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Family doctors and European definition may disappear in Italy

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Keywords: General practice; family medicine; European family doctor; EURACT

One of the disturbing implications hidden in the new indicative Italian Laws about Primary Care is that the WONCA – EURACT European Definition of General Practice may disappear. Even the concept of personal care is put under question.

At first reading, the government draft shows a dangerous picture for both doctors and patients. In recent months many people tried to divide doctors between H16 and H24, but it is curious to note how the much more worrying deletion of the words "Family Medicine" (replaced with a generic "Primary Care") passed over in silence. In practice it is as if tomorrow the Italian Republic is simply called Italy in official acts.

This simple change of a word could change the target of primary care. This is already suggested in the draft of Article 22 of the Health Pact, with the proposal for the institution of a Postgraduate School in Community Medicine and Primary Care, while trying to abolish the three years of formation (never recognized as real School of Specialization) in Family Medicine/General Practice.

These initiatives may indicate an intention to shift from a system of primary care aimed at the care of single individuals and their families, to a reductionist concept of primary care for a community of people.
It is not surprising that the draft document indicates that primary care should have some perhaps absurd purposes: such as reducing access to the emergency rooms or the achievement of district local goals. I naively ask: why do not you put in an objective simply about curing people?

Also it should be noticed that from the National Contract is removed the recognition of professional training for Primary Care according to the principles expressed by the European Definition of General Practice / Family Medicine by WONCA Europe (the European branch of the World Association of Family Physicians), which instead it was present in the previous agreement of 2005.

One of our trainees wrote in Internet that he wanted to become an "European Family Doctor": this could be difficult when the draft political Contract states that he can become a primary care doctor operating on selected cycles, or operating on an hourly basis. And he says he is unhappy about the term itself, recalling the programmes for laundry (the colored garments cycle, and the timer for time programming). This similarity in terminology made me remember the "doctors as obedient washing machines" theorized by Prof. Ivan Cavicchi [1].

Italian primary care physicians are worrying about this Contract: in fact the doctor representative of Local Medical Aggregations will be a sort of Head, who,

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appointed by the Administrative Director General (a political nomination), may bring against his colleagues minor disciplinary measures inappropriately, mainly concerning very strict guidelines and even merely bureaucratic matters.

Finally, the text include tragicomic aspects such as paragraph d) article 1 of Annex 2 which reads: the doctor will ‘‘refrain from participating in the performance of their functions, decision-making or activities which may involve direct or indirect financial or non-financial interests own, and of the spouse, relatives and relatives up to the fourth degree and life partners’’.

So being the general practitioners in clinical work from 08:00 am to 08:00 pm will make it impossible to even attending banks and the post offices remain open only during the day.

Our trainee told us that his girlfriend has already commented that perhaps now it is better to postpone their wedding. He wonders whether it is a tactic to keep him paying his and her bills. Or if she, having already one washing machine at home, thinks that another one will be useless.

Our NHS on dismantling

We have 20 Regional Councils, but only some of them ‘‘organize’’ specific Courses for GP Trainees. In many Regions General Practitioners are obliged to try to enter through the closed number taking only a general MCQ text on all clinical matters. Here there is no vocational control and interview at all. The system would be vulnerable to, for example, failed oculists trying to enter this way and taking the place of possible vacated future GPs.

Also some Regional Councils have promulgated a concourse as medical head of the ‘‘3 years of specific course forming in general practice’’ with clauses totally out the European Definition, the EURACT Educational Agenda, the EURACT Statements of Specialist Training, the EURACT Statement on Minimum Core Curriculum.

Also, the persons, just to be candidates, must work full time as regional practitioners accepted in the Regional Health System, and have to agree by written declaration, to all issues and decisions taken from the Regional Council (not made by doctors). They further have to control, as first line, that teaching would consider at first all the assets, regulations and “change’’s in resources. Implicitly, this may be accepting what really is against patients’ interests and health protection.

To summarize, 3 pages are attached to the concourse announcement on this Regional Bulletin with a list of unusual aspects and law references (in reality it is just a sequence of numbers) and dates as found in the Regional Council Law Journal. Duties for the perfect and ideal Head of the 3 years Specific Course include no real reference to the European Statements and book lists.

The same processes affect undergraduate work as only GPs full time will be possible lecturers, a disposition understandable only for tutors teaching in their practices.

Lectures on core competences and similar are considered unimportant in this kind of context. This is built implicitly through public concourses with pages of citations of decisions and ratifications taken by administrative clerks in NHS and the Regional Health System. So, also reducing about teaching , the creative step, the Health System is really going, silently and progressively, to be dismantled as critiqued by Chris van Weel and Clare Gerada and myself in an internationally cited paper published on British Journal of General Practitioners not too long time ago [2].

This paper already has indicated that global medicine education is under danger for many reasons and different ways in so many different countries, with results that are similar. Departments close, courses close or number of students and trainees is reduced. Our Health System and Medical Education as first step in quality for future doctors are under changes that are not under doctors’ control (not to say from students and patients). This is mainly for economic reasons because medicine costs growing more and more in the years (older population asking for more expensive sophisticated exams, etc.), also because of external economic groups looking to enter creating own market, making profit, possible when cutting everywhere and pushing to teach that this has to be called ‘‘appropriateness’’. Will be doctors able to survive at the level of European Definition and save education common principles and medicine principles of solidarism and universality?

Conflict of interest

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

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References

[1] Cavicchi I. Medici di base: eliminiamo i privilegi ma salvaguardiamo il sistema. 15 settembre 2015. http://www.ilfattoquotidiano.it/2015/09/15/medici-di-base-eliminiamo-i-privilegi-ma-salvaguardiamo-il-sistema/2033435/. Accessed: October 18, 2016.
[2] Van Weel C, Carelli F, Gerada C. Reforming primary care: innovation or destruction? Br J Gen Pract 2012;62:43-4.

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Original Article

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Effects of lithium chloride and methylprednisolone on experimental spinal cord injury

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ABSTRACT

Objectives. Antioxidant effects of lithium chloride (LiCl) and methylprednisolone were investigated in an experimental spinal cord injury. ***Methods.*** Spinal cord injury was performed by cerebral vascular clip with a closing force of 40 g; the duration of epidural compression was 30 seconds after T9-11 total laminectomy in the rat spine. The study was conducted in 4 groups. Group 1: sham (n=8), group 2: 0.9% saline (n=8), group 3: LiCl (n=8), group 4: methylprednisolone (n=8). Ketamine (60 mg/kg) and 2% xylazine (5 mg/kg) were used intraperitoneally as anesthesia protocol for the groups. The rats were sacrificed 24 hours after the injury and blood samples were taken. Total oxidant status (TOS), total antioxidant status (TAS), malondialdehyde (MDA) and tumor necrosis factor-α (TNF-α) level were analyzed. ***Results.*** Median (q1-q3) levels of TAS, TOS, MDA and TNF-α were statistically analyzed for the study groups. The TAS values of LiCl yielded statistically significant differences compared with group 1, 2 and 4 ($p<0.05$). The MDA values of LiCl and methylprednisolone groups were found to significantly differ between the sham and saline groups ($p<0.05$). There were no statistical differences between the study groups for the TNF-α and TOS values ($p>0.05$). ***Conclusions.*** LiCl seems to be an effective drug for experimental spinal cord injuries.

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Keywords: Spinal cord injury; experimental; treatment; lithium chloride; methylprednisolone

Introduction

Lithium chloride (LiCl) is used for the treatment of bipolar affective disorder [1, 2]. Treatment results of patients with spinal cord injury are still poor despite various treatment approach and efforts. The aim of the entire treatment effort is to prevent secondary tissue damage [3-5]. There are reports suggesting that LiCl protects the cultured neurons against glutamate-induced excitotoxicity and apoptosis mediated by N-methyl-D-aspartate (NMDA) receptors [6]. It has also been reported that pretreatment with LiCl inhibits

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Ca^{+2} influx into the cultured cerebellar granule cells by approximately 50% [6]. This study aims to evaluate the antioxidant effect of LiCl on experimental spinal cord injury.

Methods

The ethical committee of the Osmangazi University School of Medicine, Eskisehir, Turkey, approved the study. Male and female adult Spraque Dawley rats (250–350 g) were randomly assigned to four experimental groups (n=8 each): Group 1 (sham), laminectomized but without spinal cord injury or treatment; Group 2 (saline), spinal cord injury with 0.9% saline treatment; Group 3 (LiCl), spinal cord injury with 50 mg/kg lithium chloride treatment; and, Group 4 (methyl prednisolone), spinal cord injury with 30 mg/kg methylprednisolone treatment. Spinal cord injury was performed following T_9–T_{11} total laminectomy using a cerebral vascular clip, (closing force 40 g, epidural compression duration 30 seconds). Saline, lithium chloride or methylprednisolone was given intraperitoneally one hour after the trauma. Ketamine (60 mg/kg) and 2% xylazine (5 mg/kg) were administered intraperitoneally to induce anesthesia in all groups. The rats were euthanized 24 hours after spinal cord injury and blood samples were obtained for biochemical analysis. Total oxidant status (TOS), total antioxidant status (TAS), malondialdehyde (MDA) levels and tumor necrosis factor-α (TNF-α) levels were measured using commercially available assays. The TOS value was expressed in μmol H2O2 Eq./l, the TAS value was expressed in mmol Trolox Eq./l, and the TNF-α level value was expressed in pg/ml.

MDA levels were determined using the method of Ohkawa et al. [7]. Briefly, 0.5 ml plasma was mixed with 0.2 ml of 8.1% sodium dodecyl sulfate, 1.5 ml of 20% acetic acid (pH 3.5), and 1.5 ml of 0.8% thiobarbituric acid, and heated at 95 °C for 60 minutes. After cooling, 5 ml n-Butanol/Piridin (15:1 v/v) was added and the samples were centrifuged at 4000 rpm for 10 minutes. The supernatant was collected and the absorbance at 532 nm was measured using a Shimadzu UV-1201 spectrophotometer (Shimadzu Corp, Japan). The MDA level was calculated using 1,1,3,3-tetra-ethoxy-propane as a standard and was expressed in nmol/ml.

Statistical Analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA). Variables were expressed as median (25^{th} percentiles-75^{th} percentiles). Comparisons of continuous variables between the groups were performed using the Kruskal Wallis one-way analysis of variance and Dunn's Post Hoc test and using a Bonferroni t test with a corrected p value of 0.05/4. A two-sided $p<0.05/4$ was considered statistically significant.

Results

We compared the effects of lithium chloride and methylprednisolone in an experimental spinal cord injury model. Multiple measures of oxidative or inflammatory status, including TOS, TAS, and the levels of MDA and TNF-α were studied. Median TOS values were not significantly different between the treatment groups (Table 1) ($p=0.463$). Median TAS values, however, were significantly reduced in the lithium-treated rats (Table 2) ($p<0.001$). Both LiCl and methylprednisolone treatments lowered the median levels of MDA, a marker of lipid peroxidation, relative to the control and sham groups (Table 3) ($p<0.001$). There were no statistically significant differences between the TNF-α levels of the treatment groups (Table 4) ($p=0.574$).

Table 1. TOS values (μmol H_2O_2 Eq./l) for the groups

Groups	TOS	Median (q1-q3)	*p*
Sham (n=8)	11.43	8.32-19.07	
Control (n=8)	21.72	5.6-35.44	0.463
Lithium (n=8)	8.23	5.26-13.32	
Methylprednisolone (n=8)	8.57	6.40-18.15	

TOS= total oxidant status

Table 2. TAS values (mmol Trolox-Equ./l) for the groups

Groups	TAS	Median (q1-q3)	*p*
Sham (n=8)	1.25	1.16-1.33	
Control (n=8)	1.39	1.20-1.58	<0.001[a, b, c]
Lithium (n=8)	1.06	0.99-1.11	
Methylprednisolone (n=8)	1.23	1.13-1.37	

TAS=total antioxidant status, [a]There is significant difference between Lithium and Methylprednisolone groups, [b]There is significant difference between Lithium and Sham groups, [c]There is significant difference between Lithium and Control groups

Table 3. MDA values (nmol/ml) for the groups

Groups	MDA	Median (q1-q3)	*p*
Sham (n=8)	1.50	1.40-1.65	
Control (n=8)	1.85	1.65-1.90	<0.001[a, b]
Lithium (n=8)	1.00	0.85-1.16	
Methylprednisolone (n=8)	1.20	1.10-1.45	

MDA= malondialdehyde, [a]There is significant difference between Lithium and Sham groups, [b]There is significant difference between Lithium and Control groups

Table 4. TNF-α values (pg/ml) for the groups

Groups	TNF-α	Median (q1-q3)	*p*
Sham (n=8)	45.88	36.65-69.06	
Control (n=8)	54.19	26.79-75.41	0.574
Lithium (n=8)	30.81	25.99-62.79	
Methylprednisolone (n=8)	40.27	28.61-54.32	

(TNF-α)=tumor necrosis factor-α

Discussion

Methylprednisolone is used to treat a variety of neurological disorders involving white matter injury, including multiple sclerosis, acute disseminated encephalomyelitis, and spinal cord injury [8-11]. LiCl is used to treat to bipolar affective disorder, and schizophrenia [1, 2, 12].

Boku *et al.* [13] reported that LiCl and glucocorticoids affected adenosine diphosphate (ADP) proliferation, which is regulated by glycogen synthase kinase 3 beta (GSK-3β) and β-catenin/T-cell factor (TCF) pathways. Young [14] reported that chronic administration of LiCl increased the levels of neurotropic factors in the brain. LiCl stimulates not only regeneration but also neurogenesis both in-vitro and in-vivo. LiCl causes new neurons to be produced in both injured and uninjured hippocampus. The mechanism appears to involve Wnt/β-catenin signaling pathway. LiCl is also described as a potent neuroprotective agent [14]. Dill *et al.* [15] reported that the administration of GSK-3β inhibitors may facilitate the development of an effective treatment to white matter injuries including spinal cord trauma given the wide use of lithium in humans and that the inactivation of GSK-3β promotes axonal growth and recovery in central nervous system.

Lee *et al.* [9] demonstrated in-vivo (spinal cord injury in rat), and in-vitro that methylprednisolone reversed AMPA-(alpha-amino-3-hydroxy-5-methylisoxazole-4 propionate) induced decreases in the expression of antiapoptotic Bcl-xL, caspase-3 activation, and DNA fragmentation in oligodendrocyte by the glucocorticoid receptor, and not by neurons. These protective effects were inhibited by the glucocorticoid receptor antagonists: mifepristone (RU486) and small interfering RNA (siRNA). Bailly Maitre *et al.* [16] reported that the same antiapoptotic effects were seen in human and rat hepatocyte cultures by dexamethasone. Methylprednisolone (30 mg/kg, iv) used in an in-vivo rat study. The spinal cords were

examined 24 hours after the spinal cord injury for molecular sign of apoptosis. Methylprednisolone was found selectively to attenuate oligodendrocyte cell death and demyelination [9].

Xu *et al.* [11] demonstrated that methylprednisolone selectively inhibits oligodendrocyte death via glucocorticoid receptor and upregulates the expression of B-cell lymphoma-extra large (Bcl-xL). They also found that signal transducer and activators of transcription 5 (STAT5) plays a key role in mediating the protection of oligodendrocytes by the methylprednisolone/glucocorticoid receptor signaling pathway. However, the subsequent molecular cascades underlying the upregulation of Bcl-xL remained unknown. It has been reported that methylprednisolone upregulates the expression of Bcl-xL via direct binding of the glucocorticoid receptor /STAT5 complex on the putative STAT5 binding site [11]. Antiapoptotic Bcl-xL is seated on the outer membrane of mitochondria, which include intrinsic apoptotic pathway, thus provide maintenance of membrane integrity [17]. Nesic-Taylor *et al.* [18] suggested that antiapoptotic Bcl-xL has an important role on adult neural cells, which promote neuronal survival. Cittelly *et al.* [19] reported that phosphorylation of Bcl-xL is a proapoptotic event in the neurons and also after spinal cord injury.

Mohn *et al.* [20] reported that NMDA receptors represent a subclass of glutamate receptors that play a critical role in neural development and physiology. NMDA receptor blockers cause behavioral alteration (schizophrenia) due to increased dopamine level such as phencyclidine intoxication mimicking schizophrenia. Phencyclidine is a noncompetitive antagonist of NMDA receptors. Nieollon *et al.* [21, 22] reported that glutamate and dopamine exhibit reciprocal actions at subcortical cell, therefore dopamine receptor blockade may act to balance glutamatergic insufficiency [20, 23, 24].

Nonaka *et al.* [6] reported that LiCl protects to the cultured neurons against glutamate-induced excitotoxicity and apoptosis mediated by NMDA receptors. Javitt [25] reported that NMDA receptor antagonists cause glutamatergic dysfunction, which causes schizophrenic symptoms. On the other hand, hyper-glutamatergic neurotoxicity can cause cognitive deficit in schizophrenia [26]. These reports support our findings, which showed that LiCl and methylprednisolone results in NMDA receptor blockade.

Our results suggest that LiCl causes glutamate dysfunction via NMDA receptor blockade, which protects neuronal apoptosis. The MDA and TAS levels found in this paper support this hypothesis. Our result showed that lithium chloride had an antioxidant effect on the experimental rat spinal cord injury. The TAS level of the LiCl group was significantly higher than the other groups. MDA levels of the LiCl and methylprednisolone groups were statistically lower than the other groups. These results suggest that LiCl has a potent antioxidant activity as strong as methylprednisolone. Our results support the effecting mechanism of LiCl on glutamate-induced excitotoxicity and apoptosis mediated by NMDA receptors. Li inhibits Ca^{+2} influx into neural cells.

Conclusions

In conclusion, LiCl seems to be an effective drug as strong as methylprednisolone on experimental spinal cord injury.

Conflict of interest

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

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References

[1] Findling RL, Kafantaris V, Pavuluri M, McNamara NK, McClellan J, Frazier JA, et al. Dosing strategies for lithium monotherapy in children and adolescents with bipolar I disorder. J Child Adolesc Psychopharmacol 2011;21:195-205.

[2] Licht RW. Lithium: still a major option in the management of bipolar disorder. CNS Neurosci Ther 2012;18:219-26.

[3] Bains M, Hall ED. Antioxidant therapies in traumatic brain and spinal cord injury. Biochim Biophys Acta 2012;1822:675-84.

[4] Werndle MC, Zoumprouli A, Sedgwick P, Papadopoulos MC. Variability in the treatment of acute spinal cord injury in the United Kingdom: results of a national survey. J Neurotrauma 2012;29:880-8.

[5] Whittaker MT, Zai LJ, Lee HJ, Pajoohesh-Ganji A, Wu J, Sharp A. et al. GGF2 (Nrg1-β3) treatment enhances NG2+ cell response and improves functional recovery after spinal cord injury. Glia 2012;60:281-94.

