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Gülhane Medical Journal (Gulhane Med J) is the official, scientific, peer-reviewed, international journal of Gülhane Faculty of Medicine, University of Health Sciences Turkey. The journal accepts submissions on all aspects of general medicine. Featured article types include original articles, case reports, reviews, and letters to the editor. The history of the Gülhane Medical Journal dates back to 1871 and it was named with its current title in 1999.

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Gülhane Medical Journal (GMJ) is an international, multidisciplinary and peer reviewed journal for researchers and health-care providers. It is published four times a year, and accepts submissions in English. It is the official journal of the Gülhane Faculty of Medicine, University of Health Sciences Turkey.

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Type of article	Abstract	Word count*	Number of authors	Number of references	Table/figure
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Review article	250	2000 to 4000	3	50	3
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Gülhane Tıp Dergisi

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Medical Journal
Gülhane Tıp Dergisi

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Up to six keywords should be included in the manuscript.

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It should be divided into the following sections: Introduction; Methods; Results; Discussion.

A case report should be structured as follows; introduction, Presentation of Case, Discussion, Conclusion.

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Gülhane Tıp Dergisi

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Gülhane Medical Journal

Gülhane Tıp Dergisi

Contents

Gülhane
Medical Journal
Gülhane Tıp Dergisi

Message from the Editor-in-Chief

It has been five months since the first cases with atypical pneumonia were reported in Wuhan, China, on December 31, 2019. During this period, one of the most severe pandemics of the last century was announced by the World Health Organization due to Covid-19 disease.

In the first half of the year, despite the confusing state among healthcare professionals and academics due to the Covid-19 disease, interest in publishing original articles, case reports, or review articles has never declined. The number of submissions to the GMJ showed an increase during the days we have been fighting with the pandemic. Therefore, I would like to express my gratitude to all the contributing authors, reviewers, and editors in this context.

With the growing number of submissions in the last two years, we were in need of expanding our editorial board. I am honored to welcome Prof.Dr. Ahmet Coşar, Prof.Dr. Mesut Gürdal, Associate Prof. Ömer Karadaş, and Assistant Prof. Bilgin Bahadır Başgöz to the editorial board in the new term. Their contribution will undoubtedly enhance our manuscript evaluation process and the quality of published articles.

In the second half of the year, we will continue as a whole with our fight against not only the Covid-19 disease but also the challenges of new normal life in our hospitals and medical schools. As the journal's publishing team, we will also continue to work hard to provide the readers with high-quality papers, and the authors with the most efficient evaluation process, thanks to our most experienced reviewers.

Prof. Dr. Omer Azal
Editor-in-Chief

GÜLHANE MEDICAL JOURNAL
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Immunohistochemistry expression of EMA, CD10, CEA, and Bcl-2 in distinguishing cutaneous basal cell from squamous cell carcinoma: A systematic review

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Keywords: Squamous cell carcinoma, basal cell carcinoma, immunohistochemistry, differential diagnosis

ABSTRACT

Cutaneous basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most popular neoplastic entities in cutaneous medicine. These two neoplasms are commonly well recognized on the basis of their clinical and histopathological features and the differentiation between the two mentioned carcinomas is clinically important as there is a significant difference in their rates of aggressiveness and metastatic potential. In case of difficulties in distinguishing BCC from SCC, in addition to the well-defined histological criteria, immunohistochemistry methods can be used and, in the literature, numerous studies underline their usefulness. Therefore, the present systematic review aimed to assess the expression of epithelial membrane antigen (EMA), cluster of differentiation 10 (CD10), carcinoembryonic antigen (CEA), and B-cell lymphoma-2 (Bcl-2) in distinguishing cutaneous BCC from SCC. A comprehensive search was done from 1983 to September 2017 in the PubMed/Medline, Web of Science, and Scopus databases without language restriction. The studies had a cross-sectional design on human tissue. The pooled staining of biomarkers showed that staining results of EMA and CEA in SCC tissues were significantly more positive than in BCC tissues ($p<0.00001$ and $p=0.008$, respectively), as well as CD10 and Bcl-2 in BCC tissues, were significantly more positive than in SCC tissues ($p<0.00001$ and $p<0.00001$, respectively). Findings demonstrate that the use of these markers will be very useful in mentioned cases in which routine microscopy is not able to distinguish between these two entities.

Introduction

Basal cell carcinoma (BCC) is the most frequent cutaneous neoplasm, accounting for around 70% of all skin cancers. It is regionally aggressive and its metastases are rare (1). The second most common malignancy in humans is cutaneous squamous cell carcinoma (SCC), with around double metastases compared to BCC (2). Therefore, BCC and SCC are the most commonly found tumoral entities in cutaneous medicine. They are commonly well-recognized on the basis of their clinical and histopathological features and differentiation between these two carcinomas is clinically important as there is a significant difference in their rates of aggressiveness and metastatic potential. In case of difficulties in the differential diagnosis between the two entities; in addition to the well-defined histological criteria, immunohistochemistry (IHC) methods can be of help and, in the literature, many studies have previously reported their role (3-5). The cluster of differentiation 10 (CD10) is an enzyme of the cell surface with metalloendopeptidase activity and reduces cellular response to peptide hormones by regulating local peptide hormone concentrations (4). CD10 is correlated with biological invasions in human malignancies, but this marker is more commonly used for diagnosis and prognosis with a more complexity (6). B-cell lymphoma-2 (Bcl-2) protein suppresses cell death and thus may be considered

to allow malignant cells for proliferation (7). In addition, Bcl-2 protein preserves cell against apoptosis caused by various death-inducing signals (8). Carcinoembryonic antigen (CEA) is a complex macromolecule with high glycosylation and is used as a marker in carcinomas worldwide (9). Epithelial membrane antigen (EMA) is another highly glycosylated protein with expression mainly in normal and tumor epithelium (10). The differences in biologic behavior mandate the application of more accurate diagnostic methods distinguishing between SCC and BCC. In the literature, there was just one study (11) that checked EMA, CD10, CEA, and Bcl-2 markers together and other studies used one or two markers for distinguishing between cutaneous BCC and SCC. Therefore, the present systematic review aimed to assess the expression of EMA, CD10, CEA, and Bcl-2 in distinguishing cutaneous BCC from SCC.

This systematic review was achieved based on the guidelines for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA (12).

Search strategies

A comprehensive search was conducted starting from 1983 to September 2017 using the search terms of "squamous cell carcinoma" (or "SCC") or basal cell carcinoma (or "BCC") and "EMA" (or "epithelial membrane antigen") or "CEA" (or "carcinoembryonic antigen") or "CD10" (or "cluster of differentiation 10") or "Bcl-2" (or "B-cell lymphoma 2") in the PubMed/Medline, Web of Science, and Scopus databases without language restriction. In addition, we manually checked the references of eligible articles to our subject for finding possible missed studies.

Study selection and eligibility criteria

One author (M.S) searched and selected the relevant studies. The second author (M.R) re-checked the studies. All articles in this study were examined for the evaluation of the expression of EMA, CD10, CEA, or Bcl-2 in distinguishing between cutaneous BCC and SCC. The studies included in the systematic review involved the following inclusion criteria: a) cross-sectional design; b) human tissue; and c) IHC staining of EMA, CD10, CEA, or Bcl-2. The exclusion criteria were as follows: a) duplication of a previous publication; b) review or case-series; c) conference paper; d) no full-text; and e) no relevant data.

Data extraction

Two authors (M.S & M.R) checked the studies involved in the systematic review and extracted the relevant data. The third author (E.Z) re-checked the data. We extracted the author's name, publication year, country, the number of BCC or SCC patients/tissues; the number of BCC or SCC tissues with positive IHC of each marker, used antibody and cut-off from each study were included in the systematic review.

Quality assessment

The quality of each study was evaluated by the Newcastle-Ottawa Scale (13). One author (M.R) checked the quality of the studies. The maximum total score was nine for cross-sectional studies. A high-quality study was considered as a study with ≥7 scores.

Statistical Analysis

The data were analyzed applying SPSS version 22 software (IBM Corp., Armonk, NY, USA) and the chi-square test. $P < 0.05$ (two-sided) was considered statistically significant.

Results

Study selection

Out of 250 studies retrieved in the databases, after excluding duplicates and not relevant studies, 38 full-text studies were assessed for eligibility (Figure 1). Then, seven studies were excluded for some reasons (one article was animal study, two articles were review studies, two articles reported mean score of markers, one article mixed BCC and SCC patients as one group, and one article duplicated with another study). At last, a total of 31 studies were entered and analyzed in the systematic review.

Characteristics of the studies

The characteristics of the 31 studies covered in the systematic review are presented in Table 1. The studies were published between 1983 and 2017. Eight studies (3,14-20) were from USA, four (4,5,11,21) from Iran, three (22-24) from UK, three (25-27) from Japan, two (28,29) from Turkey, two (30,31) from Egypt, and also Australia (32), Austria (33), Netherlands (34), Taiwan (35), China (36), Croatia (8), Romania (37), India (38), and Germany (39) each with one study. All studies in the systematic review included 694 BCC and 536 SCC patients/tissues. Fifteen studies reported Bcl-2 and included 339 BCC and 263 SCC patients; eight studies reported CD10 and included 257 BCC and 180 SCC patients; five studies reported CEA and included 111 BCC and 87 SCC patients; and ten studies reported EMA and included 177 BCC and 158 SCC patients. Other characteristics such as the number of patients/tissues with positive staining for each marker, used antibody and cut-off are shown in Table 1.

IHC staining

The pooled staining of biomarkers based on mentioned cut-offs in each study showed that staining results of EMA and CEA in SCC tissues were significantly more positive than BCC tissues ($p<0.00001$ and $p=0.008$, respectively), as well as CD10 and Bcl-2 in BCC tissues, were significantly more positive than SCC tissues ($p<0.00001$ and $p<0.00001$, respectively) (Table 2). Therefore, these markers can be useful biomarkers for distinguishing between both BCC and SCC.

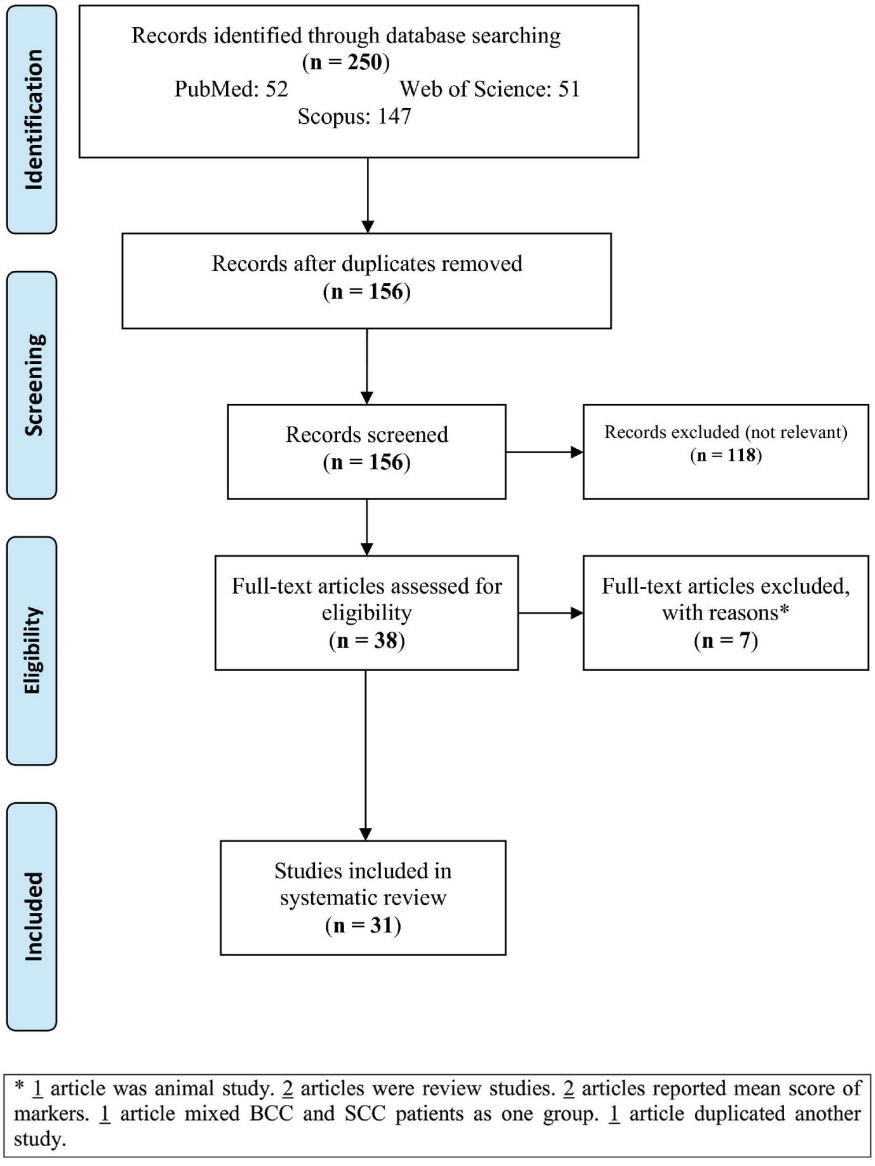

Figure 1. Flow-chart of the study

Quality assessment

The quality assessment of each study is shown in Table 3. A mean score of 6.7 was reported for all studies and twenty-six studies had high quality.

Discussion

It is critical to differentiate SCC from BCC clinicopathologically (21). In most cases, the differentiation of SCC and BCC is straightforward in routine H&E staining (4). The distinction of these neoplasms is clinically important because of the more aggressive behavior and metastatic potential of SCC, which mandates more radical treatment and closer follow-up (4,21). The SCC recurrence rate is about twice higher than that of BCC. So, more aggressive treatment is needed for SCC (21). Due to similarity in histopathology, differentiation between SCC and BCC is sometimes difficult (30). In fact, keratotic and metatypical BCCs may be indistinguishable from basaloid SCC (bSCC) in routine histopathology slides (3,4). Therefore, differentiation between BCC and SCC is mostly performed by routine histopathology, which may cause difficulty in superficial small biopsies. CD10 and Bcl-2 markers are of benefit in this condition (31). The present systematic review evaluated IHC staining of four biomarkers including EMA, CD10, CEA, and Bcl-2 in BCC compared to SCC tissues. BCC presentation is typically an ulcerated pearly papule/nodule with telangiectasia (40,41). SCC presentation is typically shallow crusted ulcer with raised margin accompanying actinic damage (40). Differentiation between SCC and BCC is very important in

Table 1. The characteristics of the included studies in the systematic review (n=31)

First author (year)	Country	Number of BCC patients or tissues	Number of SCC patients or tissues	Number of tissues with positive marker: (BCC/SCC)	Antibody manufacturer	Cut-off value
Scurry and de Boer (32)	Australia	10	10	CEA: (1/10)	DAKO & IMULOK	NR
Heyderman et al. (22)	UK	23	15	EMA: (8/15) CEA: (8/12)	Sigma	NR
Cerroni and Kerl (33)	Austria	20	20	Bcl-2: (20/0)	DAKO	NR
Nakagawa et al. (25)	Japan	15	4	Bcl-2: (15/4)	DAKO	5%
Morales-Ducret et al. (14)	USA	23	20	Bcl-2: (23/2)	DAKO	NR
Rodriguez-Villanueva et al. (15)	USA	17	11	Bcl-2: (17/0)	DAKO	NR
Wikonkal et al. (34)	Netherlands	17	22	Bcl-2: (13/6)	M0887 (DAKO A/S)	1%
Chang et al. (35)	Taiwan	10	8	Bcl-2: (10/0)	DAKO	NR
Swanson et al. (16)	USA	45	22	Bcl-2: (41/4)	Clone 124 (DAKO)	1%
Delehedde et al. (17)	USA	17	14	Bcl-2: (17/0)	Clone 124 (DAKO)	NR
Sinard (18)	USA	16	14	EMA: (1/11)	Anti–BCA-255 (BRST-1)	NR
Beer et al. (23)	UK	39	23	EMA: (0/22) CEA: (8/7)	EMA: Clone E29 (DAKO) & CEA: Clone 11-7 (DAKO)	5%
Niu et al. (36)	China	40	33	Bcl-2: (40/1)	NR	1%
Yada et al. (26)	Japan	51	9	CD10: (44/0)	DAKO	NR
Coflkun and Çobanolu (28)	Turkey	20	20	Bcl-2: (18/4)	NR	1%
Aiad and Hanout (30)	Egypt	21	16	CD10: (20/13)	Clone 56C6 (Zymed, Cat)	10%
Serarslan et al. (29)	Turkey	22	10	Bcl-2: (10/8)	Neomarkers-Biogen, mouse	10%
Wagoner et al. (3)	USA	16	13	CD10: (14/0)	NR	1%
Puizina-Ivić et al. (8)	Croatia	20	20	Bcl-2: (20/0)	M887 (DAKO)	1%
Sramek et al. (19)	USA	6	9	EMA: (0/6)	E29 (DAKO)	10%
Ansai et al. (27)	Japan	10	10	EMA: (0/9) CEA: (1/2)	EMA: E29 (DAKO) & CEA: Polyclonal (DAKO)	6%
Heidarpour et al. (21)	Iran	30	26	CD10: (26/1)	N-vision (DAKO)	10%
Abu Juba et al. (37)	Romania	14	10	Bcl-2: (12/5)	Clone 124 (DAKO)	1%
Sari Aslani et al. (5)	Iran	55	50	CD10: (52/0)	N-vision (K4061, DAKO)	10%
Mulay et al. (38)	India	18	25	EMA: (0/25)	Clone E29 (Cell Marque)	1%
Sabeti et al. (4)	Iran	27	17	CD10 (20/2)	RTU-CD10-270 (Novocastra)	10%

Table 1. Continued

First author (year)	Country	Number of BCC patients or tissues	Number of SCC patients or tissues	Number of tissues with positive marker: (BCC/SCC)	Antibody manufacturer	Cut-off value
Gaballah and Ahmed (31)	Egypt	30	20	Bcl-2: (24/0) CD10: (16/0)	CD10: 56C6 (DAKO) & Bcl-2: 100/D5 (Thermo Scientific)	10%
Plaza et al. (20)	USA	21	22	EMA: (0/16)	DAKO	1%
Mittal et al. (24)	UK	8	10	EMA: (0/5)	M0614 (DAKO)	1%
Ramezani et al. (11)	Iran	29	29	Bcl-2: (29/10) EMA: (0/4) CEA: (0/10) CD10: (22/0)	EMA: Clone E29,N1504 (DAKO) & CD10: M0727 (DAKO) & CEA: Clone II-7, N1586 (DAKO) & Bcl-2: Clone 124, N1587 (DAKO)	EMA: 1%, CD10:10%, CEA: 1%, Bcl-2: 5%
Schmitz et al. (39)	Germany	4	4	EMA: (0/4)	Clone E29. N0613 (DAKO)	NR

NR: Not reported, BCC: Basal cell carcinoma, SCC: Squamous cell carcinoma, EMA: Epithelial membrane antigen, CD10: Cluster of differentiation 10, Bcl-2: B-cell lymphoma 2, CEA: Carcinoembryonic antigen, IHC: Immunohistochemistry

Table 2. The comparison of biomarkers staining in tumor cells of basal cell carcinoma and squamous cell carcinoma tissues

Marker	BCC tissue, n (%)	SCC tissue, n (%)	p value
EMA: N (%)			
Positive	9 (5.1)	117 (74)	<0.001
Negative	168 (94.9)	41 (26)	
CD10: N (%)			
Positive	214 (83.2)	16 (8.9)	<0.001
Negative	43 (16.8)	164 (91.1)	
CEA: N (%)			
Positive	18 (16.2)	41 (47.1)	0.008
Negative	93 (83.8)	46 (52.9)	
Bcl-2: N (%)			
Positive	309 (91.1)	44 (16.7)	<0.001
Negative	30 (8.9)	219 (83.3)	

N: Number, BCC: Basal cell carcinoma, SCC: Squamous cell carcinoma, EMA: Epithelial membrane antigen, CD10: Cluster of differentiation 10, Bcl-2: B-cell lymphoma 2, CEA: Carcinoembryonic antigen

clinic and laboratory (21,30). Out of ten studies in systematic review to check EMA (11,18-20,22-24,27,28,39), five studies (22,23,27,38,39) showed EMA as positive in ≥90% SCC tissues and eight studies (12,20,21,25,28-31) did not show EMA as positive in BCC tissues (0%). In addition, out of five studies that checked CEA (11,22,23,27,32), two studies (22,32) showed CEA as positive in ≥80% SCC tissues and three studies showed ≤10% BCC tissues. Out of eight studies included in the systematic review that checked CD10 (3-5,21,26,30,31), six studies (3,5,21,26,30,31) reported CD10 as positive in more than 85% BCC tissues and five studies (3,5,11,26,31) did not show CD10 as positive in SCC tissues (0%). In addition, out of fifteen studies that checked Bcl-2 (8,11,14-17,25,28,29,31,33-37), thirteen studies (8,11,14,17,25,28,31,33,35-37) identified Bcl-2 as positive in ≥80% BCC tissues and eight studies (8,14,15,17,31,33,35,36) identified Bcl-2 as positive in ≤10% SCC tissues. Therefore, BCC and SCC can be readily distinguished using routine IHC for these markers. Based on the results of the systematic review, at least, if tumor cells were CD10 and BCl-2 positive, this would favor BCC over SCC and if tumor cells were EMA and CEA positive, this would favor SCC over BCC diagnosis.

In most cases, BCCs and SCCs are manifested on sun-damaged skin, suggesting a main role for ultraviolet (UV) radiation and their incidence is rising in Whites (37,40). UV-rays, for example, trigger new mechanisms (molecular changes in protein structure, the release of proinflammatory cytokines, and oxidative stress) overlapping those of the cutaneous carcinogenesis process (37).

Basosquamous carcinoma (bSCC) of the skin is an uncommon variant with histopathological aspects of BCC and SCC. Some authors consider it as a variant of BCC, while others as an aggressive entity (42). In the research of Beer et al. (23), a panel of antibodies was used. They found that all cases of BCCs were stained positively for the Ber EP4 antibody (Antibody to Ep-CAM/Epithelial Specific Antigen), with no staining of SCCs. bSCC demonstrated areas of

Table 3. Quality assessment based on the Newcastle-Ottawa Scale

First author, year	Selection (score)	Comparability (score)	Exposure/Outcome (score)	Total score
Scurry and de Boer (32)	4	1	3	8
Heyderman et al. (22)	0	1	3	4
Cerroni and Kerl (33)	3	1	3	7
Nakagawa et al. (25)	4	1	3	8
Morales-Ducret et al. (14)	3	1	3	7
Rodriguez-Villanueva et al. (15)	3	1	3	7
Wikonkal et al. (34)	3	1	3	7
Chang et al. (35)	0	1	3	4
Swanson et al. (16)	3	1	3	7
Delehedde et al. (17)	0	1	3	4
Sinard (18)	3	1	3	7
Beer et al. (23)	3	1	3	7
Niu et al. (36)	3	1	3	7
Yada et al. (26)	3	1	3	7
Coflkun and Çobanolu (28)	0	1	3	4
Aiad and Hanout (30)	3	1	3	7
Serarslan et al. (29)	3	1	3	7
Wagoner et al. (3)	3	1	3	7
Puizina-Ivić et al. (8)	4	1	3	8
Sramek et al. (19)	4	1	3	8
Ansai et al. (27)	3	1	3	7
Heidarpour et al. (21)	3	1	3	7
Abu Juba et al. (37)	2	1	3	6
Sari Aslani et al. (5)	3	1	3	7
Mulay et al. (38)	3	1	3	7
Sabeti et al. (4)	3	1	3	7
Gaballah and Ahmed (31)	3	1	3	7
Plaza et al. (20)	3	1	3	7
Mittal et al. (24)	3	1	3	7
Ramezani et al. (11)	3	1	3	7
Schmitz et al. (39)	3	1	3	7
Mean score				6.7

BerEp4 positivity. In this paper, BCCs did not stain with EMA, but most of the SCCs did. Only one bSCC showed a focal EMA positivity. The authors concluded that the distinction between BCCs and SCCs was possible by using BerEp4 and EMA, and that identification of bSCC could also be achieved with these antibodies.

Another challenging entity is bSCC, a quite rare type of SCC, which may resemble BCC with squamous metaplasia. In this context, BerEp4 is unreliable for differentiation between the two entities, and adding the staining for cytokeratin 14 (CK14) or CK17 is needed for differentiation (43). In this regard, Winters et al. (44) have reported the use of BerEp4 as a helpful diagnostic marker for bSCC as positive in 82% of their cases, but also in 68% of SCC cases. Positivity of BerEp4 was also found in 26.3% of cases in Bowen disease, a variant of SCC *in situ*, and caused difficulty in differentiation from BCC and other keratinocyte neoplasms (45). Stanoszek et

al. (46) reviewed the histologic mimics of BCC including non-neoplastic processes (i.e., follicular induction over dermatofibromas), benign adnexal tumors (mainly of follicular origin), and cutaneous carcinomas with basaloid appearance. Distinguishing required clinicopathological correlation and IHC. A panel including PHLDA1 (Pleckstrin Homology Like Domain Family A Member 1), CK20, androgen receptor, CD10, Bcl-2, CD34, Ber-EP4, CD200, Claudin 4, EMA, CK15, and CEA was successfully used for a wide range of diagnoses. The limitations of this study were as follows: 1) in most studies, there was no sensitivity and specificity of markers between SCC and BCC, 2) sensitivity and specificity of used antibodies were different among the studies and 3) in some studies, the cut-off of markers was different. The strengths of this study were as follows: 1) most of the studies had high quality, and 2) the used method in all studies was similar (IHC).

Conclusion

The findings of the systematic review presented a high efficiency of EMA, CD10, CEA, and Bcl-2 markers in differentiating between SCC and BCC. Moreover, the use of these markers will be useful in such cases that routine microscopy cannot differentiate between the two mentioned carcinomas. Further larger studies in various environmental areas are needed to reach more precise estimates of the sensitivity and specificity of these markers.

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Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.R., E.Z., Design: M.S., Data Collection or Processing: M.R., M.S., Analysis or Interpretation: M.R., E.Z., Literature Search: M.S., Writing: M.S.

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Correlation of ADC values measured using 3T diffusion-weighted MRI and SUVs from fluorodeoxyglucose PET/CT in head and neck squamous cell carcinomas

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Keywords: Apparent diffusion coefficient, head and neck squamous cell carcinoma, diffusion-weighted magnetic resonance imaging, positron emission tomography, standardized uptake value

ABSTRACT

Aims: The aim of our study was to assess the correlations between apparent diffusion coefficient (ADC) values and standardized uptake values (SUVs) and their correlations with tumor size, tumor stage and histological grade in patients with head and neck squamous cell carcinomas (HNSSCs).

Methods: This retrospective study included 36 patients with histologically confirmed HNSSCs visible on diffusion weighted imaging (DWI) and fluorodeoxyglucose (FDG) positron emission tomography (PET/CT). Correlations of minimum ADC (ADC_{min}), mean ADC (ADC_{mean}), and minimum-mean ADC ratio ($ADC_{min/mean}$) with maximum SUV (SUV_{max}) and lean body mass SUV_{lbm} (SUV_{lbm}) were analyzed using the Spearman's correlation test. The Kruskal-Wallis one-way ANOVA test and Mann-Whitney U test were used to assess the correlations of ADC values and SUVs with tumor size, tumor stage and histological grade. Two experienced readers measured the ADC and SUVs independently, and intraclass correlation coefficient (ICC) was used to analyze the inter-observer agreement.

Results: The mean ADC_{min}, ADC_{mean}, and $ADC_{min/mean}$ for HNSSCs were $0.68\pm0.17\times10^{-3}$ mm^2/s, $0.82\pm0.17\times10^{-3}$ mm^2/s, and 0.83±0.10, respectively. The mean SUV_{max} and SUV_{lbm} were 14.65±5.5 and 10.96±5.1, respectively. The correlations between ADC values and SUVs did not reach statistical significance. There were no significant correlations of ADC values and SUVs with tumor size, tumor stage or histological grade. There was a tendency of SUVs to increase and ADC values to decrease with tumor dedifferentiation; however, the changes were not significant. Inter-observer agreement for tumor ADC values and SUVs was almost perfect (ICC>0.81).

Conclusions: Pretreatment ADC values and SUVs in HNSSCs are reproducible and independent biomarkers.

Introduction

Head and neck carcinomas account for over 6% of all malignant tumors in adults worldwide. Over 90% of malignant head and neck tumors are squamous cell carcinomas. According to the guidelines of American Joint Committee on Cancer, the tumor node metastasis staging of head and neck cancer requires histopathological diagnosis and additional imaging (1). Fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) and diffusion weighted magnetic resonance imaging (DW MRI) are increasingly recognized as important for assessing tumor malignancy in oncology.

