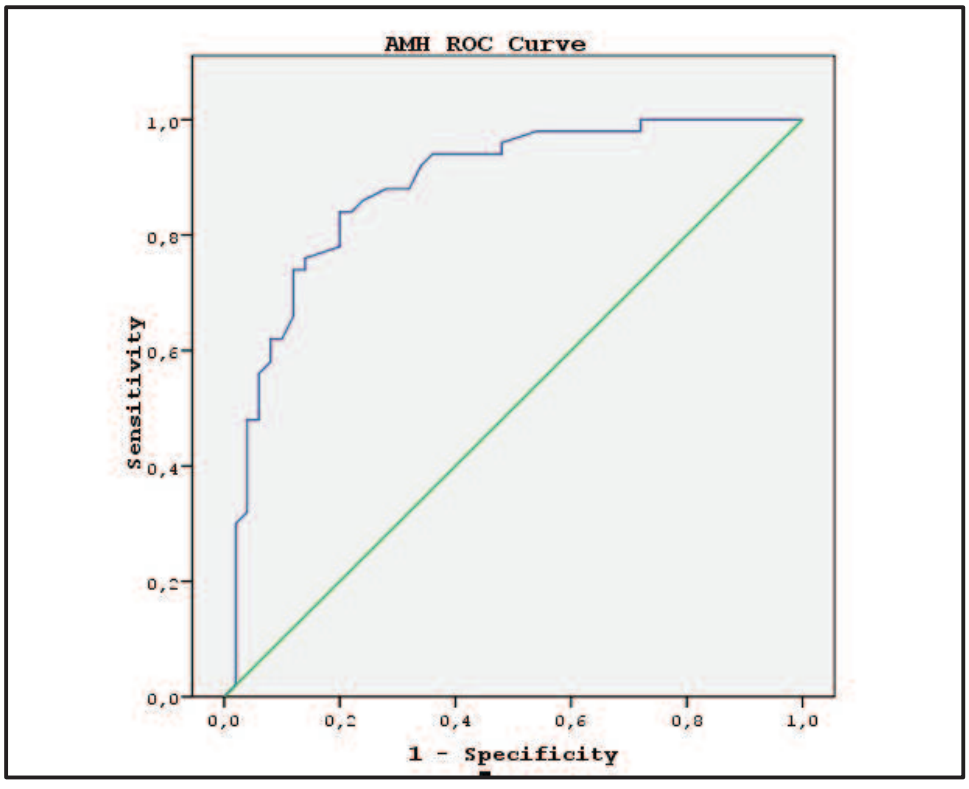

Figure 1. Anti-Mullerian lomone level ROC curve ($p < 0.001$).

Table 3. The correlation coefficients (*r*) and levels of significance (*p*) between anti-Mullerian homone and mean ovarian volume, mean stromal thickness and mean number of follicles

	r	*p*
Mean ovarian volume	0.037	0.797
Mean stromal thickness	0.024	0.866
Mean number of follicles	0.562	< 0.001

[22]. AMH has a negative role in follicular recruitment and causes follicular atresia [23]. Also, AMH reduces the sensitivity of preantral and antral follicles to FSH [24]. According to many studies, serum AMH levels have shown a greater increase in PCOS patients than in normo-ovulatuory women [25].

In the present studies, differences in AMH levels between different PCOS subgroups were evaluated and checked; the results included additional features involved in the pathogenesis of PCOS, for example, androgens, gonadotropins, and sonographic parameters. Next to sonographic parameters and androgens, which were used in the streaming of PCOS patients, patients with severe PCOS also showed higher levels of AMH and LH and higher LH/FSH ratios than did patients with mild PCOS and controls. AMH appears one of the single best and useful parameters to determine different degrees of PCOS at the group level [12, 13, 18, 19]. Similar results were found in our study: the AMH levels of the PCOS group was higher than those of the control group; this was statistically significant ($p < 0.001$).

AMH and the antral follicle count demonstrated comparable diagnostic potential for the indication of severe and mild PCOS in recent studies. It is known that the antral follicle count is strongly associated with AMH, as proven by several studies also in our analyses [26, 27]. AMH levels seem to be more appropriate for reflecting PCOS severity at the group level, but not necessarily in PCOS diagnosis, as shown by the diagnostic potency of AMH and antral follicle count in the studies [19]. Piouka *et al.* [12] demonstrated that, conversely to AMH levels, the antral follicle count did not differ significantly between severe and mild PCOS subgroups; however, AMH levels differed significantly. As indicated by Dewailly *et al.* [13] higher sensitivity and specificity in the diagnosis of severe PCOS were found for AMH compared to follicle numbers, qualifying AMH as a potential alternate marker for antral follicle count in PCOS diagnosis. As a result, AMH and antral follicle count both are appropriate diagnostic tools for determining PCOS severity. On the other hand, the ovarian volume demonstrated substantially lower diagnostic potency compared to antral follicle count [19]. In our study, the AMH levels of Group 2 were higher than those of Group 1, but the subgroup difference in AMH levels wasn't statistically significant. This may be due to the insufficient number of patients in the subgroups.

Dewailly *et al.* [13] analyzed a population with severe PCOS and detected a threshold of 5 ng/ml for the diagnosis of severe PCOS. Köninger et al. [19] found the optimal threshold of AMH for both mild and severe PCOS to be 3.5 ng/ml, with 84% sensitivity and 89% specificity for severe PCOS and 71% sensitivity and 89% specificity for mild PCOS. In our study, in the ROC analyses of AMH, the estimated AUC was found to be 0.88. We found the optimal AMH cut-off value to be 4.1 ng/ml to distinguish healthy women from PCOS patients, with 84% sensitivity and 80% specificity.

In de Vet *et al.*'s study [28], the number of small-growing follicles which show ovarian reserve in ovaries decreased with advancing age, and showed a relationship between the reduced stock of primordial follicles and the number of follicles that were little developed. Women < 25 years of age had higher serum AMH concentrations than those aged 35 years and above, and when women were tracked for a period of 1-7 years, there was a decrease in serum AMH levels, with levels becoming undetectable when menopause was reached [29]. Similarly, in our study, a statistically significant positive correlation was found between the average number of ovarian follicles and AMH levels ($p < 0.001$).

The Limitations of the Study

Our study limitations are the number of the subgroups may be more thus we could assess the PCOS severity at the group level better. Nevertheless the complete data set was from a single center and the same physician performed all the ultrasonographic procedures. Thus, this could better accomplish interobserver discrepancies.

Conclusions

Studies analyzing PCOS have noticed that AMH serum levels provide suitable results for detecting PCOS severity at the group level. AMH serum levels in PCOS patients shows similar results to AFC in the diagnosis of PCOS cases. Furthermore, for the detection of mild PCOS, AMH seems to be the most definitive diagnostic tool next to sonographic views. In patients where vaginal examination is not possible or in patients without hyperandrogenemia, AMH may be utilized as a believable alternate parameter in PCOS diagnosis. More studies are suggested for further research into the diagnostic potency of AMH, considering different PCOS subgroups to detect optimal AMH thresholds.