[6] Nonaka S, Hough CJ, Chuang DM. Chronic lithium treatment robustly protects neurons in the central nervous system against excitotoxicity by inhibiting N-methyl-D-aspartate receptor-

mediated calcium influx. Proc Natl Acad Sci U S A 1998;95:2642-7.
[7] Ohkawa H, Ohishi N, Yagi K. Assay For Lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal Biochem 1979;95:351-8.
[8] Bracken MB. Steroids for acute spinal cord injury. Cochrane Database Syst Rev 2012;18:1:CD001046.
[9] Lee JM, Yan P, Xiao Q, Chen S, Lee KY, Hsu CY, et al. Methylprednisolone protects oligodendrocytes but not neurons after spinal cord injury. J Neurosci 2008;28:3141-9.
[10] Miller SM. Methylprednisolone in acute spinal cord injury: a tarnished standard. J Neurosurg Anesthesiol 2008;20:140-2.
[11] Xu J, Chen S, Chen H, Xiao Q, Hsu CY, Michael D, et al. STAT5 mediates antiapoptotic effects of methylprednisolone on oligodendrocytes. J Neurosci 2009;29:2022-6.
[12] Small JG, Klapper MH, Malloy FW, Steadman TM. Tolerability and efficacy of clozapine combined with lithium in schizophrenia and schizoaffective disorder. J Clin Psychopharmacol 2003;23:223-8.
[13] Boku S, Nakagawa S, Masuda T, Nishikawa H, Kato A, Kitaichi Y, et al. Glucocorticoids and lithium reciprocally regulate the proliferation of adult dentate gyrus-derived neural precursor cells through GSK-3beta and beta-catenin/TCF pathway. Neuropsychopharmacology 2009;34:805-15.
[14] Young W. Review of lithium effects on brain and blood. Cell Transplant 2009;18:951-75.
[15] Dill J, Wang H, Zhou F, Li S. Inactivation of glycogen synthase kinase 3 promotes axonal growth and recovery in the CNS. J Neurosci 2008;28:8914-28.
[16] Bailly-Maitre B, de Sousa G, Boulukos K, Gugenheim J, Rahmani R. Dexamethasone inhibits spontaneous apoptosis in primary cultures of human and rat hepatocytes via Bcl-2 and Bcl-xL induction. Cell Death Differ 2001;8:279-88.
[17] Lindsten T, Zong WX, Thompson CB. Defining the role of the Bcl-2 family of proteins in the nervous system. Neuroscientist 2005;11:10-5.
[18] Nesic-Taylor O, Cittelly D, Ye Z, Xu GY, Unabia G, Lee JC, et al. Exogenous Bcl-Xl fusion protein spares neurons after spinal cord injury. J Neurosci Res 2005;79:628-37.
[19] Cittelly DM, Nesic-Taylor O, Perez-Polo JR. Phosphorylation of Bcl-xL after spinal cord injury. J Neurosci Res 2007;85:1894-911.
[20] Mohn AR, Gainetdinov RR, Caron MG, Koller BH. Mice with reduced NMDA receptor expression display behaviors related to schizophrenia. Cell 1999;98:427-36.
[21] Nieoullon A, Kerkerian L, Dusticier N. Inhibitory effects of dopamine on high affinity glutamate uptake from rat striatum. Life Sci 1982;30:1165-72.
[22] Nieoullon A, Kerkerian L, Dusticier N. Presynaptic dopaminergic control of high affinity glutamate uptake in the striatum. Neurosci Lett 1983;43:191-6.
[23] Carlsson A, Hansson LO, Waters N, Carlsson ML. Neurotransmitter aberrations in schizophrenia: new perspectives and therapeutic implications. Life Sci 1997;61:75-94.
[24] Tsai G, Coyle JT. Glutamatergic mechanisms in schizophrenia. Annu Rev Pharmacol Toxicol 2002;42:165-79.
[25] Javitt DC. Glutamatergic theories of schizophrenia. Isr J Psychiatry Relat Sci 2010;47:4-16.
[26] Olney JW, Farber NB. Glutamate receptor dysfunction and schizophrenia. Arch Gen Psychiatry 1995;52:998-1007.

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Impact of previous percutaneous coronary intervention on postoperative outcomes of coronary artery bypass grafting

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ABSTRACT

Objectives. The widespread use of percutaneous coronary intervention (PCI) has resulted in an increasing number of patients who have undergone prior PCI being referred for coronary artery bypass graft grafting (CABG). The aim of this study was to determine the association between previous PCI and early and midterm outcomes after CABG. ***Methods.*** A total of 54 patients undergoing elective CABG (group 1) between January 2008 and January 2009 were compared to 46 patients who had a history of bare metal stent implantation before CABG (group 2). Mean follow-up was 12 months. ***Results.*** The average time interval to CABG following initial PCI was 18.5 months. There was no significant difference in demographic features and risk factors between the two groups (p>0.05). There were also no significant differences in intraoperative and postoperative data, and no significant differences for in-hospital mortality, cardiac mortality and total mortality and in the number of rehospitalizations for cardiac or for all-cause reasons (p>0.05). ***Conclusions.*** In this study, previous PCI did not significantly influence the outcomes of CABG in a 12-month follow-up period.

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Keywords: Coronary artery bypass grafting; percutaneous coronary intervention; coronary artery disease; postoperative outcomes

Introduction

In the last 15 years, the number of percutaneous coronary intervention (PCI) has been continuously increasing [1]. Widely use of PCI has already caused that a great number of PCI-applied patients become part of the patient group to have coronary artery bypass grafting (CABG). Due to PCI failure (10-30% intra-stent stenosis) or the progression of disease, CABG has to be performed for patients who previously had PCI [2]. The relationship between CABG and previous PCI history is a subject that should be discussed. The results of the studies that compare the relationship between CABG and PCI are controversial. Some authors report that initial PCI may increase postoperative morbidity and mortality, others

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report the opposite [2, 3].

The aim of this study was to examine short and medium term postoperative outcomes of patients who had successful PCI prior to CABG due to recurrent symptoms and to compare these results with those of patients who had undergone CABG alone.

Methods

A total of 100 patients were included in this retrospective study between January 2008 and January 2009 at Bursa Yuksek Ihtisas Training and Research Hospital. Patients were divided into two groups as to whether they had PCI history or not. Fifty-four patients having elective CABG were determined as control group (Group 1: 42 males,12 females, average of age 59.43±10.04) and 46 patients previously having PCI and then CABG were determined as study group (Group 2: 37 males, 9 females, average of age 56±9.50). Patients have been operated on consecutively. Patients having CABG history, patients requiring concomitant surgery, patients requiring emergency surgery, patients having renal dysfunction and patients whose ejection fraction (EF) was <30% were excluded from the study. Demographic characteristics, cardiac histories and perioperative data of patients were obtained from hospital records. Institutional Review Board approved the study protocol, and informed consent was obtained from each patient undergoing the surgical procedure described herein.

Preoperative Data Analyzed

1) Basic patient characteristics: Age, gender, New York Heart Association (NYHA) classification, EF. 2) Risk factors for ischemic heart disease: Diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HL), obesity, smoking history. 3) Coexisting diseases: Recent myocardial infarction (MI), cerebrovascular disease, chronic obstructive pulmonary disease, peripheral arterial disease, renal failure history were questioned. 4) Euro SCORE was calculated. Previous coronary intervention type and time passing from PCI to CABG were determined for the study group.

Surgical Technique

In all patients, standard incision and median sternotomy were performed. Cardiopulmonary bypass (CPB) was applied by the cannulation of ascending aorta and right atrium appendix. Left internal mammary artery graft was anastomosed to left anterior descending coronary artery in all of the patients. During operation, moderate hypothermia (28°C-30°C) was applied. Roller pump and membrane oxygenators were used. Myocardial protection was achieved by antegrade cardioplegia by the cardioplegia cannula. It was ensured that pump flow was 2.2–2.4 l/min/m^2 and non-pulsatile and mean artery pressure remained at 50–60 mmHg level during cross clamp. Hematocrit was kept between 20-25% during CPB. After proper blood pressure and cardiovascular stability were ensured, CPB was ended. Patients were followed by taking into intensive care unit during postoperative period. Patients whose clinical course was normal were taken into service.

Intraoperative Evaluation

Aortic cross clamp time (minute), cardiopulmonary bypass time (minute), total number of veins bypassed, the veins bypassed, whether perioperative MI and arrhythmia were developed, whether there was an intra-aortic balloon pump (IABP) support or not, whether positive inotropic support was required or not were evaluated.

Postoperative Evaluation

Postoperative MI and arrhythmia, mechanic ventilation time (hour), total drainage amount (mL), duration of intensive care stay (day), duration of hospital stay (day), complication, re-hospitalization reasons and death were evaluated. All patients were followed during postoperative 12 months.

Statistical Analysis

When evaluating all data obtained from the study, SPSS 16.0 program was used. Data were given as mean±standard deviation. Data were statistically evaluated by Fisher's Exact Test, Pearson Chi Square Test and Independent Samples Test. $p<0.05$ value was accepted as statistically significant.

Results

Mean age of patients was 59.43±10.04 in group 1 and 56±9.50 in group 2. When considering the distribution by genders, female/male rate was 12/42 in group 1 and 9/32 in group 2 (Table 1). There is no significant difference between both groups with

Table 1. Patient characteristics

	Group 1 (n=54)	Group 2 (n=46)	*p*
Age	59.43±10.04	56±9.50	0.175
Female gender	12 (22%)	9 (20%)	0.745
DM	18 (33%)	15 (33%)	0.939
HT	28 (52%)	23 (50%)	0.854
HL	26 (48%)	19 (41%)	0.493
Obesity	18 (33%)	12 (26%)	0.431
Smoking	26(48%)	24(52%)	0.688
Previous TIA	3(6%)	2(4%)	1.000
COPD	5 (9%)	2 (4%)	0.447
PAD	6 (11%)	3 (7%)	0.501
Previous MI in 90 days	9 (17%)	12 (26%)	0.249
NYHA	2.22±0.46	2.41±0.50	0.050
EF%	48.17±9.62	46.78±9.93	0.481
Euro SCORE	2.65±1.96	2.52±1.97	0.750
Ventricle scoring	8.93±2.80	9.20±1.97	0.585

Data are shown as mean±standard deviation or number (%). Group 1=having elective CABG, Group 2=having previous PCI and then elective CABG, COPD=chronic obstructive pulmonary disease, DM=diabetes mellitus, EF=ejection fraction, HL=hyperlipidemia, HT=hypertension, MI=myocard infarction, NYHA=New York Heart Association, PAD=peripheral arterial disease, TIA=transient ischemic attack

regards to demographic characteristics and risk factors (p>0.05). Preoperative patient characteristics, coexisting diseases, mean NYHA, EF %, Euro SCORE and ventricular scoring values are shown (Table 1). The average time interval between stent implantation and CABG was 18.5 months (1 month-3 years) in group 2. In group 2, 22 patients had stenting of the LAD artery, 14 of the circumflex artery and 18 of the right coronary artery before the CABG. Three patients had stenting LAD and circumflex artery, 2 patients had stenting circumflex and right coronary artery, 2 patients had stenting LAD and right coronary artery and1 patient had stenting LAD, circumflex and right coronary artery before the CABG.

Considering the intraoperative patient data, although the number of distal anastomosis in the group having PCI was lower (3.00±0.87) and the cross clamp time and pump time were shorter (71.54±26.90 min. 90.91±29.56 min. respectively), it was seen that there was no statistically significant difference (p>0.05) (Table 2). All the patients in both groups had anastomoses to the LAD. 35 had anastomoses to the circumflex artery and 19 patients did not have anastomoses to the circumflex artery in group 1 while 32 had anastomoses to the circumflex artery and 14 patients did not have anastomoses to the circumflex artery and in group 2. All the patients in group 1 had anastomoses to the right coronary artery. Twenty-six had anastomoses to the right coronary artery, 20 patients did not have anastomoses to the right coronary artery in group 2. Inotrope was used for 9 patients in group 1 and for 10 patients in group 2, IABP was used for 7 patients in group 1 and for 5 patients in group 2. Twenty-four-hour drainage amounts were 424.53±233.21 cc in group 1 and 440.22±264.29 cc in group 2. While atrial fibrillation developed in 21 patients in group 1, it developed in 14 patients in group 2. Mean EF in control ECHO was 47.42±11.36% in group 1 and 45.09±10.42 % in group 2 (Table 3). When comparing both groups with regards to these

Table 2. Operative data

	Group 1	Group 2	*p*
Number of grafts	3.28±0.86	3.00±0.87	0.112
X klemp (minute)	79.31±27.71	71.54±26.90	0.160
CPB (minute)	98.80±32.61	90.91±29.56	0.212

Data are shown as mean±standard deviation. Group 1=having elective CABG, Group 2=having previous PCI and then elective CABG

Table 3. Postoperative data

	Group 1	Group 2	*p*
Inotropic agents	9 (17%)	10 (22%)	0.519
IABP	7 (13%)	5 (11%)	0.748
Bleeding (cc)	424.53±233.21	440.22±264.29	0.754
AF	21 (39%)	14 (30%)	0.377
EF % (Postop. 2. month)	47.42±11.36	45.09±10.42	0.303

Data are shown as mean±standard deviation or number (%). Group 1=having elective CABG, Group 2=having previous PCI and then elective CABG, AF=atrial fibrillation, EF=ejection fraction, IABP=intra-aortic balloon pump, Postop=postoperative

data, it was seen that there was no statistically significant difference ($p>0.05$).

In both groups, it was seen that there was no significant difference in intra-hospital mortality, cardiac related mortality and total mortality ($p>0.05$). In both groups, there was 1 intra-hospital mortality (2%). Cardiac related mortality was 2 patients (4%) in group 1 and 3 patients (7%) in group 2. Cardiac related deaths were the ones occurred due to MI, cardiac arrhythmia, resistant low cardiac output. Total mortality was 3 patients (6%) in group 1 and 4 patients (9%) in group 2 (Table 4).

Cardiac related hospitalization and total hospitalization rates in postoperative 1st month were 1/2 in group 1 and 1/2 in group 2. At the end of 1 year which was the follow-up time, cardiac related hospitalization and total hospitalization rate were 2/5 in group 1 and 3/6 in group 2 (Table 5). When comparing both groups, it was seen that there was no statistically significant difference between these data ($p>0.05$).

Discussion

Nowadays, the number of cases undergoing to CABG increased in parallel with the increase in frequency of ischemic CAD and evolution of PCI treatment. Therefore, many patients already having PCI become a part of cardiac surgery. Restenosis is the main restrictor of PCI. In the treatment of cases in which post-stent restenosis develops, re-stent, drug eluting stent, brachytherapy, cutting balloon, coronary bypass surgery are the main ones of preferred methods. In the studies, post-stent revascularization rates were reported as 14-30%. While 22% of these

Table 4. Mortality data

	Group 1	Group 2	*p*
In-hospital mortality	1 (2%)	1 (2%)	1.000
Cardiac mortality in 1 year	2 (4%)	3 (7%)	0.659
Total mortality in 1 year	3 (6%)	4 (9%)	0.700

Data are shown as number (%). Group 1=having elective CABG, Group 2=having previous PCI and then elective CABG

Table 5. Rehospitalization data

	Group 1	Group 2	*p*
Cardiac reasons			
Postop. 1. month	1 (2%)	1 (2%)	1.000
Postop. 1. year	2 (4%)	3 (7%)	0.659
All reasons			
Postop 1. month	2 (4%)	2 (5%)	1.000
Post. 1. year	5 (10%)	6 (14%)	0.538

Data are shown as number (%). Group 1=having elective CABG, Group 2=having previous PCI and then elective CABG, Postop=postoperative

patients are referred to CABG, 78% of whom have recurrent PCI [4, 5]. Most of these interventions are generally applied to the same coronary artery. Studies made on bare metal stents (BMS) have showed that CABG is applied to 6-13% of patients within 1 year after PCI and to 13-26% of patients within 10 years [6]. There is an increasing tendency to CABG in case of failure of PCI in early period or for patients in whom PCI is inadequate in long period. Post-PCI CABG is applied for about 12 months [7]. In our study, post-PCI CABG was applied average of 18.5 months.

There are publications reporting the poor results after non-cardiac surgery following PCI [7]. Moreover, there are studies on the fact that PCI affects adversely the results in recurrent PCIs [9]. Considering the post-PCI bypass results, there are lots of mechanisms affecting the results of post-PCI CABG. These mechanisms include; 1) PCI may limit the number of bypass. If stent is placed to distal in patients having occluded stent, it is technically difficult to place graft to distal. Moreover, graft is not placed to the veins having patent stent if there is not a stenosis in stent distal; because graft patency rates, especially arterial ones reduce for lack of significant stenosis. However, veins left only with patent stent without placing the graft may cause postoperative MI due to postoperative pro-thrombotic case and perioperative stopping of antiplatelet treatment. 2) Also PCI affects the patency rates of previous grafts. The first one in-stent restenosis was associated with early venous graft failure [10]. The second one stent presence causes the placement of grafts to more distal. Due to stents which are adjacent or overlapping, coronary obstruction or occlusion occurs, this affects the coronary run-off and bypass graft patency and endangers collateral blood flow. It is not possible to displace the stent intraoperatively and the graft anastomosis has to be made to thinner distal part of target vein and the run-off and patency rate are affected adversely. 3) Drug-eluting stents (DES) generally affect coronary endothelial function [11]. Although it is well-known that DESs cause endothelial dysfunction, it is likely that BMSs endanger endothelial function with changes in inflammation and coagulation status. Pathophysiological response to intravascular foreign body may affect adversely the results after surgery. 4) Patients having post-PCI CABG form the patient group having more aggressive atherosclerosis [12]. In fact, as the reason of poor results of post-stent surgery, it is discussed that this is not caused by previous stent application but by more aggressive course of atherosclerotic disease in patients requiring an intervention again [10].

There are many studies showing the poor results. Massoudy *et al.* [13] examined the results of 29,928 patients underwent CABG in a multicenter analysis. They compared 3 group patients (no PCI, having one PCI and having two or more PCI) with regard to intra-hospital mortality and intra-hospital major cardiac event (MCE) (MI, low cardiac output syndrome, cardiac death). In their conclusion, it was found that single PCI application did not affect the results, but multiple PCI history increased intra-hospital mortality and MCE incidence following the CABG. In our study, single stent was applied to 40 (87%) patients and 2 and more stents were applied to 6 (13%) patients. It was found that there was no statistically significant difference between them with regards to mortality and major cardiac event. Tran *et al.* [14] compared 1,537 patients having diabetes and not having PCI before CABG and 221 patients having PCI with regards to surgical and major perioperative complications. In their conclusion, patients having DM and having PCI during 2-year follow-up were found as having increased risk for operative death, perioperative complications. Likewise, Bonaros *et al.* [15] compared 306 patients having elective PCI in recent 24 months before CABG and 452 patients not having elective PCI with regards to 30-day mortality, MCE and perioperative complications. They reported that patients having PCI had poorer results than those not having PCI. Hassan *et al.* [16] compared the CABG results of 919 patients having PCI and 5,113 patients not having. Although there was less serious CAD and less comorbidity in the group having PCI, it was defined that previous PCI was an independent risk factor on hospital mortality. In our study, intra-hospital mortality was similar (2%) in both groups.