Although DW imaging (DWI) and FDG PET/CT are based on different physical principles, both techniques are highly successful in oncology clinical practice and widely applied in tumor diagnosis (2). DWI is based on the assessment of

Brownian motion at the molecular level. The more restricted the movement of extracellular water molecules, the brighter it will be on DWI sequences. Malignant tumors exhibit hypercellularity, increased nucleus-to-cytoplasm ratios, and less extracellular space resulting in decreased apparent diffusion coefficient (ADC) values on ADC map. Based on previous studies, it appears that most malignant tissues have lower ADC values compared to normal tissue because of their higher cellular density (3). On the other hand, FDG PET/CT is a simple and reliable method of evaluating the glucose uptake capacity of tumors in vivo. Hypercellular tumor cells show increased intracellular accumulation of the glucose analog FDG, which is expressed by an increased standardized uptake value (SUV) (4). Since both SUV and ADC provide information on tumor cellularity, some degree of correlation between these two quantitative imaging parameters could be expected (4,5). An inverse association has been demonstrated between SUV and ADC values in studies of gastrointestinal stromal tumor, cervix cancer, rectal cancer, breast cancer, lung cancer and lymphoma (5-8). Previous reports found diverging results with either no correlation or significant correlation between SUV and ADC values in head and neck squamous cell carcinomas (HNSCCs).

The present study aimed to assess the reproducibility and correlations between ADC values and SUVs and their correlations with tumor size, tumor stage and histological grade in the same patients with biopsy-proven primary HNSSCs. Present review focuses on the promises of noninvasive imaging modalities in the initial diagnostic and prognostic assessment of patients with HNSSCs.

Methods

Ethical approval

Approval for the study was granted by the Ethics Committee of Ege University Faculty of Medicine (approval date: February 12, 2013, approval number: 13-1/50). It was conducted in accordance with the Declaration of Helsinki.

Patients

This study retrospectively analyzed 36 patients with histologically proven HNSSCs, who underwent head and neck MRI, DWI and whole-body FDG PET/CT examinations between October 2011 and September 2013. The mean time between FDG PET/CT and MRI was 7 days. Biopsy was performed 10-20 days after FDG PET/CT and MRI examinations (average time 15 days). The inclusion criteria for this study were as follows: patients at least 18 years of age who were previously untreated for head and neck carcinomas, no palpable neck lymph nodes, and available pretreatment FDG PET/CT, head and neck MRI and DWI. The exclusion criteria included the presence of palpable metastatic neck lymph nodes, a history of previous treatment for HNSSCs, distant metastasis at initial presentation, poor image quality. A total of 16 patients were excluded owing to susceptibility to artifacts that jeopardized image quality. Eight patients, who received radiotherapy (RT), were also excluded from the study. Therefore, 36 patients with HNSSCs were finally included in this study.

MRI and DWI

A 3-T whole-body system (Verio, Siemens Medical Systems, Germany) with a neck array coil was used to perform MRI examinations. The maximum gradient capability was 40 mT/m, and the maximum slew rate was 200 mT/m. The MRI protocol included the following imaging sequences: axial T1-weighted imaging [repetition time (TR)/echo time (TE), 623/9; NEX, 2; matrix, 320 × 224; field of view (FOV), 27 cm; slice thickness, 4 mm; intersection gap, 1.5 mm; 20 sections], sagittal T1-weighted imaging (TR/TE, 730/9.6; NEX, 2; matrix, 384 × 269; FOV, 27 cm; slice thickness, 5 mm; intersection gap, 1.5 mm; 20 sections), coronal T1-weighted imaging (TR/TE, 803/9.6; NEX, 2; matrix, 384 × 288; FOV, 27 cm; intersection gap, 1.5 mm; slice thickness, 5 mm; 20 sections), axial Turbo Inversion Recovery Magnitude (TIRM) [TR/TE/inversion time (TI), 3480/56/220; NEX, 2; matrix, 320 × 224; FOV, 27 cm; slice thickness, 4 mm; intersection gap, 1 mm; 20 sections], sagittal TIRM (TR/TE/TI, 4110/55/220; NEX, 2; matrix, 320 × 240; FOV, 27 cm; slice thickness, 5 mm; intersection gap, 1 mm; 20 sections), and coronal TIRM (TR/TE/TI, 4462/55/220; NEX, 2; matrix, 320 × 240; FOV, 27 cm; intersection gap, 1 mm; slice thickness, 5 mm; 20 sections). Axial DWI was performed using a fat suppression single-shot echo-planar technique (TR/TE/TI, 14200/77/220; NEX, 2; matrix, 100 × 100; FOV, 27 cm; slice thickness, 4 mm; no intersection gap; 52 sections). ADC values were determined using the following two b factors: b 0 and b 800 s/mm^2. ADC maps were automatically formed on a pixel-by-pixel basis by an MRI software system. To locate the solid tumor portion accurately, 0.1 mmol/kg gadolinium-DTPA-enhanced T1-weighted spin-echo imaging with fat suppression was performed after DWI. The ADC values were measured on ADC maps by drawing a region of interest (ROI) around the largest solid portion of the tumor avoiding any cystic or necrotic areas identified on the TIRM and T1-weighted post-contrast MR images. ROI examples are shown in Figure 1. The size of the ROI was 16-56 mm^2. The minimum ADC (ADC_{min}, the lowest ADC value within the ROI, which is based on a single pixel), mean ADC (ADC_{mean}, the mean ADC value of all the pixels within the ROI), and minimum-mean ADC ratio ($ADC_{min/mean}$) were calculated within the same ROI.

FDG PET/CT

The PET-CT scanner used in this study was a Biograph 16-slice PET/CT scanner (Siemens Healthcare, Germany). The patients were instructed not to eat food for six hours before the PET/CT imaging. In patients whose preparation

was adequate, the blood glucose level was checked and, at the time of FDG injection, serum glucose levels were 150 mg/dL or less. In all patients, fluorine-18 FDG (^{18}F-FDG) of 3.7 MBq/kg body weight was intravenously injected. After the injection, the patients were requested to rest for one hour. At the end of the resting period, the patients were asked to empty their bladder. All the patients were scanned from the vertex to the proximal thigh. PET emission scans were performed with 1.8 min per bed position for a total of 7 to 10 beds. PET images were scatter-corrected and reconstructed using an ordered-subset expectation maximization iterative reconstruction algorithm. The reconstruction parameters were as follows: three iterations and twenty one subsets. The CT parameters were as follows: tube voltage, 130 kVp; tube current, 120 mA; collimation, 16 × 1.5; FOV, 500 mm; matrix, 512 × 512; gantry rotation, 0.6 s; gantry feed per rotation, 30 mm; slice width, 5 mm. The PET/CT images were shown on a monitor. Tumor was distinguished on PET/CT images, and a 3D ROI, which included the whole lesion in the sagittal, coronal and axial planes, was placed in the PET dataset. ROI examples are shown in Figure 1. The SUV by body weight was calculated using this formula: SUV = [radioactivity concentration in tissue (Bq) / tissue weight (g)] / [total injected dose (Bq) / patient's body weight (g)]. The maximum SUV (SUV_{max}) is merely a single-voxel value representing the most intense FDG uptake of the structure delineated by the ROI. The SUV normalized to lean body mass (SUV_{lbm}) was defined as follows: SUV = (activity in the 9 maximal pixels in mCi/mL) / (total injected dose / lean body mass). The corresponding volume measured automatically by the software was marked as metabolic tumor volume (MTV). DW MRI and PET/CT measurements were performed by two board-certified radiologists. The radiologists were informed on the clinical diagnosis of HNSSCs but were blinded to the pathologic findings and the patients' previous history. The readers measured ADC values and SUVs, independently, using the predefined ROI size. The measured values were recorded.

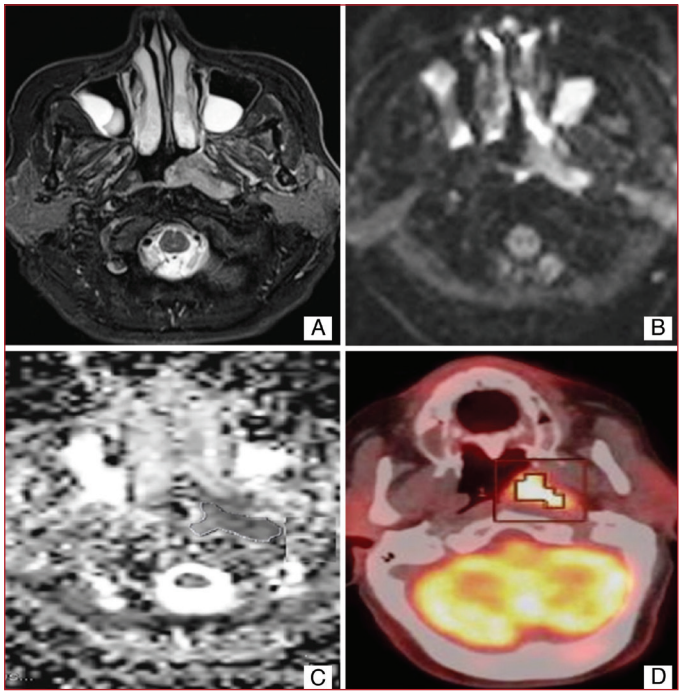

Figure 1. A 58-year-old woman with left well-differentiated nasopharyngeal cancer. The tumor is clearly delineated on axial Turbo Inversion Recovery Magnitude imaging (A). The tumor shows high signal intensity on diffusion-weighted imaging (b: 800) (B) and low signal intensity in an apparent diffusion coefficient map (C). Fluorodeoxyglucose positron emission tomography/computed tomography shows strong uptake in the tumor (D). Regions of interest are shown in C and D

Statistical Analysis

The relationships between ADC values (ADC_{min}, ADC_{mean}, and $ADC_{min/mean}$) and SUVs (SUV_{max} and SUV_{lbm}) were determined by the Spearman's rank test. The Kruskal-Wallis One-Way analysis of variance (ANOVA) test and Mann-Whitney U test were used to examine the associations of SUVs and ADC values with tumor size, MTV, tumor stage, and tumor histological grade (9). According to Donner and Koval (10), Landis and Koch (11), intraclass correlation coefficients (ICCs) values for inter-observer agreement with 95% confidence intervals were represented as follows: ≤0, no agreement; 0.01-0.20, none to slight agreement; 0.21-0.40, fair; 0.41-0.60, moderate; 0.61-0.80, substantial; and 0.81-1.00, almost perfect agreement. Statistical data were analyzed using the SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at p-value of ≤0.05.

Results

This retrospective study was conducted on 36 patients (20 men and 16 women) with HNSSCs.

The mean age was 56.4±9.8 years (range, 18-80 years). The primary tumor sites were as follows: nasopharynx (n=14), larynx (n=8), hypopharynx (n=4), oral cavity (n=4), oropharynx (n=3), paranasal sinuses (n=2), and external auditory canal (n=1). The mean tumor size according to the longest tumor diameter measured in the axial plane was 5.26±2.04 cm (range, 1-10 cm). The mean tumor volume was 22.3±26.9 cm^3 (range, 3.2-104 cm^3). Among the 36 tumors, 10 (27.8%) were poorly differentiated, 20 (55.5%) were moderately differentiated, and 6 (16.7%) were well differentiated. The diagnosed head and neck carcinomas were staged as T1 (n=6, 16.7%), T2 (n=16, 44.4%), T3 (n=11, 30.6%), and T4 tumors (n=3, 8.3%) with no additional nodal or distant metastases.

ADC values and SUVs in HNSSCs

Table 1 summarizes the ADC values and SUVs for all the HNSSCs. The mean ADC_{min}, ADC_{mean}, and $ADC_{min/mean}$ for the HNSSCs were 0.68±0.17 × 10^{-3} mm^2/s, 0.82±0.17 × 10^{-3}

Table 1. Apparent diffusion coefficient values and standardized uptake values for head and neck squamous cell carcinomas

Biomarker	HNSSC (n=36) Mean±SD	Median	Minimum	Maximum
ADC_{min} (10^{-3} mm^2/s)	0.68±0.17	0.69	0.33	0.99
ADC_{mean} (10^{-3} mm^2/s)	0.82±0.17	0.81	0.44	1.25
$ADC_{min/mean}$	0.83±0.10	0.84	0.53	0.97
SUV_{max}	14.65±5.50	13.10	7.60	29.10
SUV_{lbm}	10.96±5.10	9.40	5.00	22.50
MTV	22.30±26.90	10.30	3.20	104.00

n: Number of tumors, HNSSC: Head and neck squamous cell carcinoma, ADC: Apparent diffusion coefficient, ADC_{min}: Minimum ADC, ADC_{mean}: Mean ADC, $ADC_{min/mean}$: Minimum-mean ADC ratio, SUV: Standardized uptake value, SUV_{max}: Maximum SUV, SUV_{lbm}: Lean body mass-based SUV, MTV: Metabolic tumor volume, SD: Standard deviation

Table 2. Correlations between apparent diffusion coefficient values and standardized uptake values in head and neck squamous cell carcinomas

	ADC_{min}	ADC_{mean}	$ADC_{min/mean}$
SUV_{max}	r=-0.050	r=-0.084	r=-0.160
	p=0.777	p=0.630	p=0.359
SUV_{lbm}	r=-0.057	r=-0.090	r=-0.141
	p=0.746	p=0.606	p=0.419

p and r - values were obtained using the Spearman's rank test.
ADC: Apparent diffusion coefficient, ADC_{min}: Minimum ADC, ADC_{mean}: Mean ADC, $ADC_{min/mean}$: Minimum-mean ADC ratio, SUV: Standardized uptake value, SUV_{max}: Maximum SUV, SUV_{lbm}: Lean body mass-based SUV

mm^2/s, and 0.83±0.10 mm^2/s, respectively. The mean SUV_{max}, SUV_{lbm}, and MTV were 14.65±5.5, 10.96±5.1, and 22.3±26.9 cm^3, respectively.

Correlations of ADC values and SUVs in HNSSCs

There were no significant correlations between the ADC values (ADC_{min}, ADC_{mean}, and $ADC_{min/mean}$) and the SUV values (SUV_{max} and SUV_{lbm}) (Table 2).

Correlations of ADC values and SUVs with tumor size and MTV

ADC values and SUVs were not significantly associated with tumor size and MTV.

Correlations of ADC values and SUVs with tumor histological grade

For well-differentiated tumors, the mean ADC_{min}, ADC_{mean}, $ADC_{min/mean}$, SUV_{max}, and SUV_{lbm} were 0.72±0.23 × 10^{-3} mm^2/s, 0.89±0.17 × 10^{-3} mm^2/s, 0.79±0.15, 13.30±4.7, and 9.5±3.6, respectively. For moderately differentiated tumors, the mean ADC_{min}, ADC_{mean}, $ADC_{min/mean}$, SUV_{max}, and SUV_{lbm} were 0.72±0.19 × 10^{-3} mm^2/s, 0.84±0.21 × 10^{-3} mm^2/s, 0.86±0.08, 15.30±5.6, and 11.4±5.1, respectively. For poorly differentiated tumors, the mean ADC_{min}, ADC_{mean}, $ADC_{min/mean}$, SUV_{max}, and SUV_{lbm} were 0.64±0.14 × 10^{-3} mm^2/s, 0.78±0.15 × 10^{-3} mm^2/s, 0.82±0.10, 15.5±7.2, and 12.8±7.4, respectively (Table 3). There was a tendency for the SUVs to increase and the ADC values to decrease with tumor dedifferentiation; however, these changes were not significant.

Correlations of ADC values and SUVs with tumor stage

The mean ADC_{min}, ADC_{mean}, $ADC_{min/mean}$, SUV_{max}, and SUV_{lbm} were 0.69±0.19 × 10^{-3} mm^2/s, 0.82±0.16 × 10^{-3} mm^2/s, 0.85±0.08, 12.10±4.1, and 9.37±3.3 for T1-2 stage, and 0.67±0.16 × 10^{-3} mm^2/s, 0.80±0.20 × 10^{-3} mm^2/s, 0.81±0.11, 16.15±5.6, and 11.89±5.5 for T3-4 stage, respectively (Table 3). Although statistically insignificant, a trend towards higher SUVs and lower ADC values was observed in T3-4 stage (Table 3).

Inter-observer agreement

Inter-observer agreement for tumor ADC_{min}, ADC_{mean}, SUV_{max} and SUV_{lbm} values was almost perfect (ICC>0.81) (Table 4).

Discussion

Our study found no significant associations between the ADC values and the SUVs. Additionally, correlations between the ADC values and the SUVs with tumor size, tumor stage or tumor histological grade did not reach statistical significance.

ADC values for HNSSCs

In the present study, the ADC values (ADC_{min}, ADC_{mean}, and $ADC_{min/mean}$) were calculated from b values of 0 and 800 s/mm^2. High b values eliminate the perfusion effect (12). The ADC values in our study were obtained at 3 T. With the exception of one study (13), previous studies found that the ADC values were independent of the magnetic field strength (14-16). ADC measurements at 1.5, 3 and 7 T found no statistically significant difference for ADC values either in the breast, head and neck or in the abdomen, provided that the parameters of the DWI used were identical (14-16). The ADC values for the HNSSCs in the present study are similar to those reported in previous studies (17-29). In the present study, the mean ADC_{min}, ADC_{mean}, and $ADC_{min/mean}$ for the HNSSCs were 0.68±0.17 × 10^{-3} mm^2/s (range, 0.33-0.99 × 10^{-3} mm^2/s), 0.82±0.17 × 10^{-3} mm^2/s (range, 0.44-1.25 × 10^{-3} mm^2/s), and 0.83±0.10 mm^2/s (range,

Table 3. Correlations of apparent diffusion coefficient values and standardized uptake values with tumor stage and the histological grade of head and neck squamous cell carcinomas

Biomarker	Histologic grade	Number	Mean±SD	p*	Biomarker	Tumor stage	Number	Mean±SD	p*
ADC_{min} (10^{-3} mm^2/s)	WDC	10	0.72±0.23	0.526	ADC_{min} (10^{-3} mm^2/s)	T1-2	22	0.69±0.19	0.745
	MDC	20	0.72±0.19			T3-4	14	0.67±0.16	
	PDC	6	0.64±0.14						
ADC_{mean} (10^{-3} mm^2/s)	WDC	10	0.89±0.17	0.274	ADC_{mean} (10^{-3} mm^2/s)	T1-2	22	0.82±0.16	0.820
	MDC	20	0.84±0.21			T3-4	14	0.80±0.20	
	PDC	6	0.78±0.15						
$ADC_{min/mean}$	WDC	10	0.80±0.15	0.540	$ADC_{min/mean}$	T1-2	22	0.84±0.08	0.757
	MDC	20	0.86±0.08			T3-4	14	0.83±0.11	
	PDC	6	0.82±0.10						
SUV_{max}	WDC	10	13.30±4.7	0.983	SUV_{max}	T1-2	22	12.10±4.1	0.622
	MDC	20	15.30±5.6			T3-4	14	16.15±5.6	
	PDC	6	15.5±7.2						
SUV_{lbm}	WDC	10	9.5±3.6	0.677	SUV_{lbm}	T1-2	22	9.37±3.3	0.934
	MDC	20	11.4±5.1			T3-4	14	11.89±5.5	
	PDC	6	12.8±7.4						

*p values were obtained using the Mann-Whitney U test.
ADC: Apparent diffusion coefficient, ADC_{min}: Minimum ADC, ADC_{mean}: Mean ADC, $ADC_{min/mean}$: Minimum-mean ADC ratio, SUV: Standardized uptake value, SUV_{max}: Maximum SUV, SUV_{lbm}: Lean body mass-based SUV, WDC: Well differentiated carcinoma, MDC: Moderately differentiated carcinoma, PDC: Poorly differentiated carcinoma, SD: Standard deviation

Table 4. Inter-observer agreement for apparent diffusion coefficient and standardized uptake value measurements

Biomarker	Intraclass correlation coefficient	%95 confidence interval	Reproducibility interpretation*
ADC_{min}	0.88	0.73-0.94	Almost perfect
ADC_{mean}	0.81	0.60-0.88	Almost perfect
SUV_{max}	0.90	0.81-0.99	Almost perfect
SUV_{lbm}	0.95	0.87-0.99	Almost perfect

*Reproducibility interpretation was obtained according to Landis and Koch.
ADC: Apparent diffusion coefficient, ADC_{min}: Minimum ADC, ADC_{mean}: Mean ADC, SUV: Standardized uptake value, SUV_{max}: Maximum SUV, SUV_{lbm}: Lean body mass-based SUV

0.53-0.97 × 10^{-3} mm^2/s), respectively. A wide range of ADC values has been found in different studies, and this is probably due to tumor cystic or necrotic component, tumor cellularity, and presence of fibrosis (17-29). In the present study, there were no significant correlations between the histological tumor grade and the ADC values, although the mean ADC_{min}, and ADC_{mean} values tended to be lower in poorly differentiated (0.64 × 10^{-3} mm^2/s, and 0.78 × 10^{-3} mm^2/s, respectively) HNSSCs than in well-differentiated (0.72 × 10^{-3} mm^2/s, and 0.89 × 10^{-3} mm^2/s, respectively) and moderately differentiated (0.72 × 10^{-3} mm^2/s, and 0.84 × 10^{-3} mm^2/s, respectively) HNSSCs. Increased cellularity in poorly differentiated tumors reduces the diffusion space of water protons in the extracellular matrix, with a resultant decrease in ADC. Similar results have been reported in other studies (19,22,29,30). With the exception of one study that found a significant positive correlation (31), most studies found no significant correlations between the T stage and the ADC values (19,22,29,32). Present study reports lower ADC_{min}, and ADC_{mean} values in T3-4 tumors (0.67 × 10^{-3} mm^2/s, and 0.80 × 10^{-3} mm^2/s, respectively) than in T1-2 tumors (0.69 × 10^{-3} mm^2/s, and 0.82 × 10^{-3} mm^2/s, respectively). Previous studies have indicated no significant correlations between the ADC values and tumor size or MTV (19,30), and our findings are consistent.

SUVs for HNSSCs

PET/CT is highly successful in oncological clinical practice and widely applied in the diagnosis of HNSSCs and treatment

response evaluation. Hypercellular tumor cells show increased intracellular accumulation of the glucose analog FDG, which is expressed by an increased SUV. SUV is a convenient simple way of quantifying glucose uptake. FDG uptake is positively related to tumor cellularity and the growth rate (30,32,33). Similar to the results reported in previous studies (19,24,34-36), in the present study, the mean SUV_{max} and SUV_{lbm} for the HNSSCs were 14.65±5.5 (range, 7.60-29.10) and 10.96±5.1 (range, 5.00-22.50), respectively. A wide range of SUV has been found in different studies and this is probably due to tumor cellularity, cellular turnover, tumor volume, and presence of tumor necrotic component (35,36). An increase in tumor dedifferentiation can activate glucose metabolism, with a resultant increase in FDG uptake. In the present study, there were no significant differences in the SUVs among well, moderately, and poorly differentiated carcinomas, although the mean SUV_{max}, and SUV_{lbm} tended to be higher in poorly differentiated (15.5, and 12.8, respectively) HNSSCs than in well-differentiated (13.3, and 9.5, respectively) and moderately differentiated (15.3, and 11.4, respectively) HNSSCs. A similar trend has been reported in other studies (7,8,30,34,37,38). One study found a significant positive correlation between SUVs and T stage (19). We found no significant correlations between the SUVs and T stage; however, mean SUV_{max}, and SUV_{lbm} were higher in T3-4 tumors (16.15, and 11.89, respectively) than in T1-2 tumors (12.10, and 9.37, respectively). With the exception of one study (39), previous studies have reported positive correlations between SUVs and MTV (32,33,36,38). However, in the present study, the correlations between SUVs and MTV did not reach statistical significance.

Correlations between ADC values and SUVs in HNSSCs

It is important to assess whether the ADC values and the SUVs are statistically independent or correlated, as recent data suggest that both types of biomarkers may be associated with cell proliferation and may predict the response to RT and chemotherapy (19). Recent researches suggest that these two biomarkers may be correlated with tumor cellularity, cell proliferation, and tumor necrosis (19). The present study did not identify significant correlations between the SUVs and the ADC (800) values, indicating that these biomarkers are independent in HNSSCs. With the exception of one study that found a significant inverse correlation of these two quantitative parameters (19), previous studies reported results similar to our findings (18,20,24,34-36,40).

Inter-observer agreement

Previous analyses reported almost excellent interreader agreement for SUV_{max} values for lung cancer, sarcomas, breast cancer and HNSCCs. These studies have shown that the SUV_{max} is reproducible and observer-independent value. The present study identified almost perfect inter-observer agreement for the ADC values and the SUVs. Compared to the previous data, we found slightly inferior interreader reliability [ICC = 0.81-0.88 versus 0.96 (reported)] for ADC values (24) and almost equal interreader reliability [ICC = 0.90-0.95 versus 0.97 (reported)] for SUVs (24).

Our study has several limitations. This study was retrospective and involved a small number of patients. From this small sample size, it is difficult to draw firm conclusions. Further validation is required with a large number of cases. Different acquisition parameters including matrix size and slice thickness affect both the quality and quantitative values of MRI and PET images in the current study.

Conclusion

In conclusion, our results suggest that pretreatment ADC values and SUVs for HNSSCs are independent and reproducible biomarkers, with almost perfect inter-observer agreement. The ADC values tended to be lower and the SUVs tended to be higher in T3-4 stage and poorly differentiated HNSSCs; however, the findings were not significant. Further large-scale, multi-institutional studies should be performed to provide standardized pretreatment ADC and SUV cut-offs for characterization, prediction, treatment response assessment, and the detection of post-treatment changes and recurrent head and neck tumors.

Ethics

Ethics Committee Approval: Approval for the study was granted by the Ethics Committee of Ege University Faculty of Medicine (approval date: February 12, 2013, approval number: 13-1/50).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.C., S.B., O.A., Concept: E.C., S.B., Design: E.C., S.B., Data Collection or Processing: E.C., S.B., O.A., Analysis or Interpretation: E.C., S.B., O.A., R.S., M.E., Literature Search: E.C., S.B., O.A., R.S., M.E., Writing: E.C., S.B., O.A.

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The analysis of learning needs and level of awareness for patients who underwent thoracic surgery

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Keywords: Learning needs, mindfulness, thoracic surgery

ABSTRACT

Aims: The aim of this study is to define learning needs and level of mindfulness in patients that underwent thoracic surgery.

Methods: This cross-sectional descriptive study was conducted on 100 patients, who underwent thoracic surgery at the thoracic surgery clinic of a university hospital between December 2014 and May 2016. Data collection form consisted of three parts, namely Sociodemographic Data Form, Patient Learning Needs Scale (PLNS) and Mindful Attention Awareness Scale (MAAS).

Results: The mean age of participants was 35.74±17.87 years and 83.8% were male. The mean score obtained from the PLNS was 200.06±37.48. Participants obtained the highest scores from the "Treatment and Complications" (37.01±6.89) and "Activities of Living" (36.01±8.88) subscales of the PLNS. The lowest score was obtained from the "Feelings related to Condition" subscale (19.01±4.75). The relationship between the socio-demographic characteristics of the patients and Patient Educational Needs Scale was not statistically significant. Besides, no statistically significant relationship was found between the scores obtained from the PLNS and MAAS.

Conclusions: Our study revealed that the majority of patients needed information on "treatment and complications". Since the levels of mindfulness of the patients may change over time, it is deemed appropriate to conduct patient education with repeated interviews.

Introduction

Recently, patients and their families want to receive high quality healthcare that is parallel to the global standards (1). They demand correct and sufficient information about health status and to actively engage in treatment process (2). Within this context, informing the patient and families about the health status of the patient is an important patient right (3). Patient education aims to correct health behaviors, helps the patients to cope with their disease and improves their skills on self-decision-making (4). Standards for patient education have been developed and guaranteed by the JCAHO (5). Personalized and unique discharge plans have been proven to shorten hospital stay and reduce hospital readmission rates (6). Discharge education and care plans for home healthcare are highly important to prevent or reduce post-discharge complications of patients that underwent surgical operation (7). Learning needs, personal characteristics and preferences of the patients, content, place and duration of education, and available resources should be taken into consideration while determining patient education methods and techniques (8). Well-planned preoperative and postoperative pulmonary rehabilitation education programs are required to get patients that underwent thoracic surgery back to their daily lives (9). Pulmonary rehabilitation programs should be designed according to the clinical characteristics and learning

needs of the patients (10). Patient's learning needs include the situation of disease, procedures of treatment and post-discharge homecare. Patients are mostly interested in daily activities, possible complications, drug use, access to health services, skin care, diet, exercise, wound care, and the management of pain and physical impairment. Delays in recovery, deterioration in the quality of life and increase in hospital readmission rates are observed for the patients that have not been sufficiently informed about their status by health professionals (11). Treatment and care of patients undergoing surgical operation vary depending on the type of the operation (7). In case of thoracic surgery, therapeutic compliance of patients that have received patient education are higher than those that have not. The aims of educating the patient and families include providing information about health status, increasing therapeutic compliance and enabling the patient to take the responsibility for self-care (12). Various factors, including mindful awareness, or mindfulness, influence patient education. Mindfulness, which is highly related to consciousness, is associated with maturity. "Psychological consciousness" is defined as the ability to engage in self-evaluation and perceive the relationship between emotions, ideas and behaviors in order to comprehend the reasons behind one's life and behaviors (13). Studies that evaluate the relationship between mindfulness and education show that people may not focus on the subject or remain indifferent to the education if the attractiveness of the education is not maintained. This, in turn, leads to a failure in patient education. On the other hand, attractive education programs increase mindfulness and the success rates of the program (14). Within this context, nurses should search answers the questions of "how can the patient and families be educated?" and "how do the patients learn?". They should collect information on mental competence, levels of mindfulness, and educational, sensory, psychosocial, physical and emotional development status of the patients. Identifying patients' learning needs and levels of mindfulness of the patients will contribute to positive changes in patients' attitudes and behaviors. This study aims to identify learning needs and levels of mindfulness of patients that underwent thoracic surgery.