Conflict of interest

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Oxidative stress in relation to adenosine deaminase, nitric oxide, nitric oxide synthase and xanthine oxidase in oral cavity cancer

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ABSTRACT

Objective. Inflammation and oxidative stress are considered as the main pathways in oral cavity carcinoma. The aim of this study was to evaluate the activity levels of adenosine deaminase (ADA), nitric oxide (NO), nitric oxide synthase (NOS), and xanthine oxidase (XO) in oral cavity carcinoma, to determine their potential roles in carcinogenesis with relation to oxidative stress. ***Methods.*** Seventeen patients with oral cavity cancer underwent surgery as the primary therapy, were consisted in the study. Resected oral cavity carcinoma tissues were compared with the adjacent tumor-free control tissues of the same patients; ADA, NO, NOS, XO activity levels were evaluated in terms of difference. ***Results.*** There is a significant increase of ADA activity in squamous cell cancer tissues, which indicates a difference between the normal and tumor tissues at enzyme levels (p<0.001). ***Conclusion.*** Elevated ADA activity might be an attempt to supress formation of the immunosupressed niche which promotes the onset of neoplasia and/or to inhibit tumor progression and metastasis.

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Keywords: Adenosine deaminase, nitric oxide, nitric oxide synthase, oral cancer, oxidative stress, xanthine oxidase

Introduction

Oral cavity cancer is the most common in the head and neck cancers and has a high morbidity and mortality. Certain risk factors for the development of oral cavity carcinoma including tobacco, alcohol, nutrition, viral infection, poor dentition are known; these factors explain 90-95% of the cases especially with squamous cell carcinoma [1].

Carcinogenesis studies emphasize that carcinogenic substances are needed to be metabolized by the enzyme systems. As regarding to this accepted hypothesis, these chemicals turn into the electrophilic metabolites (radicals) in the body and lead to the

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activation of oncogenes caused by DNA damage [2-4]. We think that these enzyme systems are more significant in relation to oxidative stress in cancer types, in which predisposing factors such as oral cavity cancers are frequent.

Nitric oxide (NO) is a free oxygen radical that has significant immune functions and produced from L-arginine by NO synthase (NOS). The specific effect of NO in carcinogenesis probably depends on its local concentration and it is suggested that NO facilitates tumor growth and increases angiogenesis. The effects of NO in carcinogenesis are; advancing tumoral vascularization and angiogenesis, facilitating tumoral cell adhesion to endothelial cells and, increasing the vascular permeability. All of these effects can facilitate the rapid growth of the primary tumor [5].

Adenosine deaminase (ADA) and xanthine oxidase (XO) are enzymes that participate in purine and DNA metabolism. These enzymes are needed for the turnover of nucleic acids in tissues. ADA irreversibly converts adenosine and deoxyadenosine to inosine and deoxyinosine. This pathway increases the formation of hypoxanthine and xanthine which is finally converted to uric acid by XO. These enzymes are shown as the central mechanism of FORs formation [6, 7].

The research question of our study is whether there is a difference between tumor and tumor-free tissue in terms of enzyme levels in relation to oxidative stress. The aim of this study was to evaluate the activity levels of ADA, NO, NOS and XO in tumor tissues of oral cavity, to determine their potential roles in carcinogenesis with relation to oxidative stress.

Methods

Patients

This study consisted of seventeen patients who underwent surgery for oral cavity cancer (median age of 58 years, range: 27 to 84 years) in Ear, Nose and Throat Departments of two tertiary referral centers. All patients were histologically diagnosed by incisional biopsy prior to surgical procedures. None of the patients had a history of prior radiotherapy and/or chemotherapy. All patients were staged by the TNM classification according to American Joint Committee on Cancer (AJCC).

The approval was taken from the institutional research committee (GU117) and informed consents were obtained from from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Samples

Surgical resection was performed on all patients under general anestesia. After the surgical resection, tumor and adjacent tumor-free samples from oral epithelial tissue (which are confirmed histologically) with 2-3 mm diameter were put immediately in eppendorf tubes (with 1-2 cc of 0.9% saline) and transfered in liquid nitrogen to the biochemistry laboratory, where the samples were preserved for 6 months at -80 °C temperature until the time of analysis.

Biochemical Measurements

On the analysis day, the tissues were first washed with deionized water to separate blood then homogenized in a homogenizator (Heidolph DIAX 900 model; Heidolph Instruments GmbH & Co. KG, Scwabach, Germany). The upper clear layer was taken to be used in the assays after centrifugation at 5000 g for about 20 minutes.

Measurements of ADA Activity

ADA activity was measured spectrophotometrically by Guisti method [8] which is based on the direct measurement of the ammonia and the results were expressed as unit per mililiter (IU/ml).

Measurement of NOS and NO Activity

NOS activity and NO pool ($NO.+NO_2-$) were measured as described, respectively. NOS activity method is based on the diazotization of sulfanilic acid by nitric oxide at acid pH and subsequent coupling to N-(1-napthyl-ethylene diamine), which is the modification of a previous study [9]. Measurement of the NO pool (mainly consisting of $NO.+NO_2-$) is also based on the same chemical reaction, in which to a greater extent of nitric oxide (NO.), and to a lesser extent of nitrite anion (NO_2-), give a diazotization reaction with sulfanilic acid. The absorbance of complexone formed with N-(1-napthyl-ethylene diamine) reflects the sum of NO. and NO_2- levels in the reaction medium, which is termed the NO pool in the present study. In this method, sodium nitroprusside is used as the chemical standard and the reaction scheme given for the NOS activity measurement,

except for the incubation of the sample with arginine, is followed [10]. The results were expressed as unit per mililiter (IU/ml) for NOS and milimol (mM) for NO.

Measurement of XO Activity

XO activity was determined spectrophotometically by measuring uric acid formation from xanthine at 293 nm [11]. The results were expressed as unit per mililiter (IU/ml).

Statistical Analysis

The correlation between clinicopathological features and the enzyme, molecular activity levels were studied. Statistical analysis was performed with SPSS for Windows, Version 15.0. Chicago, SPSS Inc. The continuous variables was evaluated by visual (Histogram) and statistical methods (Shapiro–Wilk and Kolmogorov and Smirnov Tests) and it was seen that the data did not follow normal distribution. Thus non parametric tests were used. The results were evaluated statistically by using Wilcoxon Signed Rank Test, Kruskal-Wallis Variance Analysis and Spearman Correlation Analysis Test with statistical significance being accepted at 0.05.

Results

The distribution of localization of the oral cavity squamous cell carcinoma of the patients is given in Table 1. Smoking habit was determined in 70.6% (n 12) of the patients and the habit of alcohol usage was 5.9% (n=1).

Clinical and pathological TNM staging were done pre- and postoperatively. The agreement between clinical and pathological staging was assessed as significant (Cohen's kappa/ κ =1,00/ p<0.001). The numbers and percentages of clinical and pathological TNM staging of the patients are given in Table 1.

The ADA activities were significantly increased in cancer tissues compared with the adjacent tumor-free control tissues of squamous cell carcinoma (p<0.001). NO and NOS activities were decreased but not statistically significant (p=0.070 and p=0.796, respectively). No statistically significant difference was observed in terms of XO activities (p=0.233) (Table 2).

No significant correlations were determined between the activity levels of enzyme-molecule (normal and tumor tissue) and age with Spearman correlation analysis test (Table 3). Clinicopathological T stage was classified as T1, T2 and T3+4 and there was no correlation between the activity levels of enzyme-molecule (tumor tissue) and clinicopathological T stage with Kruskal-Wallis variance analysis test (Table 4).