Thielman *et al.* [17, 18] have two publications on this subject. In the first publication, they compared the results of 2,626 patient firstly having CABG but not having PCI, 360 patients having PCI for once and 289 patients having multiple PCI. In the other study, they compared 621 patients having diabetes and three vascular diseases with 128 patients. In both studies, they found that PCI applied before CABG in patients increased independently intra-hospital deaths and MCE [17, 18]. Some of the authors also reported that CABG patients with previous stent implantation have a poorer quality of life and a higher rate of unstable angina and re-intervention compared to the patients

underwent CABG only [19, 20].

Mannacio *et al.* [21] grouped and examined 7,855 patients and reported that previous PCI increased operation mortality and perioperative complications and reduced survival during 5-year follow-up. Songur *et al.* [22] reported that prior PCI can adversely affect graft patency after surgery.

In a study on 162 patients having PCI and 149 patients not having PCI, Gaszewska-Zurek *et al.* [23] reported that previous PCI did not significantly affect the CABG results but angina-related symptoms were observed frequently in patients having PCI during 3-year follow-up.

Velicki *et al.* [24] examined 950 patients during 18-month period and published that PCI did not affect the morbidity and mortality in low risk group. Additionally, in a multicenter comprehensive study in which medium term results of more than 13,000 patients were researched, Yap *et al.* [25] followed 11,727 patients not having PCI and 1,457 patients having PCI during 3.3±2.1 years on average. In their conclusion, it was reported that previous PCI did not increase short and medium term post-CABG mortality and good results could be obtained in this patient population.

In a study in which Barakate *et al.* [2] compared 361 patients having PCI and 11,909 patients not having PCI and in a study in which Judith *et al.* [26] compared 113 patients having PCI and 1,141 patients having isolated CABG, successful PCI did not affect the post-CABG results negatively. In the first meta-analysis made by Ueki *et al.* [27] in which 174,777 patients and 23 comparative studies were examined, it was shown that PCI increased intra-hospital mortality.

There is no current information on the reason why PCI increases the risk of CABG. There is a possibility that stent implantation causes a prolonged inflammatory response [28] and it adversely affects the anastomosis site of the graft. New types of stents (Polymer-coated drug eluting stents and nitric oxide-coated bioactive stents) are developed for preventing neo-intimal hyperplasia and reducing the rates of restenosis. Studies about efficacy and effectivity of nitric oxide-coated bioactive stents are still ongoing [29].

In our study, there was BMS use in all our patients. Even if poor results were published in post-stent CABG, this negative effect of stent on short and medium term surgery results could be not shown in our study.

The Limitations of the Study

The retrospective nature and low number of patients in our study are its most important limitations. However, these results may result from our patient selection. Event free surgical results may be correlated with low Euro SCORE of patients included in the study (about 2.5). This study is also a study including patients preferring the stent type only as BMS. Our results may be affected by our treatment methods. It is a single-centered study in which patient number is low in a selected patient group having post-PCI CABG. Therefore, the results cannot be generalized. It examined the operations and results made by different surgeon groups. This complicates the standardization. Our patients were followed during 12 months; therefore we have no available data for the following periods. We have no sufficient data on the number of patients who died after PCI and so could not have CABG. Multicenter studies especially with DESs are required in order to confirm the short and long term effects of pre-CABG PCI.

Conclusions

In our study, we showed that PCI was not a predictor for mortality or MCE and did not affect adversely survival in 12-month follow-up. It was found that there was no correlation between previous PCI and mortality. It was also found that there was no statistically significant different between both groups with regards to short and long term re-hospitalization and postoperative major complications. If recurrent angina develops in patients having successful PCI, CABG is a good choice.

Conflict of interest

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

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References

[1] Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2007 update: a report from the American Heart

Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2007;115:e69-171.
[2] Barakate MS, Hemli JM, Hughes CF, Bannon PG, Horton MD. Coronary artery bypass grafting (CABG) after initially successful percutaneous transluminal coronary angioplasty (PTCA): a review of 17 years experience. Eur J Cardiothorac Surg 2003;23:179-86.
[3] Kalaycioglu S, Sinci V, Oktar L. Coronary artery bypass grafting (CABG) after successful percutaneous transluminal coronary angioplasty (PTCA): is PTCA a risk for CABG? Int Surg 1998;83:190-3.
[4] Yock CA, Yock PG. The drug-eluting stent information gap. Am Heart Hosp J 2004;2:21-5.
[5] Cutlip DE, Chhabra AG, Baim DS, Chauhan MS, Marulkar S, Massaro J, et al. Beyond restenosis: five-year clinical outcomes from second-generation coronary stent trials. Circulation 2004;110:1226-30.
[6] Mercado N, Wijns W, Serruys PW, Sigwart U, Flatter MD, Stables RH, et al. One-year outcomes of coronary artery bypass graft surgery versus percutaneous coronary intervention with multiple stenting for multisystem disease: a meta-analysis of individual patient data from randomized clinical trials. J Thorac Cardiovasc Surg 2005;130:512-9.
[7] Johnson RG, Sirois C, Thurer RL, Sellke FW, Cohn WE, Kuntz RE, et al. Predictors of CABG within one year of successful PTCA: a retrospective, case-control study. Ann Thorac Surg 1997;64:3-7.
[8] Wilson SH, Fasseas P, Orford JL, Lennon RJ, Horlocker T, Charnoff NE, et al. Clinical outcome of patients undergoing non-cardiac surgery in the two months following coronary stenting. J Am Coll Cardiol 2003;42:234-40.
[9] Holmes DR Jr, Savage M, LaBlanche JM, Grip L, Serruys PW, Fitzgerald P, et al. Results of Prevention of REStenosis with Tranilast and its Outcomes (PRESTO) trial. Circulation 2002;106:1243-50.
[10] Gaudino M, Cellini C, Pragliola C, Trani C, Burzotta F, Schiavoni G, et al. Arterial versus venous bypass grafts in patients with in-stent restenosis. Circulation 2005;112(Suppl):I265-9.
[11] Muhlestein JB. Endothelial dysfunction associated with drug-eluting stents what, where, when, and how? J Am Coll Cardiol 2008;51:2139-40.
[12] Stone PH, Coskun AU, Yeghiazarians Y, Kinlay S, Popma JJ, Kuntz RE, et al. Prediction of sites of coronary atherosclerosis progression: in vivo profiling of endothelial shear stress, lumen, and outer vessel wall characteristics to predict vascular behavior. Curr Opin Cardiol 2003;18:458-70.
[13] Massoudy P, Thielmann M, Lehmann N, Marr A, Kleikamp G, Maleszka A, et al. Impact of prior percutaneous intervention on the outcome of coronary artery bypass surgery: a multicenter analysis. J Thorac Cardiovasc Surg 2009;137:840-5.
[14] Tran HA, Barnett SD, Hunt SL, Chon A, Ad N. The effect of previous coronary artery stenting on short- and intermediate-term outcome after surgical revascularization in patients with diabetes mellitus. J Thorac Cardiovasc Surg 2009;138:316-23.
[15] Bonaros N, Hennerbichler D, Friedrich G, Kocher A, Pachinger O, Laufer G, et al. Increased mortality and perioperative complications in patients with previous elective percutaneous coronary interventions undergoing coronary artery bypass surgery. J Thorac Cardiovasc Surg 2009;137:846-52.
[16] Hassan A, Buth KJ, Baskett RJ, Ali IS, Maitland A, Sullivan JA, et al. The association between prior percutaneous coronary intervention and short-term outcomes after coronary artery bypass grafting. Am Heart J 2005;150:1026-31.
[17] Thielmann M, Leyh R, Massoudy P, Neuhauser M, Aleksic I, Kamler M, et al. Prognostic significance of multiple previous percutaneous coronary interventions in patients undergoing elective coronary artery bypass surgery. Circulation 2006;114(1 Suppl):I441-7.
[18] Thielmann M, Neuhäuser M, Knipp S, Kottenberg-Assenmacher E, Marr A, Pizanis N, et al. Prognostic impact of previous percutaneous coronary intervention in patient with diabetes mellitus and triple-vessel disease undergoing coronary artery bypass surgery. J Thorac Cardiovasc Surg 2007;134:470-6.
[19] Rao C, De Lisle R, Chikwe J, Pepper J, Skapinakis P, Aziz O, et al. Does previous percutaneous coronary stenting compromise the long-term efficacy of subsequent coronary artery bypass surgery? A microsimulation study. Ann Thorac Surg 2008;85:501-7.
[20] Chocron S, Baillot R, Roucleau JL, Warnica WJ, Block P, Johnstone D, et al.; IMAGINE Investigators. Impact of previous percutaneous transluminal coronary angioplasty and/or stenting revascularization on outcomes after surgical revascularization: insights from the imagine study. Eur Heart J 2008;29:673-9.
[21] Mannacio V, Di Tommaso L, De Amicis V, Luchetti V, Pepino P, Musumeci F, et al. Previous percutaneous coronary interventions increase mortality and morbidity after coronary surgery. Ann Thorac Surg 2012;93:1956-62.
[22] Songur MC, Ozyalcin S, Ozen A, Simsek E, Kervan U, Tasoglu I, et al. Does really previous stenting affect graft patency following CABG? A 5 year follow-up: The effect of PCI on graft survival. Heart Vessels 2016;31:457-64.
[23] Gaszewska-Zurek E, Zurek P, Kazmierski M, Kargul T, Duraj P, Jasinski M, et al. Coronary artery bypass grafting in patients with relatively recent previous stent implantation: three years follow-up results. Cardiol J 2009;16:312-6.
[24] Velicki L, Cemerlic-Adjic N, Panic G, Jung R, Redzeg A, Nicin S. CABG mortality is not influenced by prior PCI in low risk patients. J Card Surg 2013;28:353-8.
[25] Yap CH, Yan BP, Akowuah E, Dinh DT, Smith JA, Shardey G, et al. Does prior percutaneous coronary intervention adversely affect early and mid-term survival after coronary artery surgery? JACC Cardiovasc Interv 2009;2:758-64.
[26] van den Brule JM, Noyez L and Verheugt FW. Risk of coronary surgery for hospital and early morbidity and mortality after initially successful percutaneous intervention. Interact Cardiovasc Thorac Surg 2005;4:96-100.
[27] Ueki C, Sakaguchi G, Akimoto T Shintani T, Ohashi Y, Sato H. Influence of previous percutaneous coronary intervention on clinical outcome of coronary artery bypass grafting: a meta-analysis of comparative studies. Interact Cardiovasc Thorac Surg. 2015;20:531-7.
[28] Taguchi I, Yoneda S, Abe S, Toyoda S, Nasuno T, Nishino S, et al. The late-phase inflammatory response after drug-eluting stent implantation. Heart Vessels 2014;29:213-9.
[29] Alagem-Shafir M, Kivovich E, Tzchori I, Lanir N, Falah M, Flugelman MY. The formation of an anti-restenotic/anti-thrombotic surface by immobilization of nitric oxide synthase on a metallic carrier. Acta Biomater 2014;10:2304-12.

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The effectiveness of final intraoperative endoscopic control in conventional septoplasty

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ABSTRACT

Objectives. Septoplasty operation is a very common procedure and can be performed with endoscopic or conventional techniques. In some cases, preoperative nasal endoscopy can not be performed due to severe anterior deviations, and computerized tomography assessment causes to radiation exposure and increased cost. Our aim was to investigate the effectiveness of final endoscopic control in conventional septoplasty operations. ***Methods.*** Fifty-one subjects who underwent conventional septoplasty with intraoperative endoscopic control and thirty age-sex matched patients who were being performed conventional septoplasty without endoscopic control were enrolled in this prospective study. Surgeon satisfaction intraoperatively and patient satisfaction 3 months later from surgery obtained with using 5 point Likert scale. Additional pathologies which observed by using intraoperative endoscopy and the rate of performed additonal surgeries were recorded. ***Results.*** Using this technique, surgeon satisfaction improved (p=0.02), but there was no significant difference on patient satisfaction (p=0.642). Additional pathologies were seen in 25% of patients and additonal surgeries performed in 21% of patients. All observed additonal pathologies were diagnosed and treated with endoscope easily. ***Conclusion.*** Final intraoperative endoscopic control in conventional septoplasty is an effective method and improves the surgeon satisfaction in surgery.

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Keywords: Endoscopy; septoplasty; conventional

Introduction

Septoplasty is one of the most common rhinologic procedures and is generally performed to treat nasal obstruction caused by nasal septum deviation (NSD) that is resistant to medical therapy (intranasal steroids, decongestants, etc.) [1, 2]. According to the literature, the prevalence of NSD in adults is nearly 90% [3]; however, the majority of these patients do not need any surgical interventions.

Endoscopic septoplasty has gained popularity in recent years due to improvements in visualization technology. Compared to the conventional technique, endoscopic septoplasty offers significant benefits such as low morbidity, limited postoperative mucosal edema due to limited dissection and an improved field of vision, especially posteriorly [4, 5]. Nevertheless, the functional results of endoscopic septoplasty are

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identical to conventional septoplasty [2].

Although nasal endoscopy is widely used in the assessment of NSD, in some circumstances, preoperative nasal endoscopy cannot be performed due to severe septal deviations. Our aim was to demonstrate the effectiveness of intraoperative endoscopic assessments immediately following suturing in conventional septoplasty and the outcomes in relation to patient and surgeon satisfaction in such cases.

Methods

This prospective study was approved by Institutional Review Board (2016/3-7). Written informed consent was obtained from each patient, and the study was conducted in accordance with the principles of the Declaration of Helsinki. Fifty-one subjects who underwent conventional septoplasty with intraoperative endoscopic control (CSEC) and 30 age- and sex-matched patients who underwent conventional septoplasty (CS) without endoscopic control were enrolled in this prospective study. The patients' characteristics like age and sex were recorded. Patients under 18 years of age, and those with known sinonasal disease (allergic rhinitis, infection, etc.), nasal surgery history and any other complaints beyond nasal obstruction (like facial pain, anosmia, rhinorrhoea, etc.) were excluded from the study.

All surgeries were performed by the same surgeons (CB, SD) using the same technique. In the CSEC group, both the nasal passage and nasopharynx were assessed with 0° rigid endoscopy immediately following suturing, but in the CS group, no further procedure was done. After the operation, the surgeons were asked if they derived any benefits from the endoscopic control, if they encountered any additional pathology or, if they performed additional surgery, if they observed another pathology with endoscopy. The surgeons were asked intraoperatively and the patients three months following surgery to rate their satisfaction according to a 5-point Likert scale where 5 indicated very satisfied and 1 denoted very dissatisfied with the procedure.

Conventional septoplasty procedure

All procedures were performed under general anaesthesia using a headlight. Local anaesthetic (Jetocaine® ampules, lidocaine HCI 20 mg/ml and epinephrine HCI 0.0125 mg/ml combination, Adeka, Samsun, Turkey) was infiltrated into the nasal mucosa. During each procedure, a hemitransfixation incision was made, the mucoperichondrial flaps were elevated, the spurs and deviated parts of the nasal septum were excised and, finally, transfixation sutures were applied. After the suturing had been completed, a nasal passage assessment was performed with rigid nasal endoscopy in the CSEC group. Nasal tampons were then placed in the nasal cavity.

Statistical Analysis

Statistical analysis was performed using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL). The satisfaction scores between the groups were compared using a chi-squared test, while age and sex distribution were compared using the Mann-Whitney U test and Fisher's exact test, respectively. The p value of <0.05 was considered statistically significant.

Results

The patients' mean age was 27.98±7.83 years (range;18 to 46 years) for the CSEC group and 29.46±6.90 years (range;18 to 42 years) for the CS group (Table 1). There were no observed benefits of endoscopic control in 18 (35%) cases. The surgeons described the method as useful although they could not find any additional pathology and did not perform any other surgeries in 20 (39%) patients. In two cases,

Table 1. Age and sex distrubution of groups

Demographic data	CSEC group (n=51)	CS group (n=30)	*p*
Age (year)	28.00±7.78	29.46±6.90	0.288¥
Female, n (%)	9 (17.6%)	5 (16.7%)	0.910§

Data are shown as mean±standard deviation or number (%). CS=conventional septoplasty, CSEC= conventional septoplasty with intraoperative endoscopic control
¥ Mann Whitney U test, § Fishers exact test

Table 2. Distrubution and comparison of satisfaction scale answers in patients between groups

Patient Satisfaction Scale	CSEC group (n=51)	CS group (n=30)	*p*‡
1	1 (1.9%)	2 (6.6%)	
2	1 (1.9%)	1 (3.3%)	
3	6 (11.7%)	5 (16.6%)	0.642
4	26 (50.9%)	11 (36.6%)	
5	17 (33.3%)	11 (36.6%)	

CS=conventional septoplasty, CSEC=conventional septoplasty with intraoperative endoscopic control
‡ Chi square test

Table 3. Distrubution and comparison of satisfaction scale answers in surgeons between groups

Patient Satisfaction Scale	CSEC group (n=51)	CS group (n=30)	*p* ‡
1	0 (0%)	2 (6.7 %)	
2	0 (0%)	0 (0%)	
3	4 (7.8%)	7 (23.3%)	0.020
4	27(52.9%)	16 (53.3%)	
5	20 (39.2%)	5 (16.7%)	

CS=conventional septoplasty, CSEC=conventional septoplasty with intraoperative endoscopic control
‡ Chi square test

adenoid tissue that obliterated the choana to less than 50% was found, and the surgeons stated that endoscopic control was useful in these cases although no additional surgery was performed. In 13 (25%) patients, additional pathologies were seen, and further surgeries were performed in 11 (21%) of these patients. The observed pathologies were concha bullosa (1 patient, treated with lateral side resection), polypoid degeneration of the posterior portion of the inferior turbinate (3 patients, treated with excision and cauterization), posterior obstruction due to inadequate bony nasal septum excision (2 patients, treated with wider excision), adenoid tissue (1 patient, treated with adenoidectomy) and nasal polyps (3 unilateral and 1 bilateral, all four polyp cases were in the middle meatus and treated with simple polypectomy). There was no difference in patient satisfaction between the two groups (p=0.642), but the surgeons' satisfaction was significantly improved in the CSEC group compared to the CS group (p=0.02) (Tables 2 and 3).