Methods

Since this study was a non-invasive clinical research, we obtained informed consent of the participants and ethics committee approval. This study was approved by Gülhane Non-invasive Investigation Ethics Committee (8 December 2014, no: 2377).

The study was conducted on 100 patients at the thoracic surgery clinic of a university hospital. Adult patients, who were admitted to the thoracic surgery clinic of the hospital and underwent thoracic surgery during the research period, constituted the universe of this cross-sectional descriptive study. Patients above the age of 18 years, who agreed to participate, could communicate, underwent thoracic surgery and would be discharged, constituted the sample of the study. Data were collected between January 2014 and May 2016 by using face-to-face interview method. Interviews were conducted 24 hours before patient discharge. Each interview took about 15-20 minutes on average. Data collection form consisted of three parts, namely Socio-Demographic Data Form, Patient Learning Needs Scale (PLNS) and Mindful Attention Awareness Scale (MAAS). The Socio-Demographic Data Form was prepared by the researchers by using the relevant literature. The form included questions on age, gender, education, marital status, profession, people that the participants lived with, chronic diseases, smoking habits, previous admission to hospital, duration of clinical stay, and discharge education. The PLNS was developed by Bubela et al. (15). Validity and reliability of the Turkish version of the scale was performed by Catal and Dicle (16). We obtained necessary permissions to use these scales in our study. The PLNS consisted of 50 items and seven subscales. Table 1 shows the subscales, items and the minimum and maximum scores for each subscale. Items were rated on a 5-point Likert type scale ranging from 1 (of no importance) to 5 (extremely important). Patients were asked to rate the items that defined their learning needs and priorities before discharge. The scale generated subscale scores and a total scale score that ranged between 50 and 250. Cronbach's alpha for the total scale was 0.95 and ranged from 0.69 to 0.88 for the subscales.

Table 1. Patient Leaning Needs Scale, subscales, items and min.-max. scores

Subscales	Number of items	Items	Min.-max. scores
Medications	8	3,8,16,18,37,39,44,45	8-40
Activities of living	9	2,5,14,17,27,28,29,30,48	9-45
Community and follow-up	6	6,9,22,31,36,41	6-30
Feelings related to condition	5	7,24,32,35,42	5-25
Treatment and complications	9	1,4,10,19,20,23,26,38,47	9-45
Enhancing quality of life	8	11,13,15,21,34,40,46,50	8-40
Skin care	5	12,25,33,43,49	5-25
Total	50		50-250

Min.: Minimum, Max.: Maximum

The MAAS is a 15-item scale, which was developed by Brown and Ryan (17), in order to explore the presence or absence of attention to and awareness of what is occurring at the moment. Reliability and validity of the Turkish version of the MAAS was performed by Ozyeşil et al. (14). MAAS has a single factor and generates a single total score. Items are rated on a 6-point Likert scale ranging from 1 (almost always) to 6 (almost never), where higher scores indicate higher levels of mindfulness. Cronbach's alpha internal consistence coefficient of the Turkish version of the MAAS was 0.80 and test-retest correlation coefficient was 0.86. Turkish version of the MAAS is a proper data collection tool to determine mindfulness of people in Turkish society.

We conducted a single interview with the participants before their discharge. Interviews after the patient discharge may be conducted in future research. Besides, we did not provide patient education to increase mindful awareness.

This research mainly attempts to answer the following question: "Do the levels of mindfulness influence the learning needs of the patients that underwent thoracic surgery?"

This study also attempts to answer the following sub-question: "Do the sociodemographic characteristics influence the learning needs of patients that underwent thoracic surgery?"

Expected relationships between the independent and dependent variables of this study are the followings:

H0: Patients with high levels of mindfulness are not aware of their learning needs.

H1: Patients with high levels of mindfulness are aware of their learning needs.

Patient-centered approach has been adopted by health centers and the importance of patient engagement in healthcare has been underlined in recent years. The model, known as "Multidimensional Framework for Patient and Family Engagement in Health and Healthcare", aims to maintain active participation of the patients to clinical decisions. The model provides information about patient and family engagement at three levels, namely, direct care, organizational design and governance, and policy making. Factors related to patient, organization and the society have positive and negative effects on patient engagement. Patient education and mindfulness, which are the subjects of this research, are among the main components of active patient engagement (18,19).

Statistical Analysis

SPSS 22.0 statistical software was used for data analysis. Number, percentage, mean and standard deviation were used for descriptive data. Normal distribution of continuous variables was tested with the Kolmogorov-Smirnov test. For intergroup comparison, we used the chi-square test for discrete variables and ANOVA and Student's t-test for continuous variables. Linear relationship between variables was evaluated by the Pearson correlation test. Statistical significance was set at 0.05.

Results

The mean age of the participants was 35.74±17.87 and 24.15±3.86 years, respectively. The majority of the participants were male (83.8%). More than half of the participants were single (63.6%), and nearly half of them were graduates of secondary and high schools (47.5%). 63.6% were self-employed, 19.2% were civil servants and 17.2% were retired. 67.7% of the participants were admitted to the hospital for the first time. 91.9% lived with their families and 62.6% had an income that met their expenditures. 41.4% had chronic diseases, including hypertension (n=20), diabetes (n=11), cardiovascular diseases (n=7) and chronic obstructive pulmonary disease (n=4). 26.3% used medications regularly. Nearly half of the participants stated that they received discharge education and one-third smoked. Descriptive characteristics of the participants are summarized in Table 2. The mean PLNS total score of the participants was 200.06±37.48. Participants received the highest mean score from the 'treatment and complications' (37.01±6.89) subscale and the lowest score from the 'feelings related to condition' subscale (19.01±4.75). Subscale that was scored the highest importance level was 'treatment and complications' (4.11), which was followed by 'enhancing quality of life' (4.08), and 'medications' (4.05), respectively. On the other hand, subscales that had the least mean importance levels were 'community and follow-up' (3.81) and 'feelings related to condition' (3.80), respectively. Table 3 shows the mean PLNS and MAAS scores of the patients. We did not find any statistically significant relationship between the socio-demographic characteristics of the patients and their mean PLNS scores. Besides, there was no statistically significant relationship between the mean MAAS scores and mean scores obtained from the PLNS and its subscales. Finally, we found a positive and statistically significant relationship between the total PLNS score and the scores obtained from the 'medications' ($r=0.922$, $p<0.001$) and 'treatment and complications' subscales ($r=0.914$, $p<0.001$).

Discussion

Patient education, which provides information to patients on their health status and treatment and recovery processes, is an important element of holistic patient care (20). It maintains active patient engagement in recovery process and helps patients to comprehend the surgical operation that they will undergo (21). Discharge education and care plans for home healthcare should be prepared to prevent or decrease complications for patients undergoing surgical operation. Discharge planning should start prior to the surgery (7,20). Learning needs of the patients are knowledge and skills that are missing due to the recent developments in the lives of the patients (22). Patient education

Table 2. Descriptive characteristics of the participants

Characteristics			
Age (Mean ± SD)		**35.74±17.87**	
		n	**%**
Gender	Female	16	16.2
	Male	83	83.8
Marital status	Married	36	36.4
	Single	63	63.6
Education	Primary school	26	26.3
	Secondary and high schools	47	47.5
	University and above	26	26.3
Profession	Self-employed	63	63.6
	Civil servant	19	19.2
	Retired	17	17.2
Admission to hospital	First time	67	67.7
	More than once	32	32.3
Income	Income equal to expenditure	62	62.6
	Income less than expenditure	26	26.3
	Income more than expenditure	11	11.1
Living with	Alone	8	8.1
	Family	91	91.9
Chronic illness	Yes	41	41.4
	No	58	58.6
Regular medication use	Yes	26	26.3
	No	73	34.3
Smoking	Yes	34	40.4
	No	65	65.7
Discharge education	Received	47	47.5
	Did not receive	52	52.5
Total		99	100

SD: Standard deviation

is crucial for the recovery of all patients undergoing surgical operation (12). This study identified the learning needs of the patients that underwent thoracic surgery before their discharge. We found that the participants obtained the highest scores from the treatment and complications and enhancing quality of life subscales of the PLNS. The mean total PLNS score of the participants in our study was relatively high and resembled to the findings of Catal and Dicle (16), Tan et al. (23), and Ozel (24). Studies that used PLNS for other patients in general surgery clinics also found high total PLNS scores. Similar to other studies, our study explored the need for informing the patients undergoing surgical operation and the preparation of patient education plans in line with patients' learning needs. Most of the patients in our study expressed their need to be informed about treatment and complications. Other studies, mostly on general surgery patients, had similar results. For example, the study of Tan et al. (23) on 575 general surgery patients found that the patients received the highest scores from the 'medications' and 'enhancement of quality of life' subscales of the PLNS whereas the lowest scores were received from the subscales of 'feelings related condition' and 'community and follow-up'. Similarly, the study of Ozel et al. (24) on 114 pre-discharged patients of general surgery clinic found that PLNS scores obtained from the 'medications' and 'enhancing the quality of life' were high. Deniz et al. (25) conducted a study on 57 general surgery patients and found that the most important learning needs were treatment and complications, which were parallel to our findings. Polat et al. (26) conducted a study on 1190 patients that would be discharged from a university hospital and found that 'treatment and complications' and 'skin care' were the subscales of the PLNS with the most and the least scores, respectively. Incidence of pulmonary complications after thoracic surgery, which ranges from 7% to 36%, prolongs hospital stay and increases morbidity and mortality rates. Repeated patient education decreases incidences of pulmonary complications (10,27-29). Pulmonary complications are especially more important for the patients

Table 3. Average Patient Learning Needs Scale and Mindful Attention Awareness Scale scores of the participants

	Average score Mean ± SD	Min.-max.	Importance level (mean)
Medications	32.42±6.48	12.00-40.00	4.05
Activities of living	36.01±8.88	14.00-91.00	4.00
Community and follow-up	22.91±5.18	7.00-30.00	3.81
Feelings related to condition	19.01±4.75	6.00-25.00	3.80
Treatment and complications	37.01±6.89	14.00-45.00	4.11
Enhancing quality of life	32.68±6.17	13.00-40.00	4.08
Skin care	20.00±4.01	6.00-25.00	4.00
PLNS total score	200.06±37.48	76.00-287.00	-
MAAS score	63.13±15.10	36.00-144.00	-

PLNS: Patient Learning Needs Scale, MAAS: Mindful Attention Awareness Scale, Min.: Minimum, Max.: Maximum, SD: Standard deviation

undergoing thoracic surgery. Discharged patients are especially nervous and demand information on how to use the ordered medications and what to do in case of complications. Patient education in thoracic surgery involves three dimensions: time required to answer the questions of the patients, information about the treatment and healthcare processes as a patient right, and content of patient education and materials. Content of patient education involves two parts: general information on thoracic surgery and information about specific surgeries, including pneumonectomy, lobectomy, wedge resection and mediastinal mass excision (20). The study of King et al. (12) on preoperative and postoperative learning needs and education given to 10 patients undergoing lung cancer surgery found that the participants found preoperative education, especially on respiratory physiotherapy, useful and expressed their learning need for postoperative pain management. On the other hand, ambulatory surgical patients have sufficient time before the operation. However, discharge education for these patients is given mostly during the postoperative period. Preoperative patient education should be simple and learning types of the patients and their satisfaction should be taken into consideration. These educations are highly important to reduce postoperative complications (28). Most of the patients that have undergone thoracic surgery have poor knowledge about modifiable life changes (30). A study on patients undergoing lung resection in the UK found that the patients identified lack of support, failure to meet patient expectations before and after surgery, underutilization of written information and their demand to face-to-face discussion with health professionals as key gaps in the experience of care (29). Our study found that the main learning needs of the participants were medications, treatment and complications and enhancing the quality of life. Patient education that deals with these subjects may contribute to patient recovery after discharge.

Discharge education that takes personal characteristics of surgical patients, including age, marital status, education, profession and prior surgical experience, into consideration are more realistic and effective to meet learning needs (31). Studies that explore sociodemographic characteristics and learning needs of the patients will have important contributions to postoperative education plans, which adapt patient demands. Our study did not find a statistically significant relationship between learning needs of the participants and their levels of mindfulness. This finding may be explained with reference to the severity of thoracic surgery, which causes anxiety and fear among the patients, irrespective of their sociodemographic characteristics. Some of the studies on sociodemographic characteristics of other surgical patients had similar findings. For example, the study of Fredericks et al. (32) that analyzed the relationship between learning needs and demographic characteristics of 38 patients, who underwent coronary artery bypass graft surgery, found no significant relationship between education levels and learning needs. However, the relationship between age, gender and cultural background of the patients and learning needs was statistically significant. Dursun and Yılmaz (33), who analyzed patients that underwent abdominal surgery found that discharge education need was higher for the graduates of high school and university. Similar to our findings, Yılmaz and Ozkan (34), and Ozkan (18) did not find a statistically significant relationship between the PLNS scores and educational levels of the patients.

Nearly 50% of the participants of our study were graduates of secondary and high schools. Our data were collected during the postoperative period. It is no accidental that participants with different educational levels shared similar ideas and feelings. In our study, participants with different sociodemographic characteristics shared similar fears and concerns before and after the thoracic surgery. Due to this reason, irrespective of their socio-demographic characteristics, all patients undergoing thoracic surgery should be provided education on subjects that will decrease their fears and concerns.

The study of Alkubati et al. (11) on patients that underwent coronary artery bypass graft surgery found a statistically significant relationship between the learning needs and sociodemographic characteristics of the patients. Learning needs of male, younger and middle-aged, highly educated, and working patients were higher compared to female, older, uneducated and non-working patients, respectively. Another study on 1190 patients, who were planned to be discharged from different clinics, found that learning needs of the participants varied according to age, gender, profession, education, department that the patient was treated and the existence of caregiver (26). Besides, the study suggested the use of verbal questions and visual materials to explore the learning needs of the patients with lower level of education. The study of Suhonen et al. (35), which compared the information wanted and received by the patients, founded that female patients gave more importance to information and evaluation of informational areas. The study concluded that further studies to develop new methods in order to determine learning needs, evaluate the content of information and form special information packages for different patients should be conducted.

Patient learning process encompasses both preoperative and postoperative periods. During the preoperative learning period, the patient comprehends his/her role to facilitate recovery. Since thoracic surgical interventions are major interventions, patients need more information. Patient education is not completed at once; rather it is a process that covers the period from admission to hospital to the post-discharge period. Fear and concerns are widespread, especially for the patients diagnosed with tumor, since they have no knowledge about the extent or risks of planned surgery. Surgeons explain the

risks and benefits of the surgery and the alternative treatment methods. They also answer the questions of the patients at different times. Comprehending the information provided by health professionals and processing of this information at intellectual and emotional levels takes time (20). Consequently, learning needs of the patients are influenced by their levels of perceptions (22).

This study found no statistically significant relationship between the levels of mindfulness and the learning needs of the patients. Mindfulness may be defined as "the state of being attentive to an aware of what is taking place in the present" (17). Our study conducted a single interview with the patients, who underwent thoracic surgery and would be discharged. The absence of a meaningful relation between the level of mindfulness and learning needs of the participants may be explained with reference to the absence of any intervention or education program given to the participants. In other words, mindfulness levels may change over time and the levels of mindfulness of the patients were low at the time of interviews. In order to raise their mindfulness, patient education programs on medication use and complication prevention should be conducted before hospital discharge of all patients undergoing thoracic surgery, irrespective of their sociodemographic characteristics.

Conclusion

This study did not find a statistically significant relationship between the level of mindfulness and learning needs of the participants that underwent thoracic surgery. However, the study found that most of the participants needed information on treatment and complications.

Based on the findings, we may conclude that, irrespective of their sociodemographic characteristics, level of mindfulness of patients that underwent thoracic surgery may change over time. Due to this reason, level of mindfulness at a particular time should be identified and different patient education methods should be used to increase the level of mindfulness.

Ethics

Ethics Committee Approval: The study were approved by the Gülhane Non-invasive Investigation Ethics Committee (8 December 2014, no: 2377).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.K., Concept: Ö.K., Design: Ö.K., G.T., Data Collection or Processing: Ö.K., G.T., K.K., Analysis or Interpretation: Ö.K., K.K., Literature Search: Ö.K., G.T., Writing: Ö.K., G.T.

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Prognostic factors in patients operated for intracerebral hematoma

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Keywords: Intracerebral hemorrhage, hemorrhage volume, prognosis, surgery

ABSTRACT

Aims: Intracerebral hemorrhages (ICH) are usually seen in patients with stroke. In this pathology; ICH volume, location of the hemorrhage and hemorrhage expanding into the ventricular system are the main factors affecting the mortality respectively. Increase in ICH volume often results in neurological deterioration. Our aim is to determine the prognostic factors in patients who underwent surgical treatment for ICH.

Methods: We retrospectively evaluated 52 patients operated in our department due to ICH which occurred spontaneously or were caused by the other etiological factors between 2017 and 2019. The parameters were the Glasgow Coma Scale (GCS) score, ICH volume in computed tomography scan, and ventricular expansion of the hemorrhage.

Results: The mortality rate in our series was 61.5%. Mortality was significantly increased in patients with hematoma larger than 60 cm^3. Nineteen of 24 (46%) patients with GCS scores between 3 and 8 died in the postoperative period. The mean duration of hospital stay was 33 days. 73% of the hematomas were seen in the lobar region.

Conclusions: Low GCS score at admission and high ICH volume are prognostic factors for patients who have undergone surgery for ICH.

Introduction

Primary intracerebral hemorrhage (ICH) is a vascular disease of the brain, caused by hemorrhage into the brain parenchymal tissue (cerebrum, cerebellum, brain stem). ICH account for 12% of all strokes (1). In the other studies, this ratio also counts for 8-18% (2,3). Short-term outcome of patients with ICH is very poor; about half of these patients die within 30 days (4,5). In these patients, early survival is associated with present state of consciousness, hematoma volume, and the existence of intraventricular hemorrhage (6,7). The annual incidence of ICH is 30.9/100.000 in the USA and 52/100.000 in Japan (8).

Advanced age, hypertension, alcohol and tobacco usage, the presence of ischemic stroke history and anticoagulant use are the accepted risk factors for ICH (9). Despite the improvements in the treatment of hypertension and a decrease in the frequency of ICH, the overall incidence did not change because of increase in bleeding due to antithrombotics and cerebral amyloid angiopathy (CAA) in elder people (10,11).

In the sixth month after the acute event, only 20% of patients can function independently in daily life and more than 50% are lost in the first year (12,13). Acute ICH treatment is a multidisciplinary effort that requires close collaboration among doctors, nurses and technicians working in neurology, neurosurgery, radiology, intensive care and emergency medicine.

Clinical features of ICH depend on the location, size, enlargement, presence of intraventricular blood and associated medical problems. Cognitive disturbances, hemiparesis/hemiplegia, visual dysfunctions, cranial nerve deficits, sensory deficits, gait and coordination problems may occur as neurological deficits. Clinical deterioration in ICH is more rapid than in ischemic stroke. Moreover, nausea, vomiting and

headache are more frequent in patients with ICH (14). Distortion occurs in the state of consciousness earlier; this is more common in massive hemorrhages, obstructing ventricular flow leading to hydrocephalus, and brain stem hemorrhage (15).

Diagnosis is mainly based on the detection of hyperdense hemorrhage in the brain tissue and/or ventricles on computed brain tomography (CT). Radiological imaging not only shows ICH but also reveals the cause of hemorrhage. A management plan is prepared based on some characteristics such as the site of bleeding, age of patient, and risk factors. The patient may be expected to become clinically stable for diagnostic imaging, unless the presence of a lesion requiring an intervention in the acute period, such as aneurysm, is suspected. The presence of hypertension and the location of the bleeding are the most important factors in understanding the underlying pathology.

In patients presenting with deep location (putamen, head of the caudate nucleus, thalamus, pons, cerebellum) bleeding, the etiology is usually hypertension. In patients presenting with more superficial (lobar) bleeding, it is necessary to obtain brain magnetic resonance imaging (MRI) including FLAIR, weighted gradient echo or susceptibility weighted imaging and non-contrast/contrast-enhanced T1-weighted sequences to exclude other underlying pathologies (tumors, vascular pathologies, and infections).

In patients with ischemic stroke, diffusion-weighted imaging and magnetic resonance venography combined with clinical findings may be used for the recognition of hemorrhage within the infarction region. Although non-invasive techniques such as magnetic resonance angiography (MRA) and CT angiography (CTA) are widely used in the detection of vascular pathologies including arteriovenous malformation (AVM) and aneurysm, catheter-based cerebral angiography is still the ultimate research method. In general, the detection of an underlying lesion by vascular imaging is easier in patients younger than 45 years-old and without hypertension (16). Although the use of these methods differs even in developed centers, it is an ideal approach to investigate vascular pathology in all patients with ICH at least with a non-invasive method such as MRA or CTA.

Methods

This retrospective study was approved by Gülhane Non-Interventional Ethics Committee (number: 19/311, date: 08.10.2019).

Patients

We retrospectively reviewed the data of 52 patients who underwent surgery for ICH between 2017 and 2019. Twenty-seven (52%) patients were male and 25 (48%) were female. The youngest patient was six months old and the oldest was 89 years old (mean age=62 years). Most of the bleedings were spontaneous in our series. In addition, other etiological factors were as follows; trauma, iatrogenic, vascular diseases, gunshot injuries, coagulation disorders, etc. (Table 1). 63.4% (n=33) of patients were given anticoagulant or antiaggregant treatment for different reasons. Bleeding into the ventricles was observed in 35 (67.3%) of the cases. When the bleeding was evaluated according to location, it was most commonly seen in the lobar region. Other locations were Thalamus, Putamen, Parafalcian region, Cerebellum etc. (Table 2) (Figure 1, 2).

Evaluation and surgical procedure

All patients were examined by non-contrast CT scan at admission according to the severity of neurological status. CTA and/or MRI was performed when vascular pathology was

Table 1. Distribution of cases according to etiological factors

Etiology	Number	Frequency (%)
Spontaneous	31	59.6
Trauma	10	19.2
Iatrogenic	4	7.6
Vascular diseases (AVM, aneurysm)	4	7.6
Others (TPA usage etc.)	3	5.7

AVM: Arteriovenous malformation

Table 2. Frequency of hematomas according to anatomical location

Hematoma location	Number	Frequency (%)
Lobar	38	73
Thalamic	6	11.5
Putaminal	3	5.7
Cerebellar	3	5.7
Parafalcine	2	3.8

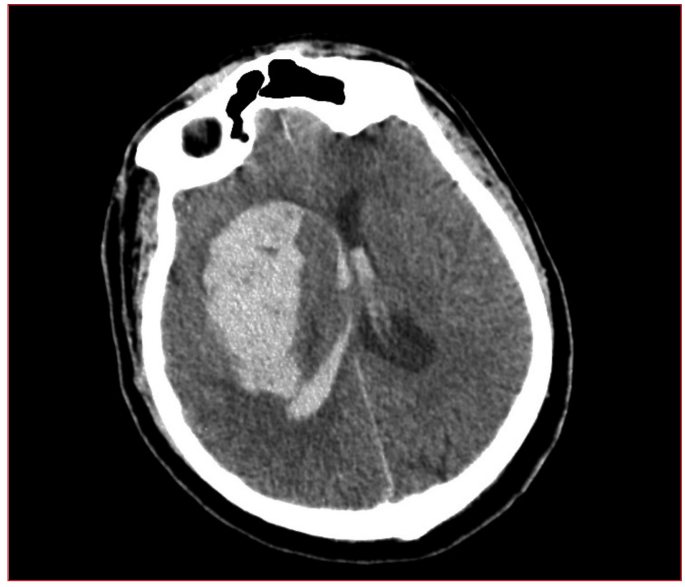

Figure 1. Computed tomography scan of a patient with acute left putaminal intracerebral hemorrhages opened to the lateral ventricle

suspected according to the location of ICH and risk factors of the patient. The patients underwent general and neurological evaluation as soon as they were first seen in the emergency department.

The patients were evaluated according to the Glasgow Coma Scale (GCS) at the first neurological examination. Hematoma volume in patients can be determined by simple, validated A x B x C / 2 formula on brain tomography (A: the largest diameter of the hemorrhage, B: the largest bleeding diameter perpendicular to A in the same section, C: multiplying of the number of sections and section thickness of the bleeding).

Antihypertensive agents suitable for blood pressure regulation were started. Vitamin K and Fresh Frozen Plasma (FFP) supplementation was provided in the patients using coumadin. Erythrocyte suspension and FFP were prepared before the operation. Basic interventions such as raising the head, using analgesics and lowering the body temperature were performed to reduce intracranial pressure. All patients were operated under general anesthesia. Craniotomy and endoscopic removal were used as a surgical technique in all cases.

Results

The smallest hematoma volume was 6 cm^3 and the largest hematoma volume was 205 cm^3. When our cases were evaluated, we found that mortality was significantly increased in cases with hematoma greater than 60 cm^3 (Table 3). The duration of hospital stay was at least 1 day and at most 195 days with the mean hospital stay that was 33 days. In two of the cases, burr holes were used for hematoma evacuation; on the other hand, in all other cases, craniotomy of various sizes was performed initially. In patients who underwent craniotomy, bone flap was not placed in 9 patients after the evacuation of the hematoma due to brain swelling. In 6 of the cases, only external ventricular drainage (EVD) was inserted for the relief of intracranial hypertension. In addition, EVD was inserted in 3 of the other patients who underwent craniotomy for the evacuation of the hematoma. Considering the location and nature of bleeding, additional CTA revealed middle cerebral artery aneurysm in 3 patients and AVM in 1 patient. In these patients, in addition to hematoma evacuation, primary vascular pathology was treated. In 2 cases, hematoma was evacuated endoscopically.

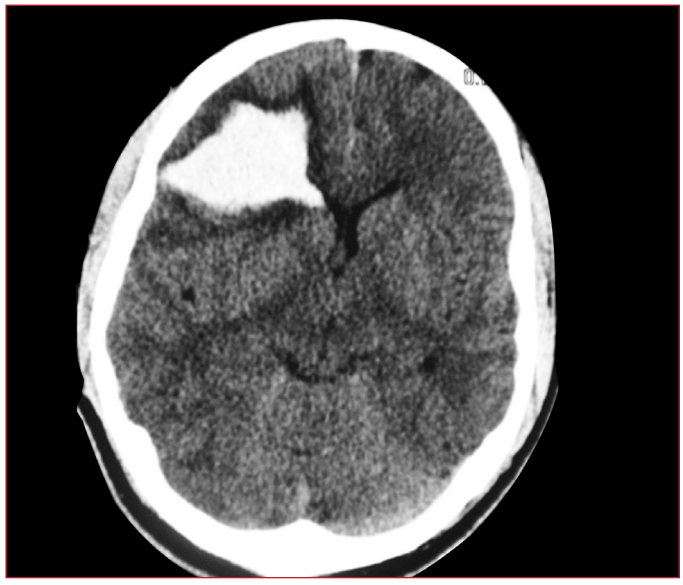

Figure 2. Computed tomography scan of a patient with acute lobar (left frontal) intracerebral hemorrhages

Discussion

Spontaneous ICH constitutes the majority of bleeding in the brain parenchyma. In our clinical study, 31 (59.6%) patients had spontaneous ICH. Van Asch et al. (17), in a review of ICHs, especially between the ages of 45 and 54 years, 85 years and older than seen more, there is no gender difference in mortality due to ICH. The incidence of ICH is 25/100.000, The highest rate is in Asians (51.8/100.000) and the lowest is in the Spaniards (19.6/100.000). In our clinical study, the majority (76.9%) of the cases were between the ages of 50 and 80 years. The male/female ratio was 1.08.