Table 1. Localization and the TNM staging of the oral cavity squamous cell carcinoma of the patients

Variable	Patients (n=17)	%
Tumor Localization		
Tongue	9	52.9
Retromolar trigon	2	11.8
Lip	3	17.7
Gingiva	1	5.9
The floor of mouth	2	13.3
TNM Staging		
Tumor		
1	4	23.5
2	8	47.1
3	2	11.8
4	3	17.6
Nodal		
0	9	52.9
1	4	23.5
2	3	17.6
3	1	5.9
Distant Metastasis		
0	16	94.1
1	1	5.9

Table 2. The activities of ADA, NO, NOS, XO between normal and tumor tissues

	Normal tissue (IU/ml)	Tumor tissue (IU/ml)	*p*-value*
ADA	6.85 (2.45-10.89)	17.98 (9.78-36.45)	p=0.001
XO	0.16 (0.02-0.23)	0.06 (0.04-0.07)	p=0.233
NO	89 (49-163.8)	69.6 (23-170)	p=0.070
NOS	6.02 (5.20-9.70)	5.63 (4.64-7.78)	p=0.796

Data are shown as median (min-max) values. ADA=adenosine deaminase, NO=nitric oxide, NOS=nitric oxide synthase, XO=xanthine oxidase, *=statistical analysis with the Wilcoxon signed rank test

Table 3. The correlation between the age and the activities of ADA, NO, NOS, XO of the normal and tumor tissues

	Normal tissue *p* value*	Tumor tissue *p* value*
ADA	0.670	0.842
XO	0.913	0.105
NO	0.083	0.132
NOS	0.713	0.459

ADA=adenosine deaminase, NO=nitric oxide, NOS=nitric oxide synthase, XO=xanthine oxidase, *=statistical analysis with the Spearman correlation analysis test

Table 4. The correlation between T stage and the activities of ADA, NO, NOS, XO of the tumor tissues

	ADA	NO	NOS	XO
Asym. Sig. (*p* value)*	0.397	0.805	0.797	0.883

T stage describes tumor staging of 1-4, ADA=adenosine deaminase, NO=nitric oxide, NOS=nitric oxide synthase, XO=xanthine oxidase, *=statistical analysis with the Kruskal-Wallis variance analysis test

Discussion

The biological and molecular mechanisms in head and neck cancer were investigated in many studies in recent years. The results are controversial, may be according to the complexity and alteration of the mechanisms. Risk and predisposing factors such as tobacco, alcohol, poor dentition etc. are common (90-95%) in oral cavity carcinoma cases, especially squamous cell carcinoma [1-4]. Although chronic inflamation, free oxygen radical formation, activation of oncogenes and DNA damage are the main steps, pathways are variable for different types of cancer.

In this context, enzyme studies performed with the tumoral and peritumoral tissues are valuable and thought to be effective to understand the carcinogenesis process especially relation with oxidative stress. Although recent studies were limited to blood, serum, secretions etc. and especially focused on as the diagnostic, prognostic or follow-up parameters. In the present study, the role of oxidative stress is elucidated in relation to ADA, NO, NOS and XO activities in patients with oral cavity carcinoma. To our knowledge, this is the first study concerning the measurement of ADA, NO, NOS and XO activities in tumor tissues of patients with oral cavity carcinoma.

ADA is the key enzyme in purine salvage pathway of mammalian, that catalyzes the conversion of adenosine to inosine and deoxyadenosine to deoxyinosine. Due to the irreversibility of the reaction, it is the one of rate-limiting steps in adenosine degradation [6, 7]. Adenosine is present in the interstitial fluids at low levels in physiological conditions. In pathophysiological conditions such as ischemia, inflammation, trauma etc., it can rapidly increase as a result of releasing from intracellular space. It behaves as an 'alarm' that constitutes various responses to restore tissue homeostasis. In the acute phase, adenosine activates pathways that aim to promote healing process however in the chronic phase, it may trigger immune supression or promote unremitting wound healing process such as fibrotic remodelling. In the carcinogenesis process, the increase of adenosine is not a passive product of cancer tissues [12]. It not only generates 'an immunosupressed niche' to promote the onset of neoplasia, an angiogenic and matrix remodelling environment but also activates tumor progression and metastasis indirectly [13, 14].

ADA enzyme activities in head and neck cancer tissues have presented controversial results in literature review [15-19]. Altered purine metabolism in various cancer types which is affected actively by genetic alterations may be one of the reasons for this discrepancy [20]. Ashok *et al.* [15] reported that serum ADA levels in head and neck cancer cases was significantly increased and a highly significant correlation was found between the serum ADA activity and the stage of the disease. After the treatment of the disease by different modalities, the

serum ADA levels were determined to be decreased [15]. Few published clinical studies about the activity of ADA in the oral cavity carcinoma are available in the literature. In the study by Rai *et al.* [16] salivary ADA activity in patients with squamous cell carcinoma of tongue was assessed significantly increased compared with the control group and as the disease stage progressed from stage I to stage III in both genders. In another study by Kelgandre *et al.* [17] statistically significant increase in serum ADA levels was observed in oral cavity carcinoma cases compared with the control group. Also serum ADA levels increased significantly with the histopathological grade. They suggested that serum ADA levels in squamous cell carcinoma of tongue and oral cavity carcinoma might be a useful diagnostic and prognostic biomarkers in clinical practice [16, 17]. In contrast Saracoglu *et al.* [19] found that ADA was significantly lower in saliva of the patients with oral cavity cancer compared with larynx cancer patients and control subjects. However, a statistically significant difference in preoperative and postoperative activity levels of ADA were not observed in patient groups. The low ADA activities in patients with the oral cavity cancer were reported as a compensatory mechanism to the high metabolism of purine and DNA [19, 20]. Our study reveals that ADA activity was increased in the tumor tissues of the patients with oral cavity carcinoma. Our results are in agreement with the studies that showed high ADA activity in patients with various head and neck cancer types [15-17] as a compensatory mechanism against toxic accumulation of its substrates. However there was a significant correlation between serum and salivary ADA activity and tumor stage or histopathological grade in the studies [16-18], in the present study no significant correlations were determined between the activity levels of enzyme-molecule (normal and tumor tissue) and age or clinicopathological T stage (Tables 3 and 4). This finding in agreement with some studies [19-20] can be explained as increased ADA activity is independent from the stage of the tumor.

Another substantial finding of our study is no statistically significant difference was observed in terms of XO activities, in spite of increased activity levels of ADA in the same pathway. ADA and XO enzymes are consecutive enzymes that participate in purine salvage pathway. As thought to be a compensatory mechanism against toxic accumulation of its substrates, XO activities is also be expected to increase. Our results can be explained as elevated ADA enzyme activity is not only a compensatory mechanism against toxic accumulation of its substrates but also an active process.

NO has many critical roles as vasodilatation, regulation of wound healing, non-specific immune response to infection, host defense, cytotoxicity, etc. [21]. In carcinogenesis process, the effect of NO depends on the local concentration of the molecule. It can show both tumoral and antitumoral effects like a 'double-edged blade'. In high concentrations NO inhibits tumor growth however in low concentrations contributes to the tumor development [22]. It is known that endogen NO is cytotoxic and induce the death of tumoral cells [23]. NO and NOS assume potential roles in carcinogenesis with regard to their oxidant and antioxidant effects on the process of inflammation. NO is also one of the nonspecific protective factors against pathogenic microorganisms in the oral cavity. However, the excessive amount of NO can cause the destruction of tumor tissue in tumor metabolism. Therefore NO and NOS may be effective in the development of the oral cavity cancers. In the study by Avci *et al.* [24] NO level and NOS activity were found decreased in the malign lesions compared with the benign lesions. They suggested that decrased NO might be an attempt to supress angiogenesis and/or malign lesions might supress NO production for rapid proliferation [24].