Discussion

The following were the main findings of this study: 1) Intraoperative endoscopic control of the nasal passage following suturing is an effective method for assessing coexisting pathologies; 2) Using this method surgeon satisfaction improved, but there was no change in patient satisfaction; 3) The co-existing nasal pathologies were not complex disorders, and all of them could be easily treated with endoscopy. We therefore suggest that there may be no need for preoperative computerized tomography (CT) imaging in NSD patients who have only nasal obstruction complaint.

Traditional septoplasty consists of headlight illumination and limited visualization with a nasal speculum; therefore, surgery may sometimes be quite difficult to perform in circumstances where the patient has a narrow nose or there is posterior deviation [4]. Although the endoscopic technique has gained popularity in recent years, conventional septoplasty is still widely used.

There is no single diagnostic test that can be considered as the gold standard for NSD. Anterior rhinoscopy and nasal endoscopy may be used to diagnose the severity and location of NSD in a decongested nose, but inter-rater variability is a significant problem in these assessments [6]. In a clinical consensus statement, nasal endoscopy was not found to be necessary to make a diagnosis of NSD, and this highlighted the possibility that it may provide useful information about coexisting pathologies such as polyps, rhinosinusitis and tumours. Patient history and physical examination have been mentioned as the gold standard for diagnosing NSD [7]. Chaitanya *et*

al. [8] evaluated 80 patients and divided them into 2 equal groups. Only conventional septoplasty was performed in the first group, while septoplasty with endoscopy was done to observe the remnants of the septum and associated lateral wall pathologies in the second group. The researchers made a few additional observations: 1 polypoid middle turbinate, 2 accessory ostia and 1 nasal polyp. They also compared the nasal symptoms of both groups in the preoperative and postoperative periods, and stated that symptom relief was better in the endoscopically controlled group. Contrarily, there was no improvement in patient satisfaction in our study, but the surgeons were significantly satisfied with the use of endoscopy intraoperatively. We observed additional pathologies in 25% (13/51) of the patients, and the surgical plans had to be altered in 11 (21%) of these cases. Accordingly, we determined that intraoperative endoscopic control following suturing is an effective method in conventional septoplasty.

The preoperative requirement that every patient undergoing septoplasty have a CT scan is a controversial issue. Aziz *et al.* [6] indicated that CT can provide an accurate diagnosis of NSD, but its negative aspects are exposure to radiation and the high cost. In their retrospective study, Karatas *et al.* [9] divided 76 patients into two groups, one for which preoperative CT was performed (40 patients) and the other for which it was not (36 patients). They performed endoscopic sinus surgery for 8 patients and concha bullosa resection for 14 patients. They therefore stressed that preoperative CT is helpful when determining the location and type of surgery. On the other hand, it has been stated that CT may not show the degree of NSD accurately [7]. Vural *et al.* [10] could not find a significant relationship between preoperative nasal obstruction symptom evaluation (NOSE) scores and the severity of NSD using CT, and stated that preoperative CT is unnecessary. Similarly, Sedaghat *et al.* [11] reported that the septoplasty surgery decision should not be based on imaging findings. In their retrospective blinded study, they investigated the correlation between a CT scan and a physical examination (anterior rhinoscopy and nasal endoscopy) on different septal locations but only found a correlation for the osseous septum.

Gunbey *et al.* [12] did not recommend preoperative CT for all patients undergoing septoplasty. Although performing CT preoperatively changed the surgery decision in 8.3% of patients, the researchers reported that CT was highly sensitive but had low specificity for NSD. They recommended CT in conditions such as deviation in the posterior area cannot be assessed endoscopically if there is severe anterior deviation, chronic rhinosinusitis, osteomeatal complex pathology or a polyp or mass in endoscopy [12]. However, there was no mention about the rate of additional pathologies in the posterior nasal area observed with CT which could not be assessed with endoscopy. In our study, additional pathologies were diagnosed and treated endoscopically. According to the results of this study, intraoperative final endoscopic assessment provides improved surgical satisfaction, and should be performed in patients after conventional septoplasty surgery.

The Limitation of the Study

Small sample size is a limitation of our study.

Conclusions

Intraoperative endoscopic control is an effective method in conventional septoplasty and improves surgeon satisfaction. Additional pathologies can be easily diagnosed and treated using this method. We did not encounter complex disorders when using nasal endoscopy in the final assessment, further studies are needed to clarify the superiority of CT and endoscopy to determine additional nasal pathologies.

Conflict of interest

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

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References

[1] Sedaghat AR, Busaba NY, Cunningham MJ, Kieff DA. Clinical assessment is an accurate predictor of which patients will need septoplasty. Laryngoscope 2013;123:48-52.

[2] Champagne C, Ballivet de Regloix S, Genestier L, Crambert A, Maurin O, Pons Y. Endoscopic vs. conventional septoplasty: a review of the literature. Eur Ann Otorhinolaryngol Head Neck Dis 2016;133:43-6.

[3] Mladina R, Cujic E, Subaric M, Vukovic K. Nasal septal deformities in ear, nose, and throat patients: an international study. Am J Otolaryngol 2008;29:75-82.

[4] Hwang PH, McLaughlin RB, Lanza DC, Kennedy DW. Endoscopic septoplasty: indications, technique, and results.

Otolaryngol Head Neck Surg 1999;120:678-82.
[5] Bothra R, Mathur NN. Comparative evaluation of conventional versus endoscopic septoplasty for limited septal deviation and spur. J Laryngol Otol 2009;123:737-41.
[6] Aziz T, Biron VL, Ansari K, Flores-Mir C. Measurement tools for the diagnosis of nasal septal deviation: a systematic review. J Otolaryngol Head Neck Surg 2014;43:11.
[7] Han JK, Stringer SP, Rosenfeld RM, Archer SM, Baker DP, Brown SM, et al. Clinical Consensus Statement: Septoplasty with or without Inferior Turbinate Reduction. Otolaryngol Head Neck Surg 2015;15:708-20.
[8] Chaitanya VK, Janardhan N, Kumar SR, Rakesh G. Does the use of an endoscope in conventional septal surgery provide benefit in patients of deviated nasal septum? Sch J App Med Sci 2014;2:1824-27.
[9] Karatas D, Yuksel F, Senturk M, Dogan M. The contribution of computed tomography to nasal septoplasty. J Craniofac Surg 2013;24:1549-51.
[10] Vural S, Tas E, Gursel AO. [Evaluation of septoplasty patients with health status scale, rhinomanometry and computed tomography]. Kulak Burun Bogaz Ihtis Derg 2008;18:166-70. [Article in Turkish]
[11] Sedaghat AR, Kieff DA, Bergmark RW, Cunnane ME, Busaba NY. Radiographic evaluation of nasal septal deviation from computed tomography correlates poorly with physical exam findings. Int Forum Allergy Rhinol 2015;3:258-62.
[12] Gunbey E, Gunbey HP, Uygun S, Karabulut H, Cingi C. Is preoperative paranasal sinus computed tomography necessary for every patient undergoing septoplasty? Int Forum Allergy Rhinol 2015;5:839-45.

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Hysteroscopy before the first in vitro fertilization: a 7-year experience from a single center

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ABSTRACT

Objective. This study aims to evaluate the importance of performing hysteroscopy prior to the first attempt of in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) by specifying the incidence of intrauterine pathologies and the success of IVF/ICSI cycle. ***Methods.*** This is a retrospective review of 357 women who underwent their first cycle of IVF/ICSI treatment during a 7- year period. All women had primary infertility due to various factors: Polycystic ovary syndrome (n=101), male factor (n=84), tubal factor (n=78) and unexplained infertility (n=94). ***Results.*** The majority of the patients had normal hysteroscopic findings whereas 29.4% of them had an intrauterine pathology. Abnormal hysteroscopic findings included endometrial polyps (13.7%), submucous myomas (5.9%), uterine septa (4.5%), endometrial adhesions (3.1%), endometritis (1.4%) and cervical stenosis (0.8%). When compared to the women with normal hysteroscopy (n=252), the women with corrected hysteroscopic abnormalities (n=105) had significantly higher fertilization rate (p=0.045), implantation rate (p=0.038), clinical pregnancy rate (p=0.022) and live birth rate (p=0.022). When compared to the women with normal transvaginal ultrasonography and hysteroscopy findings (n=252), the women with normal ultrasonography and abnormal hysteroscopy (n=35) had significantly higher implantation rate (p=0.044), clinical pregnancy rate (p=0.032) and live birth rate (p=0.030). ***Conclusions.*** The utilization of hysteroscopy before the first IVF cycle would allow the detection and treatment of intrauterine pathologies and structural uterine abnormalities that might be responsible for the failure of IVF and, thus, result in improved pregnancy rates.

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Keywords: Hysteroscopy; in vitro fertilization; intracytoplasmic sperm injection; infertility; intrauterine pathology

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Introduction

In vitro fertilization (IVF) is an effective and expensive treatment which ends up with successful outcome in only a third of treatment cycles. The major underlying reason for this relatively lower success rate is the implantation failure is usually attributed to embryo quality and/or uterine receptivity [1, 2].

It is well known that uterine factor exists in 15% to 20% of the infertile couples. The presence of uterine pathology may negatively affect the chance of implantation. It has been found that the prevalence of uterine pathology can be up to 50% in asymptomatic women with implantation failure. Therefore, the visualization of uterine cavity by means of hysteroscopy has been proposed for women undergoing IVF treatment [3-5].

Hysteroscopy is the gold standard test for the assessment of uterine cavity. It is generally performed as a diagnostic method for the evaluation of abnormal findings detected by hysterosalpingography or saline hysterosonography which are performed during the investigation of infertile women. Besides allowing accurate visual assessment of the uterine cavity, hysteroscopy also provides an opportunity to treat any intrauterine pathology detected during the examination. The development of smaller and narrower hysteroscopes has made the use of outpatient or office hysteroscopy available as a routine examination [6-10].

Current evidence indicates that performing hysteroscopy before initiating an IVF cycle can increase the chance of pregnancy in the subsequent IVF treatment in women who have undergone one or more unsuccessful IVF attempts. However, the routine use of hysteroscopy before starting the first IVF treatment cycle is still a matter of debate [11, 12].

The present study aims to evaluate the importance of performing hysteroscopy prior to the first attempt of IVF or intracytoplasmic sperm injection (ICSI) by specifying the incidence of intrauterine pathologies in a selected group of infertile women and determining the success of first IVF/ICSI cycle after the hysteroscopic procedures.

Methods

This is a retrospective review of 357 women who underwent their first cycle of IVF/ICSI treatment at the study center during a 7-year period between January 2007 and January 2014. All women had primary infertility due to various factors: Polycystic ovary syndrome (n=101), male factor (n=84), tubal factor (n=78) and unexplained infertility (n=94). All of the hysteroscopy and the embryo transfer procedures were performed by one operator (S.H.). All patients gave written informed consents before the initiation of treatment. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Hysteroscopic procedures

Before the procedure, all patients had a transvaginal ultrasonography and all abnormal findings were recorded. Hysteroscopy was performed under general anesthesia using a 9-mm, 0° angle hysteroscope with an external sheath of 9-mm diameter providing inflow, outflow, and 5F working channels (Karl Storz, Tuttlinger, Germany). After vaginal disinfection and cervical dilatation, the hysteroscope was inserted into the external cervical os, and the scope was inserted through the cervical canal into the cavity with gentle movements. Uterine cavity distention was achieved with normal saline installation.

In patients with noted uterine cavity distortion, or pathology, appropriate surgical management was administered in the same setting. Adhesiolysis was performed with the use of micro scissors. Uterine septa (the diagnosis of which was based on the extent of midline protrusion into the cavity estimated in relation to the length of micro scissors and on its structure) and/or endometrial polyps (with a maximum diameter less than 2 cm) were excised with the use of micro scissors and micro forceps, or with the bipolar resectoscope electro surgery system (Gynecare, Ethicon, Somerville, NJ). In patients with endometrial polyps with a maximum diameter of more than 2 cm or submucous myomas, removal of the lesions was achieved using monopolar diathermy through cutting loops and glycine as distending medium. During the postoperative period, all women were prescribed a four-day-long course of oral doxycycline (100 mg bid) in order to prevent any intrauterine infections.

Assisted reproduction procedures

Controlled ovarian hyper stimulation was started using a long protocol (mid-luteal gonadotropin-releasing hormone (GnRH) analog and stimulation

with recombinant follicle stimulating hormone (recFSH) after confirmation of downregulation), short protocol (GnRH analog from cycle day 2 and recFSH from cycle day 3), or a flexible antagonist protocol (recFSH from cycle day 2 and the addition of a GnRH antagonist when the leading follicles reached 14–15 mm in diameter). Transvaginal ultrasonography guided oocyte retrieval was performed about 35 hours after the administration of 10000 IU of human chorionic gonadotropin. The women were assigned to the same protocol that was used in the previous trial before hysteroscopy.

Based on the infertile couple's diagnostic workup, traditional IVF or ICSI was performed with the respective male partner's spermatozoa. Sequential culture media was used for all procedures. In the case of frozen/thaw cycles, embryo thawing and transfer were synchronized according to the serum luteinizing hormone (LH) surge on a natural cycle. Embryos are usually transferred on day 3 and sometimes on day 5 depending on the decision of the embryologist. All embryo transfers were performed with a catheter under ultrasonography guidance. The number of transferred embryos depended on multiple factors including female age, embryo availability and quality. Luteal phase support was achieved using vaginal progesterone suppositories (200 mg daily).

Statistical analysis

Collected data were analyzed by Statistical Package for Social Sciences version 18.0 (SPSS IBM, Armonk, NY, USA). Continuous variables were expressed as mean±standard deviation (range: minimum-maximum) whereas categorical variables were denoted as numbers or percentages. $p<0.05$ value was accepted as statistically significant.

Results

The demographic characteristics of the participants including age, partner age and duration of infertility are demonstrated in Table 1. The majority of the patients had normal hysteroscopic findings whereas nearly 30% of them had an intrauterine pathology (Table 2). Abnormal hysteroscopic findings included endometrial polyps (13.7%), submucous myomas (5.9%), uterine septa (4.5%), endometrial adhesions (3.1%), endometritis (1.4%) and cervical stenosis (0.8%). Complete resection was achieved in all patients with endometrial abnormalities and the endometrial cavity was assessed with hysteroscopy after the operation. The hysteroscopic appearance of the endometrial pathology was confirmed with the histopathological findings.

Table 1. Demographic characteristics of the 357 participants

Characteristics	Data
Age (years)	28.7±3.4 (23-35)
Partner age (years)	33.1±2.9 (26-40)
Duration of infertility (years)	6.8±1.5 (2-12)

Data are shown as mean±standard deviation (min-max)

Table 2. Hysteroscopic findings of the 357 participants

Findings	Data
Normal hysteroscopy	252 (70.6)
Abnormal hysteroscopy	105 (29.4)
Endometrial polyps	49 (13.7)
Submucous myomas	21 (5.9)
Uterine septa	16 (4.5)
Endometrial adhesions	11 (3.1)
Endometritis	5 (1.4)
Cervical stenosis	3 (0.8)

Data are shown as number of cases (%)

All patients underwent transvaginal ultrasonography and hysterosalpingography before hysteroscopy. No patients had saline infusion sonography. Pre-procedural transvaginal ultrasonography was able to visualize endometrial polyps in 44 patients (89.8%), submucous myomas in 17 patients (81%), uterine septa in only five patients (31.3%) and endometrial adhesions in only two patients (18.2%). Transvaginal ultrasonography failed to specify either endometritis or cervical stenosis in none of the affected patients. Pre-procedural hysterosalpingography was able to detect endometrial polyps in 25 patients (51%), submucous myomas in 10 patients (47.6%), uterine septa in 14 patients (87.5%) and endometrial adhesions in 6 patients (54.5%). Hysterosalpingography was unable to determine either endometritis or cervical stenosis in none of the affected patients.

Table 3 compares the characteristics of the first IVF/ICSI cycles of the participants with respect to the hysteroscopy findings. When compared to the women with normal hysteroscopy, the women with corrected hysteroscopic abnormalities had significantly higher fertilization rate ($p=0.045$), implantation rate ($p=0.038$), clinical pregnancy rate ($p=0.022$) and live birth rate ($p=0.022$).

Table 3. IVF/ICSI characteristics of the participants with respect to hysteroscopy findings

	Normal hysteroscopy (n=252)	Abnormal hysteroscopy (n=105)	*p* value
Age (years)	28.5±3.1	29.1±3.4	0.077
Partner age (years)	32.9±3.1	33.6±2.4	0.124
Duration of infertility (years)	6.6±1.7	7.1±1.9	0.188
Cause of infertility			0.110
Polycystic ovary syndrome	70 (27.8%)	35 (29.5%)	
Male factor	60 (23.8%)	24 (22.9%)	
Tubal factor	57 (22.6%)	21 (20.0%)	
Unexplained infertility	65 (25.8%)	29 (27.6%)	
Collected oocytes per cycle	12.7±5.8	12.1±4.7	0.212
Metaphase II oocytes per cycle	6.6±2.3	6.5±3.1	0.186
Fertilized oocytes per cycle	4.2±1.7	3.4±2.2	0.106
Transferred embryos per cycle	1.5±0.9	1.2±0.4	0.128
Fertilization rate	1058/1663 (63.6%)	357/682 (52.3%)	0.045*
Implantation rate	94/378 (32.9%)	52/126 (41.3%)	0.038*
Clinical pregnancy rate	91/378 (24.1%)	50/126 (39.7%)	0.022*
Live birth rate	89/378 (23.5%)	49/126 (38.9%)	0.022*

*$p<0.05$ was accepted to be statistically significant, IVF/ICSI=in vitro fertilization/intracytoplasmic sperm injection

Table 4 summarizes the characteristics of the first IVF/ICSI cycles of the participants with respect to the combination of transvaginal ultrasonography and hysteroscopy findings. When compared to the women with normal transvaginal ultrasonography and hysteroscopy findings, the women with normal ultrasonography and abnormal hysteroscopy had significantly higher implantation rate (p=0.044), clinical pregnancy rate (p=0.032) and live birth rate (p=0.030).

Discussion

Despite the significant improvement in the area of assisted reproductive techniques, implantation rates per embryo transfer still remain relatively low. The two key factors in question for this problem are the quality of the embryo and the receptivity of the endometrium. Although it is possible to assess the embryo quality by microscopy, there are no definitive methods for the evaluation of endometrial receptivity.