The main causes of spontaneous ICH are hypertension, CAA, vascular diseases, and coagulopathies (18,19). Eighteen of our cases were found to be using anticoagulants or antiaggregants for the treatment of their primary pathologies. Among them, the most important risk factors were older age, acute or chronic hypertension. Cheung and Zou (20) emphasized that 72-81% of patients with ICH were hypertensive. Ruiz-Sandoval et al. (21) found the most frequent underlying factor of ICH as hypertension (69%) and then obesity. Forty-one (78.8%) of our patients had a history of hypertension and 24 (75%) of these patients with hypertension died in the postoperative period. The etiological factors in our clinical series for non-spontaneous ICH are shown in Table 1.

Mortality rate in ICHs is much higher than in other stroke types (19). To date, many studies have been conducted in the literature on surgical indications and treatment outcomes of ICHs (22,23). The main purpose of surgical management is the prevention of death and the second purpose is to lower the risk of neurological sequelae. Except for superficial lobar ICH, the superiority of surgery has not been demonstrated in deeply localized spontaneous ICHs (17,24). The aim of our surgical

Table 3. Relationship between hematoma volume and prognosis

Hematoma volume	Died (n=32)	Alive (n=20)	Total (n=52)
<10 cm^3	0	2	2
10-30 cm^3	7	9	16
30-60 cm^3	9	3	12
>60 cm^3	16	6	22

treatment in ICH is to eliminate the mass effect of hematoma, to prevent secondary brain stem compression, to decrease intracranial hypertension and to shorten the recovery time. In terms of prognosis, initial consciousness of the patients, size and localization of the hematoma and ventricular spreading are important factors (20,25). The group with the best prognosis according to location is lobar hematomas (20).

GCS was evaluated during the patient's admission at hospital and 19 of 24 (46%) patients having scores between 3 and 8 died in the postoperative period. High mortality rate was mostly associated with low GCS score.

Early surgical intervention was performed following the evaluation of the patients. It was evaluated that early intervention had a positive effect on the survival of patients having low GCS and ventricular bleeding. Mendelow and Unterberg (26) have shown that early surgery is associated with better prognosis in lobar hemorrhages. However, in another study, drainage of lobar hematomas larger than 20 mL and deep ICHs by craniotomy within the first 4 hours after the onset of complaints increased the risk of bleeding and therefore, the study was terminated early (27).

Currently, indications for early surgical intervention are life-threatening lobar hemorrhages and cerebellar hemorrhage with the largest diameter above 3 cm (28). Surgical intervention can be performed with open craniotomy or stereotactic approaches in the case of clinical or radiological deterioration in any ICH patient with an acceptable prognosis.

The prognosis of severe brain stem hemorrhage and massive dominant hemisphere hemorrhage is generally very poor. The placement of EVD during surgery or alone allows both the measurement of intracranial pressure and the treatment of cerebrospinal fluid drainage. Only 6 of our patients underwent EVD application and 5 of these patients recovered with benefit from treatment.

In the literature, different rates of bleeding location have been reported, and putaminal hematomas constitute the most common group with a rate of 34%, followed by lobar and thalamic hematomas in order of frequency (29). In our case series, 73% of the hematomas were seen in the lobar region and 11.5% in the thalamic region (Table 2).

Low GCS score at admission (<8), advanced age, infratentorial location, high ICH volume and intraventricular hemorrhage were found to be independently associated with poor prognosis (30). Hematoma volume and ventricular hematoma are the most important determinants of mortality associated with ICH (6,7). ICH volume is a very important prognostic indicator. In a CT-based study, only one of 71 patients with parenchymal bleeding greater than 30 cm^3 was able to live independently in daily life after 30 days following the acute event (7). In our cases, as shown in Table 3, only 6 of 22 cases with more than 60 cm^3 survived.

In another study performed by Garde et al. (25) based on CT scan, ventricular opening rate was found to be 43% and it was more frequent especially in central and thalamic hematomas. Thirty-five (67.3%) of our ICH cases were found to open to any ventricle (lateral ventricle, third ventricle, fourth ventricle) and this rate was high compared to the literature.

Long-term mortality rates for ICH have not been reported in most of the previous studies. One-month mortality rate in spontaneous ICH was reported as 34.4% by Nakayama et al. (31). In another investigation by Karnik et al. (24), one-month mortality rate was 37.1% and annual mortality rate was 49.6%. In the study of Kanaya (32) published in 5255 cases, which is the largest series ever published, 22% postoperative mortality has been reported. Kaneko et al. (29) published 7 mortality cases in 100 patients who they operated urgently.

In our series, we evaluated that hematomas opening to ventricles and hematomas larger than 60 cm^3 in general increased mortality significantly. In addition, GCS score was significant in terms of prognosis at admission.

Conclusion

Initial low GCS score and large hematoma volume are poor prognostic factors in patients who have undergone surgery for ICH.

Ethics

Ethics Committee Approval: This retrospective study was approved by Gülhane Non-Interventional Ethics Committee (number: 19/311, date: 08.10.2019).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.K., S.Y., Design: A.K., Data Collection or Processing: A.K., S.Y., Analysis or Interpretation: A.K., S.Y., Literature Search: A.K., S.Y., Writing: A.K., S.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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Electrophysiological assessment in spinal intradural tumors

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Keywords: Spinal tumor, intradural, surgery, electrophysiology

ABSTRACT

Aims: To present our spinal intradural tumor series and to evaluate the reliability of electrophysiological assessment in patients treated for these tumors.

Methods: We retrospectively evaluated the data of patients treated for spinal intradural tumor between 2010 and 2019. The demographic, surgical and histological features of patients were evaluated and compared with their pre- and postoperative electrophysiological data. Somatosensory evoked potentials (SEP) were used as electrophysiological test.

Results: A total of 69 patients with spinal intradural tumor was evaluated. Thirty-one of them had extramedullary and 38 had intramedullary tumor. The mean age was 48.3 years for extramedullary and 26.3 years for intramedullary tumors. In preoperative period, SEP was prolonged in 25 patients with intramedullary tumor while it was prolonged in 8 patients with extramedullary tumor. In postoperative period, recovery in SEP values was detected in 5 of 25 patients with intramedullary tumor but it was observed in 7 of 8 patients with extramedullary tumor.

Conclusions: Electrophysiological evaluation is a safe and reliable method to assess the patients surgically treated for spinal intradural tumor. It is an objective method to evaluate the neurological recovery of patients with extramedullary tumor.

Introduction

Tumors of the spine and spinal cord make up about 15% of all central nervous system (CNS) tumors (1). Its annual incidence is 2-10 per 100,000 people. Spinal tumors are divided into two groups as intradural and extradural (2). These tumors are mostly located in the extradural region (55-60%) and cancer metastases are the most common type of extradural spinal tumors (3). Spinal intradural tumors are rarer and more difficult to diagnose. These tumors may develop in adults as well as in children (4). The frequent symptoms are back and/or neck pain (based on the site of tumor), radicular pain, weakness, paresthesia, gait disturbances, and bowel and bladder dysfunctions (5). Common diagnostic methods for spinal tumors are computed tomography (CT) and magnetic resonance imaging (MRI) (3).

Intradural tumors are categorized into two as intramedullary and extramedullary depending on the relationship with the spinal cord (5,6). Extramedullary tumors are rare. They constitute nearly 40-45% of all tumors of the spine. They are separated from intramedullary tumors because of their extra axial location. Extramedullary tumors usually occur in the age range of 45-50 and have male predominance. Its annual incidence is 0.4 per 100,000 people (7,8). Most frequent tumors of the extramedullary region are meningioma, nerve sheath tumors and filum terminale ependymomas (7-9). Diagnosis is made by contrast-enhanced T1 and T2-weighted MRI. Main treatment is surgery and total resection is usually possible using standard microsurgical techniques. The results of surgery in extramedullary tumors are often promising and satisfactory (6,9,10).

Intramedullary tumors are less common spinal cord tumors, potentially causing serious neurological deficits, poor quality of life, and even death (11). The rate of all primary spinal tumors is 20-30% (12). 80% of these tumors are glial tumors (12). Each tumor has its own characteristics and its behavior varies depending on its radiological and clinical features (13). Diagnosis is often difficult. T1 and T2-W spinal MRI is the gold standard for the diagnosis of intramedullary tumors. Transverse myelitis, multiple sclerosis and other autoimmune and inflammatory diseases of the spinal cord are in the differential diagnosis of these

tumors. Treatment is primarily surgical (14,15). Preoperative neurological condition and histopathological features of the tumor are the factors that determine further treatment. Early diagnosis provides rapid treatment protocols (16,17).

Electrophysiologic evaluation is performed preoperatively and postoperatively for all spinal tumors (18). This evaluation is an objective method especially for postoperative neurological follow-up of patients. Although sensory evoked potentials (SEP) are generally used, motor evoked potentials (MEP) are also important. Currently, the most common median and tibial nerve SEPs are measured (19). Their latencies and amplitudes are measured and evaluated. Prolonged SEP latencies are an important clinical marker especially in spinal intramedullary tumors. In addition, decrease in amplitude in cortical responses as a result of median and tibial stimuli is the finding supporting neurological effect. Changes in these parameters following the surgery suggest that patients may be evaluated more objectively from a neurological point of view (18).

The aims of our study were to analyze pre- and postoperative SEP records of spinal intradural tumor patients and to compare the changes with the clinical outcomes.

Methods

The ethical approval of this study was obtained from the Ethics Committee of Keçiören Training and Research Hospital (date: 13.02.2017 and no: 1332). A total of 157 spinal tumor cases operated in our clinic between 2010 and 2019 and their data were reviewed retrospectively. MRI was used in all patients and CT was performed in patients with bone involvement or calcification. Contrast enhanced images were preferred for the detection of tumors. The tumor was intradural in 69 (44%) of 157 patients and these patients were examined. Laminectomy/laminotomy was performed with standard midline approach and tumor resection was performed using microsurgical techniques. Myelotomy was performed for intramedullary tumors. Extramedullary tumors were removed after dural opening. Meticulous microsurgical dissection was performed during the tumor removal in order to protect the spinal cord and spinal roots. The radiological, electrophysiological and clinical data of these 69 patients were reviewed retrospectively. All patients underwent electrophysiological evaluation with SEPs preoperatively and postoperatively. Integrated electrical stimulators and electrodes (Medtronic Dantec®, Denmark) were used for electrophysiological assessment. Latency and amplitude of the posterior tibial and median nerve evoked sensory potentials were measured in all patients. The stimuli were given from the posterior tibial and median nerves. Responses were recorded from the somatosensorial cortex. P37 and N20 responses were used for median and posterior tibial nerves respectively. These SEP results were compared with preoperative results. In addition, intraoperative neuromonitorization (IONM) was performed during the operation. In IONM, MEP and free-running methods were applied. MEP recordings were performed before, during and just after the tumor removal. We evaluated the neurological condition of each patient prior to surgery, 24 hours following the surgery, and then three months after the discharge. Postoperative SEP recordings and neurological outcomes were compared. The mean follow-up period was 1.2 years.

Results

Sixty-nine patients who were operated for spinal intradural tumor during the last 10 years and who had preoperative and postoperative electrophysiological test records were included in this study. There were extramedullary tumors in 31 patients and intramedullary tumors in 38 patients (Table 1). The most frequent location of intramedullary tumors was cervical region (n=13). Thoracic spine was the frequent site of extramedullary tumors (n=12). The most common extramedullary tumor was meningioma and was detected in 15 patients (Figure 1). This was followed by schwannoma, neuroepithelial cyst, neuroenteric cyst and lymphoma metastasis. The most common intramedullary tumor was ependymoma and was observed in 23 patients. This was followed by astrocytoma (Figure 2),

Table 1. The distribution of patients based on demographic features, tumor locations and histological types

Variable	Number (%)
Sex	
Female	30 (43.5%)
Male	39 (56.5%)
Total	69 (100%)
Location	
Extramedullary	31 (44.9%)
Intramedullary	38 (55.1%)
Total	69 (100%)
Intramedullary tumors	
Ependymoma	23 (60.5%)
Astrocytoma	5
Lipoma	4
Epidermoid tm	3
Paraganglioma	2
Ganglioglioma	1
Total	38 (100%)
Extramedullary tumors	
Meningioma	15 (48.4 %)
Schwannoma	12
Neuroepithelial cyst	1
Neuroenteric cyst	1
Lymphoma metastasis	2
Total	31 (100%)

lipoma, epidermoid tumor, paraganglioma, ganglioglioma. In astrocytomas, 2 patients had the diagnosis of glioblastoma and they died in follow-up period. The mean age of patients with intradural extramedullary tumors was 48.3 years and ranged from 2 to 75 years. Nineteen of these patients were female and 12 were male. The mean age of patients with intradural intramedullary tumors was 26.3 years and ranged from 0 to 66 years. Eleven of these patients were female and 27 were male (Table 1).

No neurological deterioration was observed in any patient. Neurological improvement was observed in 28 (90.3) of 31 patients with extramedullary tumor while it was seen in 23 (60.5%) of 38 patients with intramedullary tumor. In the preoperative period, 25 of 38 patients with intramedullary tumors had prolonged SEP responses, whereas 8 of 31 patients with extramedullary tumors had longer responses. Postoperatively, SEP responses were improved in 5 (20%) of 25 patients in the intramedullary group and 7 (87.5%) of 8 patients in the extramedullary group. The clinical and electrophysiological improvement is better in extramedullary tumor group than the intramedullary tumor group.

Two patients with intramedullary tumor died in the postoperative period. The histological diagnosis of these patients was glioblastoma and the location of tumor in both patients was thoracic spinal cord. Cerebrospinal fluid collection after surgery was occurred in 4 patients but resolved in the long-term follow-up period.

Discussion

Preoperative and postoperative electrophysiological evaluation of spinal intradural tumors is an objective method for evaluating the outcomes of surgery. In this retrospective study, we analyzed the results of 69 patients with spinal intradural tumor. We found that the electrophysiological improvement was correlated with clinical improvement especially in intradural extramedullary tumors. We also emphasized that pre- and postoperative electrophysiological assessment of the patients is a reliable method to predict the outcome of surgery.

Spinal tumors are rare malignancies that can seldom be fatal but usually cause serious morbidity (2). The spine and spinal cord are the most common sites of neoplasia after the brain in the CNS. However, not all spinal tumors have the same characteristics (3). They are a heterogeneous group of tumors (1). Therefore, classifications were made according to different characteristics. The most accepted classification is the classification based on the location of tumor. Spinal tumors are divided into two as intradural and extradural according to their relationship with the dura mater. Intradural tumors are tumors located within the dura mater and have no direct relationship with the spine and vertebrae. Extradural tumors are tumors

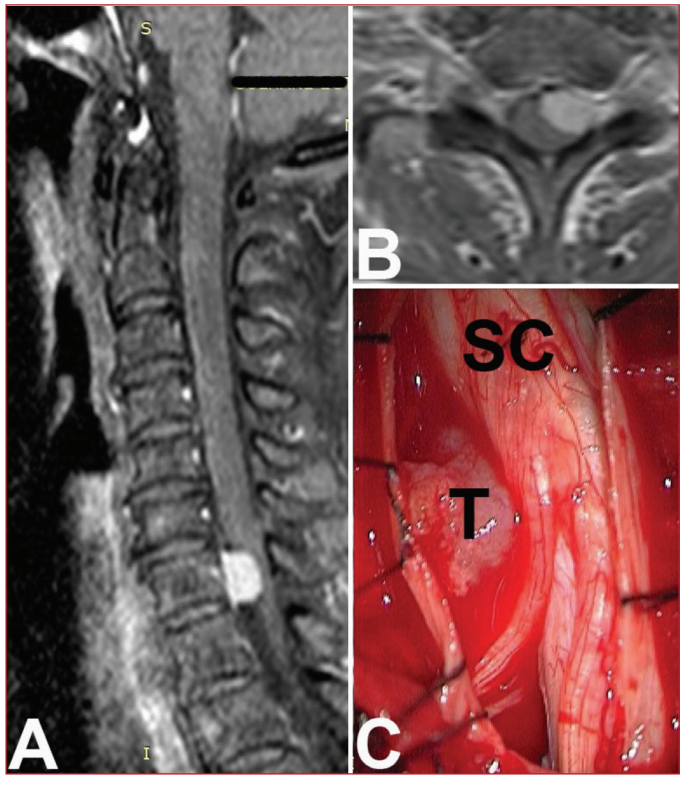

Figure 1. T1-W sagittal (A) and axial (B) magnetic resonance imaging of a patient with intradural extramedullary tumor. It was removed using posterior approach (C) and the histological diagnosis was meningioma

T: Tumor, SC: Spinal cord

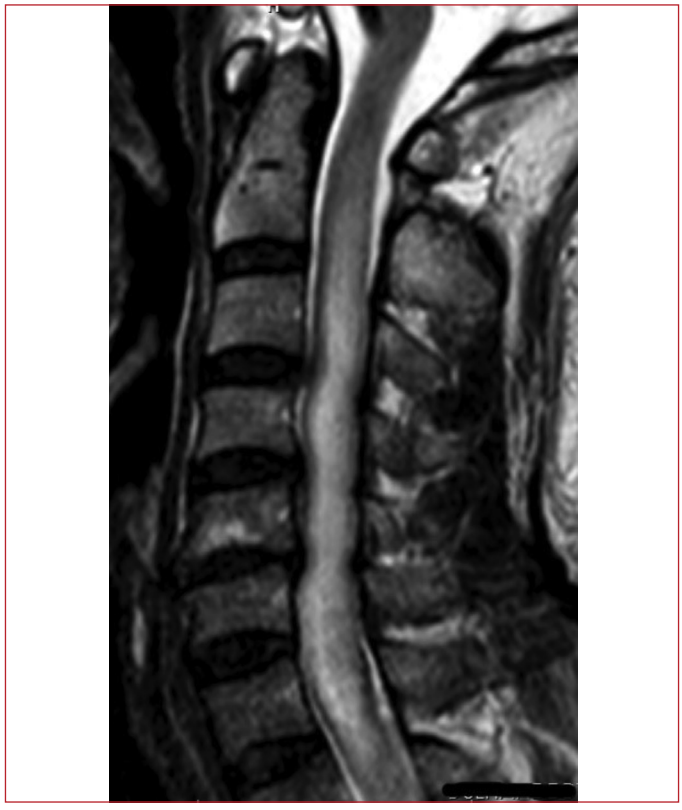

Figure 2. T2-W sagittal magnetic resonance imaging of a patient with cervical intradural intramedullary tumor. The patient underwent surgical treatment and the histological diagnosis was anaplastic astrocytoma

located outside the dura mater and usually involve the spine and its elements. Intradural tumors are classified as intramedullary (located within the spinal cord) and extramedullary (located outside the spinal cord) according to the medulla spinalis (spinal cord) in the dura mater. Extramedullary tumors are meningiomas and schwannomas originating from dura mater or spinal roots. Intramedullary tumors are usually glial origin and astrocytomas and ependymomas are the most common types of tumor. In our series of 69 intradural tumors, the most common intramedullary tumors were ependymomas (60%) and astrocytomas (13%) followed by lipoma, epidermoid tumor, paraganglioma and ganglioglioma. The most common extramedullary tumors were meningiomas (48%) and schwannomas (38%) followed by neuroepithelial cysts, neuroenteric cysts and metastases.

Ottenhausen et al. (6) stated that technological improvements in radiological and electrophysiological techniques, less invasive methods as well as radiation therapy provide better clinical results in spinal tumors located intradurally. They also pointed out that the clinical results of intramedullary malignant spinal tumors are still poor. Ahn et al. (7) reported the results of 11 patients with intradural extramedullary tumors and they emphasized that the level of neurological symptoms was corresponding to the amount of tumor within the intradural space. They also recommended aggressive surgical excision in patients with long-term symptoms or serious neurological deficits. In our series, we have similar results with Ahn et al. (7) and the clinical symptoms of our patients with extramedullary tumors improved rapidly, as well as electrophysiological tests were also improved gradually after surgery.

Electrophysiological tests are widely used in the diagnosis of spinal tumors (18,19). Although MRI and CT are the gold standard in the diagnosis of spinal tumors, electrophysiological tests are useful methods to objectively assess the neurological condition of the patients (3). Especially SEP is frequently used before surgery. Evoked potentials can be defined as the electrical activities of the CNS in response to short sensory stimuli. SEPs are usually measured from the posterior tibial and median nerves and response from the cortex is measured. SEP is often used in the disorders of brain, spinal cord or nerve root and diseases. SEPs may help to identify lesions on any part of somatosensorial pathways. However, the SEP findings should be interpreted together with the neurological examination and radiological imaging results (19). Although MEP may also be used in the diagnosis of spinal tumors, it is generally not preferred preoperatively because it is more difficult and complicated to perform and interpret, but it is used in IONM (20-22). Pusat et al. (19) analyzed the results of 30 patients and concluded that the latency of tibial nerve response may be prolonged in the early time period after spinal intradural tumor surgery. They also pointed out that electrophysiological findings are not predictive for patients with spinal tumor. Ishida et al. (22) reported the significance of IONM for the resection of intradural extramedullary spinal tumors to anticipate the possible neurological disturbances in a 6-month follow-up period after surgery. Meanwhile, SEPs are more easily and widely used both pre- and postoperatively. In our series, 69 patients with intradural tumors underwent SEP preoperatively and postoperatively and the results were recorded. We also performed IONM in all patients. In the preoperative period, 25 of 38 patients with intramedullary tumors had prolonged SEP responses, whereas 8 of 38 patients with extramedullary tumors had longer responses. Postoperatively, SEP responses were improved in 5 of 25 patients in the intramedullary group and 7 of 8 patients in the extramedullary group. These improvements were in parallel with the improvement in the neurological condition of the patients. In addition, no electrophysiological deterioration was observed during the surgery for extramedullary or intramedullary tumors.

Conclusion

Electrophysiological evaluation of spinal intradural tumors either in preop- or postoperative period is very important. This is also indispensable during the surgery. Electrophysiologic tests are useful for objective neurological evaluation of the patients especially in the postoperative follow-up period.

Ethics

Ethics Committee Approval: The ethical approval of this study was obtained from the Ethics Committee of Keçiören Training and Research Hospital (date: 13.02.2017 and no: 1332).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.Y., A.K., Design: S.Y., Data Collection or Processing: A.K., Analysis or Interpretation: A.K., S.Y., Literature Search: S.Y., Writing: S.Y.

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Autologous stem cell transplantation in patients with extragonadal germ cell tumors: A single center experience

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ABSTRACT

Aims: In extragonadal germ cell tumors (EGGCT), chemosensitivity and prognosis are worse than in GCT tumors. There is no standard salvage chemotherapy regimen for relapsed/refractory EGGCT patients. Autologous stem cell transplantation (ASCT) has increasingly been used in recent years as a second or third salvage therapy. In this study, we aimed to share our experience with the relapsed/refractory EGGCT patients who underwent ASCT.

Methods: The data of patients who underwent ASCT and were followed up according to tango in EGGCT between 1991 and 2015 at the University of Health Sciences Turkey, Gülhane Training and Research Hospital, Ankara, Turkey, were retrospectively analyzed.

Results: This study included 30 patients. The most common involvement site was the retroperitoneum (n=20, 66.7%), followed by the mediastinum (n=10, 33.3%). Retroperitoneal lymph node dissection was performed in 14 patients. Due to relapse, 27 patients received 3 cycles of TIP (paclitaxel, ifosfamide and cisplatin) and three patients received 3 cycles of VIP (etoposide, ifosfamide and cisplatin) treatment as the first salvage. Complete response was achieved in 10 patients. Progression was recorded in five patients. As the second salvage, 13 patients received VIP and three patients received TIP. In addition, 10 patients underwent ASCT as the second salvage and 20 patients had the third salvage. Nine patients died and 21 patients were still under follow-up.

Conclusions: Although the chemosensitivity and prognosis are worse in patients with EGGCT than in those with gonadal GCT, their survival seems to be increased significantly with multimodal treatments and ASCT.

Introduction

Testicular cancer is the most common solid malignancy in men aged 15-35 years, 95% of which are germ cell tumors (GCT) (1). GCT is primarily located in the gonadal region and rarely occurs in an extragonadal area such as the mediastinum and retroperitoneum. Extragonadal GCT (EGGCT) are formed by malignant transformation of gonadal cells that have not completed their migration during embryogenesis without a gonadal primary mass in ultrasonographic evaluation (2). EGGCT accounts for 2-5% of all GCT and has an approximate incidence of 1/1,000,000 (3).

Although EGGCT has similar histological, serological and cytogenetic characteristics as gonadal GCT, their behavior is different clinically and biologically. EGGCT has a worse chemosensitivity and prognosis than gonadal tumors (4,5). The treatment of EGGCT patients is similar to the treatment of gonadal GCT, and after histological separation as seminoma and non-seminoma, chemotherapy (CT) is applied according to risk classification. Surgical resection is also performed in patients with residual tumors. This multimodal treatment increases efficacy and survival (6,7). There is no standard salvage CT treatment for relapsed/refractory EGGCT patients. Autologous

stem cell transplantation (ASCT) therapy for EGGCT patients has started to increase gradually and is mostly applied as second or third salvage (8).

The aim of this study was to share our single center experience with patients who underwent salvage ASCT with the diagnosis of relapse/refractory EGGCT.

Methods

In this study, 30 patients with EGGCT who underwent high dose CT (HDCT) and ASCT between 4 February 1991 and 12 May 2015 at the University of Health Sciences, Gülhane Training and Research Hospital, Medical Oncology Clinic, Ankara, Turkey were evaluated retrospectively. The study was approved by the Ethics Committee of Gülhane Training and Research Hospital with the decision number 18/159. Patient interview information, patient files and electronic system data were used to obtain data. Patients' demographic status, tumor localization, first recurrence dates, salvage CT protocols and treatment responses, HDCT and ASCT time, and HDCT and ASCT recurrence and final status were noted.

The primary endpoint is overall survey (OS) and progression free survey (PFS). The diagnosis date was accepted as the start date for the general OS value of the patients, the end point was the last control date for the surviving patients, and the exitus date for the ex-patients. In order to calculate OS values after HDCT and ASCT, start date HDCT and ASCT date is accepted. Endpoint for OS is the last control date for living patients, exitus date for ex patients.

The PFS values of the patients after the first step treatment were calculated as PFS1. In addition, the time to recurrence after HDCT and ASCT was calculated as PFS2; HDCT and ASCT dates were taken as the starting date, relapse date for the relapse as the endpoint, and the last control date for the non-relapse.

Patients with pathologic evidence of EGGCT who had relapsed after first-line treatment and who had HDCT and ASCT were included in the study. Patients who did not have HDCT and ASCT and whose files and follow-up information were missing were excluded from the study.

Statistical Analysis

Statistical Package for Social Sciences version 24.0 was used for conducting statistical analysis of data (IBM Corp, Armonk, NY, USA). Descriptive statistics for expressing continuous (quantitative) variables were mean, standard deviation, minimum and maximum values, while the categorical variables were expressed as number (n) and ratio (%). The suitability of the variables to the normal distribution was evaluated by visual and analysis methods and nonparametric tests were used because they did not fit the normal distribution. The chi-square and Fisher's exact tests were used to determine the demographic characteristics of the patients. The Kaplan-Meier was used for univariate survey analysis and log rank test was used. In multivariate analyses, the Cox regression test was used. The Spearman's rank correlation test was used for univariate correlation analysis. Statistically significant value was accepted as that less than 0.05.

Results

A total of 30 patients who underwent HDCT and ASCT were included in the study. The median age of the patients was 41 years (range: 21-60). First line 4 cycles of BEP (bleomycin, etoposide, cisplatin) were applied to all patients. During follow-up, all patients relapsed and the median PFS1 was 16 (range: 3-45) months. TIP (paclitaxel, ifosfamide and cisplatin) was given to 27 (90%) patients after the relapse and VIP (etoposide, ifosfamide and cisplatin) salvage CT was applied to 3 (10%) patients. After Salvage CT, complete response (CR) in 10 (33.3%), partial response (PR) in 12 (40%), stable response in three (10%) and progression in five (16.7%) patients were observed. A total of 20 (66.7%) patients who did not receive CR underwent second salvage CT. Four (20%) of the patients who underwent second salvage CT were treated with TIP; 16 patients (80%) received VIP treatment. In 6 (33.3%) CR, 9 (49%) PR and 3 (17.7%), stable responses were observed in the second salvage CT. The primary characteristics were summarized in Table 1.