In our study NO and NOS activities were decreased in tumor tissue but not statistically significant. This finding is compatible with the knowledge that NOS expression is mainly in peritumoral and tumoral tissues [22], owing to the control samples were adjacent tumor free tissues. The activity in the tumoral tissue may thought to be the result of carcinogenesis and in the peritumoral tissue, inflammation may be the reason.

The Limitation of the Study

However there are some limitations of our study as 3 of the cases that are lip cancer. The etiological factors involved in lip cancer development are different from other oral cavity cancers such as environmental ultraviolet light exposure is the most common factor. Although smoking has also been associated with the development of lip cancer [1], this difference in the etiology cannot be ignored but oxidative stress has been thought to be the common pathway.

Conclusions

ADA enzyme activity of the tumor tissues was found to be increased compared with tumor free tissues in oral cavity carcinoma patients. Adenosine which is a tumor promoting substrate in carcinogenesis process, generates this effect in the onset of neoplasia, progression and metastasis processes [13, 14]. Degradation of this substrate is the main outcome of increased ADA enzyme activity and contributes to free oxygen radicals development.

In this context, elevated ADA activity might be an attempt to supress formation of the immunosupressed niche which promotes the onset of neoplasia and/or to inhibit tumor progression and metastasis. We think that further studies especially animal and invivo studies are needed to clarify the effectiveness of ADA in this field.

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Ectoparasitic infestations of the eye: Three cases with three different arthropods

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ABSTRACT

Parasitic infestations of the external eye are uncommon and more often prevalent in tropical and developing countries. We present three cases with ocular infestation caused by three different arthropods admitted to the ophthalmology department of a tertiary health care centre during two months. The first case was infected with the larvae of *Oestrus ovis*, the second case with *Phthiriasis palpebrarum*, and the third case with a tick, *Ixodes ricinus*. All patients in this report were living in city center of Bursa, one of the most industrialized cities of Turkey. Ocular ectoparasitic infestations should be taken into consideration in differential diagnosis of conjunctivitis, blepharitis and eyelid mass, even if patients living in urban areas. Due to the rarity of ocular ectoparasitic infestations and overlapping symptoms with more commonly occuring ophthalmic conditions, a careful ophthalmic examination is required to avoid misdiagnosis and delay in treatment.

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Keywords: Ocular ectoparasitic diseases, ophthalmomyiasis, phthiriasis palpebrarum, ocular tick infestation

Introduction

Parasitic infestations of the external eye are uncommon. They usually cause mild symptoms, so most cases of ocular infestations caused by arthtopods are late or misdiagnosed. Generally, damage of the eye is a result of the direct mechanical effects of the parasite or its larvae, or pathogens transmitted by these arthropods [1-3]. The diagnosis usually depends on detecting the arthropod on the ocular surface with a detailed slit-lamp examination. If the arthropod or its larvae are found on the ocular surface or eyelids, the most effective treatment is removing them mechanically as soon as possible. Nevertheless, some ectoparasites can invade the globe and cause temporary or permanent loss of vision. Ocular ectoparasitic diseases commonly seen are ophthalmomyiasis, phthiriasis palpebrarum, and tick infestations [1, 4]. In this report, we presented three different cases infected by three different arthropods, and then referred to ophthalmology department of a tertiary health care center of Bursa, Turkey.

Case Presentations

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Case 1

A 21-year-old male presented to ophthalmology clinic with a 4-hour history of foreign body sensation, itching and lacrimation in his left eye. The symptoms began immediately after some muddy water was splashed to his left eye while he was working on the land. Biomicroscopic examination of the left eye revealed an about 1-2 mm-length-larva moving on the surface of the bulbar conjunctiva. Pulling down the inferior eyelid enabled visualization of two larvae moving away from the light on the fornices (Figure 1). Totally eight larvae was detected on the ocular surface. On microscopic examination, the prominent features of the larvae were the segmented translucent body and white cephalopharyngeal skeleton with characteristic pair of curved, dark oral hooklets.

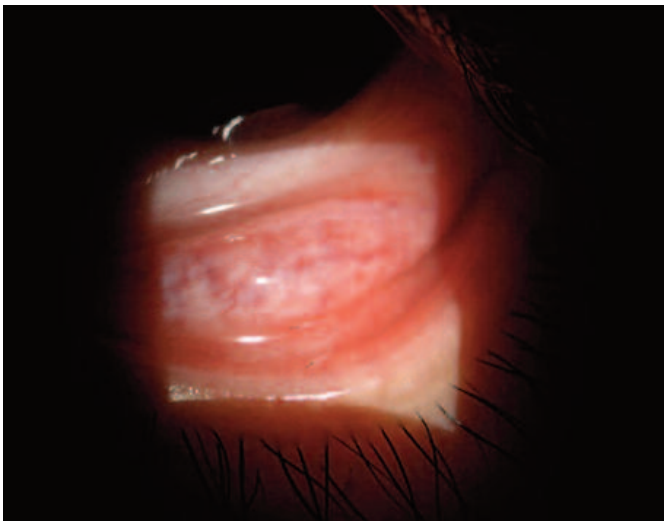

Figure 1. *Oestrus ovis* larvae on lower fornix. The larvae had segmented translucent body, and white cephalopharyngeal skeleton with characteristic pair of curved, dark oral hooklets.

Case 2

A six-year-old boy was admitted to ophthalmology clinic with symptoms of moderate itching and irritation of his both eyelids for about a month. On external examination, exfoliative lesions and mild edema in the eyelids were observed. Slit-lamp examination revealed multiple mobile and semitransparent lice at the base of the eyelashes and numerous, translucent, white nits were adherent to the eyelashes at both upper eyelids (Figure 2a and 2b) and the left lower eyelid.

Case 3

A 51-year-old male was referred to our clinic with a small light brown lesion on his left upper eyelid. He noticed this lesion two days before and he claimed it has been enlarging ever since without pain. He had a history of being in a rural area two days before presentation. Mild swelling of the left upper eyelid was observed, with a light brown lesion at the center. The lesion was on the lid margin between the eyelash roots (Figure 3a). Biomicroscopic examination of the lesion showed that it was the body of an alive tick (Figure 3b), some part of it was buried in the eyelid.