Table 4. IVF/ICSI characteristics of the participants with respect totTransvaginal ultrasonography and hysteroscopy findings

	Normal ultrasonography & Normal hysteroscopy (n=252)	Normal ultrasonography & Abnormal hysteroscopy (n=35)	*p* value
Age (years)	28.5±3.1	29.0±3.2	0.117
Partner age (years)	32.9±3.1	33.3±2.9	0.118
Duration of infertility (years)	6.6±1.7	6.8±1.9	0.184
Cause of infertility			0.108
Polycystic ovary syndrome	70 (27.8%)	10 (28.6%)	
Male factor	60 (23.8%)	8 (22.9%)	
Tubal factor	57 (22.6%)	8 (22.9%)	
Unexplained infertility	65 (25.8%)	9 (25.7%)	
Collected oocytes per cycle	12.7±5.8	12.0±4.7	0.112
Metaphase II oocytes per cycle	6.6±2.3	5.5±3.1	0.186
Fertilized oocytes per cycle	4.2±1.7	3.2±1.2	0.099
Transferred embryos per cycle	1.5±0.9	1.1±0.1	0.125
Fertilization rate	1058/1663 (63.6%)	112/192 (58.3%)	0.055
Implantation rate	94/378 (32.9%)	16/39 (41.0%)	0.044*
Clinical pregnancy rate	91/378 (24.1%)	15/39 (38.5%)	0.032*
Live birth rate	89/378 (23.5%)	14/39 (35.9%)	0.030*

*$p<0.05$ was accepted to be statistically significant, IVF/ICSI=in vitro fertilization/intracytoplasmic sperm injection

It has been hypothesized that structural abnormalities of the uterine cavity such as polyps, myomas, adhesions and septa may impair endometrial receptivity by interfering with implantation. Therefore, it would be prudent to assume that the diagnosis and treatment of those abnormalities can restore uterine cavity, optimize uterine environment and thus improve IVF success rates [13-16].

There is an ongoing debate on the utilization of routine hysteroscopy in the management of infertile women who have no diagnosis or suspicion of intrauterine pathologies. Currently, the European Society of Human Reproduction and Embryology (ESHRE) guidelines indicate hysteroscopy to be unnecessary, unless it is for the confirmation and treatment of doubtful intrauterine pathology. This recommendation is based on the facts that hysteroscopy is an invasive procedure and an intrauterine pathology has inaccurate effects on fertility [17]. Shokeir *et al.* [18] reported that 26% of the patients with normal hysterosalpingography had abnormal hysteroscopic findings. A meta-analysis of six studies also showed that the incidence of uterine abnormalities in patients undergoing hysteroscopy ranges between 10 and 59% [12]. Data presented in this meta-analysis indicates that hysteroscopy performed in the cycle preceding the ovarian stimulation cycle could improve IVF outcome in asymptomatic patients who were undergoing their first IVF cycle and who had normal transvaginal ultrasonography findings. Both the clinical pregnancy and live birth rates were found to be higher in the hysteroscopy group than the control group. On the other hand, these data should be interpreted carefully as there was considerable methodological and statistical heterogeneity among the reviewed studies. In addition, only one of the six studies was randomized and was published as a conference abstract [12].

As for the present study, nearly 30% of the women who were to undergo their first IVF/ICSI cycle were diagnosed with an intrauterine pathology and only 35.5% of the pregnancies conceived by first IVF/ICSI attempt occurred in women who had intrauterine pathologies that were corrected by hysteroscopy. These findings suggest that hysteroscopy may not be as effective as it has been anticipated in women who would have their first IVF/ICSI treatment. The relatively narrow extent of improvement in IVF outcome after hysteroscopy may be attributed to the lower burden of intrauterine pathology expected in those having their first IVF cycle. That is, the women having their first IVF cycle probably have different fertility potentials compared to those who have gone through one or more failed IVF attempt. Therefore, the degree of improvement in IVF outcome observed after hysteroscopy prior to the first IVF cycle seems to be lower than that observed after hysteroscopy following previous IVF failure. This may consequently result in a higher number of women who should undergo hysteroscopy in order to achieve an additional clinical pregnancy [19, 20].

Office hysteroscopy is a simple, safe and minimally invasive procedure that could be readily integrated into IVF programs in most assisted reproduction centers. The possible benefits of hysteroscopy include the correction of intrauterine pathologies, procurement of easier embryo transfer, provision of more accurate embryo placement and enhancement of endometrial receptivity secondary to endometrial stimulation [21].

The limitations of the study

Despite the statistical similarities in demographic and clinical characteristics of the normal and abnormal hysteroscopy groups, there was a significant increase in the implantation, clinical pregnancy and live birth rates. This increase implies that the utilization of hysteroscopy before the first IVF cycle improves the pregnancy rates. However, the power of these findings is limited by its retrospective design, relatively small and heterogeneous cohort, absence of standardization in ovulation induction protocols and lack of longitudinal data related with the ultimate fertility outcome of the women who had hysteroscopic treatment of intrauterine pathologies.

Conclusions

The utilization of hysteroscopy before the first IVF cycle would also allow the detection and treatment of intrauterine pathologies and structural uterine abnormalities that may be responsible for the failure of IVF and, thus, result in improved pregnancy rates. This would also protect the infertile couples from additional costs of IVF cycles, where failures occur because an intrauterine pathology is missed on other screening tools such as hysterosalpingography.

Further research is warranted to clarify the benefits of hysteroscopy in asymptomatic women who would undergo their first IVF/ICSI cycle.

Conflict of interest

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References

[1] Coughlan C, Ledger W, Wang Q, Liu F, Demirol A, Gurgan T, et al. Recurrent implantation failure: definition and management. Reprod Biomed Online 2014;28:14-38.
[2] Timeva T, Shterev A, Kyurkchirev S. Recurrent implantation failure: the role of the endometrium. J Reprod Infertil 2014;15:173-83.
[3] Fatemi HM, Popovic-Todorovic B. Implantation in assisted reproduction: a look at endometrial receptivity. Reprod Biomed Online 2013;27:530-8.
[4] Moini A, Kiani K, Ghaffari F, Hosseini F. Hysteroscopic findings in patients with a history of two implantation failures following in vitro fertilization. Int J Fertil Steril 2012;6:27-30.
[5] Cenksoy P, Ficicioglu C, Yildirim G, Yesiladali M. Hysteroscopic findings in women with recurrent IVF failures and the effect of correction of hysteroscopic findings on subsequent pregnancy rates. Arch Gynecol Obstet 2013;287:357-60.
[6] Pundir J, El Toukhy T. Uterine cavity assessment prior to IVF. Womens Health (Lond) 2010;6:841-7; quiz 847-8.
[7] Papathanasiou A, Bhattacharya S. Prognostic factors for IVF success: diagnostic testing and evidence-based interventions. Semin Reprod Med 2015;33:65-76.
[8] Bosteels J, Weyers S, Puttemans P, Panayotidis C, Van Herendael B, Gomel V, et al. The effectiveness of hysteroscopy in improving pregnancy rates in subfertile women without other gynaecological symptoms: a systematic review. Hum Reprod Update 2010;16:1-11.
[9] Bettocchi S, Achilarre MT, Ceci O, Luigi S. Fertility-enhancing hysteroscopic surgery. Semin Reprod Med 2011;29:75-82.
[10] Bosteels J, Kasius J, Weyers S, Broekmans FJ, Mol BW, D'Hooghe TM. Hysteroscopy for treating subfertility associated with suspected major uterine cavity abnormalities. Cochrane Database Syst Rev 2015;2:CD009461.
[11] Makrakis E, Pantos K. The outcomes of hysteroscopy in women with implantation failures after in-vitro fertilization: findings and effect on subsequent pregnancy rates. Curr Opin Obstet Gynecol 2010;22:339-43.
[12] Pundir J, Pundir V, Omanwa K, Khalaf Y, El-Toukhy T. Hysteroscopy prior to the first IVF cycle: a systematic review and meta-analysis. Reprod Biomed Online 2014;28:151-61.
[13] Coughlan C, Ledger W, Wang Q, Liu F, Demirol A, Gurgan T, et al. Recurrent implantation failure: definition and management. Reprod Biomed Online 2014;28:14-38.
[14] Vlachadis N, Vrachnis N, Economou E, Siristatidis C. Zooming in on the definition of "recurrent implantation failure". Reprod Biomed Online 2014;29:144-5.
[15] Evans-Hoeker EA, Young SL. Endometrial receptivity and intrauterine adhesive disease. Semin Reprod Med 2014;32:392-401.
[16] Campo S, Campo V, Benagiano G. Adenomyosis and infertility. Reprod Biomed Online 2012;24:35-46.
[17] Crosignani PG, Rubin BL. Optimal use of infertility diagnostic tests and treatments: The ESHRE Capri Workshop Group. Hum Reprod 2000;15:723-32.
[18] Shokeir TA, Shalan HM, EI Shafei MN. Significance of endometrial polyps detected hysteroscopically in eumenorrheic infertile women. J Obstet Gynecol 2004;30:84-9.
[19] Fatemi HM, Kasius JC, Timmermans A, van Disseldorp J, Fauser BC, Devroey P, et al. Prevalence of unsuspected uterine cavity abnormalities diagnosed by office hysteroscopy prior to in vitro fertilization. Hum Reprod 2010;25:1959-65.
[20] Yu HT, Wang CJ, Lee CL, Huang HY, Chen CK, Wang HS. The role of diagnostic hysteroscopy before the first in vitro fertilization/intracytoplasmic sperm injection cycle. Arch Gynecol Obstet 2012;286:1323-8.
[21] Di Spiezio Sardo A, Di Carlo C, Minozzi S, Spinelli M, Pistotti V, Alviggi C, et al. Efficacy of hysteroscopy in improving reproductive outcomes of infertile couples: a systematic review and meta-analysis. Hum Reprod Update 2016;22:479-96.

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Comparison of bupivacaine and levobupivacaine for treatment of post-thoracotomy pain through thoracic paravertebral block

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ABSTRACT

Objectives. The aim of this study was to compare postoperative pain and respiratory functions of lobectomy patients who were given bupivacaine or levobupivacaine with fentanyl through a paravertebral catheter. ***Methods.*** ASA I-II patients (n=40, 18-65 years old) randomized into two groups. While Group B was administered 0.25% bupivacaine with fentanyl, Group L was administered 0.25% levobupivacaine with fentanyl at a rate of 0.1 ml/kg/hr through paravertebral catheter for patient controlled analgesia. Visual analog scale (VAS), arterial blood gases and respiratory function tests were assessed. ***Results.*** There were no significant differences in terms of demographic characteristics and surgery durations between the groups ($p>0.05$). VAS scores recorded at the 1st postoperative hour were higher in both groups compared to the following hours ($p<0.001$), but there was no difference between the groups. FEV1 and FVC measured in the postoperative period were significantly lower than preoperative values in both groups ($p<0.001$); however, there was no significant difference between the groups. There was no significant difference between the two groups regarding side effects, mean values of PaO_2, $PaCO_2$ and SpO_2 ($p>0.05$). ***Conclusion.*** Bupivacaine and levobupivacaine had equivalent efficiency and could be safely used in treatment of post-thoracotomy pain through thoracic paravertebral block.

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Keywords: Bupivacaine; levobupivacaine hydrochloride; post-thoracotomy pain; thoracic paravertebral block

Introduction

Pulmonary lobectomy is a common surgical procedure that removes one lobe of the lung, is used to treat fungal infections, benign tumors, emphysema, lung abscesses, and tuberculosis. A thoracotomy involves an incision between two ribs on the one side of chest. Successful treatment of the thoracotomy pain

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is one of the most important aspects of optimal postoperative management of surgery and anesthesia. Severe pain contributes to postoperative pulmonary dysfunction [1, 2]. As it adversely affect coughing and deep breathing, such a pain may lead to hypoxia, atelectasis, lung infection or respiratory failure. Delay in the initiation of pain treatment may lead to life-threatening situations [3, 4]. There are many pain sources related with thoracostomy, such as location of surgery incision, damage on ribs and intercostal nerves, inflammation of the chest wall around the incision, incision or crushing of pulmonary parenchyma and pleura, placement/implantation of single or multiple drains [5]. Paravertebral block is the injection of local anesthetics on the spinal nerves located in the paravertebral space. Local anesthetics infused alongside the vertebral column enable ipsilateral analgesia. Although it is mainly used for unilateral surgeries, such as chest wall trauma, breast surgery, cholecystectomy, hernia repair and renal surgery, it can be performed for bilateral surgeries as well. Paravertebral block is also applied for chronic pain and treatment of benign or malignant neuralgia [6, 7].

In this study, we aim to compare the influence and side effects of continuous of bupivacaine-fentanyl and levobupivacaine-fentanyl infusion through a paravertebral catheter on postoperative pain, pulmonary functions and arterial blood gas values of patients who underwent thoracic surgery.

Methods

The study was carried out after the approval of the Local Research Ethics Committee and the provision of informed consents of the patients. The study included 40 ASA (American Society of Anesthesiologists) I-II patients, aged between 18 and 65 years, who were scheduled to have elective surgical lobectomy under general anesthesia. Exclusion criteria consisted of infection in the area where the catheter should be installed, allergy to local anesthetics and opioids, kidney failure or liver dysfunction, pregnancy or breast-feeding, using anticoagulant drugs, and unwillingness for the study. Additionally, the patients who could not be provided with an extrapleural pocket were not included in the study. The patients were randomized into two groups according to the sealed envelope method. Twenty milliliters of 0.5% bupivacaine (Marcaine®, AstraZeneca, Istanbul, Turkey) was gived to Group B and 20 ml of 0.5% levobupivacaine hydrochloride (Chirocaine®, Abbott, Istanbul, Turkey) was gived to Group L through an epidural catheter placed in the paravertebral area.

PaO_2, $PaCO_2$ and SpO_2 values were recorded on the day before the surgery. FEV1 and FVC values were recorded preoperatively while the patient in the room air by the pulmonary function test performed with a portable spirometer (ContecTM SP10, China). None of the patients received premedication. Patients taken to the operating theater were monitored for non-invasive arterial blood pressure, heart rate, DII lead electrocardiogram, and SpO_2. After 3 minutes preoxygenization with 3 mL/minute 100% O2, 0.03-0.05 mg/kg iv midazolam, 2 mcg/kg fentanyl, 1 mg/kg 2% lidocaine, 2-3 mg/kg propofol and 0.6 mg/kg rocuronium were administered to induce general anesthesia. 50% oxygen/air and 2% sevoflurane were used for the maintenance of anesthesia. Patients were intubated with a double-lumen endobronchial tube, and the position of the tube was checked with fiberoptic bronchoscopy. At the end of the operation, the surgeon placed an epidural catheter (Perifix®, Braun, Germany) by inserting an 18-G Tuohy needle percutaneously 2.5-3 cm lateral to the incision and advancing it perpendicularly to the skin by spinous process towards the paravertebral area. After the pleural space was closed, Group B was given 20 ml of 0.5% bupivacaine and Group L was given 20 ml of 0.5% levobupivacaine through the catheter. For patient controlled analgesia, solutions of 425 mg of 0.25% bupivacaine+350 mcg fentanyl, and of 425 mg of 0.25% levobupivacaine+350 mcg fentanyl were used for Group B and Group L, respectively. Both groups received a continuous 48 hour infusion at a rate of 0.1 ml/kg/hr for patient controlled analgesia.

Patients' pain levels during rest, movement and coughing were measured at the 1st, 6th, 24th and 48th postoperative hours using the Visual Analog Scale (VAS) (0=No pain, 10=Severe pain). Patients with a VAS score of >3 were administered 1 mg/kg im pethidine (Aldolan-Gerot ®, LibaLab, Istanbul, Turkey). Application times and doses were recorded. PaO_2, $PaCO_2$, SpO_2, FEV1 and FVC values were recorded at the 24^{th} and 48^{th} postoperative hours. Side effects, such as hypotension, bradycardia nausea, vomiting and pain, were recorded postoperatively.

Statistical Analysis

Statistical analysis of the study was carried out using Statistical Package 13.0 for Windows (SPSS Inc., Chicago, USA). Shapiro-Wilk test was used as

normallity test. Continuous variables were compared using Mann-Whitney U test when the data were not normally distributed. Wilcoxon Signed rank test was used for dependent groups. Categorical variables were compared using Pearson's chi-squared test and Fisher's exact test. The *p* value of <0.05 was considered statistically significant and the values were expressed as "median" or as a number. Results were given as median values.

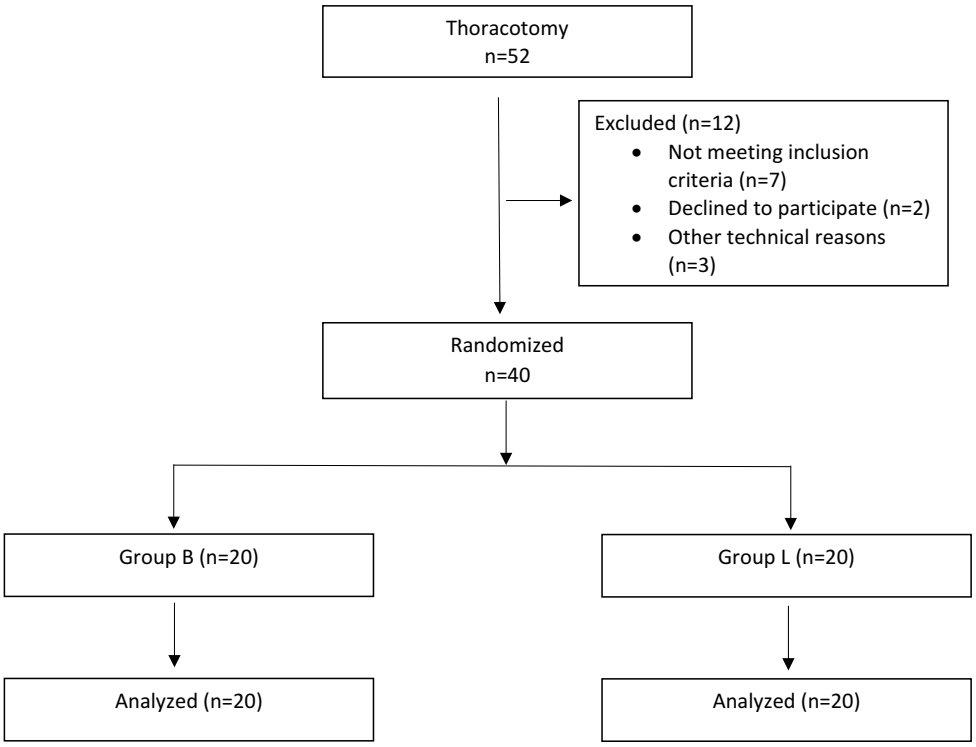

Figure 1. Flow chart of patient enrollment and analysis

Results

Out of 52 patients undergoing elective lobectomy, 40 patients were included in the study. Twelve patients were excluded (not meeting inclusion criteria, declined to participate, etc). A total of 40 patients were assessed statistically (Figure 1). There was no statistically significant difference between the groups in terms of their demographic characteristics (p>0.05) (Table 1).