Table 1. Primary characteristics

Primary site, n (%)	Retroperitoneal	20 (66.7)
	Mediastinal	10 (33.3)
Pathology, n (%)	Embryonal carcinoma	3 (10)
	Teratoma	10 (33.3)
	Mixed nonseminoma	8 (26.7)
	Choriocarcinoma	7 (23.3)
	Yolk sac	2 (6.7)
Metastasis, n (%)	Yes	16 (53.3)
	No	14 (46.7)
Metastasis-site, n (%)	Brain	4 (25)
	Bone	1 (6.3)
	Lung	7 (43.8)
	Liver	1 (6.3)
	Multiple organs	3 (18.8)
RPLND, n (%)	Yes	14 (46.7)
	No	16 (53.3)
RPLND pathology, n (%)	Necrosis	7 (50)
	Viable tm	7 (50)
Metastasectomy, n (%)	Yes	3 (10)
	No	27 (90)

Table 1. Continued

Relapse site, n (%)	Retroperitoneal lymph node	17 (56.7)
	Mediastinal lymph node	8 (26.7)
	Lung	3 (10)
	Bone	1 (3.3)
	Brain	1 (3.3)
Salvage CT, n (%)	TIP	27 (90)
	VIP	3 (10)
Salvage CT response, n (%)	CR	10 (33.3)
	PR	12 (40)
	Stable	3 (10)
	Progression	5 (16.7)
Second salvage CT, n (%)	Yes	20 (66.7)
	No	10 (33.3)
Second salvage CT p, n (%)	TIP	4 (20)
	VIP	16 (80)
Second salvage CT, n (%)	CR	6 (33.3)
	PR	9 (50)
	Stable	3 (16.7)
Relapse after ASCT, n (%)	Yes	9 (30)
	No	21 (70)
Last status, n (%)	Exitus	9 (30)
	Alive	21 (70)

RPLND: Retroperitoneal lymph node dissection, CT: Chemotherapy, TIP: Paclitaxel, ifosfamide, cisplatin, VIP: Etoposide, ifosfomaide, cisplatin, CR: Complete response, PR: Partial response, ASCT: Autologous stem cell transplantation

All patients underwent HDCT and ASCT between 4 February 1991 and 12 May 2015. In our study, the follow-up period after diagnosis was 137 months (range: 30-353 months); the median follow-up period after HDCT and ASCT was 110 months (range: 29-327 months).

Patients who relapsed after the first step treatment were included in the study. The median PFS1 value of patients until the first relapse after the first cure was 16 months (range: 3-45 months). The patient relapsed for 9 months (30%) after HDCT and ASCT. The median value of PFS2 after HDCT and ASCT is 101 months (range: 26-235 months). All patients who recurred after HDCT and ASCT were ex.

According to our current data, 9 (30%) patients died and 21 (70%) patients were alive. The median $OS_{diagnosis}$ value after diagnosis was 136 months (range: 31 to 353 months), and the median OS_{ASCT} value after HDCT and ASCT was 103 months (range: 29-327 months).

The 2-year $OS_{diagnosis}$ value of the patients in our study group was 97.6%; the 5-year $OS_{diagnosis}$ value was 93.2% and the 10-year $OS_{diagnosis}$ value was 84.7%. The 2-year OS_{ASCT} value of our patients was 93.7%; the 5-year OS_{ASCT} value was 88.4% and the 10-year OS_{ASCT} value was 78.3%. The 2-year PFS_{ASCT} value of our patients was 92.6%; the 5-year PFS_{ASCT} value was 87% and the 10-year PFS_{ASCT} value was 77.5%.

Factors affecting $OS_{diagnosis}$

The median $OS_{diagnosis}$ value of the patients after diagnosis was 136 (range: 31 to 353) months. The mediastinal or retroperitoneal (RP) localization of the disease did not affect $OS_{diagnosis}$ significantly (p=0.072). While the median $OS_{diagnosis}$ was found to be 140 months (range: 30-319) in patients with RP, the median was 133 months (66-353) in those with the mediastinum (Figure 1).

When the relationship between the pathologies and $OS_{diagnosis}$ was evaluated, the median was 186 months (range: 118-223) for embryonic carcinoma, the median was 136 months for teratoma (range: 30-218), the median was 130 months (range: 51-319) for mixed nonseminoma, the median was 107 months (range: 66-162) for patients with choriocarcinoma; the median was 222 months (206-240) in the yolk sac.

$OS_{diagnosis}$ was significantly affected by the relapse region of the patients (p=0.001). The median $OS_{diagnosis}$ was 135 months (range: 51-240) in patients with relapse RP, and 150 months (range: 86-353) in patients with recurrent mediastinal region, 118 months (range: 66-218) in patients with recurrence of the lung, 30 months only in the case of recurrence in the bone and 319 months in the only case of recurrence in the brain. When the subgroup analysis was performed, it was found that the relapse in the bone where the significance was caused by bone had a significantly lower $OS_{diagnosis}$ value than the others.

There was a significant relationship between recurrence

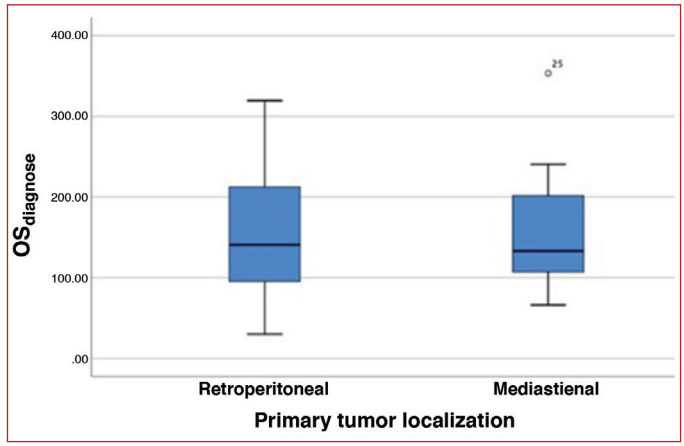

Figure 1. Relationship between $OS_{diagnose}$ and primary tumor localization
$OS_{diagnose}$: Overall survival from the time of diagnosis

after HDCT and ASCT and $OS_{diagnosis}$ (p=0.001). The median value of $OS_{diagnosis}$ after HDCT and ASCT was 136 months (range: 51-353) and the median $OS_{diagnosis}$ value was 130 months (range: 30-240).

Factors affecting OS_{ASCT}

The median OS_{ASCT} value after the ASCT date was 103 (range: 29-327) months. Primary mediastinal or RP did not significantly affect OS_{ASCT} (p=0.075). While the median OS_{ASCT} was 101 months (range: 29-304) in patients with RP and 103 months (49-327) in patients with primary mediastinum.

OS_{ASCT} was found to have a significant effect on the relapse region (p=0.006). The median time was 114 months (range: 51-304) in patients with relapse RP and 90 months (range: 36-327) in patients with mediastinal area, 80 months (range: 45-153) in patients with lung recurrence, 29 months in a single case with bone and 50 months in a single case of recurrence in the brain. When the subgroup analysis was performed, it was found that the bone recurrent case had a significantly lower OS_{ASCT} value than the others (Figure 2).

When the relationship between OS_{ASCT} and the pathology of the patients was evaluated, the median was 172 months for embryonal carcinoma (range: 80-202), 109 months (range: 29-153) for teratoma, 88 months (range: 45-304) for mixed nonseminoma, 48 months (range: 36-117) for choriocarcinoma and 197 months (143-200) for yolk sac.

Unlike $OS_{diagnosis}$, OS_{ASCT} was significantly affected by the age of the patients. The median OS_{ASCT} value of patients aged 40 years and under was 47 months (range: 28-118), whereas for those over 40 years, this value was 148 months (range: 50-327) (p=0.012) (Figure 3).

Factors affecting PFS2 (PFS_{ASCT})

The median value of PFS2 (PFS_{ASCT}) after HDCT and ASCT was 101 months (range: 26-235). All patients who recurred after HDCT and ASCT died. PFS2 did not significantly affect the mediastinal or RP primer (p=0.070). While the median PFS2 was 101 months (range: 26-304) in patients with RP primer, the median PFS2 was 101 months (45-327) in those with mediastinal primer.

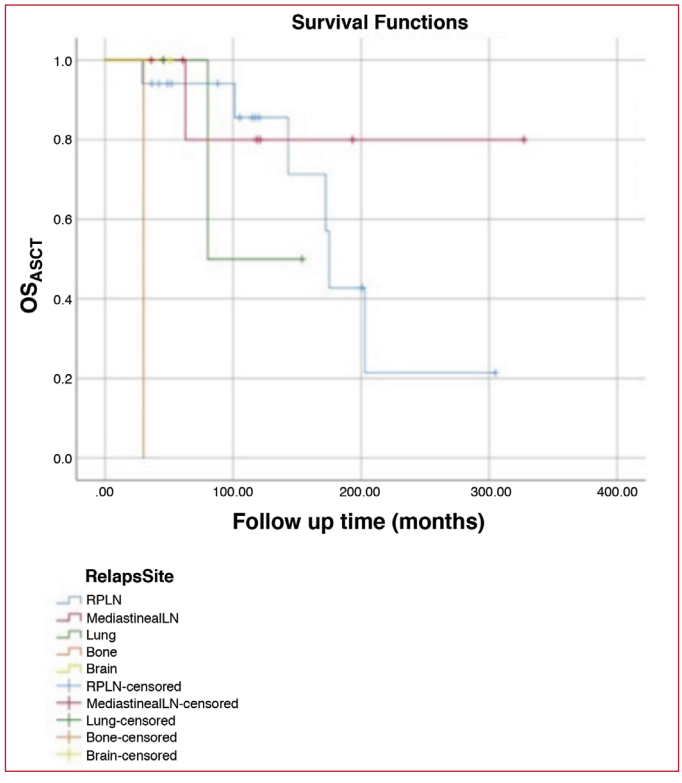

Figure 2. Relation of OS_{ASCT} to relapse site

OS_{ASCT}: Overall survival from the time of autologous stem cell transplantation, RPLN: Retroperitoneal lymph node, Mediastinal LN: Mediastinal lymph node

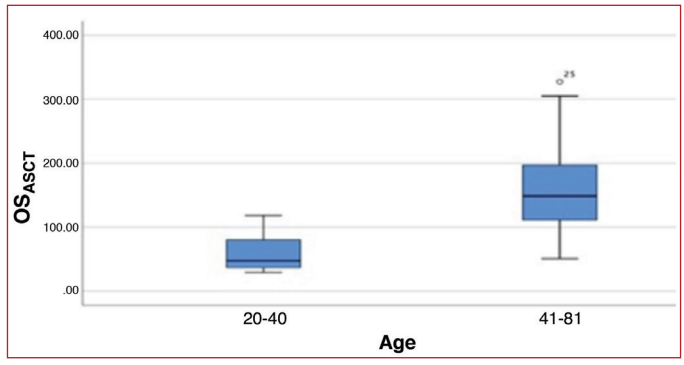

Figure 3. Evaluation of the relationship between OS_{ASCT} and age

OS_{ASCT}: Overall survival from the time of autologous stem cell transplantation, RPLN: Retroperitoneal lymph node, Mediastinal LN: Mediastinal lymph node

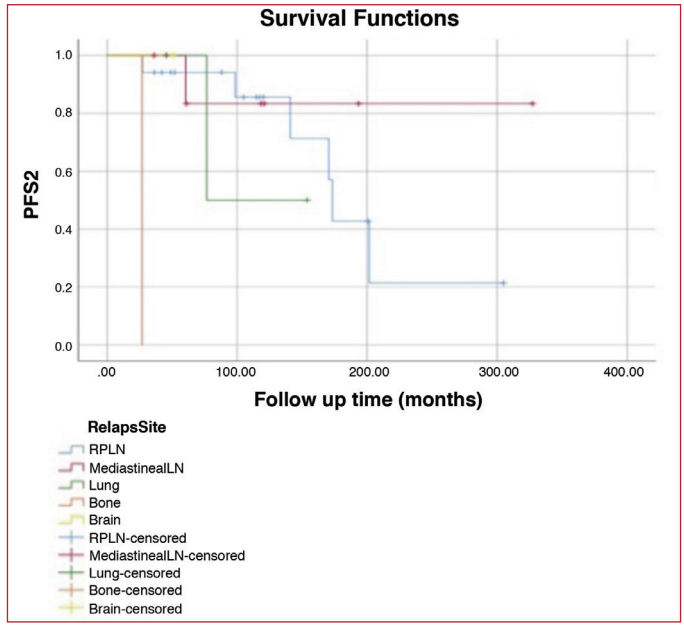

Figure 4. The relationship between PFS2 and relapse site

PFS2: Progression free survival from the time of autologous stem cell transplantation, RPLN: retroperitoneal lymph node, Mediastinal LN: Mediastinal lymph node

The relapse region of the patients was significantly affected by PFS2 (p=0.001). the median PFS2 was 112 months (range: 27-27304) in patients with relapse RP, and 86 months (range: 35-327) in patients with mediastinal recurrence. It was 76 months (range: 40-153) in patients with lung recurrence, 26 months in bone recurrence, and 48 months in single brain recurrence. When subgroup analysis was performed, it was found that the recurrent bone case had a significantly lower PFS2 value than the others (Figure 4).

When the relationship between PFS2 and patients' pathology was evaluated, it was found that the median PFS2 was 170 months (range: 76-201) in embryonal carcinoma, 109 months in teratoma (range: 26-153), 88 months in mixed nonseminoma (range: 43-304), 48 months in choriocarcinoma (range: 36-117) and 197 months (143-200) in the yolk sheet.

PFS2 was significantly affected by the age of patients at the time of ASCT. The median PFS2 value was 45 months (range: 26-118) for patients aged 40 years and younger, and 147 months (range: 48-327) for those over 40 years of age (p=0.010).

Discussion

In relapsed/refractory GCT patients, HDCT and ASCT have been used as standard salvage treatment and are often used for second or third salvage purposes (9). However, due to the low number of relapsed/refractory EGGCT patients, the efficacy of HDCT and ASCT in these patients could not be clearly demonstrated due to the lack of randomized trials. In this study, we evaluated the demographic characteristics, progression-free and total survival data retrospectively in our center to demonstrate the efficacy of treatment in relapsed/refractory EGGCT patients who underwent HDCT and ASCT for second or third salvage purposes.

All of our EGGCT patients had histopathology in the non-seminomatous group and all of them were in the poor prognostic group according to IGCCG (9,10). We performed HDCT and ASCT as the second salvage in 10 of our patients and as the third salvage in 20 of our patients. There was no significant relationship between salvage application step and OS and PFS. There is a high chance of success in the studies performed in GCT patients in the third step and before, and it provides duration of response even in the next steps (11).

In many studies, VIP as the first salvage regimen is preferred primarily (12,13), but in our patients we preferred TIP treatment as the first salvage, as in the study of 69 patients included by Ko et al. (14). There is no study designed to compare the advantages of TIP and VIP regimens as salvage treatment.

Total survival in EGGCT patients varies according to primary tumor localization, relapse status, relapse duration and IGCCCG criteria. While 5-year OS is 65% in primary RP EGGCT, this rate decreases to 40-45% in mediastinal EGGCT patients (2,12,15,16). In a study conducted by Schmoll et al. (17), the disease-specific survival of RP EGGCT patients who underwent HDCT and ASCT was reported to be 76%. In our study, the 5-year OSASCT value was reported as 88.4% and clearly shows the efficacy of the treatment.

In our study, the mean age was 41 years and 15 years older than the median age in the literature (18,19). The average age is high compared to the literature, decreases bone marrow reserve, causes neutropenia and febrile neutropenia complications, and may lead to an increase in mortality rate. In addition, in the literature (20), the average rate of advanced disease was 30%, whereas in our study, this rate was 50% and the mortality risk was high. In our study, nine patients died and despite this high risk, this rate is significantly lower than in the literature. In addition, in our study, an unspecified result was obtained in the literature and OS_{ASCT} and PFS2 were significantly better in patients over 40 years of age, who underwent HDCT and ASCT.

Hege et al.'s (21) study revealed that treatment-related mortality was found to be 5.5% in HDCT and ASCT patients and Adra et al. (22) also presented treatment-related mortality as 2.4% (21). In our study, no patients died in association with the treatment.

Considering the limitations of our study, the study consisted of a report on rare case series that underwent AHSCT due to relapsed or refractory EGGCT; therefore, it included a small sample size of patients. Also, it had a heterogeneous patient population with regard to indications for AHSCT and it was a retrospective study.

Conclusion

As a result, for patients with relapsed/refractory EGGCT, high dose ifosfamide/carboplatin/etoposide regimen was safe and and an effective treatment choice. Although the chemosensitivity and prognosis of EGGCT patients are worse than GCT patients, their survival is significantly increased with multimodal treatments and ASCT. Future prospective randomized studies should reveal more reasonable and effective survival results.

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Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Gülhane Training and Research Hospital with the decision number 18/159.

Informed Consent: Retrospective study.

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Authorship Contributions

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Absolute lymphocyte count is a predictor of outcome after splenectomy for immune thrombocytopenia

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ABSTRACT

Aims: Splenectomy is still the standard salvage therapy in immune thrombocytopenia (ITP) cases refractory to corticosteroid therapy. The aim of this study was to evaluate adult ITP patients who underwent splenectomy and to analyze the predictive factors of response to splenectomy.

Methods: A retrospective analysis was performed from 2009 to 2018 using the data of 46 patients with ITP who underwent splenectomy in our hospital. The diagnosis and response to treatment were evaluated according to the International Working Group recommendations. A complete response (CR) was accepted as any platelet count >100×10^9/L. A partial response (PR) was accepted as any platelet count from 30-100×10^9/L or a doubling of basal platelet count.

Results: After splenectomy, 38/46 (82.7%) patients achieved CR and 6/46 (13.0%) achieved PR. Fifteen (34.0%) responders relapsed with a median time of 61.9 months. Compared to the non-responders and relapsed patients (NR + relapsed, n=17), the stable responders (CR + PR, n=29) had lower absolute lymphocyte count (ALC) (ALC, ×10^9/L) at the time of diagnosis [1.8 (0.84-4.32) vs 2.47 (1.4-5.1); p=0.018]. Patients with ALC ≤1.85×10^9/L at the time of diagnosis had a better response to splenectomy to splenectomy than those with ALC >1.85×10^9/L (p=0.031). According to the Cox-Regression module, we demonstrated that the increase in initial ALC would increase the relapse rate after splenectomy (Hazard ratio: 1.003, 95% confidence interval: 1.001-1.005; p=0.009).

Conclusions: Splenectomy is a safe treatment with a long-term CR rate of 58.6% for ITP patients. The findings highlighted that ALC at the time of diagnosis was the only predictive variable of long-term response to splenectomy in patients with ITP.

Introduction

Immune thrombocytopenia (ITP) is an autoimmune disease characterized by increased thrombocyte destruction and impaired thrombocyte production which can lead to isolated thrombocytopenia and spontaneous (1). The incidence of primary ITP in adults ranges between 1.6 and 3.9/100.000 people/year (2). With the development of new drugs such as thrombopoietin receptor agonists, splenectomy remains the second-line treatment for ITP patients unresponsive to corticosteroids (1,3,4). The cure rate of splenectomy has been reported to be higher than that of other treatments, at 60-70% in 5 years (5). In addition, no clear international guidelines for the order of treatment of ITP have been proposed and the selection of treatment has been seen to be based on physician and patient preference rather than on the evidence of clinical experience (6).

The criteria and parameters that can predict response to splenectomy and prognosis are currently of great interest to researchers. The most frequently studied predictive and prognostic factors in splenectomy are age, the response to steroid treatment before splenectomy, the time from diagnosis to splenectomy (duration of disease), and pre-postoperative platelet count. There are conflicting results in different studies and no factor has been determined to consistently predict the

response. Therefore, there is still a need for disease-specific parameters which can be used in clinical practice. The aim of this retrospective study was to evaluate adult ITP patients who underwent splenectomy in our hospital during the last 9 years and to analyze the predictive factors of response to splenectomy.

Methods

Ethical approval and informed consent

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by University of Health Sciences Turkey, Ankara Diskapi Yildirim Beyazit Research and Training Hospital Ethics Committee (protocol no: 57/12, date: 17.12.2018).

A retrospective examination was performed from the records of patients diagnosed with ITP and followed up in the Hematology Clinic of University of Health Sciences Turkey, Diskapi Yildirim Beyazit Training and Research Hospital. A total of 46 patients who underwent splenectomy for therapeutic purposes were included. For all the patients examined, a record was made of demographic information, date of diagnosis, treatments received, responses to treatments, date of splenectomy, complete blood count follow-up after splenectomy and total follow-up period. Using these data, analysis was applied to response rates to splenectomy, relapse rates after splenectomy, and relapse-free survival (RFS) rates. Of the hematological parameters at the time of diagnosis, the effects of platelet count, absolute lymphocyte count (ALC), plateletcrit (PCT), platelet distribution width (PDW), mean platelet volume (MPV), platelet/lymphocyte ratio (PLR), lactate dehydrogenase (LDH), ferritin and vitamin B12 levels were examined on relapse rates and RFS rates after splenectomy.

The diagnosis of chronic ITP was based on the International Working Group (IWG) standard of a peripheral blood platelet count of $<100\times10^9$/L continuing for more than 1 year after discounting other reasons of thrombocytopenia (7). The response to treatment to treatment was evaluated according to the IWG recommendations. A complete response (CR) was accepted as any platelet count $>100\times10^9$/L. A partial response (PR) was accepted as any platelet count from $30\text{-}100\times10^9$/L or a doubling of basal platelet count. No response (NR) was accepted as platelet count $<30\times10^9$/L or an increase of less than double basal platelet count. Corticosteroid dependency is defined as platelet count maintained at a minimum of 30×10^9/L and/or a need for continuous or repeated application of corticosteroids to prevent bleeding for a period of more than 2 months (7). To exclude other hematological diseases and evaluate megakaryocyte count, bone marrow biopsy was performed to all patients.

Statistical Analysis

Statistical analyses of the study data were made using SPSS Statistics 20 software (IBM, Armonk, NY, USA). Descriptive data were reported as number (n) and percentage (%). For survival analysis, the Kaplan-Meier method was used. RFS was calculated as the time from response obtained following splenectomy to the time of relapse. Comparisons between the patient groups were made using the Log-Rank test. In the comparison of 2 independent variables with measurement values with normal distribution, the Independent Samples t-test was used and if there was not normal distribution, the Mann-Whitney U test (Z-table value) was employed. In the examination of the relationships between 2 qualitative variables, the chi-square cross tables were used according to the levels of the expected values. The optimal cut-off value was determined using the ROC curve analysis. A value of $p<0.05$ was accepted as statistically significant.

Results

The patient characteristics are presented in Table 1. Evaluation was performed on a total of 46 patients, comprising 31 (67.3%) females and 15 (32.7%) males with a mean age of 43.52±15.89 years. Splenectomy was performed at a mean standard deviation (SD) patient age of 37.57 (17.25) years at a mean (SD) 41.93 (75.61) months after ITP diagnosis. Accessory spleen was determined in 4 patients relapsed after splenectomy and surgical removal was applied. All the patients were treated with corticosteroids at least once before splenectomy. Corticosteroid dependency was determined in 28 (60.8%) and NR to corticosteroids was observed in 18 (39.2%). The follow-up period after splenectomy was mean (SD) 60.70 (80.31) months. The mean (SD) total period from diagnosis to final follow-up was 102.62 (111.06) months.

The response to splenectomy was evaluated in 1 month postoperatively and at the final follow-up examination. In 1 month after splenectomy, a response was obtained in 44 of 46 patients (95.6%) as CR in 38 and PR in 6 patients, and NR was

Table 1. General characteristics of the patients

Variable (n=46)	
Gender Female Male	 31 (67.4%) 15 (32.6%)
Age at diagnosis (yrs) (Mean ± SD)	34.00±19.43
Current age (yrs) (Mean ± SD)	43.54±15.89
Age at splenectomy (yrs) (Mean ± SD)	37.57±17.25
Time from diagnosis to splenectomy (months) (Mean ± SD)	41.93±75.61
Time from splenectomy to last follow-up (months) (Mean ± SD)	60.70±80.31
Time from diagnosis to last follow-up (months) (Mean ± SD)	102.63±111.06

Yrs: Years, SD: Standard deviation

obtained in 2 (4.4%) patients. Relapse occurred during follow-up in a total of 15 patients as 4 with PR and 11 with CR. The time to relapse was median 61.9 months. In the 4 relapsed patients with prior PR, the relapse occurred within first 1 year. In the total follow-up period, 27 patients had CR; therefore, the long-term response rate of splenectomy was determined as 58.6% (27/46) (Table 2).

The total 17 patients including 2 patients with NR to splenectomy and 15 patients relapsed after splenectomy compared to the 29 patients with a stable response (CR + PR) who received no treatment and had no relapse throughout the follow-up period. No statistically significant difference was determined between the groups in respect of age, gender, response to steroids before splenectomy, immunosuppressive drug usage, comorbidities, time from diagnosis to splenectomy (months), age at splenectomy (years), platelet count, and PCT, MPV, PLR, PDW, LDH, vitamin B12 and ferritin levels (p>0.05). ALC in patients with a stable response was determined to be significantly lower than that of patients with NR or subsequent relapse (p=0.018) (Table 3). The optimal ALC cut-off value was determined as 1.85 with 86.7% sensitivity and 51.7% specificity (AUC=0.717; p<0.05). Patients with ALC ≤1.85×10^9/L at the time of diagnosis were determined to have a better response to splenectomy than those with ALC >1.85×10^9/L (p=0.031) (Table 4).

Table 2. Response rates to splenectomy

	1 month after splenectomy	Long-term follow-up
Complete response	38/46 (82.7%)	27/46 (58.6%)
Partial response	6/46 (13.0%)	2/46 (4.3%)
No response	2/46 (4.3%)	2/46 (4.3%)
Recurrence	-	15/44 (34.1%)

To identify the determinants of a permanent response to splenectomy, RFS analysis was applied to a total of 44 patients with CR and PR after splenectomy. The 1, 3, and 5-year RFS rates after splenectomy were determined as 90.9%, 86.3% and 84.0%, respectively. As a result of the Cox-Regression model applied according to the response to splenectomy, ALC at the time of diagnosis was seen to have a statistically significant effect on RFS (HR=1.003, p=0.009). No effect was determined in any of all the other parameters examined in the multivariate analysis (Table 5).

Discussion

In patients with primary ITP, when platelet count remains stable at <30×10^9/L, treatment is needed to reduce the risk

Table 3. Comparison of parameters according to long-term response to splenectomy

	Patients with stable response (CR+PR) (n=29)	Patients with recurrence and no response (NR+relapse) (n=17)	p
Age at diagnosis (yrs) (Mean ± SD)	36.62±20.13	29.53±17.87	0.236
Gender			
Female	20 (69.0%)	11 (64.7%)	0.766
Male	9 (31.0%)	6 (35.3%)	
Response to steroids			
No response	10 (34.5%)	8 (47.1%)	0.533
Dependent	19 (65.5%)	9 (52.9%)	
Immunosuppressive usage			
No	23 (79.3%)	15 (88.2%)	0.691
Yes	6 (20.7%)	2 (11.8%)	
Time from diagnosis to splenectomy (months) (Mean ± SD)	10.5 (0.5-392.6)	13.5 (0.0-133.9)	0.955
Age at splenectomy (yrs) (Mean ± SD)	40.48±17.71	32.59±15.71	0.136
At the time of diagnosis			
Platelet count (×10^9/L)	8.0 (1.0-43.0)	12.0 (2.0-40.0)	0.516
PCT	0.0 (0.0-0.4)	0.0 (0.0-0.1)	0.666
MPV (fL)	8.5 (4.7-19.0)	9.4 (4.5-11.9)	0.909
Lymphocyte count (×10^9/L)	1.8 (0.84-4.32)	2.47 (1.4-5.1)	**0.018**
PLR	5.9 (0.7-16.8)	4.3 (0.8-20.8)	0.674
PDW	16.9 (12.2-85.7)	16.3 (12.1-60.3)	0.446
LDH (/l)	222.1 (136.0-488.0)	230.3 (133.0-432.0)	0.387
Vitamin B12 (pmol/L)	265.0 (111.0-2000.0)	275.0 (143.0-1101.0)	0.936
Ferritin (ng/mL)	50.0 (2.4-202.0)	55.4 (2.2-225.0)	0.828

MPV: Mean platelet volume, PCT: Plateletcrit, PLR: Platelet/lymphocyte ratio, PDW: Platelet distribution width, LDH: Lactate dehydrogenase, Yrs: Years, SD: Standard deviation, CR: Complete response, PR: Partial response, NR: No response

Table 4. Absolute lymphocyte count according to long-term response to splenectomy

	Patients with stable response (n=29)	Patients with recurrence and no response (n=17)	Total (n=46)	p
Absolute lymphocyte count ($\times 10^9$/L)				
≤1.85	15 (51.7%)	3 (17.6%)	18 (39.1%)	**0.031**
>1.85	14 (48.3%)	14 (82.4%)	28 (60.9%)	

Table 5. Factors affecting relapse-free survival (multivariate analysis)

	Relapse-free survival		
	HR	95% CI	p
Gender	0.245	0.028-2.161	0.205
Age at diagnosis	1.316	0.666-2.600	0.429
Lymphocyte count	1.003	1.001-1.005	**0.009**
Platelet count	1.032	0.967-1.100	0.342
PCT	1.089	0.967-1.212	0.122
MPV	0.591	0.334-1.049	0.072
Response to steroids	0.091	0.003-2.737	0.167
Age at splenectomy	0.843	0.433-1.641	0.616
Time from diagnosis to splenectomy	1.010	0.927-1.101	0.813

MPV: Mean platelet volume, PCT: Plateletcrit, CI: Confidence interval, HR: Hazard ratio

of serious bleeding. While approximately 70-80% of patients respond to corticosteroid treatment, relapse is widespread. When various factors are taken into consideration such as the patient's history of bleeding, suitability for surgery, comorbidities, tolerance of side-effects, lifestyle and preferences, a choice can be made between more advanced medical treatments and splenectomy for patients who are steroid-resistant (6). Although splenectomy is used less often now than in the past due to the emergence of new drugs, it remains the standard second-line treatment for ITP patients unresponsive to corticosteroids (1,3,4).