As a beginning all of the patients were treated by removing the ectoparasites mechanically by a blunt forceps. The species of the arthropods were identified as *Oestrus ovis* in the first case, *Phthirus pubis* in the second case and *Ixodes ricinus* in the third case by the microbiology laboratory. Topical antibiotics and corticosteroids were prescribed for preventing secondary bacterial contamination and reducing the inflammation. After one week, the ocular symptoms of all patients completely resolved and no residual ectoparasites could be found on the ocular surface. In

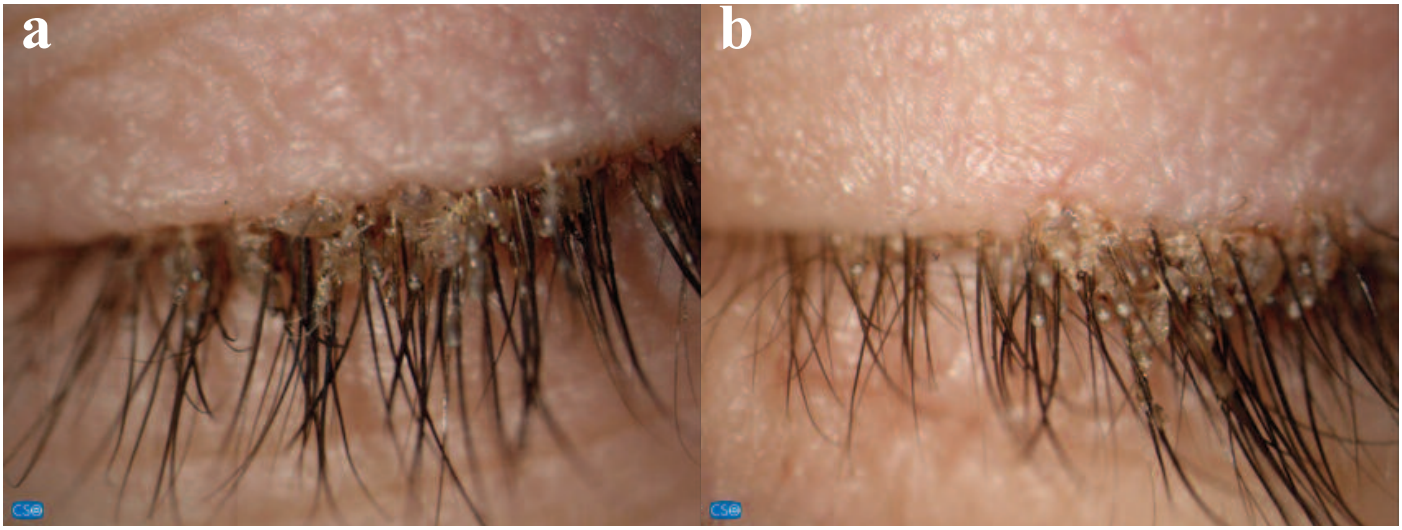

Figure 2. Multiple semitransparent lice, *Phthirus pubis*, at the base of the eyelashes and numerous, translucent, white nits adherent to the eyelashes at right (a) and left (b) upper eyelid.

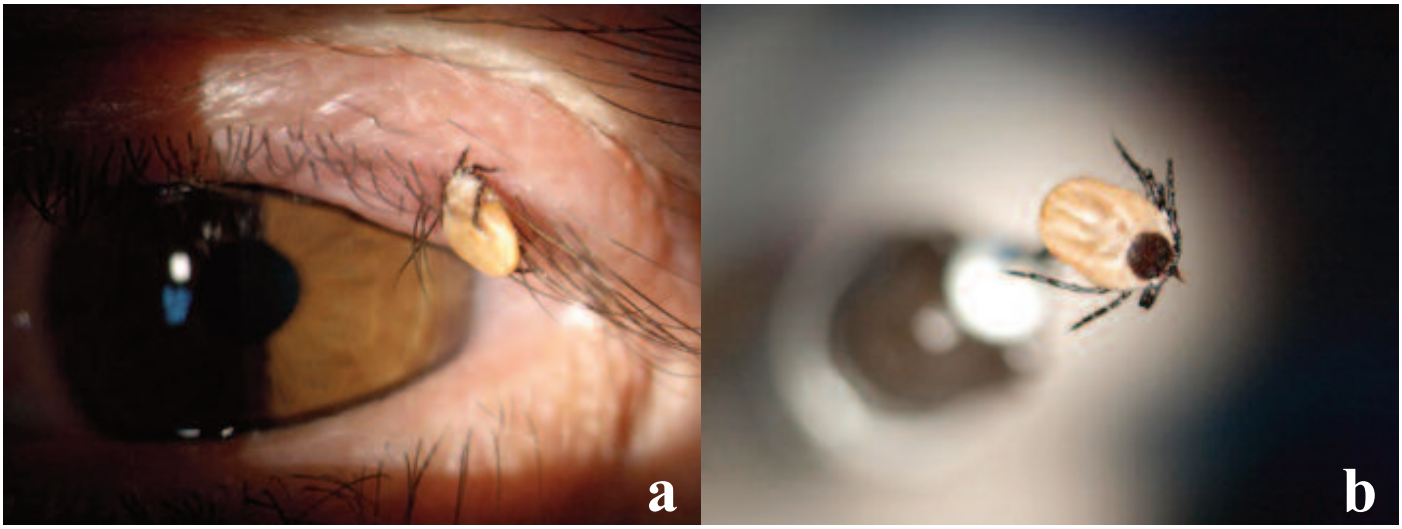

Figure 3. The alive tick on the lid margin, some part of it was buried in the eyelid (a). The tick was identified as *Ixodes ricinus* (b).

case 3, subsequent serological tests for zoonoses were negative and there was no sign of systemic disease during six month of follow-up.

Discussion

Ophthalmomyiasis externa is an infestation of the superficial external ocular structures with larvae of most commonly sheep nasal botfly (*O. ovis*) [3]. It is a large, yellowish gray fly about 10-12 mm long. The larval stage of *O. ovis* takes place in the nasal cavities of the sheep, cattle or horse. Humans may serve as an accidental host when the botfly releases its larvae on to the eye while it is flying [5]. Although it is reported that this infestation is more common in rural areas and sheep raising areas [4, 5], our first case was working in an area closer to a hippodrome in the city center when his symptoms were first started.

Phthiriasis palpebrarum is a rare eyelid infestation caused by the louse, *Phthirus pubis* [4, 6]. This parasite is primarily adapted to living in pubic hair and transferred from the genital area to the eyelashes by hand or sexual contacts [6, 7].The symptoms range from pruritic lid margins to blepharitis and marginal keratitis. Therefore, semitransparent lice and nits can be easily overlooked and phthiriasis palpebrarum can be misdiagnosed as allergic conjunctivitis due to pruritis [1, 6].

Tick infestation of ocular tissues is rare. Ticks can become embedded in the meibomian gland orifices and may be appear to be a mass at the eyelid margin [4, 8]. If a segment of the tick is left in situ after removal, granulomasor abscesses can occasionally develop [9]. Unlike other ectoparasites, ticks are important vectors for the transmission of zoonoses. The parasite should be completely removed as soon as possible [8], because the risk of systemic disease transmission increases significantly after 24 hours of attachment [8, 10].

Ectoparasitic infestations are more common in geographical areas where enviromental factors and poor hygienic conditions facilitate the parasitism between human and animals [3]. All patients in this report were living in city center of Bursa, one of the most developed and industrialized city in Turkey. *Oestrus ovis* and *I. ricinus* may be seen in our city due to its closeness to villages having sheep and goat farms. *Phthirus pubis* infestation generally associated with poor hygiene and overcrowding may be increasingly diagnosed as a result of rural-urban migration. To our best knowledge, this is the first report that three different ocular ectoparasitic infestations presented from the same ophthalmology clinic.

The most effective treatment of ocular ectoparasitic infestations is removing the arthropod mechanically if it is possible. Besides that pilocarpine 4% slows or paralyzes parasite's movement. Also, washing with 5% povidine iodine solution, cryotherapy, argon laser photocoagulation, fluorescein eye drops 20%, physostigmine 25%, yellow mercuric oxide oinment 1% and oral ivermectin are different treatment options [1].