When the VAS scores during rest, movement and coughing were compared, the scores obtained at the 1st postoperative hour were significantly lower than the scores measured at the 6th, 24th and 48th hours in both groups (p<0.001) (Figures 2, 3 and 4). Rest, movement, and coughing VAS scores did not show significant difference between the two groups at any time (p>0.05).

The average pethidine use was 155±117.9 mg in Group B and 142.5±144.4 mg in Group L. There was no significant difference between the two groups regarding the use of pethidine (p>0.05).

Table 1. Distribution of demographic characteristics, operation time

	Group B (n=20)	Group L (n=20)	*p*
Age (year)	51.1±10.88	50.9±11.96	0.956
Male/Female	13/7	15/5	0.490
Height (cm)	167.45±7.9	168.2±8.9	0.780
Weight (kg)	74.65±11.7	75.4±10.7	0.835
ASA I/II (n)	6/14	7/13	0.600
Operation time (minute)	139±56.6	150±61.5	0.640

Data are shown as mean ± standard deviation or number. ASA=American society of anesthesiologists

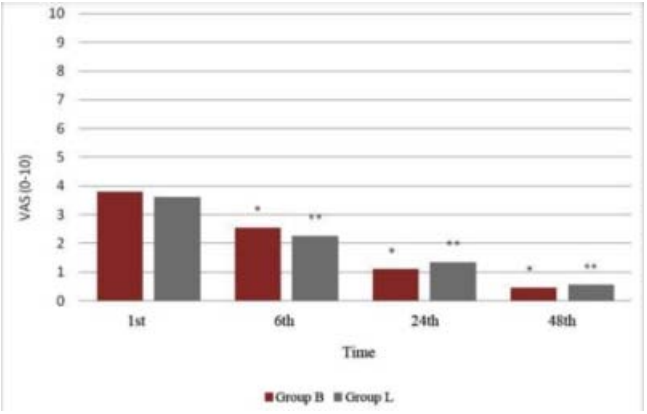

Figure 2. Mean values of VAS according to groups at the rest. VAS=Visual analogue scale, *p<0.001 (difference between 1st, 6th, 24th and 48th hours in Group B), **p<0.001 (difference between 1st, 6th, 24th and 48th hours in Group L)

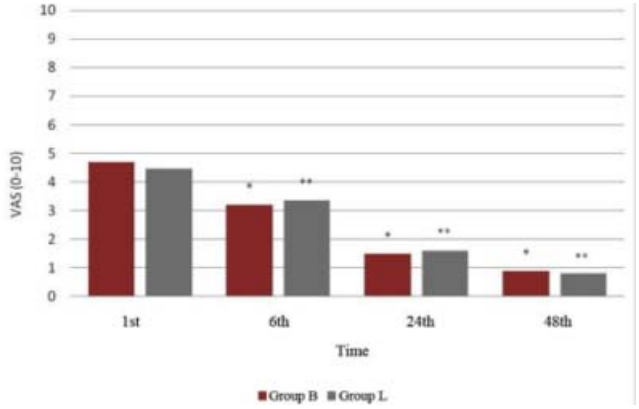

Figure 3. Mean values of VAS according to groups at the movement. VAS=Visual analogue scale, *p<0.001 (difference between 1st, 6th, 24th and 48th hours in Group B), **p<0.001 (difference between 1st, 6th, 24th and 48th hours in Group L)

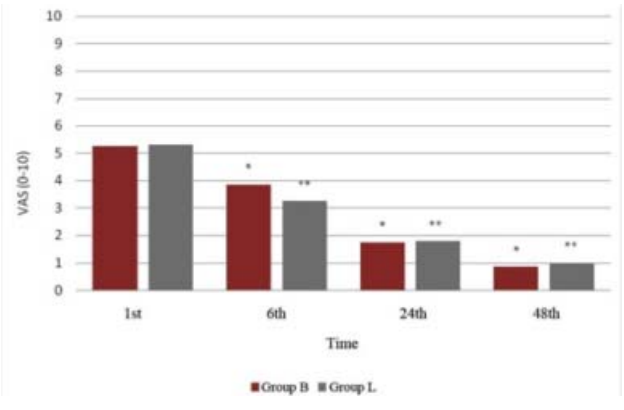

Figure 4. Mean values of VAS according to groups during the cough. VAS=Visual analogue scale, *p<0.001 (difference between 1st, 6th, 24th and 48th hours in Group B), **p<0.001 (difference between 1st, 6th, 24th and 48th hours in Group L)

The preoperative FEV1 values did not show any significant difference between Group B and Group L (p>0.05). However, in both groups, the FEV1 values measured at the 24th and 48th postoperative hours were found to be significantly lower than the preoperative FEV1 values (p<0.001) (Figure 5). The FEV1 value of both groups decreased approximately to 68% and 83% of the preoperative FEV1 value at the 24th and 48th postoperative hours, respectively. The FEV1 values measured at the 24th and 48th postoperative hours were no significant difference in both groups (p>0.05).

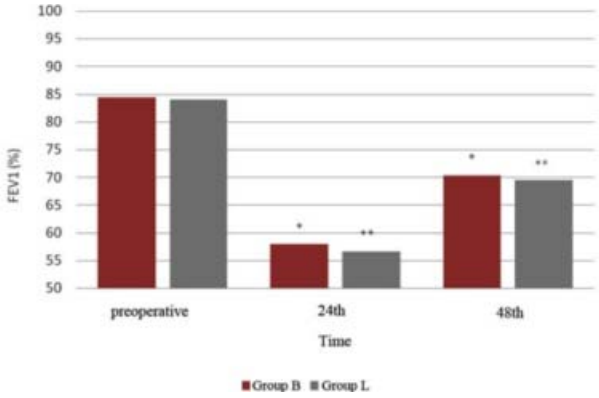

Figure 5. Mean values of FEV1 according to groups. FEV1=forced expiratory volume 1 second. VAS=Visual analogue scale, *p<0.001 (difference between preoperative, 24th and 48th hours in Group B), **p<0.001 (difference between preoperative, 24th and 48th hours in Group L)

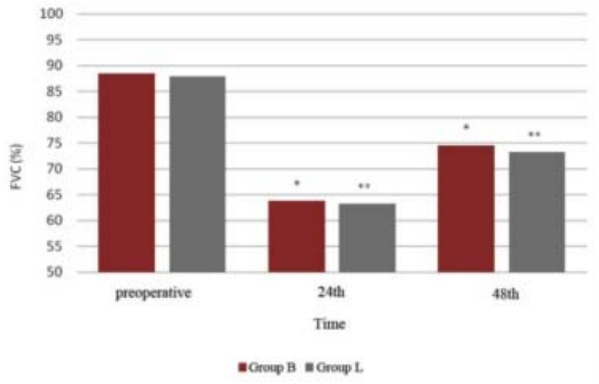

Figure 6. Mean values of FVC according to groups. FVC=forced vital capacity. VAS=Visual analogue scale, *p<0.001 (difference between preoperative, 24th and 48th hours in Group B), **p<0.001 (difference between preoperative, 24th and 48th hours in Group L)

We did not find any difference between the groups regarding the preoperative FVC values (p>0.05). In both groups, the FVC values obtained at the 24th and 48th postoperative hours were statistically significantly lower than the preoperative FVC values (p<0.001) (Figure 6). While the FVC value measured at the postoperative 24th hour was almost equal to

Table 2. PaO_2, $PaCO_2$, SpO_2 values according to groups

	Group B (n=20)	Group L (n=20)	*p*
Preoperative PaO_2 (mmHg)	91.29±6.20	91.28±5.1	0.998
Preoperative $PaCO_2$ (mmHg)	43.05±4.12	42.23±4.55	0.557
Preoperative SpO_2 (%)	79.03±3.56	83.25±3.17	0.695
Postoperative 24th hour PaO_2 (mmHg)	82.75±4.3	81.49±4.26	0.926
Postoperative 24th hour $PaCO_2$ (mmHg)	37.3±1.32	36.67±1.24	0.877
Postoperative 24th hour SpO_2 (%)	93.01±1.97	97.1±1.82	0.362
Postoperative 48th hour PaO_2 (mmHg)	80±3.83	86.32±3.05	0.573
Postoperative 48th hour $PaCO_2$ (mmHg)	37.34 ± 1.23	40.57 ± 6.03	0.300
Postoperative 48th hour SpO_2 (%)	96.11±1.3	91.76±1.94	0.325

Data are shown as mean ± standard deviation or number. PaO_2=partial pressure of oxygen in arterial blood, $PaCO_2$= partial pressure of carbon dioxide in arterial blood, SpO_2=saturation of arterial blood with oxygen

71% of preoperative FVC value, the FVC at the 48th was nearly equal to 84% of preoperative FVC. Additionally, the FVC values measured at the 24th and 48th postoperative hours did not show any significant difference between the two groups (p>0.05).

In terms of PaO_2, $PaCO_2$, SpO_2 values measured respectively preoperative period, postoperative 24th and 48th hours, there were not any significant difference between Group B and Group L (p>0.05) (Table 2).

In both groups, two (10%) patients had nausea, two (10%) patients from Group B and one (5%) patient from Group L had hypotension, which did not require therapy, and there were no significant differences between the groups (p>0.05).

Discussion

In this study, we compared the effects of bupivacaine and levobupivacaine administered through a paravertebral catheter was placed at the end of surgery for the treatment of post-thoracotomy pain. We found that bupivacaine and levobupivacaine which were combined with fentanyl and administered in equivalent doses at a fixed rate provided similar analgesia. As the thoracic epidural block, which is considered as the golden standard in thoracic surgery for the treatment of postoperative pain, has some side effects, alternative methods instead of central blocks have come into use in recent years. As a result, paravertebral block applications are becoming increasingly common [8, 9]. Some earlier studies have already reported that bupivacaine and levobupivacaine can provide sufficient analgesia in paravertebral block applications [10, 11].

Novak-Jankovic *et al.* [12] compared the efficacy of 0.25% levobupivacaine and bupivacaine infused through a paravertebral catheter, which was installed percutaneously in the preoperative period on 40 patients undergoing thoracotomy. After a bolus of morphine and 0.5% bupivacaine or levobupivacaine were administered following the placement of the catheter, morphine, clonidine and 0.25% bupivacaine or levobupivacaine were used continuously. The researchers reported that the intraoperative fentanyl requirement was less, pain scores obtained during the first 3 days of postoperative rest and during the first 2 days of exercise were lower, and the dose of the rescue analgesic was lower in the group receiving levobupivacaine. Nevertheless, pulmonary function tests and hemodynamic parameters showed similar results. In our study, patients received similar concentrations of bupivacaine and levobupivacaine infusion, which were combined with fentanyl instead of clonidine and morphine, through the paravertebral catheter which was placed at the end of the operation. Unlike the study of Novak-Jankovic *et al.* [12], the infusion rate was two times faster, and the VAS scores and rescue analgesic requirement was similar in bupivacaine and levobupivacaine groups in our study. As in the aforementioned study, the pulmonary function tests and arterial blood gas values did not show any difference between the groups in our study. In the study comparing paravertebral block and thoracic epidural block in patients having thoracotomy, Gulbahar *et al.* [13] administered 0.25% bupivacaine at a dose of 0.1 ml/kg/h using both methods and indicated that paravertebral block could provide equal and sufficient analgesia as epidural block did. In our study, we want to compare type of local anesthetic drugs administered via a paravertebral catheter, not to compare technics like that paravertebral block and thoracic epidural block. Like

this study our groups received an infusion at a rate of 0.1 ml/kg/hr bupivacaine or levobupivacaine for patient controlled analgesia. There were not any significant differences between bupivacaine or levobupivacaine groups in our study.

Garutti *et al.* [14] made comparison of three different paravertebral block applications in their study. During the operation, each patient in the three groups was infused with 0.25% bupivacaine at a rate of 0.15 ml/kg/h through a paravertebral catheter, which was percutaneously placed by the anesthesiologists in the preoperative period. While the 1st group was infused using only the paravertebral catheter, the 2nd group received subcutaneous infusion through the surgical incision. On the other hand, in the 3rd group, the percutaneous catheter was removed at the end of the operation and a new catheter was placed in the T5-T6 paravertebral space through the surgical incision. While the researchers observed that analgesia was more effective in the 2nd group, the other two paravertebral blocks were reported to ensure similar analgesic efficacy. The VAS scores of the 3rd group measured during rest, movement and coughing did not show any change at the 4th, 8th, 12th, 24th, 48th, and 72th hours. The lack of change in the VAS scores may be attributed to the fact that there was enough time for development of the block because the 1st VAS measurement took place at the postoperative 4th hour, and that the infusion rate of bupivacaine (not combined with fentanyl) was higher compared to our study.

Pintaric *et al.* [11] compared the effects of preoperative bolus dose and postoperative infusion applications in the thoracic epidural and paravertebral block on the analgesia and hemodynamics in patients undergoing thoracotomy. After catheters were placed at the beginning of the operation, a bolus of 0.25% levobupivacaine and 30 mcg/ml morphine was given through the epidural catheter and 0.5% levobupivacaine and 30 mcg/ml morphine were administered by bolus through the paravertebral catheter. The infusion was started with 200 ml of 0.125% levobupivacaine and 20 mcg/ml morphine at a rate of 0.1 ml/kg. Piritramide was used as rescue analgesic. The authors reported that there was no difference between the two groups regarding the pain scores and use of additional analgesics. Perioperative hypotension was more common in the group receiving thoracic epidural analgesia. In both groups, two (10%) patients from Group B and one (5%) patient from Group L had hypotension, which did not require therapy in our study. We also found that bupivacaine and levobupivacaine which were combined with fentanyl and administered in equivalent doses at a fixed rate provided similar analgesia and no significant difference between the two groups regarding the use of additional analgesics in paravertebral block applications.

Gulbahar *et al.* [13] indicated in the study comparing epidural block and continuous paravertebral block regarding their effects on postoperative pain and pulmonary functions after thoracotomy that both methods were effective and safe for postoperative pain treatment and improvement of pulmonary functions. In that study, postoperative the FEV1, and PEFR (peak expiratory flow rate) values showed a significant decrease compared to the preoperative values. However, there was no difference between two groups in the pre- and postoperative FEV1, and PEFR values. In the present study, the FEV1 and FVC values also showed a significant decrease in both groups at the postoperative 24th and 48th hours compared to the preoperative measurements and there was no difference between the groups regarding that decrease. We obtained similar results with the studies [13, 15] reporting significant decrease in the pulmonary function tests after thoracotomy compared to preoperative values.

The Limitations of the Study

The limitation of this study is the absence of different doses of local anesthetics. Doses we used were safe and effective, but it is need to find the minimal doses in order to optimal effectivity for both local anesthetics. The other limitation is the small number of patients involved in this study. Hence, further studies are required with a greater number of patients.

Conclusions

We concluded that bupivacaine-fentanyl or levobupivacaine-fentanyl combination infused after a bolus dose through paravertebral catheter which was inserted at the end of the operation by surgeon provided effective analgesia in patients who underwent thoracotomy. Positive effects of the catheter on pulmoner functions began second postoperative day. In conclusion, we think that the efficacy of bupivacaine and levobupivacaine is

equivalent through paravertebral catheter, and they can be safely used for post-thoracotomy pain.

Conflict of interest

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

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The authors disclosed that they did not receive any grant during conduction or writing of this study.

References

[1] Joshi GP, Bonnet F, Shah R, Wilkinson RC, Camu F, Fischer B, et al. A systematic review of randomized trials evaluating regional techniques for postthoracotomy analgesia. Anesth Analg 2008;107:1026-40.

[2] Junior Ade P, Erdmann TR, Santos TV, Brunharo GM, Filho CT, Losso MJ, et al. Comparison between continuous thoracic epidural and paravertebral blocks for postoperative analgesia in patients undergoing thoracotomy: systematic review. Braz J Anesthesiol 2013;63:433-42.

[3] Thavaneswaran P, Rudkin GE, Cooter RD, Moyes DG, Perera CL, Maddern GJ. Brief reports: paravertebral block for anesthesia: a systematic review. Anesth Analg 2010;110:1740-4.

[4] Yeung JH, Gates S, Naidu BV, Wilson MJ, Gao Smith F. Paravertebral block versus thoracic epidural for patients undergoing thoracotomy. Cochrane Database Syst Rev 2016;21;2:CD009121.

[5] Wildgaard K, Ravn J, Kehlet H. Chronic post-thoracotomy pain: a critical review of pathogenic mechanism and strategies for prevention. Eur J Cardiothorac Surg 2009;36:170-80.

[6] Piraccini E, Pretto EA, Jr, Corso RM, Gambale G. Analgesia for thoracic surgery: the role of paravertebral block. HSR Proc Intensive Care Cardiovasc Anesth 2011;3:157-60.

[7] Scarfe AJ, Hingel SS, Duncan JK, Ma N, Atukorale YN, Cameron AL. Continuous paravertebral block for post-cardiothoracic surgery analgesia: a systematic review and meta-analysis. Eur J Cardiothorac Surg 2016. pii: ezw168.

[8] Helms O, Mariano J, Hentz JG, Santelmo N, Falcoz PE, Massard G, et al. Intraoperative paravertebral block for postoperative analgesia in thoracotomy patients: a randomized, double-blind, placebo-controlled study. Eur J Cardiothorac Surg 2011;40:902-6.

[9] Marret E, Bazelly B, Taylor G, Lembert N, Deleuze A, Mazoit JX, et al. Paravertebral block with ropivacaine 0.5% versus systemic analgesia for pain relief after thoracotomy. Ann Thorac Surg 2005;79:2109-13.

[10] Burlacu CL, Frizelle HP, Moriarty DC, Buggy DJ. Pharmacokinetics of levobupivacaine, fentanyl and clonidine after administration in thoracic paravertebral analgesia. Reg Anesth Pain Med 2007;32:136-45.

[11] Pintaric TS, Potocnik I, Hadzic A, Stupnik T, Pintaric M, Novak-Jankovic V. Comparison of continuous thoracic epidural with paravertebral block on perioperative analgesia and hemodynamic stability in patients having open lung surgery. Reg Anesth Pain Med 2011;36:256-60.

[12] Novak-Jankovic V, Milan Z, Potocnik I, Stupnik T, Maric S, Stopar-Pintaric T, et al. A prospective, randomized, double-blinded comparison between multimodal thoracic paravertebral bupivacaine and levobupivacaine analgesia in patients undergoing lung surgery. J Cardiothorac Vasc Anesth 2012;26:863-7.

[13] Gulbahar G, Kocer B, Muratli SN, Yildirim E, Gulbahar O, Dural K, et al. A comparison of epidural and paravertebral catheterisation techniques in post-thoracotomy pain management. Eur J Cardiothorac Surg 2010;37:467-72.

[14] Garutti I, Gonzalez-Aragoneses F, Biencinto MT, Novoa E, Simon C, Moreno N, et al. Thoracic paravertebral block after thoracotomy: comparison of three different approaches. Eur J Cardiothorac Surg 2009;35:829-32.