According to the results of this study, while a R was obtained in 44 (95.6%) of the total 46 patients in the first month after splenectomy, relapse developed in 15 (34.0%) patients throughout the follow-up period. The median time to relapse was 61.9 months. In previous studies, the response to splenectomy in the early period was found to be 74% (8). An extremely high R rate was determined in the current study. However, as CR was obtained throughout the total follow-up period in 27 patients, the long-term response rate was determined as 58.6%. Similar studies have also shown a cure rate of approximately 58-66% (9,10). In the current study, the 1, 3 and 5-year RFS rates were found to be 90.9%, 86.3% and 84.0%, respectively. In a retrospective study that examined 54 ITP patients between 1999 and 2005, the 1, 3, and 5-year RFS rates were reported as 91.9%, 88.4% and 88.4%, respectively (11). In 4 of the 6 patients with PR, relapse developed within 1 year. This finding shows that when CR cannot be obtained after splenectomy, the early relapse rate is high. It has been reported in literature that relapse rates were higher in the early years (9).

Several factors have been previously studied in respect of capability to predict R to splenectomy. These studies have shown a young age (3,9,11,12), pre-post high platelet count (9,11-13), a good R to steroids before splenectomy (9,11,13), a short time from diagnosis to splenectomy (3,9), and a high megakaryocyte count at the time of diagnosis (9) to be effective parameters in respect of a stable response. However, there is no universally accepted marker that has been shown by all. In contrast to those previous studies, the current study results showed that although the age at diagnosis and age at splenectomy were higher in patients with a stable response compared to those with NR and relapse, the difference was not statistically significant. The duration of disease in patients with a stable response was shorter than in patients with NR and the response to steroids before splenectomy was better but these differences were not statistically significant. In a meta-analysis that examined 135 cases published between 1996 and 2004, it was shown that none of 12 preoperative factors, including age and R to steroids, were effective (10).

In the current study, when the impact of initial hematological and biochemical parameters was examined on response to splenectomy, a relationship was only found in ALC at the time of diagnosis. ALC in patients with a stable response was determined to be significantly lower than that of patients with NR or subsequent relapse (p=0.018). Patients with initial ALC ≤1.85×10^9/L were observed to have a better response to splenectomy (p=0.031). ALC at the time of diagnosis was seen to affect RFS in the Cox-Regression model applied according to the response to splenectomy (HR=1.003, p=0.009). None of the other parameters was seen to have any effect. In 4 studies of pediatric patients diagnosed with acute ITP, low baseline ALC or low lymphocyte count in the first months of the disease was shown to be significant risk factors in respect of future development of chronic ITP (14-17). Another study of 209 adult ITP patients showed that low ALC at the time of diagnosis was an independent risk factor for the development of infection (18). In the only study having similar results to the current study, Culic et al. (19) reported that there was a negative correlation between ALC and platelet count at the time of diagnosis in ITP patients and high ALC could predict a poor prognosis. In all the studies mentioned, the parameters were not studied in respect of response to splenectomy. To the best of our knowledge, the current study is the first to have examined ALC in respect of response to splenectomy, and contrary to what has

been previously known, patients with a low initial ALC were shown to have a good prognosis.

As a result of the activation of specific auto-reactive T lymphocytes, the production and proliferation of B lymphocytes producing antiplatelet antibodies is one of the most significant immunological impairments in ITP (20). In addition, impaired cellular immunity is thought to be important in the pathophysiology of ITP. There is current important evidence showing that generalized functional impairment of autoreactive T cells is a critical immunopathological cause of ITP and that antiplatelet autoantibodies are under the control of T cells (21). There are conflicting findings about the relationship of these immunological occurrences and lymphocyte count. Three significant points emerged from the results of an important study that considered lymphocyte counts: the rates of CD4+ cells in the peripheral blood of ITP patients were lower than those of the control group, CD8+ rates increased, and the CD4+/CD8+ ratio decreased. At the same time, the B lymphocytes (CD19+) were shown to be significantly higher than in the control group (22). In our study, lymphocyte subgroup analysis should be performed in order to reach the above mentioned comments. This analysis could not be performed due to the design of the study. However, when the results of these studies are considered together with those of the current study, it can be speculated that high ALC originating from both B and T cells in ITP patients impairs the immune response and could cause an increase in underlying autoantibody production leading to increase in relapse rates in the future. In contrast to these results, Yilmaz and Ayhan (20) showed that the percentages of T lymphocytes, T helper lymphocytes, regulatory T lymphocytes and storage B lymphocytes were initially significantly lower than those of the control group. However, at the end of the study, no difference was seen in these rates between patients who responded or did not respond to first stage treatment. In conclusion, it was reported that the percentages of regulatory T lymphocytes and storage B lymphocytes were not of any benefit in predicting the treatment outcomes of newly-diagnosed adult ITP patients.

There were some limitations to this study, primarily the retrospective design and smaller number of patients. However, we know that ITP is a rare disease in adults. Furthermore, the lack of lymphocyte subtype analysis and peripheral blood smear limited the interpretation and discussion of the current results.

Conclusion

Measurement of ALC at the time of diagnosis may be considered as predictive of the response to splenectomy. A low ALC at the time of diagnosis is a determining factor of a better response to splenectomy and higher RFS. Patients with a high initial ALC should be monitored more carefully and frequently. Even with splenectomy, there is a higher possibility of relapse and/or NR in this patient group. There is a need for further studies to analyze lymphocyte subgroups and the cytokine network to be able to clarify the underlying mechanisms.

Ethics

Ethics Committee Approval: The study was approved by University of Health Sciences Turkey, Ankara Diskapi Yildirim Beyazit Research and Training Hospital Ethics Committee (protocol no: 57/12, date: 17.12.2018).

Informed Consent: Retrospective study.

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Authorship Contributions

Concept: A.Y., Ç.P., Design: A.Y., M.A., Data Collection or Processing: A.Y., O.S., H.B.A.Ö., A.K., Analysis or Interpretation: A.Y., Ç.P., Literature Search: M.A., S.M., P.C., Writing: A.Y.

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Controlled hypotensive anesthesia in the beach-chair position under general anesthesia: Is it safe for shoulder arthroscopy?

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ABSTRACT

Aims: The beach-chair position (BCP) imposes a risk to cerebrovascular hypoperfusion due to deep hypotensive events (DHEs) which may progress to catastrophic neurological complications. However, a controlled hypotensive anesthesia (CHA) management is often required for arthroscopic shoulder surgery to reduce blood loss and to improve visibility of surgical field. The aim of this retrospective study was to evaluate CHA managements, DHEs, and complications in patients who underwent shoulder arthroscopy in the BCP under general anesthesia (GA) between years 2017 and 2019.

Methods: After hospital's ethic committee approval was obtained, medical records of 72 adult patients were retrospectively reviewed. Primary outcome measures were the frequency of CHA management and the incidence of DHE. Secondary outcome measures were to determine the stages of surgery at which DHEs have developed and the complications.

Results: CHA was required in 46 of total 72 patients (63.9%). Among those 46 patients, 31 (67.4%) had at least one DHE. A total of 82 DHEs were detected in 49 patients whereas mean arterial pressure limits were normal (±30% of baseline) in the remaining 23 (68.1% vs. 31.9%; $p<0.05$). DHEs were recorded most frequently after BCP ($p<0.05$). All DHEs were promptly treated with the discontinuation of CHA and administration of vasopressor drugs. No neurological complication was observed.

Conclusions: GA in BCP caused DHEs and its incidence was increased by inducing CHA. It was concluded that neurological complications could be prevented when further decrease in blood pressure was avoided or promptly treated in case of a hypotensive event.

Introduction

Arthroscopy is the most common surgical procedure for the diagnosis and treatment of orthopedic shoulder pathology and generally performed as an outpatient procedure rather than open surgery due to minimal invasive properties and low risk of morbidity (1). Shoulder arthroscopy can be performed under general anesthesia (GA), peripheral nerve block, or a combination of both techniques. Patients are positioned in either beach-chair position (BCP) or lateral decubitus position. The BCP has became more popular than lateral decubitus position because of better visualization of the joint, lower incidence of neurovascular complications, and easier conversion to open surgery (2). Common complications of shoulder arthroscopy are traction injuries in the brachial plexus, extravasation of irrigation

fluid out of the joint, air embolism, and infection irrespective of positioning and anesthetic management. However, uncommon but devastating complications like stroke, cerebral cord ischemia, and transient visual loss have been reported for the BCP. The exact mechanisms of these complications are not clear, but studies have reported that intraoperative deep hypotension events may cause cerebral hypoperfusion which is defined as a reduction in mean arterial blood pressure (BP) below 50 mmHg. It is reported that deep hypotensive events may arise from upright positioning combined with GA (3-5). For this reason, it is advocated that the mean arterial BP should be kept in a range between 50 and 65 mmHg during shoulder arthroscopy, which does not blunt cerebral blood flow and autoregulation. However, a controlled hypotensive anesthesia (CHA) technique is often required to reduce blood loss and to improve visibility of surgical field during arthroscopy which may further increase cerebral hypoperfusion (4).

The aim of this retrospective study was to evaluate the CHA management, deep hypotensive events, and complications in patients who underwent shoulder arthroscopy in the BCP under GA between years 2016 and 2018. Primary outcome measures were the frequency of CHA management and the incidence of deep hypotension events. Secondary outcome measures were to determine at which stages of the surgery deep hypotension events developed and perioperative complications.

Methods

Approval from the Local Research Ethics Committee of our tertiary hospital was obtained before initiating the study (University of Medical Sciences Turkey, Gülhane Training and Research Hospital, project no: 18/102, date: 02.05.2018). After obtaining hospital ethic committee approval, medical files and anesthesia charts of the patients who underwent arthroscopic surgery were retrospectively evaluated. Inclusion criteria were unilateral elective shoulder surgery, arthroscopic procedure, and GA in the BCP. Exclusion criteria were urgent surgery, arthroscopic surgery converted to open surgery, BCP converted to lateral decubitus position, patients with history of cerebrovascular disease or neurological injury, and missing data.

Anesthetic management

GA was induced using intravenous (IV) propofol, fentanyl, and rocuronium. Propofol infusion or sevoflurane inhalation combined with IV remifentanil was used for the maintenance. CHA was induced in patients with a normal range of mean arterial pressure (MAP); i.e. ±20% of baseline MAP after surgical team stated that the quality of surgical exposure was not adequate due to bleeding. IV metoprolol or nitroglycerine was given to achieve CHA defined as a reduction in the MAP to a range of 60-70 mmHg or ±30% of baseline levels. Non-invasive BP measurement was used for American Society of Anesthesiologists (ASA) I patients while invasive BP measurement was used for the remaining patients. A deep hypotension event was defined when the MAP reduced to <50 mmHg or systolic BP to <90 mgHg. Deep hypotensive events were treated with the discontinuation of CHA, reducing of anesthetic drug doses, IV bolus fluid replacement, and administration of 5-10 mg IV ephedrine boluses. Patients were evaluated using the modified Aldrete Scoring System (mASS) after GA in the post-anesthesia care unit, and patients with a mASS score of >9 were transferred to the service.

Following data were collected and evaluated from patient's files and anesthesia charts: a) demographic data: Gender, age, body height, weight, ASA physical status, and co-morbidity, b) duration of surgery (min.), c) anesthetic management, d) number of CHA management, e) number, duration, and stage of deep hypotensive events, f) perioperative complications, g) time to discharge (hours).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 21 (IBM SPSS Inc., Chicago, IL). Descriptive statistics were used as mean and standard deviation (Mean ± SD) for continuous data, and frequency and percentage (n, %) for categorical data. The normal distribution of the continuous data was evaluated with the Kolmogorov-Smirnov test. The abnormal distribution for continuous variables was analyzed using the Mann-Whitney U test between the groups whereas the Pearson chi-square test was employed for categorical variables. $P<0.05$ was considered as statistically significant.

Results

Records of 96 patients were evaluated, and 24 of those patients were excluded due to missing data (Figure 1). Demographic data of the remaining 72 patients were shown in Table 1. The mean age was 49.84±15.25 years and co-morbidity rate was 50% as follows: Hypertension (20.8%), coronary artery disease (9.7%), diabetes mellitus (9.7%), coronary artery disease + diabetes mellitus (4.2%), and hypertension + diabetes mellitus (5.6%).

Primary outcome measures: A minimum one episode of deep hypotensive event was recorded in 49 patients whereas the MAP levels were remained in normal range in the remaining 23 patients [49 (68.1%) vs. 23 (31.9%); $p<0.05$]. It was observed that CHA was required in 46 patients and not required in 26 patients (63.9% vs. 36.1%; $p<0.05$). Among 46 patients who received CHA, deep hypotensive event was recorded in 31 patients while arterial BP remained in normal range in other 15 patients (67.4% vs. 32.6%; $p<0.05$). On the other hand, a deep hypotensive event was recorded in 18 patients out of 26 patients who did not receive CHA [18 (69.2%) vs. 8 (30.8%); $p<0.05$]. The rate of deep hypotensive event was statistically insignificant

between patients who did receive CHA or not (67.4% vs. 69.2%; p>0.05). The total number of deep hypotensive events was 82. Primary outcome measures were summarized in Table 2.

Secondary outcome measures: It was observed that deep hypotensive events developed most often after the BCP of patients followed by intraoperative period, in other words, after the start of CHA (p<0.05; Table 2). When the anesthesia records on the chart were evaluated, it was found that the duration of deep hypotensive events did not exceed 5 minutes. A total of 9 complications, which included 7 postoperative nausea and vomiting and 2 bronchospasms, were recorded in 7 of 72 patients. No neurological complications were observed.

Table 1. Demographic data, operation and discharge time

Parameter		Result
Gender (n,%)	Female	36 (50%)
	Male	36 (50%)
Age (yrs)		49.8±15.2
Height (cm)		167.0±10.8
Weight (kg)		79.5±13.3
ASA physical status	I	36 (50.0%)
	II	28 (38.9%)
	III	8 (11.1%)
Co-morbidity	None	36 (50.0%)
	HT	15 (20.8%)
	CAD	7 (9.7%)
	DM	7 (9.7%)
	CAD+CVD	3 (4.2%)
	HT+DM	4 (5.6%)
Operation time (min.)		97.8±20.1
Discharge time (hrs)		20.8±4.7

ASA: American Society of Anesthesiologists, HT: Hypertension, CAD: Coronary artery disease, DM: Diabetes mellitus, CVD: Cerebrovascular disease, Yrs: Years, Hrs: Hours, Min.: Minimum

Table 2. Controlled hypotensive anesthesia and deep hypotensive events

Parameter		n (%)	p*
Patients received CHA (n, %)	Yes	46 (63.9%)	<0.05
	No	26 (36.1%)	
Patients with DHE (n, %)	0 episode	23 (31.9%)	<0.05
	≥1 episode	49 (68.1%)	
Patients with DHE (n, %)	Received CHA	31 (67.4%)	>0.05
	Not received CHA	18 (69.2%)	
Number of DHE (total 82)	1	21 (42.9%)	>0.05
	2	23 (46.9%)	
	3	5 (10.2%)	
Stage of DHE in the perioperative period	After induction	12 (14.6%)	<0.05
	After positioning	39 (47.6%)	
	During surgery	30 (36.6%)	
	After extubation	1 (1.2%)	
	In the ward	0 (0.0%)	

*p<0.05 was considered as statistically significant.
MAP: Mean arterial pressure, CHA: Controlled hypotensive anesthesia, DHE: Deep hypotensive event (MAP ≤50 mmHg)

Discussion

The results of this study showed that CHA was required in most of patients who underwent arthroscopic shoulder surgery. The incidence of deep hypotensive events was found to be mainly increased with the BCP combined with GA and further precipitated with the administration of CHA, but complications related to cerebral hypoperfusion were not observed throughout the procedure. Interventions to prevent further decreases in BP might preserve patient's neurological status.

As in other various surgeries, a clear and bloodless surgical exposure is important in arthroscopic shoulder surgery. It was reported that a pressure difference should be ensured between systolic BP and pressure in the subacromial space to produce a bloodless surgical field. Increasing the arthroscopic pump pressure, decreasing the systolic BP or a combination of both are generally used for this purpose. However, high irrigation pump pressure may cause excessive extra-articular fluid extravasation, which may progress to serious complications including neurovascular impingement and tracheal stenosis. So, a combination of both techniques (low pump pressure and induced hypotension) is much more preferred (6).

Intraoperative induced hypotension is known to reduce perioperative blood loss and duration of the surgery up to 50% but may cause serious complications by decreasing perfusion of vital organs (4). Especially, neurological complications related to cerebral hypoperfusion may have a potential to progress to brain and spinal cord injury (5). Although the incidence of this complication is quite low (8 in 224275 patients) during shoulder arthroscopy, it is remarkable that all events were observed in the BCP under GA (3). Upright positioning of an awake patient activates sympathetic nervous system and thereby increases peripheral vascular resistance, which results in elevation of arterial BP. However, GA blinds baroreceptor responses which is required to correct of the effects of the gravity on the cerebral perfusion pressure. In addition, GA also prevents peripheral vascular resistance. In our study, it was found that nearly half of all deep hypotensive events were developed after positioning of patients. It was reported that the rate of intraoperative hypotension could be as high as 32% during GA in upright position (7). In our study, the rate of hypotensive events was similar between the patients who received or not received CHA. According to this, it may be conceivable that the BCP combined

with GA had an great effect on deep hypotensive events without the administration of CHA.

CHA has been used for more than 60 years in anesthesia, but there are still controversies about the safe limits of the management (8). The common opinion is that the MAP should be kept above 60 mmHg, systolic BP above 90-100 mmHg while maximum reduction in MAP should not exceed 30% of basal levels (9). However, many studies revealed that regional cerebral desaturation episodes were diagnosed using near-infrared spectroscopy in about 80% of patients even intraoperative MAP was kept between ±%20 of baseline levels. However, any neurological complication was not reported (9,10).

In our study, minimum one deep hypotensive episode was recorded in 68.1% of patients. Further decreases in MAP were prevented with interventions including the discontinuation of anesthetic and hypotensive agents and administration of ephedrine and fluid boluses. In a study by Gillespie et al. (11), a minimum one episode of a decrease in systolic arterial pressure below 90 mmHg was reported in all patients and the mean rates of decrease in systolic and mean arterial BP were 36% and 42%, respectively. Among these patients, an ischemic change was detected with electroencephalography only in 3 patients without any neurological impairment. Therefore, it was advocated that the risk of neurological complications may have a relationship with the severity of the deep hypotensive events as well as with its duration. In our study, although the exact duration of deep hypotensive event was not strictly recorded during the operation, anesthesia records revealed that any of deep hypotensive event did not exceed five minutes.

Another debate continues on where the cuff of non-invasive BP or transducer of invasive arterial pressure line places to correctly measure the BP at brain level. It is not exactly established whether a non-invasive BP measurement reflects cerebral BP. Also, the question concerns whether the transducer should be adjusted according to the level of the heart or of theear (external auditor meatus) (12). One opinion is that the measurement with non-invasive BP should be corrected according to the position of the patient's head (a reduction in BP of 1 mmHg for each 1.25 cm height difference between the site of measurement and the brain) (9,13). In our daily anesthetic practice, the level of invasive pressure transducer or of non-invasive pressure cuff is adjusted to the level of the heart but corrected to the level of the external auditor meatus to measure cerebral perfusion pressure.

Our study has some limitations. Firstly, there was a lack of measurement of cerebral perfusion using electroencephalogram or near-infrared spectroscopy. Both are advanced and expensive techniques and need experience, which limit their use in daily practice. The second limitation is that the nature of the retrospective design of the study may cause selection errors and comparison bias. In order to prevent this, we tried to collect all data of patients and excluded 24 files with missing data (Figure 1).

Conclusion

As a result, it is concluded that the combination of the BCP with GA caused deep hypotensive events which were further precipitated by inducing CHA during shoulder arthroscopy. We think that neurological complications could be prevented when further decreases in BP would be avoided or promptly treated in case of a hypotensive event.

Ethics

Ethics Committee Approval: Approval of the Local Research Ethics Committee of our tertiary hospital was obtained before initiating the study (University of Medical Sciences Turkey, Gülhane Training and Research Hospital, project no: 18/102, date: 02.05.2018).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.Ö.Ö., C.Ç., Concept: M.Ö.Ö., M.B.E., U.G., Design: M.Ö.Ö., M.B.E., B.A., Data Collection or Processing: M.Ö.Ö., M.B.E., M.P., Analysis or Interpretation: M.B.E., C.Ç., M.A.S., M.P., Literature Search: M.B.E., C.Ç., B.A., Writing: M.Ö.Ö., M.B.E., U.G., B.A., M.P.

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The effect of preoperative warming on perioperative hypothermia in transurethral prostatectomies

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ABSTRACT

Aims: The aim of this study was to assess the effectiveness of warming in perioperative hypothermia, hemodynamic variables, post-anesthesia care unit discharge time, shivering, patient comfort and patient satisfaction in elderly patients undergoing transurethral resection of prostate (TURP) surgery under general anesthesia.

Methods: Patients aged between 50 and 85 years, scheduled for TURP surgery of 30-90 min under general anesthesia, were enrolled into the study. Patients were randomly allocated to either the warming (Group P) or standard care (Group C) group. Core body temperatures and hemodynamic parameters were assessed. Additionally, patient satisfaction, thermal comfort, and shivering were compared using scales.

Results: Overall, 33 patients (Group P; n=16, Group C; n=17) completed the study. Core body temperature was higher in Group P after anesthesia induction than in Group C (37.01±0.29 vs 36.61±0.21) (p=0.001). In addition, at the end of surgery, the core temperature was significantly higher in Group P (36.03±0.33) than in Group C (35.31±0.45) (p=0.001). Hypothermia was observed in four warmed and 17 unwarmed patients at the end of surgery (p=0.001). Following anesthesia induction, one warmed patient and nine unwarmed patients developed hypotension (p=0.004). Thermal comfort and patient satisfaction scores were significantly higher in warmed patients than in unwarmed patients (p<0.05), but shivering scores displayed a similar pattern between the groups (p>0.05).

Conclusions: This study demonstrated that perioperative forced-air warming helped preserve perioperative core body temperature, reduced the incidence of hypotension during the induction period, increased thermal comfort, improved patient satisfaction, but did not affect shivering in patients undergoing TURP surgery.

Introduction

Core body temperature is tightly regulated by thermoregulatory defense mechanisms such as sweating, shivering and arteriovenous shunt vasoconstriction. Perioperative hypothermia is defined as a core body temperature less than 36 °C during surgery and the postoperative period (1,2). General anesthetics represent one of the most common cause of perioperative hypothermia. They impair several thermoregulatory defenses such as vasoconstriction and shivering and lead to thermal redistribution (3).

Perioperative hypothermia is associated with several complications such as coagulopathy (4), increased transfusion requirement (5), shivering (6), thermal discomfort (2), delayed drug metabolism (7), increased risk of surgical site infection (3), tissue ischemia (8), and delayed wound healing. Additionally, it may reduce patient satisfaction, prolong length of hospital stay, and increase hospital costs (1). Perioperative hypothermia is more accentuated in the elderly population undergoing transurethral resection of prostate (TURP) surgery in part due to the excessive use of irrigation fluids and in part due to their reduced thermoregulatory capacity (9).

Cutaneous blood flow is influenced by both thermoregulation and cardiovascular homeostasis which are closely related to each other (10). Increased body temperature and accompanying vasodilation are followed by a moderate decrease in the central venous pressure and a passive redistribution of the blood flow towards the cutaneous vascular beds (10). During hypothermia, in contrast, circulating blood volume is reduced as a result of cutaneous vasoconstriction (4). Perioperative warming of the patient, in this regard, is an effective means of preserving thermal homeostasis (3) and inhibiting the hypotensive response. Warming the patient prior to anesthesia induction reduces redistribution hypothermia by increasing the temperature of peripheral tissues and lowering the core to periphery temperature gradient (4,11). Among others, forced-air warming system is the most commonly used perioperative (pre-, intra- and post-operative) warming modality (12).

The primary aim of this study was to assess the effectiveness of prewarming on perioperative hypothermia in elderly patients undergoing TURP surgery under general anesthesia. We also sought to evaluate the effects of prewarming on hemodynamic variables, post-anesthesia care unit (PACU) discharge time, shivering, patient comfort and satisfaction.

Methods

We conducted a single-center, prospective, randomized, single-blinded (assessor-blinded) study at the Training and Research Hospital between November 2018 and February 2019. The trial was approved by the Ethical Committee of the Ministry of Health Diskapi Yildirim Beyazit Training and Research Hospital in Ankara, Turkey (protocol number: 06/22, date: 17.12.2012). It was registered at www.clinicaltrials.gov (NCT01858727). All patients gave their written informed consent to participate in the study.

American Anesthesiology Association (ASA) I-III patients aged between 50 and 85 years, with a body mass index (BMI) between 15 and 36 kg/m^2, scheduled for TURP surgery of 30-90 min under general anesthesia, were enrolled in the study. Exclusion criteria were as follows: inadequate comprehension of the Turkish language, known impaired thermoregulation or thyroid disorders, presence of severe hypertension defined as a systolic blood pressure (SBP) >180 mmHg or diastolic blood pressure (DBP) >110 mmHg measured in the operating room, presence of secondary hypertension (e.g., Cushing's syndrome, pheochromocytoma, renal artery stenosis), presence of a vascular disease or poor cutaneous perfusion, presence of serious skin lesions, use of an angiotensin-converting enzyme inhibitor/angiotensin II receptor antagonist on the day of surgery, and a baseline temperature ≥37.5 °C. Preoperative visits were conducted by an anesthesiologist. Patients were randomly assigned to either the prewarming (Group P) or standard care group (Group C) using a computer-generated list.

Patients were instructed on the use of the shivering scale (0=No shivering; 1=One or more of piloerection; peripheral cyanosis without other cause but without visible muscular activity; 2=Visible muscular activity confined to one muscle group; 3=Visible muscular activity in more than one muscle group; 4=Gross muscular activity involving entire body) (13), the patient satisfaction scale (Likert scale; range: 1-7), the 100-mm visual analog scale (0 mm=Unbearably cold, 50 mm=Neutral, and 100 mm=Unbearably hot) to measure thermal comfort (14). Patients in the control group were given standard care without active warming in the admission and preoperative period. Patients in the prewarming group received 30 minutes of full-body preoperative warm-up by nurses unaware of the study using a forced-air warming device (Mistral-Air/The 37 Company, Amersfoort, the Netherlands) set to 43 °C in the preoperative waiting area, before entering the operating room. Patients were assessed every 5 minutes and the temperature was lowered to 37 °C if the patient reported discomfort (2). Hemodynamic data and core body temperature were measured and recorded at baseline and at 30th min using the zero-heat-flux thermometry sensor (3M SpotOn, St. Paul, Minnesota, USA) placed on the patients' forehead (15). The researcher stayed in the operating room and did not reach the waiting area before surgery to ensure blindness. Patients were monitored during heating for undesirable effects such as vomiting, nausea, and diaphoresis.

Each patient received an infusion of 0.9% saline at 100 mLhr^{-1}. To ensure blinding, the assessor remained in the surgery room and did not enter the preoperative waiting area. A protocol deviation was defined as a delay of 20 minutes or more between the end of warming and transfer to the surgery room. During surgery, potential warming-related adverse effects such as diaphoresis or nausea and vomiting were recorded. Premedication was not applied to the patients.

Heart rate (HR), SBP, DBP, mean arterial pressure (MAP), peripheral oxygen saturation, bispectral index (BIS, Quatro sensor and BIS VISTA monitor), room temperature and core body temperature were monitored and recorded every 15 minutes during surgery, at 0th and 20th min in the PACU and at 1st, 2nd and 12th hours in the ward by a blinded investigator using non-invasive methods. Induction of anesthesia was achieved using infusions of propofol (4 μg.mL^{-1} target effect-site concentration using the model of Schnider et al. (16) and by maintaining the BIS in the range 40-60. The attending anesthesiologist increased the concentration of propofol in increments of 1 μg.mL^{-1} if the target BIS range was not reached within two minutes. The patient was intubated following neuromuscular blockade with rocuronium 0.6 mg.kg^{-1} iv. Propofol was titrated using a target-controlled infusion adjusted for BIS between 40 and 60. The dose of remifentanil was titrated according to the systemic blood pressure response during anesthesia care. If SBP declined more than 30% from the baseline value or if MAP

was lower than 60 mm Hg, repeated doses of ephedrine 5 mg iv were administered. If the HR fell below 45 beat/min, atropine was administered. Patients were positioned similarly during the entire surgical procedure and were transferred to the PACU by using a warmed cotton blanket and a reflective foil blanket following surgery. Forced-air warming continued in the PACU (1).