Conclusion

In conclusion, even if patients living in urban areas, ocular ectoparasitic infestations should be taken

into consideration in differential diagnosis of conjunctivitis, blepharitis and eyelid mass. Due to the rarity of ocular ectoparasitic infections and overlapping symptoms with more commonly occurring ophthalmic conditions, a careful ophthalmic examination is required to avoid misdiagnosis and delay in treatment. Transmission of zoonoses and systemic evaluation should be kept in mind in ocular tick infestations.

Informed consent

Written informed consents were obtained from the patients and family of the patient (boy) for the publication photographes used in this study.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Gender dysphoria in an adolescent diagnosed with Klinefelter syndrome over a follow-up period

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ABSTRACT

Although genetic factors have been thought to be main cause for gender dysphoria, its etiology is still not clearly understood. Klinefelter syndrome is the most seen sex chromosomal disorder. In the literature, there are fewer case reports in connection with Klinefelter syndrome and gender dysphoria. Herein, we report a 16-year-old adolescent patient displaying gender dysphoria features, who has revealed Klinefelter syndrome after genetic examination, and has been treated with testosterone hormone, and his gender dysphoria symptoms have disappeared. In our case, chromosomal anomaly and lower levels of androgen could play a role in the etiopathogenesis of gender dysphoria. Bringing Klinefelter syndrome disorder to mind in gender dysphoria cases, even it is a rare disorder, could positively affect the course of the treatment as was in our case. The relation between psychiatric symptoms, which can be seen in gender dysphoria, and testosterone is not known exactly. Further studies, which are randomized-controlled ones, can help to better understand the subject.

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Keywords: adolescent, gender dysphoria, Klinefelter syndrome, depression

Introduction

It is assumed that the development of the sexual identity is completed at the end of the adolescence period with a prominent appearing the secondary sex features. Some children would experience in some degree of trouble to identify and build their gender identity by virtue of their biological features, family dynamics and environmental features. Children having trouble with their gender identity would experience some degree of discomfort regarding their biological gender, feeling themselves as having actually an opposite sex, liking with opposite sex's activities and features [1].

Gender dysphoria is generally used as a term and a clinical entity although is not yet located in Diagnostic and Statistical Mental Disorder (DSM) classification system as a diagnosis having with criteria. Its etiology is still not clearly understood yet there are studies pointing out an importance of genetic factors playing crucial role in the etiology of gender

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dysphoria based on studies carried with twins (as concordance studies) and affected family members [2, 3]. In addition, with some chromosomal anomalies reported in the cases with gender dysphoria in the literature is also presented as the possible salient facts of the underlying mechanisms of gender dysphoria [4-11].

Klinefelter's syndrome is by far the most seen sex chromosomal disorder and second frequent disorder in terms of presence an extra-chromosome. Its prevalence is 1.09 to 1.72/1000 in male sex and characterized by a 47,XXY karyotype chromosomal anomaly [12]. In the literature, still there are fewer cases reporting association of gender dysphoria and Klinefelter syndrome [10, 11].

In this report, an adolescent admitted to our department because of his complaints of sexual interest towards his own sex and feeling bothered by it. He was evaluated as having possible traits of gender dysphoria. He was diagnosed with Klinefelter syndrome over his follow-up period and his psychiatric complaints improved after treating with endocrinological approach. Therefore, the association of gender dysphoria and Klinefelter syndrome was discussed in this case report using with literature knowledge.

Case Presentation

The patient is a 16-year-old male, third grade student in a high school, living with his older brother. He admitted to our clinic by virtue of his thoughts related to their sexual identity as he is a homosexual and he wanted to us the elimination of these thoughts. He referred himself as a comfortable person except these thoughts, however, his older brother described him as aggressive and indisposed and according to older brother, he prefers being alone. He was born in a small village, he lived there with his mother, father, older brother and younger brother until he was 14. When he won a high school scholarship, he moved to the metropolis and stayed in a male hostel where located near to his high school. He has always been criticized with "talking, acting and dressing like a girl" by both his family and his relatives because of his thin voice, polite conversation attitudes, gestures and mimics that he uses when he is talking and his clothing style. Six months later when he set the hostel, some troubles emerged between him and his roommates and he moved in with his older brother since he began to work in a job and could be able to afford a flat to live in. Questioning of his sexual life, he revealed that he remembered when he was in 7-8, once he played with his male friends from his classroom as looking at their sexual organs of each other. When he was in high school, he went with it especially one male friend of him, spending lots of time together with him, he had fantasy related to him and dreamed with sexual content about him. When he told to him he was liking of him, he exposed much of opposition from his hostel friends and he had to leave from the hostel. He began to think himself about that he might be a homosexual person at that time. Then some symptoms have become to emerge which diagnosed by major depressive disorder like malaise, not to be able to enjoy from living, decrease in food intake, difficulty in falling asleep. He has always been a fine and successful student throughout the entire of educational life in school. He was excluded by his male friends because of his polite speaking style and he began to spend his time with girl friends but he couldn't be able to close to them very well and could not made close friendship.

History

He was born after a planned pregnancy. There had no expectation by his parents regarding the sex of the baby. According to older brother's report, the pregnancy was normal and his mother did not use any medication. The delivery was uneventful at full term. The neonatal period was uneventful. His developmental stages were normal.

Family history

Information reported about family history was limited because his parents who lived outside of the metropolis could not be interviewed by the clinician. There were no gender dysphoria and Klinefelter syndrome cases in his family members or relatives. According to older brother's report, when he was a toddler, his mother had a major depression and behaved him hostilely. His father also did not care about him. There were his father's humiliating and overwhelming attitudes toward his mother and him.

Psychiatric examination

Looking with little hairy face and his behaviors and talking style demonstrates childish and feminine features, his outfit is appropriate with his socioeconomic level, a male adolescent with showing truly his own age. His mood examination revealed as

depressive, his affect was anxious, his speech was clear, understandable with proper response to the questions and seen as cooperative. His perception, consciousness, orientation, attention and memory examination were normal. His thought processing was normal, accompanying with worthlessness of thought content and guilt as well as alongside with dominancy of concern for the future. There was no delusion. His intelligent quotient was normal. Clinical interview based on DSM-5 criteria [13] revealed major depressive disorder and gender dysphoria. Weekly sessions of the therapy aiming to obtain insight to him was planned. These sessions were structured with his traumatic experiences, family relations and relationship with members of it to be increased the awareness of him, ensuring separation of his individuality and make him to be realized his strength points. Daily 50 mg of sertraline, the selective serotonin re-uptake inhibitor (SSRI) was ordered. Over the follow-up period, he was referred to the endocrinology department because of his phenotypical features mentioned before. He was diagnosed with Klinefelter syndrome after evaluating and examining by the endocrinology department. Testosterone treatment began to him. After treating with testosterone, he experienced more hair on his face and his facial appearance has become masculine features with voice thickened. Diagnosed with Klinefelter syndrome during follow-up, and interpreted his gender dysphoria symptoms as having an organic and solid-based disorder by himself, had a positive effect regarding his position. At the end of the follow-up period, he has become less interested in with the same sex, with lesser extend of feminine appearance, mimic and gestures, and he became make friends with girls in sexual and emotional context and enjoyed from it with improved depressive symptoms.