[15] Concha M, Dagnino J, Cariaga M, Aguilera J, Aparicio R, Guerrero M. Analgesia after thoracotomy: epidural fentanyl/bupivacaine compared with intercostal nerve block plus intravenous morphine. J Cardiothorac Vasc Anesth 2004;18:322-6.

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Evaluation of dry eye-associated symptoms and signs after microincision cataract surgery

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ABSTRACT

Objectives. To evaluate the effects of microincision cataract surgery on dry eye-associated symptoms and signs. ***Methods.*** This prospective study included 40 eyes of 32 patients. Microincision cataract surgery was performed to eyes through 2.2 mm superior clear corneal incision. Dry eye-associated symptom scoring, corneal sensitivity test, Schirmer 1 test, tear break-up time (tBUT) were measured at 3 days before and 3 days, 10 days, 1 month, 3 months after surgery. 'One way ANOVA for repeated measures', and Pearson correlation tests were used for statistical analysis. ***Results.*** The postoperative symptom scores were significantly different from preoperative value at all consecutive examinations ($p<0.01$). The decrease in superior corneal sensitivity was significant at 3 and 10 days ($p<0.001$), and recovery to preoperative level had occured at 1 month. The decrease in tBUT was significant up to 1 month ($p=0.007$ for 3 days, $p=0.008$ for 10 days, and $p=0.018$ for 1 month). The difference in Schirmer 1 test between pre- and postoperative each visit was not significant ($p=0.32$, $p=0.12$, $p=0.092$ and $p=0.088$; respectively). Symptom score was highly correlated with operative time ($r=0.72$, $p<0.01$), and there was an inverse correlation between operative time and postoperative mean tBUT values ($r=-0.52$, $p<0.01$). ***Conclusions.*** Despite microincision cataract surgery, an aggravation of dry-eye associated symptoms, and temporary dry eye-associated signs might develop. Operative time and exposure to operating microscope light seem to an important factor on symptoms and tear film stability.

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Keywords: Microincision cataract surgery; dry eye; tear film stability

Introduction

After successful cataract surgery, dry eye-associated symptoms, such as red or watery eyes, foreign body sensation, and fatigue, frequently occur and persist in some patients. Despite good visual results after surgery, dissatisfaction of patients might reduce surgical success. Some studies have reported aggravation of dry eye symptoms and signs after cataract surgery [1, 2]. Many factors, such as topical anesthesia and eye drops containing preservatives like benzalkonium chloride, surgical incision types, exposure to light from operating microscope, disrupt to normal organization of the corneal innervation,

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might affect the ocular surface environment after cataract surgery [3-5].

The purpose of this study was to evaluate the change in tear film stability, corneal sensitivity or patients' symptoms after microincision cataract surgery, and relationships between these parameters and operative time.

Methods

Fourty eyes of 32 patients (19 men and 13 women; mean age, 65.1±8.4 years) with age-related cataract were included in this prospective study. Exclusion criteria included using of eye drops for any ocular pathology, presence of chronic ocular diseases, such as glaucoma or uveitis, disorders of the lid and nasolacrimal canal, previous ocular surgery, dry eye disease, and chronic systemic disease which might affect ocular surface, such as diabetes mellitus, collagen vascular diseases, or smokers. Patients with blepharitis, ocular allergies or pterygium were also excluded, because these factors could affect results of dry eye tests [6]. Written informed consent was obtained from each patient. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by a local ethical committee.

Phacoemulsification and intraocular lens implantation were successfully carried out by 1 surgeon in all cases and operative time was recorded for each eye. Eye drops with 2.5% phenylephrine and 0.5% tropicamide were used 3 times over half an hour to dilate pupils before cataract surgery. Topical anesthesia was achieved with 0.5% proparacaine hydrochloride. A 2.2 mm-sized clear corneal incision was made as two step grooved incision at the superior location, and two 1.0 mm-sized incisions for the side punctures were made at a 60º angle from both sides of the main incision, approximately 0.2 mm anterior to the edge of the limbal vessels. Torsional mode (OZil mode; Infinity Vision System, Alcon Laboratories Inc, Ft. Worth, TX) phacoemulsification was used for cataract surgery. All surgeries were suture-less and uncomplicated. Eye drops used after cataract surgery included moxifloxacin 4 times a day for a week, 1% prednisolone acetate 4 times daily for two weeks, 3 times daily for the third week, and 2 times a day for the fourth week. All eye drops were started 1 day after cataract surgery.

Symptom scoring, tear break-up time (tBUT), corneal sensitivity test, and Schirmer 1 test were carried out in this specific order for every patient at all visits.

Subjective symptoms were graded on a numerical scale from 0 to 4 according to the Ocular Surface Disease Index (OSDI) score [7]. The intensity of dry eye symptoms was rated from 0 to 4 as follows: 0, none; 1, mild; 2, moderate; 3, severe; 4, very severe. The frequency of dry eye symptoms was quantified as follows: 0, none; 1, some of the time; 2, half of the time; 3, most of the time; 4, all of the time. Aggravation of dry eye (when blink frequency is reduced while watching TV, driving, etc.) was quantified as follows: 0, none; 1, mild; 2, moderate; 3, severe; 4, very severe. The total score of dry eye symptoms was calculated as follows: (intensity score + frequency score + aggravation score) divided by 3. Scores ranged from 0 to 4, with higher scores indicate severe symptoms.

Corneal sensitivity was measured using a Cochet-Bonnet esthesiometer. The superior corneal surface was touched orthogonally with a defined nylon fiber. Eyelid closure was considered to be a positive response to the stimulus. The intensity of response was defined the length and the stiffness of the fiber, which was noted as millimeter.

Schirmer 1 test was measured without anesthesia. The test was lasted 5 minutes and the length of wetted paper was noted on the scale which is placed on paper. Schirmer 1 test was performed only once.

For tBUT, a fluorescein-impregnated strip wet with non-preserved saline solution was placed into inferior fornix and the patient was asked to blink several times. Using a cobalt blue filter and slit-lamp microscopy, the time which was required for the first area of tear film break-up to appear after a complete blink was noted. The test was repeated three times and the average was calculated.

All measurements were performed at 3 days before surgery, and 3 days, 10 days, 1 month and 3 months after surgery. The time interval between the tests was at least 10 minutes.

Statistical Analysis

Statistical analysis was made by using SPSS software package (SPSS 18.0). Data were analyzed by one way ANOVA for repeated measures, with Bonferroni test. The relationship between variabilities was evaluated by Pearson correlation analysis. $p< 0.05$ was regarded as statistically significant.

Results

Many patients complained of dry eye-associated symptoms, especially foreign body sensation and watery eyes after microincision cataract surgery. The symptom scores 3 days before, and 3 days, 10 days, 1 month, 3 months after cataract surgery were as follows; 0.79±1.81, 2.25±1.79, 2.29±1.53, 1.81±1.37, 1.75±1.25, respectively. The postoperative values were significantly different from the preoperative value (p<0.01 for all).

Preoperatively, the mean corneal sensitivity of superior incision location was 58.7±2.3 mm. Postoperatively, at 3 days the mean corneal sensitivity had decreased to 50.1±4.8 mm at 3 days (p<0.001) and to 53.4±5.6 mm at 10 days (p<0.001). The improvement in corneal sensitivity had continued regularly up to 1 month and recovery of corneal sensitivity to preoperative levels had occured at 1 month (Figure 1).

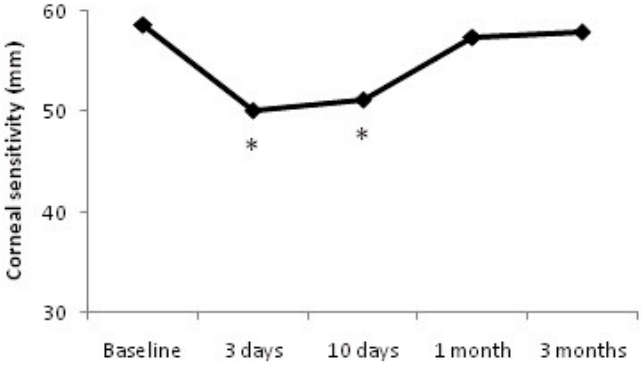

Figure 1. The mean superior corneal sensitivity from baseline to 3 days, 10 days, 1 month, 3 months (*p<0.001, Bonferroni test).

At 3 days, 10 days, and 1 month postoperatively, the decrease in tBUT was statistically significant (p=0.007, p=0.008, and p=0.018, respectively). There was no significant difference between preoperative and postoperative 3 months values (p>0.05). The difference in Schirmer 1 test between preoperative and any postoperative visits was not significant (p=0.32, p=0.12, p=0.092, p=0.088, for all consecutive visits) (Table 1).

Table 1. Changes of tear break-up time and Schirmer 1 test over time

	Preoperative	**Postoperative**			
	3 days	3 days	10 days	1 month	3 months
tBUT	11.9±2.9	6.7±3.1	6.9±2.8	8.0±4.1	9.3±3.3
p* value		0.007	0.008	0.018	0.068
ST1	12.5±3.4	13.7±4.9	13.2±4.3	12.8±3.7	12.7±5.1
***p* value&**		0.32	0.12	0.092	0.088

* Bonferroni test, compared values of tear break-up time (tBUT) between preoperative and postoperative values at specified time point, & Bonferroni test, compared values of Schirmer test 1 (ST1) between preoperative and postoperative values at specified time point.

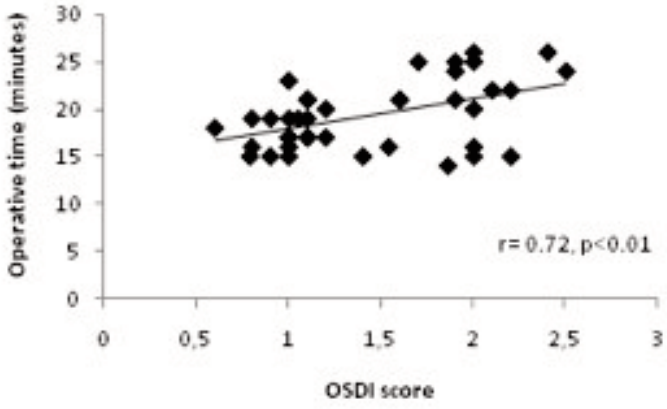

Figure 2. Correlation between OSDI score and operative time. OSDI=ocular surface disease index

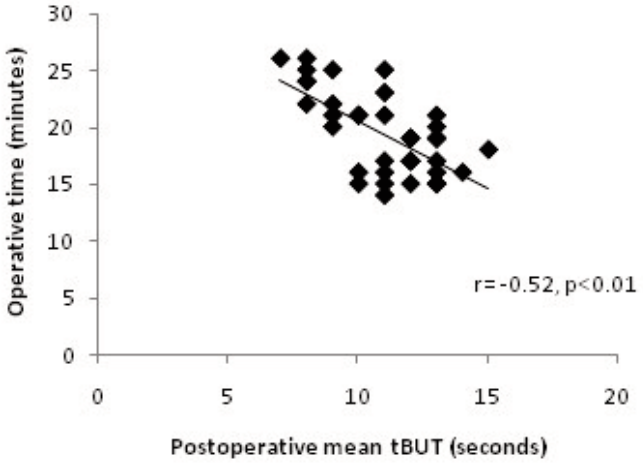

Figure 3. Correlation between tBUT values and operative time. tBUT=tear break-up time

The mean operative time was 17.4±4.9 (14-26) minutes. OSDI score was highly correlated with operative time (r= 0.72, $p<0.01$) (Figure 2), and there was an inverse correlation between operative time and postoperative mean tBUT values (r= -0.52, $p<0.01$) (Figure 3). There was no relationship between operative time and change in corneal sensitivity or Schirmer 1 test measurements ($p=0.058$ and $p=0.24$, respectively).

Discussion

In the current study, we have demonstrated that the dry eye-associated symptoms and signs increased in the early postoperative period after microincision cataract surgery. Despite microincision size which causes less damage to corneal nerves than large incision, increase of dry eye-associated symptoms and signs have indicated that the incision size is not the only mechanism of aggravation of dry eye-associated symptoms. The mechanism for the exacerbation of ocular surface damage likely includes several factors: increased inflammatory mediators due to postoperative inflammation, misuse of eye drops, toxicity from the use of benzalkonium chloride containing eye drops, decrease in corneal sensitivity which is resulted in reduced tear production, and exposure to light from the operating microscope [1-4].

Generally, dry eye-associated symptoms following cataract surgery is characterized by one of two ways. One group experienced an increase in pre-existing dry eye symptoms and the other group experienced surgically-induced dry eye. In a previous study, whether or not preoperative dry eye disease, dry eye disease symptoms occured after cataract surgery, according to NEI-VFQ25 and OSDI [1]. In our study, dissatisfaction of patients was apparent at postoperative 3 days according to symptom scores. The symptom score decreased after 10 days, but it was statistically higher than preoperative value at 1 and 3 months.

The surgical incision may potentially impact the ocular surface after cataract surgery. Historically, large incision from extracapsular cataract extractions induced damage to the corneal nerves [7, 8]. However the wounds in microincision cataract surgery seem to induce localized damage to the corneal nerves with subsequent reduced corneal sensation [6]. Sitompul *et al.* [9] reported that the corneal sensitivity decreased at the incision site and at other sites on days 1, 7, 15 after manual small-incision cataract surgery, however the change was not found statistically significant. Oh *et al.* [10] reported that the corneal sensitivity decreased significantly at 1 day postoperatively at the center and temporal incision sites, and returned to preoperative levels at 3 months after phacoemulsification with 2.8 mm corneal tunnel incision. The change in the corneal sensitivities at the other areas of the cornea was not found statistically significant. It has been reported that the corneal sensitivity had returned to preoperative levels after 3 months, in a previous study with 4.1 mm corneal incision phacoemulsification [2]. In our study, the mean corneal sensitivity of superior incision site decreased statistically significant at 3 days after micro-incisional cataract surgery with 2.2 mm clear corneal incision. The corneal sensitivity had returned to preoperative levels at 1 month postoperatively. This result indicates that the extent of incision is an important factor on recovery time of corneal sensitivity.

Depending on the damage of the corneal sensory nerves during corneal surgery, tear production decreases due to interruption of the message for tear production stimulation. Therefore, temporary dry eye symptoms might develop until the nerves regenerate again [2, 10]. Most surgical procedures, especially surgical incisions that cause denervation of the cornea, also result in impaired epithelial wound healing, increased epithelial permeability, decreased epithelial metabolic activity and loss of cytoskeletal structures associated with cellular adhesion [5]. The changes in tBUT and Schirmer tests have been reported in previous studies [1, 2, 4, 9-11]. In our study, compared with before surgery, tBUT was markedly decreased at 3 days and slightly improved up to 3 months, but it was still lower than baseline at 3 months. The change in Schirmer 1 test was not statistically significant. Irregularity of epithelium might have a role in decreased tBUT, but not in Schirmer 1 test. Small incisions may not impair reflex tear production due to less corneal sensory nerve damage.

Hazards from the optical radiation of an operating microscope can cause damage at the corneal, lenticular, and retinal levels [12]. Oh *et al.* [10] reported a decrease in the number of goblet cells in eyes with longer operative times because of more exposure to operating microscope light. We observed that for eyes which have longer operative times, dry

eye-associated symptoms according to OSDI score were more severe. After that we investigated the relationships between operative times and tear film stability tests, and found an inverse correlation between operative time and tBUT. Probably, decrease in tBUT is an important factor on dry-eye associated symptoms.

The limitations of this study

The limitations of this study were short follow-up period, and lack of histopathologic evaluation, which demonstrate squamous metaplasia and goblet cell loss.

Conclusions

In conclusion, despite microincision cataract surgery, we observed an aggravation of dry eye-associated symptoms and a decrease in corneal sensitivity and tBUT. The improvement of tests continued up to 1-3 months. However tBUT and OSDI scores had not returned to preoperative values. For this reason, patients' symptoms can be related to change in tBUT. Additionally, operative time seems an important factor on symptoms and tear-film stability. Therefore it is important to shorten the operative time and exposure to operating microscope light.

Conflict of interest

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

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References

[1] Li XM, Hu L, Hu J, Wang W. Investigation of dry eye disease and analysis of pathogenic factors in patients after cataract surgery. Cornea 2007;26(9 Suppl 1):S16-20.
[2] Khanal S, Tomlinson A, Esakowitz L, Bhatt P, Jones D, Nabili S, et al. Changes in corneal sensitivity and tear physiology after phacoemulsification. Ophthalmic Physiol Opt 2008;28:127-34.
[3] Walker TD. Benzalkonium toxicity. Clin Experiment Ophthalmol 2004;32:657.
[4] Cho YK, Kim MS. Dry eye after cataract surgery and associated intraoperative risk factors. Korean J Ophthalmol 2009;23:65-73.
[5] Kohlhaas M. Corneal sensation after cataract and refractive surgery. J Cataract Refract Surg 1998;24:1399-409.
[6] Moss SE, Klein R, Klein BE. Prevalence of and risk factors for dry eye syndrome. Arch Ophthalmol 2000;118:1264-8.
[7] Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. Arch Ophthalmol 2000;118:615-21.
[8] Lyne A. Corneal sensitivity after surgery. Trans Ophthalmol Soc U K 1982;102 (pt 2):302-5.
[9] Sitompul R, Sancoyo GS, Hutauruk JA, Gondhowiardjo TD. Sensitivity change in cornea and tear layer due to incision difference on cataract surgery with either manual small-incision cataract surgery or phacoemulsification. Cornea 2008;27:13-8.
[10] Oh T, Jung Y, Chang D, Kim J, Kim H. Changes in the tear film and ocular surface after cataract surgery. Jpn J Ophthalmol 2012;56:113-8.
[11] Ram J, Gupta A, Brar G, Kaushik S, Gupta A. Outcomes of phacoemulsification in patients with dry eye. J Cataract Refract Surg 2002;28:1386-9.
[12] Micheal R, Wegener A. Estimation of safe exposure time from an ophthalmic operating microscope with regard to ultraviolet radiation and blue-light hazards to the eye. J Opt Soc Am A Opt Image Sci Vis 2004;21:1388-92.