The shivering scale, patient satisfaction scale and the 100-mm visual analog scale to measure thermal comfort were administered and recorded at 0th and 20th min in the PACU and at 1st, 2nd and 12th hours in the ward by a blinded investigator. When the Modified Aldrett score was higher than 9 and the core body temperature was higher than 36 °C, the patient was discharged from the PACU. The time in PACU was recorded.

For analgesia, 50 mg dexketoprofen trometamol was applied at the beginning of surgery and 100 mg tramadol was intravenously administered towards the end of the surgery. For postoperative pain, intravenous 50 mg dexketoprofen trometamol was administered every 8 hours. Patients with a numerical rating scale score of 4 or more received 50 mg intravenous tramadol HCl. Patients with severe postoperative nausea and vomiting (PONV) were given i.v. 10 mg of metoclopramide. In addition to patients whose PONV complaints continued, i.v. ondansetron 4 mg was administered.

Statistical Analysis

Sample size was calculated based on an expected treatment effect of 0.5 °C at the end of surgery, which has been shown to be the smallest difference associated with hypothermia induced complications (17). Using α-error=0.05 at 80% power, we calculated the number of patients required per group as 16 and included 18 patients in each group considering potential dropouts.

Statistical Package for Social Sciences (SPSS) software version 24 was utilized for all other data analyses (SPSS, Inc., Chicago, IL, USA). Normality of continuous data was assessed using the one sample Kolmogorov-Smirnov test. Categorical data were summarized using number (percent), normally distributed data were presented using mean (standard deviation) and skewed data were summarized using median (interquartile range). Two group comparisons were conducted using the chi-square or Fisher's exact tests for categorical data, unpaired two-tailed Student's t-tests for normally distributed data and rank-sum tests for skewed data. Repeated measures analysis of variance was used to evaluate time-dependent changes in temperatures and hemodynamic values. A p value of <0.05 was considered to be statistically significant.

Results

A total of 42 patients were assessed for eligibility. Six of these were excluded as one had a thyroid disorder, three had severe hypertension, one used an angiotensin-converting enzyme inhibitor/angiotensin 2 receptor antagonist on the day of surgery, one had inadequate comprehension of the Turkish language. Overall 36 patients were included in the study. One patient in Group P and two in Group C were excluded because the duration of surgery was less than 30 min. Consequently 33 patients (Group P; n=16, Group C; n=17) completed the study. Groups were well matched with regards to age, gender, BMI, ASA classification, room temperature, amount of irrigation fluid and intravenous fluid consumption (p>0.05) (Table 1). Total rate of propofol consumption was also similar between the groups (p=0.059) (Table 1).

Baseline core body temperature was similar between Group P and Group C (p=0.122). Core body temperature was significantly higher in warmed patients than in unwarmed patients after prewarming and at 0th, 15th, 30th, 45th, 60th min after the induction of anesthesia and at the end of surgery (p=0.001, p=0.001, p=0.014, p=0.001, p=0.001, p=0.001, p=0.001 respectively) (Table 2) (Figure 1). Core body temperature was also significantly higher in warmed patients at postoperative 0th and 20th min (p=0.039, p=0.01 respectively), but remained similar between the groups at postoperative 1st, 2nd and 12th hours (p=0.093, p=0.441, p=0.122 respectively) (Figure 1). Hypothermia was observed in none of the warmed patients and in four unwarmed patients at 15th min after anesthesia induction (p=0.335); in two warmed and six unwarmed patients at 30th min (p=0.225); in three warmed and 17 unwarmed at 45th min (p=0.001); and in four warmed and 17 unwarmed patients at the end of surgery (p=0.001). Operation time and baseline core body temperature values were similar between the groups (p>0.05) (Table 1). PACU discharge time was shorter in warmed than in

Table 1. Comparing prewarmed vs control on demographics and operation factors

	Group P (n=16)	Group C (n=17)
Age (year)	66.12 (6.92)	67.12 (5.81)
ASA (I/II/III)	4/8/4	3/11/3
BMI (kg/m^2)	27.58 (3.62)	28.86 (2.03)
Ambient room temperature (°C)	21.25 (1.00)	21.35 (1.05)
Washing fluid (mL)	8437 (8545)	8070 (6007)
IV fluid (mL)	750 (274)	705 (185)
Total propofol consumption (mg)	656 (135.09)*	577 (94.96)
Operation time (minute)	52.25 (12.87)	58.23 (16.29)
PACU time (minute)	31.18 (9.57)**	45.64 (17.11)

Values are presented as mean (standard deviation), or median (first-third quartiles).
*p value compared to the control group (p=0.059).
**Significant compared to the control group (p=0.05).
PACU: Postanesthesia care unit, IV: Intravenous, BMI: Body mass index, ASA: American Anesthesiology Association

unwarmed patients (p=0.006) (Table 1). Side effects such as diaphoresis or vomiting during the prewarming intervention were not seen in any patient.

Hemodynamic variables (mean SBP, DBP, HR levels) were similar between the groups at baseline (p>0.05). Following warming, they were significantly reduced in warmed patients (p=0.001), but remained unchanged in unwarmed patients (p>0.05) and were significantly lower in warmed patients than in unwarmed patients (p=0.01) (Table 3). Following anesthesia induction, hemodynamic variables remained unchanged in warmed patients, but were significantly reduced in unwarmed patients (p=0.001), and remained similar between the two groups (p>0.05). Following anesthesia induction, one warmed patient and nine unwarmed patients developed hypotension (Table 3). Hemodynamic variables showed a similar pattern between the two groups during the rest of the follow-up period (p>0.05) (Table 3).

Thermal comfort and patient satisfaction scores were significantly higher in warmed patients than in unwarmed patients at postoperative 0th and 20th minutes (p<0.05) but were similar at postoperative 1st, 2nd and 12th hours (p>0.05) (Table 4). Shivering scores displayed a similar pattern between the groups at all assessment points (Table 4).

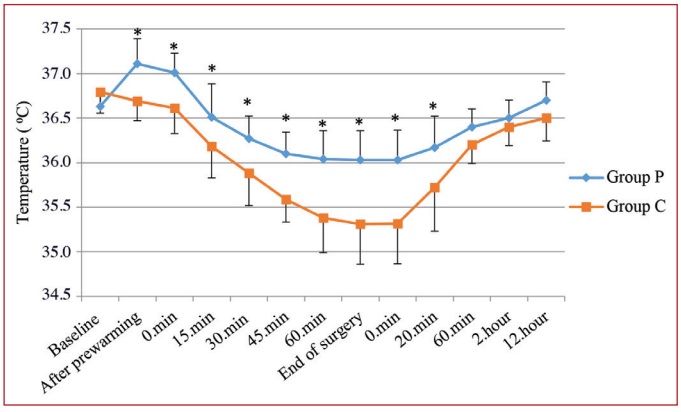

Figure 1. Mean perioperative core temperatures of the control Group C and the prewarming Group P
*p<0.05 compared to Group C

Table 2. Comparing prewarmed vs control on primary and secondary outcomes

	Group P (n=16)	Group C (n=17)	p value
Baseline (°C)	36.63 (0.16)	36.79 (0.23)	0.122
After prewarming (°C)	37.11 (0.22)	36.68 (0.28)	0.001
After induction of anesthesia (°C)	37.01 (0.29)	36.61 (0.21)	0.001
15 minutes after induction of anesthesia (°C)	36.51 (0.37)	36.18 (0.35)	0.014
End of surgery (°C)	36.03 (0.33)	35.31 (0.45)	0.001
Hypothermia in end of surgery (n/%)	4/25	17/100	0.001

Values are presented as mean (standard deviaiton), or numbers/ percentage.
All temperatures are core temperature values

Discussion

We found that warming patients during the perioperative period prevented temperature decrease in patients undergoing TURP surgery. We also observed that this intervention increased thermal comfort, improved patient satisfaction and prevented

Table 3. Hemodynamic variables

	Group P (n=16)	Group C (n=17)	p value (prewarming-control)
Baseline			
SBP (mmHg)	128 (19)	130 (20)	0.853
MAP (mmHg)	96 (16)	99 (16)	0.576
HR (beats/min)	76 (9)	75 (15)	0.915
After prewarming			
SBP (mmHg)	106 (5)*	131 (11)	0.001
MAP (mmHg)	82 (6)*	102 (11)	0.001
HR (beats/min)	65 (3)*	84 (10)	0.001
Post induction			
SBP (mmHg)	103 (7)	102 (14)**	0.136
MAP (mmHg)	78 (9)	71 (15)**	0.570
HR (beats/min)	65 (3)	70 (8)**	0.665
15.min			
SBP (mmHg)	95 (15)	98 (17)	0.526
MAP (mmHg)	72 (18)	75 (15)	0.419
HR (beats/min)	66 (17)	65 (14)	0.824
30.min			
SBP (mmHg)	107 (9)	101 (12)	0.141
MAP (mmHg)	81 (8)	76 (13)	0.149
HR (beats/min)	65 (9)	73 (14)	0.074
45.min			
SBP (mmHg)	116 (6)	108 (12)	0.092
MAP (mmHg)	91 (4)	82 (9)	0.118
HR (beats/min)	66 (6)	65 (9)	0.780
60.min			
SBP (mmHg)	119 (5)	98 (11)	0.011
MAP (mmHg)	74 (11)	68 (12)	0.772
HR (beats/min)	68 (11)	55 (3)	0.488
End of surgery			
SBP (mmHg)	115 (15)	102 (17)	0.062
MAP (mmHg)	65 (8)	72 (9)	0.083
HR (beats/min)	89 (15)	81 (18)	0.488
Hypotension in post induction	1/6.25	9/52.94	0.004

Values are presented as mean (standard deviation), or numbers/percentage.
All temperatures are core temperature values.
*p=0.001 compared to the baseline value.
**p=0.001 compared to the prewarming time value.
SBP: Systolic blood pressure, MAP: Mean arterial pressure, HR: Heart rate, min: Minute

hypotension during anesthesia induction, but did not affect shivering.

Perioperative hypothermia is a common but almost always preventable complication of elective surgery. It is associated with poor clinical outcomes and serious medical complications such as myocardial ischemia, blood loss and surgical site infection (18). TURP patients mostly belong to the geriatric age group who already present with pulmonary and/or renal comorbidities and/or adverse cardiovascular events such as hypertension and tachyarrhythmia (19). The use of high volume irrigation fluids during TURP surgery and the presence of a reduced shivering threshold further increase the risk of perioperative hypothermia (20). Prevention of hypothermia and hemodynamic instability in the elderly is therefore critical. Warming increases peripheral tissue temperature and thereby reduces core to peripheral tissue temperature gradient, a process that reduces blood redistribution following anesthetic induction and that ameliorates redistribution hypothermia. Warming the patient is usually performed using the forced-air warming system (21).

Horn et al. (21) compared the effectiveness of preoperative warming versus usual care among women receiving general anesthesia and found that the number of patients who developed hypothermia was less in warmed patients. Munday et al. (1), in contrast, found no difference in the rate of hypothermia between women who did and did not receive preoperative warming before spinal anesthesia for cesarean delivery. In the current study, we found that warmed patients had higher mean perioperative core temperatures at each assessment point during the study period. Additionally, while hypothermia was observed as early as 15 minutes after anesthetic induction in some unwarmed patients, it was observed only after 30 minutes in warmed patients. These discrepancies may be due to the differences in ambient temperature, variations in surgery duration and/or the use or non-use of intrathecal morphine.

Table 4. Comparing prewarmed vs control on postoperative data

	Group P (n=16)	Group C (n=17)	p value
Thermal comfort score			
0.minute	50 (35-50)	40 (30-40)	0.007
20.minute	50 (42.5-57.5)	40 (35-42.5)	0.001
1.hour	50 (50-50)	40 (35-50)	0.276
2.hour	50 (50-50)	50 (45-50)	0.958
12.hour	50 (50-50)	50 (50-50)	0.557
Shivering grade			
0.minute	0 (0-1)	2 (0-2.5)	0.087
20.minute	0 (0-0.75)	1 (0-1)	0.063
1.hour	0 (0-0)	0 (0-0)	0.260
2.hour	0 (0-0)	0 (0-0)	1.0
12.hour	0 (0-0)	0 (0-0)	1.0
Satisfaction scores			
0.minute	6 (5-6.75)	4 (4.5-5)	0.017
20.minute	6 (6-7)	5 (4.5-6)	0.019
1.hour	6.5 (6-7)	6 (6-7)	0.488
2.hour	6.5 (6-7)	6 (6-7)	0.683
12.hour	6.5 (6-7)	6 (6-7)	0.683

The data are presented as median (first-third quartiles)

Warming increases both peripheral tissue and core body temperatures. Increased cutaneous temperature facilitates the opening of vascular beds and indirectly increases cardiac output due to splanchnic vasoconstriction (10). Warming, in this regard, may help prevent anesthesia-mediated hypotension (10,22). Kim et al. (23) assessed the effectiveness of cutaneous warming during anesthesia preparation on temperature and hemodynamic variables in the early operative period in patients undergoing off-pump coronary artery bypass surgery. They found that MAP values remained within the normal range at the pre-induction period in warmed patients but not in unwarmed patients. Darvall et al. (22) found no difference in MAP values both at the pre-and post-induction period between patients warmed with convective forced-air one hour prior to intravenous anesthetic induction and unwarmed patients. In the current study, warmed patients developed significantly less hypotension than unwarmed patients during the post-induction period (6.25% vs 52.94%) and MAP values were significantly lower in warmed patients (4.87% vs. 30.39%).

The primary thermoregulatory defense mechanisms in humans are sweating, shivering and arteriovenous shunt vasoconstriction (4). The intensity of postoperative shivering may vary depending on the severity of intraoperative hypothermia (1). Postoperative shivering reduces patient satisfaction and comfort (2), and may augment oxygen consumption by increasing the metabolic rate by up to five folds (4). An augmentation in oxygen consumption may facilitate the development of cardiac complications such as arrhythmia, angina pectoris and myocardial infarction and may prolong the postoperative recovery time in the elderly patients who already present with comorbidities. While some studies claim that perioperative warming may prevent shivering (21), many others demonstrated that warming alone was insufficient (1,11,18) because non-thermogenic factors such as pain or anxiety also contribute to the development of shivering through the release of catecholamines (24). In the current study, although the incidence of shivering was similar between the groups, thermal comfort scores and patient satisfaction scores were higher in warmed patients. This may be related to the warming process which not only provides the warming of the patient but also allows a more personalized care which usually provides some sort of psychological comfort.

TURP surgery may be conducted by either regional or general anesthesia. General anesthesia is preferred in the elderly as they may present with disorders such as vertebral collapse, osteophytes and calcified ligamentum flavum that complicate the application of a central nerve block. In the

current study, we included only patients undergoing general anesthesia. It should therefore be noted that the effects of warming could differ in patients undergoing regional anesthesia because central nerve block application inhibits vasomotor and shivering responses and impairs autoregulation causing thermal redistribution from core to peripheral tissues (25). This dermatomal distribution may further increase the risk of intra- and post-operative hypothermia (26). Future studies that compare the effects of warming in patients undergoing regional or general anesthesia in TURP patients are warranted.

One limitation of this study is that, in control group patients, standard blankets, which are used in routine practice in many services, were used to provide passive warming. Another limitation is that after the prewarming application, cotton blankets were used in the transfer process (about 10 minutes) until the induction of anesthesia.

Conclusion

This study demonstrated that perioperative forced-air warming helped preserve perioperative core body temperature, reduced the incidence of hypotension during the induction period, increased thermal comfort, and improved satisfaction in patients undergoing TURP surgery. Warming may be recommended in patients undergoing TURP surgery.

Ethics

Ethics Committee Approval: The trial was approved by the Ethical Committee of the Ministry of Health Diskapi Yildirim Beyazit Training and Research Hospital in Ankara, Turkey (protocol number: 06/22, date: 17.12.2012).

Informed Consent: All patients gave their written informed consent to participate in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.K.A., J.E., D.Ö., Concept: F.K.A., J.E., D.Ö., İ.B.A., Design: F.K.A., J.E., G.B.A., E.A., Data Collection or Processing: F.K.A., İ.B.A., E.A., G.B.A, Analysis or Interpretation: F.K.A., D.Ö., J.E., E.A., G.B.A., Literature Search: D.Ö., G.B.A., İ.B.A. Writing: F.K.A., J.E., D.Ö., İ.B.A., E.A., G.B.A.

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Early complications of endobronchial lung volume reduction treatment with endobronchial valves

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Keywords: Endobronchial valve, emphysema, COPD, complication

ABSTRACT

Aims: Endobronchial valve (EBV) treatment is one of the main minimally invasive treatment options for emphysema management. In this study, we aimed to evaluate the early term complication rates of patients having severe emphysema and being treated with EBV.

Methods: A total of fifteen patients treated with EBV for bronchoscopic lung volume reduction between November 2017 and January 2019 were included in the study. Pretreatment demographic data, pulmonary function results and exercise capacities were recorded. All complications encountered during the first 3-month period after the EBV treatment were evaluated. The status of collateral ventilation was assessed with Chartis system. Implanted valves were appropriately chosen according to the bronchial lumens' diameter. All patients were discharged after a minimum of 72 hours of observation.

Results: Fifteen bronchoscopic lung volume reduction treatment sessions were performed for fifteen patients. All of them were male. The mean age of the patients was 66.7±6.3 years and the mean disease duration was 11.1±3.7 years. A mean of 3.46 valves were implanted per patient. Early complications were observed in five patients (33.3%) during the 3-month follow-up period after the EBV treatment. Of them, three had chronic obstructive pulmonary disease exacerbation, one had pneumothorax, and the last one had pneumonia. Only one patient died due to the early complications of the valve treatment.

Conclusions: Although the number of patients is small, our study demonstrates that EBV treatment can be safely applied with low complication rates as a bronchoscopic lung volume reduction treatment to the patients that have severe heterogeneous emphysema.

Introduction

Chronic obstructive pulmonary disease (COPD) is a widespread, preventable and treatable disease, characterized by restricted airflow and permanent respiratory tract symptoms originating from airway and/or alveolar abnormalities caused by severe exposure to harmful particles or gases (1). Emphysema, which constitutes the component of COPD other than chronic bronchitis, is a progressive condition characterized by irreversible damage to the alveolar tissue. As a result of permanent airway damage and early collapse in the small airways, air cannot be sufficiently expelled from the lungs in expirium and causes excessive lung ventilation.

The main cause of shortness of breath in patients with emphysema phenotype of COPD is this excess lung ventilation. The effect of current standard treatment approaches on excess lung ventilation is extremely limited. Although lung volume reduction surgery is an effective method in the treatment of emphysema, it is associated with a significant degree of morbidity (20-30%) and increased early mortality (the first 3-month mortality) (7.9%) (2). This has brought the use of bronchoscopic lung volume reduction treatments to the fore, as they have lower morbidity and mortality rates (3). Current studies in literature that have evaluated the efficacy of bronchoscopic lung volume reduction treatment methods have mostly been conducted on the use of endobronchial valves (EBV).

Reduction of hyperinflation of the lungs with EBV treatment is based on the principle of preventing entry in inspirium and drainage by allowing the air in the lungs with emphysema to be expelled in expirium. The aim of this study is to determine the early complications of EBV treatment in cases with advanced heterogenous emphysema.

Methods

The study was approved by the Ethics Committee for the Non-invasive Research at the Gülhane University of Health Sciences Turkey (ID/date: 163/05.04.2019).

Study design

A retrospective analysis was made of patients that applied with EBV for bronchoscopic lung volume reduction treatment in our clinic between November 2017 and January 2019. Approval for the study was granted by the Ethics Committee of Health Sciences University Turkey, Gülhane Training and Research Hospital. The cases selected for treatment were those with Gold Stage 3 and 4 COPD with advanced emphysema. The treatment was applied with Zephyr® EBV (Pulmonx Inc, Redwood City, CA, USA).

To determine the distribution of emphysema, volumetric fine-slice thoracic tomography tests were used. Two target lung lobes were determined in cases who met the study selection criteria for bronchoscopic lung volume reduction treatment. In the determination of the first and second target lobes, quantitative lung perfusion scintigraphy was used. The lung lobes which had the lowest perfusion were determined as the target lobes. For patients who had received a sufficient duration of pulmonary rehabilitation, a record was made of demographic data such as age, gender, body mass index (BMI), duration of disease and smoking status before the procedure, and post-procedure respiratory function test parameters and exercise results were also recorded. Complications that developed in the follow-up period after the treatment of the patients that applied with EBV as bronchoscopic lung volume reduction treatment were also recorded.

Patient selection criteria for EBV treatment

1. Age >18 years
2. Heterogenous emphysema
3. GOLD Stage 3 or 4
4. Expected forced expiratory volume in one second (FEV1) <50%, residual volume (RV) >150%, total lung capacity (TLC) >100%
5. RV/TLC ≥58
6. 6-minute walk test distance <500 m
7. Systolic pulmonary artery pressure <50 mmHg on echocardiography
8. Optimum use of bronchodilator treatment
9. Quitting smoking at least 8 weeks before the procedure
10. To have had pulmonary rehabilitation treatment for at least 6 weeks before the procedure

Treatment procedure

All the cases were hospitalized before the procedure. All the EBV placement procedures were applied in the bronchology unit of our clinic under intravenous total anesthesia, with a flexible bronchoscope (Olympus BF-1TQ180) having a working channel with a diameter of 2.8 mm passed through a laryngeal mask. After the selection of the target pulmonary lobes, whether or not there was collateral ventilation pre-procedure was evaluated with the Chartis system (PulmonX, Redwood City, CA, USA). In cases determined with collateral ventilation in the first target lobe, the Chartis procedure was repeated for the second target pulmonary lobe. The procedure was not applied to patients determined with collateral ventilation with the Chartis system.

In cases with negative Chartis, an EBV (Zephyr TM EBV; Pulmonx Inc., Redwood, CA, USA) was inserted unilaterally in the lobular, segmental or subsegmental bronchi, according to the anatomic status of the case, with the aim of completely isolating the target lobe. The inserted valves were selected to be compatible with airway diameters of 4.0-7.0 mm and 5.5-8.5 mm. Following the procedure, routine postero-anterior chest X-ray was taken immediately in cases with symptoms, and after two hours for those without symptoms. Patients who were stable with no complications were monitored for 72 hours with daily chest X-ray imaging and then discharged with a follow-up appointment at the end of the first week.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) for Mac 20.0 package program (SPSS Inc, Chicago, IL) was used for the statistical evaluation. Data were summarized as the mean and standard deviation for the continuous variables, as absolute value and percentages for the categorical variables.

Results

A total of fifteen cases were applied with fifteen bronchoscopic lung volume reduction treatment procedures. All the patients were male with a mean age of 66.7±6.3 years and mean disease duration of 11.1±3.7 years. A mean of 3.46 valves were placed per patient. The most common site of the procedure was the right superior lobe (n=11). All the characteristics of the study population are shown in Table 1. The mean FEV1 was 0.71±0.24 (0.35-1.35) L, and 26.5%±8.6 of the expected value, TLC was 7.12±0.76 (6.27-8.41) L and 117.1%±15.4 of the expected value, RV was 4.83±0.8 (3.57-6.49) L and 204.9%±38.3 of the expected value, and the RV/TLC ratio was 68.4%±6.6. The mean BODE index (BMI, airflow obstruction, dyspnea, and exercise capacity) was 7.3±1.4 and DLCO (diffusing capacity of the lung for carbon monoxide) was 35.1%±12.4 of the expected value. Complications were determined in five cases in the first 3-month period after the procedure.

Of these, COPD exacerbation was observed in three, pneumothorax in one, and pneumonia in one patient (Table 2). In all the cases who developed COPD exacerbation, the symptoms started in the second week. All these patients were re-hospitalized and treated with bronchodilator and systemic

Table 1. Characteristics of the patients (n=15)	
Variable	**Value±SD/(min.-max.)**
Age, year	66.7±6.3
BMI, kg/m^2	23.4±4.3
Smoking history, pack-years	42.5±6.2
Disease duration, years	11.1±3.7
Lung functions	
FVC, L	2.27±0.6 (1.5-3.3)
FVC, % predicted	65.8±17 (43-96)
FEV1, L	0.71±0.24 (0.35-1.35)
FEV1, % predicted	26.5±8.6 (13-44)
Total lung capacity, L	7.12±0.76 (6.27-8.41)
Total lung capacity, % predicted	117.1±15.4 (101-155)
Residual volume, L	4.83±0.8 (3.57-6.49)
Residual volume, % predicted	204.9±38.3 (155-281)
DLCO, %	35.1±12.4 (21-66)
Arterial blood gas	
pCO_2, mmHg	36.6±5.7
pO_2, mmHg	67.4±15.7
sO_2, %	91.9±5.0
6-minute-walk distance, m	235.5±106.2 (150-483)
mMRC score*	3.5±0.5
CAT	26.5±7
BODE index score†	7.3±1.4
Target lobe, n	
Right upper lobe	11
Right upper + right middle lobe	1
Right lower lobe	1
Left upper lobe	1
Left lower lobe	1
Number of valves, per patient	3.46±0.5
4.0 n,%	25 (48)
4.0 LP n,%	3 (6)
5.5 n,%	24 (46)
Total	52
Hospital stay, days	5.3±2.7 (3-14)

SD: Standard deviation, FEV1: Forced expiratory volume in one second, FVC: Forced vital capacity, CAT: Chronic obstructive pulmonary disease assessment test, DLCO: Diffusing capacity of the lung for carbon monoxide, BMI: Body mass index, LP: Low product, BODE: Body mass index, airflow obstruction, dyspnea, and exercise capacity, mMRC: Modified Medical Research Council, Min.: Minimum, max.: Maximum.
*mMRC dyspnea score scale ranges from 0 to 4, with higher scores indicating more severe dyspnea.
†BODE index score ranges from 0 to 10 based on a multidimensional scoring system to include FEV1, BMI, 6-minute-walk distance, and the mMRC dyspnea score. Higher scores denote a greater risk of mortality.

steroid treatment in accordance with the GOLD guidelines (4). In one of the patients with COPD exacerbation, mortality developed 34 days after the procedure because of respiratory failure. The patient who developed pneumonia presented with complaints of shortness of breath, cough, expectoration of phlegm, and fever after two weeks. Three valves had been placed in the right lung superior lobe of this patient, but the pneumonia was in the right inferior lobe. No agent could be isolated in the mucous and blood cultures, and full resolution was achieved radiologically with appropriate antibiotherapy. In the case that developed pneumothorax, the complaints started 2 hours after the procedure in the form of sudden shortness of breath and chest pain. This patient was the only case where the bronchoscopic lung volume reduction procedure had been applied to the left lung superior lobe, and collateral ventilation was determined in the Chartis procedure in the right-side superior lobe of this patient. On the pulmonary radiograph taken on this patient, almost total left-sided pneumothorax was observed (Figure 1). Drainage was immediately applied by the Thoracic Surgery Department using a 32 French chest tube. Full expansion was obtained rapidly after tube thoracostomy. On the second day after the treatment,

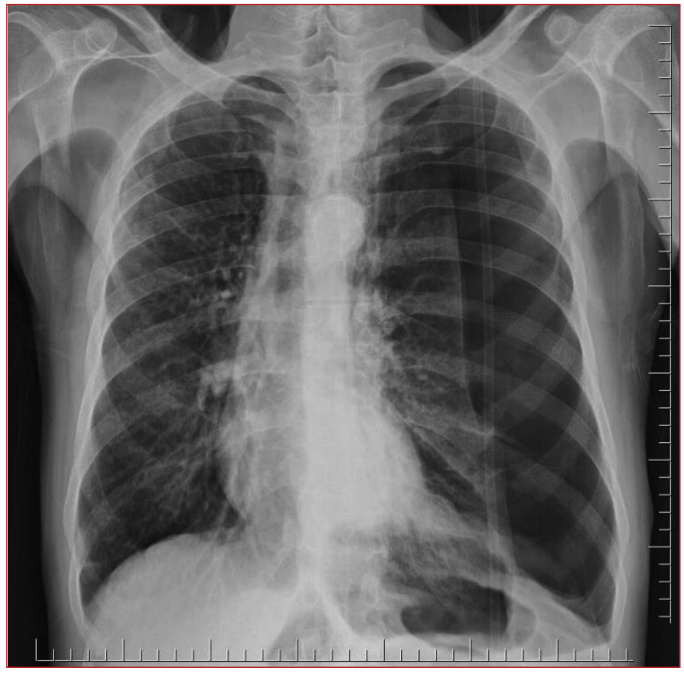

Figure 1. Left pneumothorax two hours after endobronchial valve procedure

Table 2. Serious adverse events during 3 months of follow-up	
Complication	**n (%)**
Pneumothorax	1 (6.7)
Pneumonia	1 (6.7)
COPD exacerbation	3 (20)
Death	1 (6.7)

COPD: Chronic obstructive pulmonary disease

air leakage and subcutaneous emphysema developed. When one week of air leakage had passed, it was planned to remove one of the valves, but on the 8th day, the air leakage was seen to have stopped. The chest tube was removed on the 12th day, and the patient was discharged on the 14th day. On the follow-up pulmonary radiograph taken after 4 weeks, total atelectasis was observed in the left superior lobe (Figure 2).