Discussion

Gender dysphoria is highly complex issue for evaluating in a context of biological, psychological and social variables and needed to be evaluated by multidisciplinary attitude with many areas of professionals. Genetic factors and prenatal exposure of sex hormones are thought to be responsible for underlying mechanisms of gender dysphoria. Throughout pregnancy, fetal brain develops as a male brain with under effect of androgen hormones. If there are no androgen hormones, fetal brain switches to the female characteristics. Gender identification of the brain appears later than the development of genital organs [14]. Gender dysphoria could emerge if there is a conflict between gender development of the brain and genital differentiation [1].

Klinefelter syndrome is characterized by, as in our case, longer arms and legs, feminine hip and muscle development, gynecomastia and hypergonadotropic hypogonadism. In general, their voices are thin with feminine type body hairs, very limited beard and mustache growth and their testicles are smaller with lower testosterone hormone levels [15]. Testosterone displays its biological effects via binding to the androgen receptors [16]. In Klinefelter syndrome, there have been reported a relation between some mechanisms including the androgen receptor polymorphism (longer CAG repeated), X chromosome inactivation and parental origin of extra-X chromosome and an increased prevalence of psychiatric symptoms and disorders such as depression, anxiety, autism, schizophrenia, attention deficit, hyperactivity, learning difficulties and cognitive inabilities [17]. Related to the brain volumes of Klinefelter syndrome cases, it was argued that inactivation of X chromosome might associated with an effect on gray matter of whole brain as well as left insula volume which is smaller. It is also suggested that X-linked genes would have a potential impact on the development of these volumes [17].

Yet, these hypotheses could not be clearly showed. Some studies reported longer repeated androgen receptor genes in gender dysphoria cases and Klinefelter syndrome alike compared to the healthy controls [18].

Neuroimaging studies revealed a difference between volumes of white and gray matters of the brain in affected peoples compared to the controls but it could not be enough to be used as diagnostic tool for these patients [1].

Although its prevalence is rare in etiology of gender dysphoria, chromosomal anomalies including Klinefelter syndrome should come to mind during the evaluation of patients having gender dysphoria symptoms. Like in our case, doing so might be beneficial for determining of accompanying disorder, if any, and treating to it. Testosterone treatment of Klinefelter syndrome has been shown as positively effective on symptoms of patients affected, although its mechanisms not clearly proved [19]. Testosterone treatment has been reported that it developed and improved the functions of neuromotor, speech,

cognitive and reading skills [20]. Testosterone treatment has a positive effect on some features including sleep pattern, mood and irritability symptoms [21]. In 1979, Rinieris et al. [22] reported in two cases with Klinefelter syndrome that with testosterone treatment, depressive symptoms of two cases did not recurred. In 2015, Kawahara et al. [12] showed in a case with Klinefelter syndrome and bipolar disorder that testosterone hormone treatment ended with a cease in manic attacks.

In our case, testosterone might have an effect to improve depressive symptoms accompanying with sertraline treatment. In addition, interpreting of gender dysphoria as a consequence of an organic disorder, he began to grow beard with masculine appearance of his facial contours and thickening his sound after treating with testosterone, all these developments could very well ease to establish identification of male sex and thus, it might indirectly ameliorate the depressive symptoms of him. Psychiatric symptoms improved with testosterone hormone treatment in Klinefelter syndrome is not fully proven and its mechanism of action is not yet clearly certain. Further randomized studies would be beneficial to fully understand of testosterone effects on psychiatric symptoms.

Conclusion

In our case, chromosomal anomaly and lower androgen hormone levels might play a role in the ethiopathogenesis of gender dysphoria. Nonetheless, the possible causative relation between gender dysphoria and 47-XXY is still not clearly understood. Genetic factors and hormones could very well be included to the topics for the future researches in this area. Gender dysphoria cases having different symptoms and features, as in our case, would add a valuable outlook to build new hypothesis in connection with scientific studies. Screening for the frequency of gender dysphoria in cases with Klinefelter syndrome would might contribute to better understanding the etiology of gender dysphoria.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Surgical excision of a giant cardiac fibroma in an asymptomatic child

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ABSTRACT

Cardiac fibroma is a rare primary tumor of the heart. Patients can be asymptomatic or present with palpitations, cardiac murmur, syncope, arrhythmias, symptoms of congestive heart failure, or sudden death. We report a case of successful surgical excision of a giant cardiac fibroma in an asymptomatic child.

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Introduction

Cardiac fibromas are rare benign tumors predominantly seen in the pediatric population [1]. Cardiac fibromas are connective tissue tumors derived from fibroblasts, encapsulated and extend into the surrounding myocardium. These patients may be asymptomatic for a long period of time and present with a large intramural mass [2], or present with congestive heart failure, sudden death, or arrhythmias. Although management of asymptomatic patients with cardiac fibromas is controversial, surgical resection is recommended in symptomatic cases [1].
In this paper, we present a successful resection of a large primary cardiac fibroma in an asymptomatic child.

Case Presentation

A 21-month-old male, who had been followed with cardiac mass, was referred to our clinic. A 15×23 mm cardiac tumor was identified with echocardiography when he was 2-month old with no symptom. He was followed-up with echocardiographic examination. The tumor showed rapid growth at the age of 1 year and 9 months. The two-dimensional transthoracic echocardiography revealed a hyperechoic mass with maximal size of 25×45 mm in the apical part of the left ventricle. Magnetic resonance imaging showed a solitary, well-defined intramural mass measuring 35×60 mm in the same location. Magnetic resonance imaging findings were characteristic, with homogeneous signal

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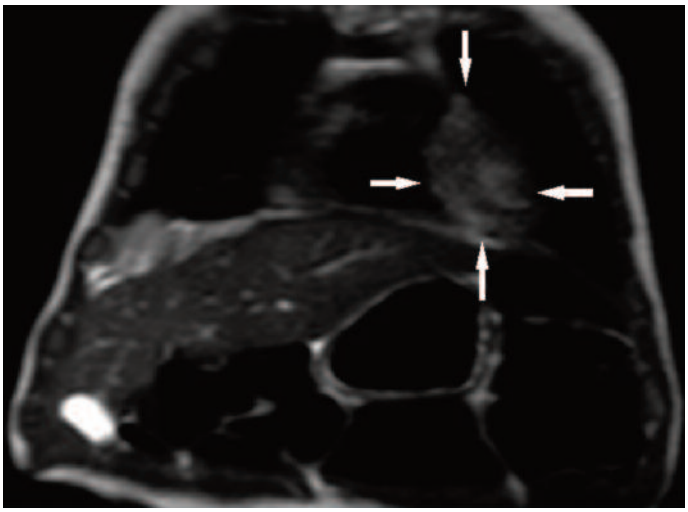

Figure 1. Magnetic resonance imaging in coronal view showing a mass in the apical area.

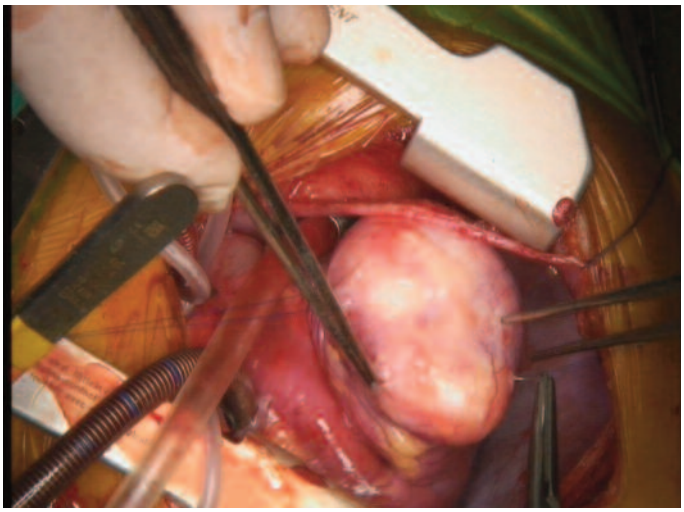

Figure 2. Intraoperative view. The gray-white tumor located in the apex.

isointense to myocardium on T1-weighted and hypointense signal on T2-weighted images (Figure 1). The patient was entirely asymptomatic at the time of these examinations. Elective surgery was recommended due to the risk of ventricular arrhythmias and of sudden cardiac death [1].

The chest was opened using a median sternotomy. Total cardiopulmonary bypass was established with aorto-bicaval cannulation and a cross-clamp was applied. Antegrade cardioplegia was used in an intermittent fashion. Macroscopically, a firm white mass was situated in the apical part of the left ventricle (Figure 2). A layer of thin myocardium was stretched over the mass. Through a limited apical ventriculotomy incision, the mass was resected en bloc by sharp dissection (Figure 3). The mass had 4.5×3×2 cm dimensions (Figure 4). Reconstruction of the left ventricular wall was performed using a Teflon felt in a fashion similar to a Dor procedure (Figure 5). At the end of the surgery, the wound surface was coated with Tisseal (Baxter). The patient was easily weaned from cardiopulmonary bypass with minimal inotropic support. The aortic cross-clamp time was 30 minutes, and the total cardiopulmonary bypass time was 53 minutes. Protamine was administered, and hemostasis was secured. The sternum was closed in the routine manner.

The postoperative course was uneventful and the patient had regular sinus rhythm. Transthoracic echocardiography showed good ventricular function. The patient was discharged from the hospital on the 6th postoperative day. Pathologic studies revealed intracardiac fibroma. At the 7-month follow-up, he was asymptomatic with no evidence of recurrence and good left ventricular function on echocardiography.

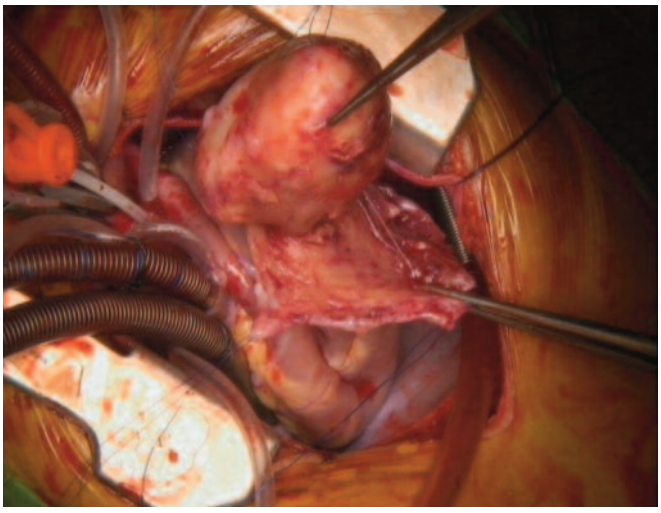

Figure 3. The solid tumor was excised by sharp dissection.

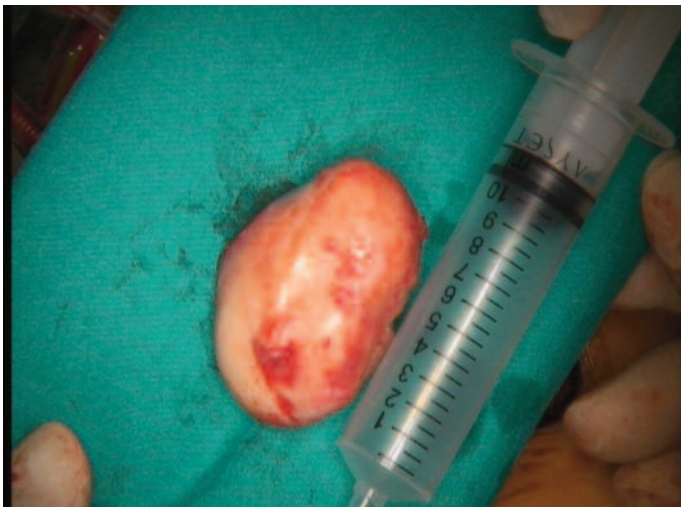

Figure 4. The huge mass after excision.

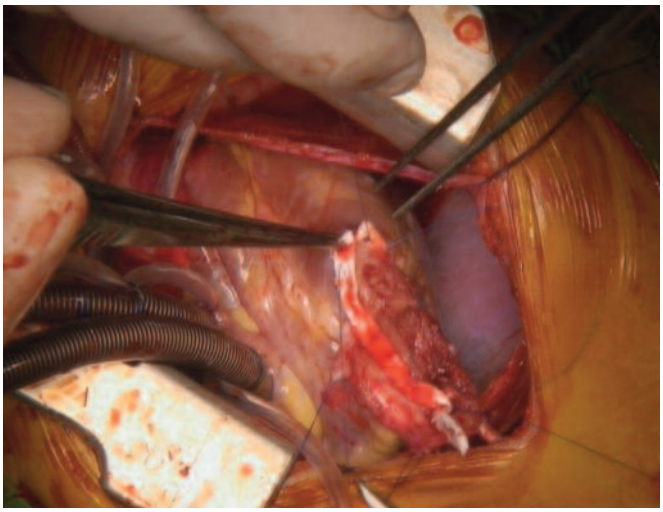

Figure 5. Left ventricle apex reconstructed using teflon felt

Discussion

Primary cardiac tumors are very rare [3] and cardiac fibromas are the third most common type of primary cardiac tumors in children, after rhabdomyomas and teratomas [4]. Fibroma accounts for 12-16% of primary cardiac tumors in children [5]. Fibromas are derived from fibroblastic structures and may invade the ventricular muscle or may extend into the ventricular conduction system, resulting in congestive heart failure or ventricular arrhythmias [4]. While patients with fibroma may manifest arrhythmias or heart failure, cyanosis, syncope, chest pain, or even sudden cardiac death, as many as one-third of them are asymptomatic [1].

Surgical resection is recommended in symptomatic patients. However, management of asymptomatic patients with cardiac fibromas is controversial. Numerous authors advocate for surgical resection due to concerns regarding sudden death associated with arrhythmias and operation is favored in patients with enlarging tumors to prevent progressive cardiac deformity and valvular dysfunction [6]. In our case, we closely followed the tumor's development and surgery was indicated because tumor had the tendency to grow fast.

Imaging techniques are very sensitive in making the diagnosis of cardiac fibromas. Echocardiography is the mainstay of non-invasive diagnostic tool that depicts tumour size, location, surrounding structures and any functional impairment [5]. Diagnostic imaging may include computed tomography or magnetic resonance imaging scanning to confirm the diagnosis and it provides sectional views of cardiac and mediastinal structures from various angles, defines the extent of tumor involvement.

Conclusion

In conclusion, cardiac fibromas are very rare. Though, one-third of them are asymptomatic, elective surgical removal should be considered before the appearance of symptoms as they have the tendency to grow and spontaneous regression rarely occurs. Surgical resection can be performed safely with good long-term prognosis.

Informed consent

Written informed consent was obtained from the patient's family for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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