Discussion

In this study, complications and the frequency at which they developed were determined in the first three months after the application of bronchoscopic lung volume reduction treatment with endobronchial one-way valves to fifteen patients with advanced stage heterogenous emphysema. COPD exacerbation was observed in three patients, pneumonia in one and pneumothorax in one patient.

EBV treatment has been shown to provide significant functional and clinical improvement in patients with advanced stage heterogenous emphysema without collateral ventilation (5-8). In the first 3-month period after the placement of the valve, bronchitis, pneumonia and/or lung infection can develop at the rate of approximately 20% (9). In addition, the most frequently encountered complications related to valve treatment have been reported to be pneumothorax, pneumonia, COPD exacerbation, and valve migration (10,11). Of these, pneumothorax is the most common complication which can develop (20-30%) and is a clinical condition that requires attention (12).

Pneumothorax complication associated with the procedure is often (86%) seen in the first 72 hours, so it is recommended that these patients are kept under observation for a minimum of 72 hours (13). In our clinical practice, patients are hospitalized and monitored for at least 72 hours after an EBV procedure. When examined in general, pneumothorax complication is seen more in-patient groups with a high treatment rate in the left superior lobe. For example, the highest pneumothorax rates have been reported as 29.2% in TRANSFORM studies and 26.6% in LIBERATE studies. The rates of right and left side superior lobe treatment were reported as 8% and 52%, respectively, in the TRANSFORM study, and 6.3% and 66.4%, respectively, in the LIBERATE study (7,8).

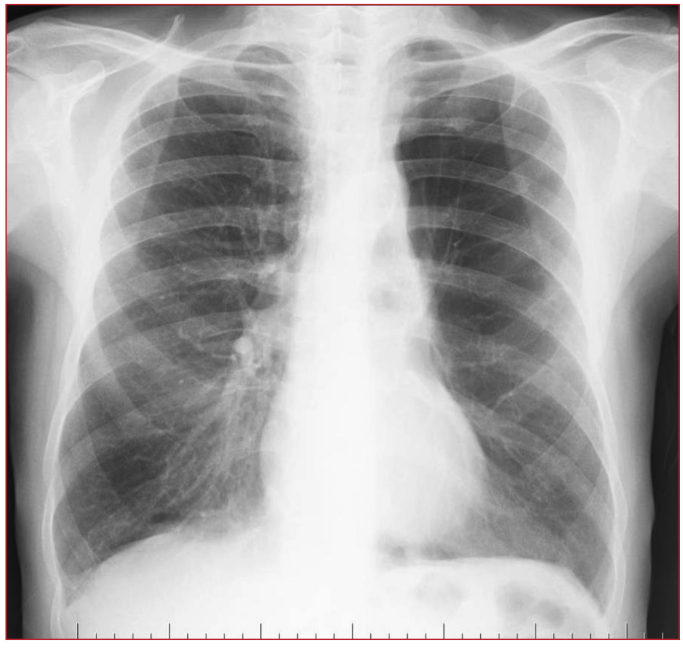

Figure 2. Total atelectasis in the left upper lobe four weeks after endobronchial valve procedure

In a study by Fiorelli et al. (14), 33 patients applied with a total of 36 procedures were followed up for 5 years, and despite left superior lobe treatment in 72%, pneumothorax complication was seen in only 6%. In the current study, pneumothorax developed in only 1 patient (6.7%). The EBV treatment had been in the left superior lobe (6.7%) and the case was treated with tube thoracostomy. On the second day of follow-up, there was seen to be air leakage and subcutaneous emphysema, then the air leakage stopped on the 8th day. This patient was followed up for 12 days with tube thoracostomy, and the case had the longest hospitalization with a total of 14 days in this series.

In patients who develop pneumothorax associated with EBV treatment, when air leakage develops and persists for more than 7 days, it is recommended that one of the valves is removed, preferably the most proximal valve. If the air leakage continues for more than 48 hours despite the removal of one valve, then all the valves must be removed (15). In the current case, as the air leakage stopped on the 8th day, there was no need to remove a valve.

Another frequently seen complication associated with EBV treatment is COPD exacerbation. In the LIBERATE study which was the first, prospective, randomized, controlled study conducted to evaluate the efficacy and reliability of Zephyr® EBV, a total of 190 patients with minimal or no collateral ventilation (128 EBV, 62 standard medical treatment) were evaluated over a 12-month period. The development of COPD exacerbation was reported at the rate of 7.8% in the first 45 days after treatment and at 23% in the subsequent period (8). The highest rate of COPD exacerbation was reported at the rate of 37.8% in the European arm of the VENT study (9). In the current study, COPD exacerbation developed in 3 patients (20%), all within the first 2 weeks. In literature, the mortality rate of patients applied with EBV treatment ranges from 0% to 8% (16,17). In the current study, of the three patients with COPD exacerbation, mortality occurred in one (7.6%) because of respiratory failure 34 days after the treatment.

The rate of pneumonia development in the early period after EBV treatment has been reported as 1.2-18% in previous studies in literature (14). In the current study, pneumonia developed in the right inferior lobe in one patient two weeks after the treatment. However, the EBV treatment had been applied to the right superior lobe in this patient. No agent could be isolated in this

patient, who was then hospitalized and treated with a diagnosis of community-acquired pneumonia. Following the treatment, full resolution was achieved clinically and radiologically. When pneumonia develops in the pulmonary lobe where the valve has been applied, the valve must be removed. However, in the case in this study, as pneumonia developed in a different pulmonary area, it was not deemed necessary to remove the valve.

The main limitation of this study was the low number of cases. However, it can be considered that, with an increased number of cases and range of procedures, the complication rate could be lower.

Conclusion

In conclusion, EBV treatment applied for bronchoscopic lung volume reduction treatment to suitable patients with advanced stage emphysema is a method which can be performed with a low rate of complications.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee for the Non-invasive Research at the Gülhane University of Health Sciences Turkey (ID/date: 163/05.04.2019).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.D., C.T., Concept: D.D., C.T., Design: C.T., Data Collection or Processing: D.D., Analysis or Interpretation: D.D., C.T., Literature Search: D.D., C.T., Writing: D.D., C.T.

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Clinical and radiological evaluation of epilepsy after ischemic cerebrovascular disease

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ABSTRACT

Aims: We aimed to evaluate the onset time, seizure type, response to treatment, etiological causes, electroencephalographic, and radiological features of epileptic seizures that occur after ischemic stroke.

Methods: A retrospective evaluation was performed using the data of 2900 patients admitted to our clinic between October 2016 and June 2019 and diagnosed with ischemic stroke. Those who had epileptic seizures within the first 15 days after ischemic cerebrovascular disease were considered as early-onset seizures (EOS), and those who started on or after day 16 were considered as late-onset seizures (LOS).

Results: The study was conducted on 46 patients who had epileptic seizures after ischemic stroke. EOS were detected in 28 of the patients (60.9%) and LOS in 18 (39.1%). When ischemia etiologies were examined, cardioembolism was found in approximately half of the cases (47.8%). Secondary generalized tonic-clonic seizure (SGTCS) (52.2%) and complex partial seizure (26.1%) were the most common ones in patients. Monotherapy was performed in 39 patients (84.8%) and polytherapy in 7 patients (15.2%). A focal epileptiform anomaly was the most frequent abnormality in electroencephalography. The most common involvement in both EOS and LOS was observed in the cortical and subcortical areas.

Conclusions: EOS were more frequent after ischemic stroke. Cortical and subcortical involvement was the most common in terms of seizures in radiological examination. The most common seizure type was SGTCS. Monotherapy was the most frequent application in the treatment. The most commonly preferred antiepileptic drug was levetiracetam. Antiepileptic drug therapy was found to be effective.

Introduction

The most common disabling disease is stroke and it is the third most common cause of death after coronary heart disease and cancer (1,2). Cerebrovascular diseases (CD) take place in the pathogenesis of epilepsy, especially in older ages, and 45% of epileptic seizures over 60 years of age are a CD (3). Epileptic seizure after hemorrhagic stroke is more common than ischemic stroke (4).

Two or more non-provoked seizures that occurred during the first week after CD were defined as post-stroke epilepsy (PSE) according to the International League Against Epilepsy (ILAE) criteria (5). Seizures that occur in the first 15 days after stroke are classified as early seizures, and those after 16 days are classified as late seizures (5).

Risk factors for developing seizures after CD include hemorrhagic stroke, cardioembolic stroke, cortical location, and multiple cortical involvements (6). In parallel with the increasing elderly population ratio, the increase in ICD patients makes the determination of possible risk factors for the prevention of PSE increasingly important (7).

In our study, we aimed to determine the clinical and radiological features and risk factors of seizures and to evaluate the relationship with seizure prognosis in early and late epilepsy patients after ischemic cerebrovascular disease (ICD).

Methods

This retrospective study was approved by the Non-Interventional Ethical Committee of Ankara Liv Hospital (no: 001-2019/003). Between October 2016 and June 2019, 2900, in patients who were admitted to the emergency department at the first 24 hours of neurological symptoms, the ischemia was diagnosed retrospectively. The data of the patients were taken from the hospital follow-up files. Patients who were diagnosed with acute ischemic stroke and who had epilepsy for the first time during the first year of follow-up were included in this study. The exclusion criteria included having pre-stroke seizure, hemorrhagic stroke, cerebral venous thrombosis, brain tumor and metastasis, cranial operation, neurological (such as multiple sclerosis) and metabolic abnormalities (hypoglycemia, ketotic or nonketotic hyperglycemic coma, hyponatremia, alcohol intoxication, hypocalcemia) and chronic systemic diseases (liver and kidney failure, cancer). Two or more non-provoked seizures that occurred one week after ICD were defined as PSE according to the ILAE criteria (5). Seizures that occur in the first 15 days after ICD are classified as early seizures, and those that occur after the 16th day are classified as late seizures (5).

Non-contrasted brain computed tomography and magnetic resonance imaging records of the patients, which were obtained within the first 24 hours after admission to the emergency room, were retrospectively evaluated by a neuroradiologist with more than five years of clinical experience. Radiological diagnosis of acute infarction would be made when the lesion was hyperintense on diffusion weighted imaging and was iso or minimal hyperintense on the T2 sequence.

Localization of lesions was recorded as; both cerebral, cerebellar hemispheres and brainstem, cortical-subcortical, basal ganglia (deep gray matter, internal capsule, periventricular white matter), cerebellum and brainstem. Lesion numbers were determined as single or multiple.

The antiepileptic drugs used by the patients were divided into two groups as monotherapy and polytherapy according to the treatment.

The prognosis was evaluated in three groups according to the frequency of seizures after the treatment. These three groups included those without seizures, those with more than 50% reduction in the frequency of seizures, and those with less than 50% reduction in the frequency of seizures after the treatment.

Statistical Analysis

SPPS-16 package program was used for Statistical Analysis. Descriptive statistical methods were used in the evaluation of the data, mean±standard deviation was used in the analysis of numerical data, and number (n) and % expressions were used in the analysis of categorical data. While comparing binary groups with numerical parameters, an independent t-test was used, and a chi-square test was employed to compare categorical data. $p<0.005$ value was considered as statistically significant (8).

Results

Eighteen of the patients were female (39.1%), and 28 were male (60.9%). The mean age of the patients was 63.72±13.50 years (29-90 years). There was no difference between genders in terms of mean ages (Table 1). Early-onset seizures (EOS) were detected in 28 (60.9%) of 46 patients with ischemic stroke in the study, and 18 late-onset seizures (LOS) were detected (39.1%). While the rates of men and women were equal in those with EOS, 77.8% (n=14) of patients with LOS were men. There was no statistical difference between genders in terms of seizure onset time (p=0.056).

When ischemia etiologies were examined, cardiac embolism was found in approximately half of the cases (n=22, 47.8%). While large arterial atherothrombosis was present in 32.6% (n=15) of the cases, 19.6% (n=9) had small artery occlusion.

When the risk factors of the patients were evaluated, hypertension (HT) was detected in 29 (63.0%) patients, atrial fibrillation in 22 (47.8%) patients and diabetes mellitus in 20 (43.5%) patients. The smoking rate was 30.4% (n=14) and the rate of hypercholesterolemia was 28.3% (n=13).

Considering the localization of the lesions, while the most common involvement in both EOS and LOS was in the cortical-subcortical area (78.6% and 72.2%, respectively), LOS were found more in those with basal ganglion involvement, and EOS in those with cerebellum involvement. There was no statistical difference between localization and time of onset of seizures.

When the number of ischemic lesions was examined, there was more than one lesion, especially in patients with LOS (p=11, 61.1%). Ischemic lesions were present in both hemispheres of the brain in 17.4% (n=8) of the patients. In more than half of the patients with EOS, the lesion was on the unilateral right side (n=16, 57.1%).

While secondary generalized tonic-clonic seizure (SGTCS) (52.2%) and complex partial seizure (26.1%) were the most common types in patients, followed by simple partial seizure (8.7%) and non-convulsive status epilepticus (SE) (8.7%), the most common seizure type in patients with EOS was SGTCS, and it constitutes 60.7% of seizure types. There was no statistically significant difference between seizure onset time and seizure types (p=0.479).

The most common finding in electroencephalogram (EEG) was focal epileptic abnormality (FEA) (45.7%). EEG results of 5 patients were evaluated as normal. The most common EEG finding in patients with EOS was FEA (53.6%), while the most common EEG finding in LOS was focal slow wave. No significant

Table 1. Demographical and clinical data of patients with post-stroke epilepsy

Variables (n=46)		Seizure time						p
		EOS (n=28)		LOS (n=18)		Total (n=46)		
		n	%	n	%	n	%	
Gender	Female	14	50.0	4	22.2	18	39.1	0.056
	Male	14	50.0	14	77.8	28	60.9	
Etiology	Atherothrombosis	9	32.1	6	33.3	15	32.6	
	Small arteries occlusion	6	21.4	3	16.7	9	6.19	0.923
	Cardiac embolism	13	46.4	9	50.0	22	47.8	
Localization	Cortical-subcortical	22	78.6	13	72.2	35	76.1	0.622
	Basal ganglia	6	21.4	7	38.9	13	28.3	0.199
	Brainstem	-	-	1	5.6	1	2.2	0.207
	Cerebellum	6	21.4	1	5.6	7	15.2	0.144
Side	Right	16	57.1	8	44.4	24	52.2	
	Left	7	25.0	7	38.9	14	30.4	0.594
	Bilateral	5	17.9	3	16.7	8	17.4	
Number of lesions	Single	14	50.0	7	38.9	21	45.7	0.551
	More than one	14	50.0	11	61.1	25	54.3	
EEG result	Normal	3	10.7	2	11.1	5	10.9	
	FSW	8	28.6	8	44.4	16	34.8	0.659
	CSW	10	35.7	5	27.8	15	32.6	
	FEA	15	53.6	6	33.3	21	45.7	
Seizure type	SGTCS	17	60.7	7	38.9	24	52.2	
	CPN	7	25.0	5	27.8	12	26.1	
	SPS	1	3.6	3	16.7	4	7.8	0.479
	NCSE	2	7.1	2	11.1	4	7.8	
	SE	1	3.6	1	5.6	2	4.3	
Treatment	Monotherapy	25	89.3	14	77.8	39	84.8	0.407
	Polytherapy	3	10.7	4	22.2	7	15.2	
Medication	LEV	21	75.0	8	44.4	29	63.0	0.036
	CBZ	6	21.4	6	33.3	12	26.1	0.370
	VA	3	10.7	2	11.1	5	10.9	0.966
	OXC	1	3.6	6	33.3	7	15.2	0.006
Risk factors	HT	20	71.4	9	50.0	29	63.0	0.142
	DM	11	39.3	9	50.0	20	43.5	0.474
	HL	8	28.6	5	27.8	13	28.3	0.953
	SM	8	28.6	6	33.3	14	30.4	0.732
	AF	13	46.4	9	50.0	22	47.8	0.813
Prognosis	Seizure-free	21	75.0	10	55.6	31	67.4	
	Seizure decreased by more than 50%	3	10.7	7	38.9	10	21.7	0.068
	Seizure decreased by less than 50%	4	14.3	1	5.6	5	10.9	

EOS: Early-onset seizure, LOS: Late-onset seizure, FSW: Focal slow wave, CSW: Common slow waves, FEA: Focal epileptic abnormality, SGTCS: Secondary generalized tonic-clonic seizure, CPS: Complex partial seizure, SPS: Simple partial seizure, SE: Status epilepticus, NCSE: Non-convulsive SE, LEV: Levetiracetam, CBZ: Carbamazepine, VA: Valproic acid, OXC: Oxcarbazepine, HT: Hypertension, DM: Diabetes mellitus, HL: Hyperlipidemia, SM: Smoking, AF: Atrial fibrillation

Table 2. Treatment management of patients with post-stroke epilepsy

Medicines	The number of drugs		n	%	p
LEV	Monotherapy (n=39)	No	17	43.6	0.028
		Yes	22	56.4	
	Polytherapy (n=7)	No	-	-	
		Yes	7	100.0	
CBZ	Monotherapy	No	30	76.9	0.272
		Yes	9	23.1	
	Polytherapy	No	4	57.1	
		Yes	3	42.9	
VA	Monotherapy	No	36	92.3	0.102
		Yes	3	7.7	
	Polytherapy	No	5	71.4	
		Yes	2	28.6	
OXC	Monotherapy	No	34	87.2	0.285
		Yes	5	12.8	
	Polytherapy	No	5	71.4	
		Yes	2	28.6	

LEV: Levetiracetam, CBZ: Carbamazepine, VA: Valproic acid, OXC: Oxcarbazepine

difference was found in seizure onset time among patients with EEG abnormalities (p=0.659).

Monotherapy was performed in 39 patients (84.8%) and polytherapy in 7 patients (15.2%). Three (10.7%) of patients undergoing polytherapy had EOS, and 4 (22.2%) had LOS. There was no significant relationship between the number of drugs used and the seizure of EOS or LOS (p=0.407) (Table 2).

When the drugs used by the patients were examined, it was observed that levetiracetam (LEV) (63.0%) was used mostly. In patients using a single medication, 56.4% (n=22) used LEV while all patients receiving polytherapy had LEV usage.

Seizure recurrence was not observed in 31 of the patients (67.4%). While more than 50% reduction in seizures of 10 patients (21.7%) were achieved, improvement in seizure recurrence of 5 patients (10.9%) was less than 50%.

Discussion

This study showed that different types of epileptic seizures occur as a complication of ICD. Cardiac embolism and atherothrombosis were found to be the most common etiology of ICD, and HT was the most common risk factor. Epileptic seizures were frequently associated with ischemic involvement with cortical-subcortical localization. Focal seizures were the most common after ICD.

In large epidemiological studies from the literature, the most common cause of partial and generalized seizure etiology has been shown as cerebrovascular disease (9). It showed different rates, such as 35%, 48%, and 54% for early seizures after stroke (10-12). In one study, the rate of seizures seen in a year after stroke was 3.4%, while 56% of patients had an early onset partial character and 72% of late seizures were observed as generalized tonic-clonic features (13). In our study, EOS were detected in 28 (60.9%) of 46 patients with ischemic stroke, and late-onset were detected in 18 (39.1%).

In a study by Barańska-Gieruszczak et al. (14), 483 cases who had epileptic seizures after stroke were evaluated and it was reported that early seizures were commonly generalized and less frequently simple partial. In our study, the most common seizure type in those with EOS was SGTCS.

In the study of Burneo et al. (15), no statistically significant difference was found between the presence of seizures and age. In our study, there was no statistically significant difference in terms of gender (p=0.056), seizure onset time, and age (0.690).

Although they did not find a significant relationship between cortical involvement and EOS in the Copenhagen stroke study, some authors showed a significant relationship between EOS and cortical involvement (16). In our study, considering the localization of the lesions, while the most frequent involvement in both EOS and LOS was in the cortical-subcortical area (78.6% and 72.2%, respectively), LOS were found more in those with basal ganglion involvement, and EOS were more common in those with cerebellum involvement.

It was reported in the literature that SE after serious stroke was more common, and in the early period (17). In our study, the SE case was seen at both one early and one in the late period.

While the prognosis of epileptic seizures developing after a stroke is well accepted, the response to monotherapy is generally good. In the literature, this rate was reported to be 88% in one study (18). In our study, 39 (84.8%) patients were treated with monotherapy, 7 (15.2%) were treated with polytherapy, and 31 (67.4%) of them had no recurrence of seizures during the follow-up.

LEV, which is one of the new antiepileptics, has been the most preferred antiepileptic in terms of side effects and tolerability considering the patient's average age. In our study, the most commonly used antiepileptic drug was LEV (63.0%), while carbamazepine and valproate were preferred less.

In our study, the group evaluated was intended to be more homogeneous, and we have evaluated ischemic stroke and seizure association from the cerebrovascular disease group. The limitations of this study were as follows; the study was retrospective, and the number of patients was small.

Seizures may be seen in the early and late periods associated with ICD. Although the seizures observed during the course of ICD are frequently focal seizures, SE (convulsive and non-convulsive) with high mortality and morbidity can also be seen. Generally, ICD patients are from the elderly population. Early

diagnosis of epileptic seizures and rapid initiation of appropriate treatment are very important in terms of prognosis.

Nevertheless, there were some limitations to our study. Firstly, this retrospective study may lead to the possibility of selection bias, and the lack of a control group was limiting the strength of the current analysis. Secondly, the study population was small, and a larger sample size could be better to find the prognosis of PSE.

Conclusion

As a result, in societies where life expectancy is longer and the elderly population is increased, the importance of ICD related seizures has increased due to its effect on mortality and morbidity. Some data obtained from the studies were found different from each other. These differences may be due to the study design, selected patient subgroups, and non-standard parameters examined. Randomized, double-blind, placebo-controlled, long-term, multicenter studies with large patient groups are needed to fully reveal the frequency, types, treatment responses, and prognosis of epileptic seizures after ICD.

Ethics

Ethics Committee Approval: This retrospective study was approved by the Non-Interventional Ethical Committee of Ankara Liv Hospital (no: 001-2019/003).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.Ö.Ö., Design: A.Ö.Ö., Data Collection or Processing: A.Ö.Ö., Analysis or Interpretation: A.Ö.Ö., F.C., Literature Search: A.Ö.Ö., F.C., Writing: A.Ö.Ö., F.C.

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Dilemmatic presentation of hemangioma of the lip: A short case report

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ABSTRACT

The hemangioma is a hamartomatous proliferation of endothelial cells that are present at birth or can develop during the neonatal period. They pose a diagnostic dilemma when they develop in adults. This is a short case report of a case of a 21-year-old female patient presenting with a polypoid mass on the upper lip of 3 weeks duration, which was diagnosed as capillary hemangioma on histopathologic examination.

Introduction

Hemangioma is one of the most common hamartomatous growth in the orofacial region. It is mainly seen in infants and children although it is also observed in middle-aged and elderly individuals (1). However, denovo appearance of capillary hemangioma is a very rare occurrence in adults. We hereby report a case of capillary hemangioma of the lip in a female patient aged 21 years, which posed a diagnostic dilemma due to its uncommon presentation.

Presentation of Case

A 21-year-old female patient presented with the complaint of growth on the left side of the upper lip with 3 weeks duration. Her medical history revealed that it started as a white pinhead sized papule. As the patient was concerned about this, she made multiple attempts to rupture it with fingernails which traumatized the lesion and resulted in minimal bleeding. The lesion then slowly grew and attained the current size. There were no prodromal symptoms or pain associated with the lesion. General examination of the patient did not reveal any abnormalities. On examination of the lip, a well-defined reddish exophytic growth measuring about 0.4*0.6 cm was seen on the left side of the upper lip (Figure 1). The surface of the lesion was covered with scabs. The surrounding tissue appeared normal. It was firm, fixed and untender. Diascopy test was negative. As the features of the lesion did not match any of the known lesions and due to esthetic concern, an excisional biopsy was planned and performed by a plastic surgeon. Bleeding encountered during excision was minimal. On histopathological examination, it showed stratified squamous epithelium with underlying vascular lesion comprising of lobules of proliferating capillary sized vessels. The vessels were lined with plump endothelial cells and an intact smooth muscle layer. The lobules were separated by thin fibrous septa suggestive of capillary hemangioma (Figure 2). The patient was recalled periodically and no recurrence was observed for 18 months.

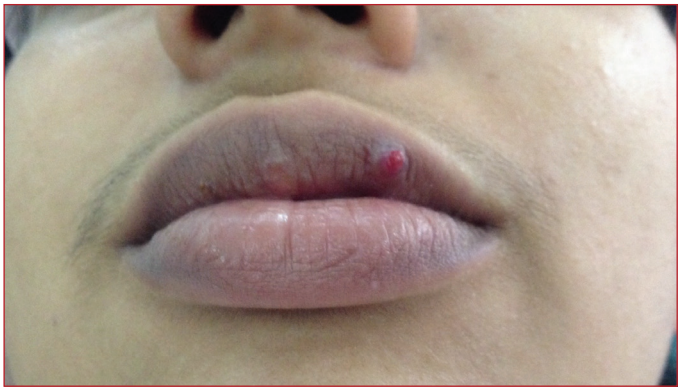

Figure 1. Well-defined reddish exophytic growth on the upper lip

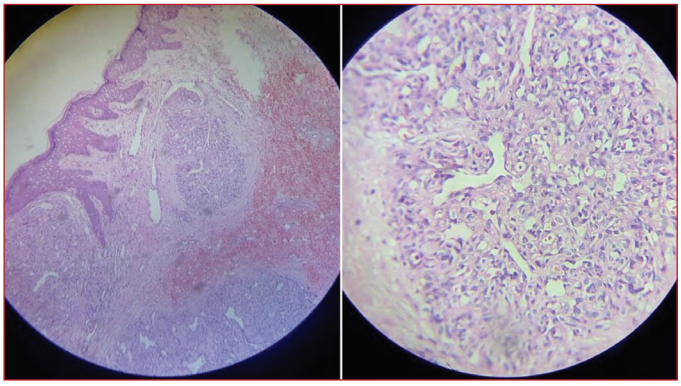

Figure 2. H&E stained sections showing stratified squamous epithelium with underlying vascular lesion comprising of lobules of proliferating capillary sized vessels lined with plump endothelial cells

Discussion

The lip is the most common site for the occurrence of many sorts of vascular lesions probably due to the fact that lip has relatively good blood supply owing to the presence of large blood vessels approximating the surface at this location than the other parts, and that the lip is often subjected to traumatic insults (1). The hemangioma is a benign hamartomatous proliferation of endothelial cells commonly seen in the head and neck region. Hemangiomas are either present at birth or can develop during the neonatal period. These lesions are three to five times more common in females (2). It is quite uncommon to see hemangiomas arising denovo in adults and hence it poses a diagnostic challenge.

The hemangioma clinically presents as a softer, smooth or lobulated, pedunculated or sessile mass, its size may vary from a few millimeters to several centimeters, and the color may vary from pink to red-purple. They are generally painless. They are firm and rubbery to palpation (3).

Although capillary hemangioma presents as an asymptomatic lesion, its location and size may demand immediate intervention. It usually presents a diagnostic challenge to the clinician. Lesions like pyogenic granuloma may also present at such locations, but is a rare occurrence without any history of chronic irritation (4). The biopsy of such lesions is mandatory for establishing a definite diagnosis. Most importantly, the surgical excision of capillary hemangioma should be performed by considering the intra-operative and postoperative bleeding (2). The factors which direct the management of hemangiomas include the patient's age and the extent and size of the lesions, also the clinical characteristics (5). The lesions of lip may be of aesthetic concern and surgical excision is a treatment option to be considered as it also provides good esthetic and functional outcome (2). The prognosis of hemangioma, in general, is excellent since it does not tend to recur or undergo malignant transformation following adequate treatment (5). No recurrence was observed in our case as well.

Conclusion

Hemangiomas, though they are common lesions, may pose a diagnostic challenge due to its uncommon presentations. Oral physicians should be aware of variety of manifestations of such lesions to avert medical emergencies.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: V.A.H., Concept: R.R.K., A.D.D., Design: R.R.K., A.D.D., Data Collection or Processing: R.R.K., A.D.D., V.A.H., Analysis or Interpretation: R.R.K., R.K., P.K.R., Literature Search: R.R.K., R.K., P.K.R., Writing: R.R.K., R.K, P.K.R.

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CONTENTS

REVIEW

ORIGINAL ARTICLES

CASE REPORT