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Red cell distribution width, other hematological parameters and atherogenic index of plasma in patients with clopidogrel and aspirin resistance

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ABSTRACT

Objectives. Chronic inflammation might favour platelet hyperactivity, which leads to inter-individual variability in antiplatelet resistance. The aim of this study was to test the hypothesis that there is a relationship between some hematological parameters reported as measures of systemic inflammation, the atherogenic index of plasma (AIP), and antiplatelet responsiveness. ***Methods.*** This retrospective study included patients receiving aspirin (100 mg) and clopidogrel (75 mg) daily before and after stenting. Platelet inhibition was assessed using the VerifyNow P2Y12 point-of-care test. Resistance to antiplatelet therapy was defined as P2Y12 reactivity exceeding 240 units (for clopidogrel) or aspirin reaction units exceeding 550 units (for aspirin). The AIP was calculated as the logarithm of triglyceride/high density lipoprotein cholesterol. The white blood cell (WBC), platelet (P), neutrophil (N), and lymphocyte (L) counts, red cell distribution width (RDW), hemoglobin (Hb), plateletcrit, mean platelet volume (MPV), platelet distribution width, and N/L and P/L ratios were evaluated. ***Results.*** Of 232 patients (73% male; median age, 63 years; range, 38-87 years), 52 (22%) were aspirin resistant and 82 (35%) were clopidogrel resistant; 7.7% were both aspirin and clopidogrel resistant. Median RDW levels were significantly higher (14.4% [interquartile rate (IQR) 3] vs. 13.9% [IQR 1.3]; p=0.01) and Hb levels significantly lower (12.0±1.6 g/dL vs. 13.2±1.7 g/dL; p<0.001) in the clopidogrel-resistant patients than in the clopidogrel responders. WBC, AIP, MPV, N/L, and P/L ratios were not statistically significant (p>0.05). Multivariate logistic regression showed that Hb (odds ratio [OR]=0.73; 95% confidence interval [CI], 0.60-0.88; p=0.001) and RDW (OR=1.26; 95% CI, 1.02-1.55; p=0.02) were independent predictors of clopidogrel resistance. ***Conclusions.*** Both RDW and Hb were independent variables associated with clopidogrel resistance, but antiplatelet resistance cannot be predicted based on other hematological parameters or AIP.

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Keywords: Red cell distribution width; hematological parameters; atherogenic index of plasma; systemic inflammation; clopidogrel resistance

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Introduction

Antiplatelet therapy is mandatory during and after percutaneous coronary intervention (PCI) for the prevention of acute stent thrombosis. To reduce the risk of stent thrombosis, dual antiplatelet therapy is currently recommended for PCI patients [1].

Stent thrombosis is more frequent when platelet inhibition by aspirin and clopidogrel is inadequate [2]. Clopidogrel and aspirin use different pathways to inhibit platelet aggregation. A combination of these drugs provides an additive effect over those of either agent alone [3]. There is wide inter-individual variability in the inhibitory effect of these drugs on platelet aggregation, some individuals exhibit a reduced or even absent antiplatelet response, and this is called antiplatelet drug resistance.

Inflammation and haemostasis are pathophysiologic processes that affect each other. Platelets influence various aspects of the inflammatory process, including interactions with leucocytes and the vascular endothelium. Recently, a number of studies have shown that chronic inflammation might favour platelet hyperactivity, which leads to inter-individual variability in antiplatelet resistance [4-6].

Mean platelet volume (MPV), platelet distribution width (PDW), red cell distribution width (RDW), neutrophil-to-lymphocyte (N/L) ratio are simple markers that indicate chronic inflammation [7]. The platelet-to-lymphocyte (P/L) ratio is an indicator of the balance between inflammation and thrombosis which is more advantageous than platelet or lymphocyte counts alone.

The atherogenic index of plasma (AIP) calculated as log triglyceride (TG)/high density lipoprotein cholesterol (HDL-C) has been universally used by practitioners as a significant predictor of atherosclerosis [8]. Plasma TG and HDL-C are basically opposite in direction with respect to measures of oxidative stress/systemic low-grade inflammation. Recently its shown that hypertriglyceridemia affects antiplatelet response [9].

We aimed to test the hypothesis that there is a relationship between inflammation-related haematological parameters, AIP and antiplatelet resistance. We also evaluated the relationship between RDW, MPV, N/L ratio, and P/L ratio, and (AIP) and antiplatelet responsiveness.

Methods

This study complies with the Declaration of Helsinki. The study protocol was approved by the Institutional Ethics Committee. This retrospective analysis was based on computerized databases in our Hospital's cardiovascular center. All study participants were hospitalized as acute coronary patients from the emergency department and were scheduled to undergo planned PCI for other coronary vessels. In addition, all patients were undergoing elective PCI, and all medical records for the cases from January to December 2015 were reviewed.

Based on medical records, patients aged >18 years and receiving 75 mg daily doses of clopidogrel, combined with 100 mg aspirin daily during 10 days to one month prior to elective PCI, were selected. Peripheral venous blood samples were obtained from subjects prior to the next dose of clopidogrel and aspirin on elective PCI day for study.

Patients with severe anaemia, thrombocytopenia, myelodysplastic syndrome, coagulopathy and recent blood transfusion, history of stroke or central nervous system damage, recent major surgery, or chronic renal insufficiency requiring dialysis were excluded.
Throughout the study, the quality of test results was validated by daily internal quality control procedures and participation in an external quality assessment scheme.

Platelet Aggregation Assays

Platelet response to aspirin and clopidogrel (P2Y12) was performed with the Verifynow point-of-care system (Accumetrics Inc., San Diego, CA) based on turbidimetric-based optical changes measurement in whole blood as platelets aggregate. Specific cartridges for the aspirin and P2Y12 pathway were used, and the degree of aggregation was quantified by a corresponding increase in light transmission and is reported as aspirin reaction units (ARU) and P2Y12 reaction units (PRU), respectively. In the literature, a value of ≥550 ARU indicates aspirin resistance, and clopidogrel resistance is indicated as PRU ≥240 [10].

Atherogenic Index

The levels of total cholesterol (T Chol), TG and HDL-C were determined using commercially available assay kits (Abbott Diagnostics, Abbott Park, IL) with an Architect C16000 auto-analyser (Abbott Diagnostics). AIP is calculated as previously described [8].

Complete Blood Cell Count

Samples were analysed in an automated haematology analysis system (Coulter LH-780 haematology analyser, Beckman Coulter Inc., Fullerton, CA) that measures platelet size and platelet count using aperture-impedance technology. The WBC, P, N and L counts, RDW, MPV and PDW were recorded, and the N/L and P/L ratios were calculated from these parameters. Patients with elevated WBC counts (>11,000/mL) and any inflammatory, infective, or malignant diseases were excluded from the study.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version 21.0 for Windows (SPSS Inc., Chicago, IL). Data are expressed as median (interquartile range) or mean±SD after normality test. The Shapiro–Wilk test was used to determine the normality of the evaluated variables. After evaluating the normality, statistically significant differences between parameters with Gaussian distributions were tested by a Student's t-test; variables with a non-Gaussian distribution were compared using the Mann-Whitney U test. Variables (PRU, ARU,T Chol, N/L and P/L ratios, MPV, RDW were evaluated using the Spearman correlation coefficients. Logistic regression analysis of the relationship between clopidogrel resistance and the variables were analysed. Statistical significance was set at $p<0.05$.

Results

A total of 232 patients (73% male, median age, 63 years) were included in the analysis. The patients were divided into two groups according to aspirin and clopidogrel response. According to our criteria, a total of 52 patients (22%) were aspirin-resistant and 82 patients (35%) were clopidogrel-resistant (Tables 1 and 2). Approximately 7.7% of the patients were both aspirin-resistant and clopidogrel-resistant.

The median ARU for the responder group was 471 (interquartile range [IQR] 80), and 590 ARU (IQR 72) for aspirin-resistants. The median PRU for the responder group was 173 (IQR 100), and for the resistant group, it was 289 (IQR 46).

Median RDW levels were significantly higher (14.4% [interquartile rate (IQR) 3] vs. 13.9% [IQR 1.3]; $p=0.01$) and Hb levels significantly lower (12.0±1.6 g/dL vs. 13.2±1.7 g/dL; $p<0.001$) in the clopidogrel-resistant patients than in the clopidogrel responders. However; WBC, AIP, MPV, N/L, and P/L ratios were not statistically significant ($p>0.05$). Our correlation analysis indicated that clopidogrel resistance as PRU was positively correlated with

Table 1. Demographic and laboratory parameters in patients (n=232)

Parameters	Aspirin responder	Aspirin resistant	*p*
Age	63 (15)	64 (12)	
Number of patients	180	52	
Female/male	43/137	20/32	
Baseline laboratory results			
PRU	206 (125)	219 (187)	
ARU	471(80)	590(72)	
Hb (g/dL)	12.7±1.9	13.0±1.4	0.831
RDW (%)	14.2 (1.6)	14.0 (1.1)	0.078
Platelet (10^3 /µL)	235 (88)	241 (80)	0.451
MPV(fL)	8.6±1.0	8.3±1.0	0.089
PCT	0.20 ±0.06	0.20±0.04	0.706
PDW (%)	16.8±0.6	16.7 ±0.6	0.290
WBC (10^3 /µL)	8.5(2.8)	8.2 (2.4)	0.235
N/L ratio	2.6±1.4	2.5±1.4	0.299
P/L ratio	117±48	120±48	0.418
T Chol (mg/dL)	182±48	200±49	0.062
Triglycerides (mg/dL)	145 (107)	162 (140)	0.287
HDL (mg/dL)	40 (12)	43 (14)	0.591
LDL (mg/dL)	104±39	118±41	0.055
Atherogenic index	0.16±0.30	0.21±0.30	0.362

Data are expressed as median (interquartile range) or mean±SD after normality test. PRU=P2Y12 reactivity unit, ARU=aspirin reaction units, N/L=neutrophile/lymphocyte, P/L=platelet/lymphocyte, MPV=mean platelet volume, PCT=plateletcrit, PDW=platelet distribution width, WBC=white blood cell, T Chol=total cholesterol, HDL=high density lipoprotein, LDL=low density lipoprotein LDL

Table 2. Demographic and laboratory parameters in patients (n=232)

Parameters	Clopidogrel responder	Clopidogrel resistant	*p*
Age	62 (15)	65 (15)	
Number of patients	150	82	
Female/male	29/121	34/48	
Baseline laboratory results			
PRU	173 (100)	289 (46)	
ARU	495 (120)	509 (83)	
Hb (g/dL)	13.2±1.7	12.0±1.6*	<0.001
RDW (%)	13.9 (1.3)	14.4 (3)*	0.001
Platelet (10^3 /µL)	240 (89)	235 (67)	0.337
MPV(fL)	8.5±1.0	8.5±0.9	0.857
PCT	0.20±0.06	0.23±0.05	0.309
PDW (%)	16.8 ±0.6	16.8 ±0.6	0.557
WBC (10^3 /µL)	8.6 (2.3)	8.0 (1.9)	0.056
N/L	2.6±1.1	2.5±1.3	0.747
P/L	118±47	121±45	0.323
T Chol (mg/dL)	191±46	178±53	0.840
Triglycerides (mg/dL)	150 (120)	175 (85)	0.632
HDL (mg/dL)	40 (12)	43 (14)	0.075
LDL (mg/dL)	110±40	102±41	0.078
Atherogenic index	0.18±0.31	0.15±0.29	0.480

Data are expressed as median (interquartile range) or mean±SD after normality test. PRU=P2Y12 reactivity unit, ARU=aspirin reaction units, N/L=neutrophile/lymphocyte, P/L=platelet/lymphocyte, MPV=mean platelet volume, PCT=plateletcrit, PDW=platelet distribution width, WBC=white blood cell, T Chol=total cholesterol, HDL=high density lipoprotein, LDL=low density lipoprotein LDL, *p<0.05

RDW (r=0.297, p<0.001), and that aspirin resistance as ARU was negatively correlated with RDW (r= –0.149, p=0.023); whereas r values point to a poor correlation between variables. Hb was negatively correlated with PRU (r= –0.35, p<0.001) and RDW (r= –0.41, p<0.001). None of the other correlations were statistically significant (Table 3).

In univariate logistic regressionanalysis; Hb, RDW, and WBC were predictors of clopidogrel resistance (Table 3). In multivariate logistic regression analysis, Hb (odds ratio [OR]=0.73; 95% confidence interval [CI], 0.60-0.88; p=0.001) and RDW (OR=1.26; 95% CI, 1.02-1.55; p=0.02) were independent predictors of clopidogrel resistance (Table 4). None of the variables we evaluated was a risk factor for aspirin resistance.

Discussion

This is the first study showing that high RDW is a significant and independent predictor of resistance to clopidogrel and that there is a negative correlation between RDW and PRU.

There are a number of studies indicating that RDW has been influenced by inflammation and oxidative stress, and a strong correlation between RDW and inflammatory markers, C-reactive protein, and sedimentation rate has been observed [11-13]. We found that inflammation-related CBC parameters were similar between the groups; however, this was not in agreement with our working hypothesis. We did not find a correlation between RDW and inflammation markers, N and WBC counts, N/L ratio, or MPV.

Table 3. Correlation between variables in all patients (n=232).

		T Chol	Atherogenic index	N/L ratio	P /L ratio	MPV	RDW
PRU	**r**	-0.08	-0.06	-0.09	-0.01	0.07	0.30
	p	0.273	0.443	0.443	0.935	0.322	<0.001*
ARU	**r**	0.11	0.10	-0.09	0.01	-0.09	-0.15
	p	0.109	0.184	0.160	0.871	0.194	0.023*

* Correlation is significant at the .05 level (2-tailed). PRU=P2Y12 reactivity unit, ARU=aspirin reaction units, T Chol=total cholesterol, N/L=neutrophile/lymphocyte ratio, P/L=platelet /lymphocyte ratio, MPV=mean platelet volume, RDW=red cell distribution width

Table 4. Evaluation of parameters tested for their ability to predict the clopidogrel resistance using univariate and multivariate logistic regression analysis

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Hb	0.65 (0.55-0.78)	<0.001*	0.73 (0.60-0.88)	0.001*
RDW	1.40 (1.17-1.68)	<0.001*	1.26 (1.02-1.55)	0.020*
WBC	1.15 (1.01-1.28)	0.056	1.14 (0.99-1.39)	0.060
N/L ratio	1.01(0.82-1.25)	0.860		
P/L ratio	1.002 (0.99-1.008)	0.550		
PLT	0.99 (0.99-1.002)	0.320		
MPV	1.02 (0.78-1.33)	0.850		
AIP	0.75(0.28-1.96)	0.550		
LDL	0.99 (0.98-1.002)	0.190		

Hb=hemoglobin, RDW=red cell distribution width, WBC=white blood cell, LDL=low density lipoprotein, N/L=neutrophile/lymphocyte, P/L=platelet/lymphocyte ratio, MPV=mean platelet volume, AIP=atherogenic index of plasma, *p<0.05

Oxidative stress may be another underlying biological mechanism that may lead to increased RDW. High oxidative stress contributes to elevated RDW by reducing RBC survival, increasing the release of large premature red blood cells into the peripheral circulation and increasing the fragility of red blood cells and affecting red cell lifespan [14]. Oxidative stress can enhance platelet aggregation to clopidogrel responsiveness in coronary artery disease patients [15]. Moreover, a recent study showed that patients under clopidogrel therapy showed different expressions of proteins involved in oxidative stress [16]. Because we did not look at the oxidative parameters, we cannot comment on if the RDW is related to the oxidant status in clopidogrel-resistants in our study group.

Tziakas *et al.* [17] described a link between RDW and lipidic composition of erythrocyte membranes. The stability of erythrocytes may be maximal within an optimal range of membrane fluidity [18]. Increases in erythrocyte membrane cholesterol levels are responsible for the deterioration of cell deformability, which affects the lifespans of circulating erythrocytes, and this results in elevated RDW values [13, 17, 18]. However, we did not find a correlation between AIP, T cholesterol, and RDW in our patients, which is in agreement with Vaya *et al.* [13]'s study. They also did not observe a correlation between RDW and T cholesterol, HDL-C, LDL cholesterol, or TG in a healthy Mediterranean population [13]. They found that RDW is associated with inflammatory markers but not with an unfavourable lipid profile.

Aspirin's effect on platelet aggregation is subject to inter-individual and intra-individual variability, which can be attributed to multifactorial reasons [20-22]. MPV, PDW, or PCT values were not different between groups, similar to Nada [21]'s study, which observed that diabetic patients receiving aspirin or clopidogrel did not show significant differences in MPV when compared with controls [19]. Hyperglycaemia may decrease the effectiveness of antiplatelet therapy by increasing reactive oxidant species and lead to aspirin resistance by binding to thromboxane receptors, whereas hypercholesterolaemia may blunt aspirin's effect on thrombin [23, 24]. Genetics also play a role in patient response to aspirin as polymorphisms of platelets membranes postulated to cause aspirin resistance. However, we could not find the variables we evaluated as a risk factor of ASA resistance.

The Limitations of the Study

There are some limitations of this study. First of all, this is a single-centre, retrospective case-control study in which the selected population may not reflect the whole cohort. A lack of CRP, erythrocyte sedimentation rate and interleukin levels as inflammatory markers is another limitation of this study. Finally, we selected the VerifyNow method for ASA and clopidogrel resistance measurements, but there are other methods of measuring antiplatelet resistance that were not chosen for this study.

Conclusions

Antiplatelet resistance cannot be predicted based on other haematological parameters or AIP. However, this result should be verified in well-designed, large-scale studies on antiplatelet therapy resistance.

Conflict of interest

The authors disclosed no conflict of interest during

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References

[1] Wassef AW, Khafaji H, Syed I, Yan AT, Udell JA, Goodman SG, et al. Short duration vs standard duration of dual-antiplatelet therapy after percutaneous coronary intervention with second-generation drug-eluting stents- A systematic review, meta-analysis, and meta-regression analysis of randomized controlled trials. J Invasive Cardiol 2016. pii: JIC2016915-2.

[2] Shirasaka Y, Chaudhry AS, McDonald M, Prasad B, Wong T, Calamia JC, et al. Interindividual variability of CYP2C19-catalyzed drug metabolism due to differences in gene diplotypes and cytochrome P450 oxidoreductase content. Pharmacogenomics J 2015;16:375-87.

[3] Manolis AS, Manolis TA, Papadimitriou P, Koulouris S, Melita H. Combined antiplatelet therapy: still a sweeping combination in cardiology. Cardiovasc Hematol Agents Med Chem 2013;11:136-67.

[4] Osmancik P, Paulu P, Tousek P, Kocka V, Vidimsky P. High leukocyte count and interleukin-10 predict high on-treatment-platelet-reactivity in patients treated with clopidogrel. J Thromb Thrombolysis 2012;33:349-54.

[5] Larsen SB, Grove EL, Kristensen SD, Hvas AM. Reduced antiplatelet effect of aspirin is associated with low-grade inflammation in patients with coronary artery disease. Thromb Haemost 2013;109:920-9.

[6] Caruso R, Rocchiccioli S, Gori AM, Cecchettini A, Giusti B, Parodi G, et al. Inflammatory and antioxidant pattern unbalance in "clopidogrel-resistant" patients during acute coronary syndrome. Mediators Inflamm 2015;2015:710123.

[7] Ozer S, Yilmaz R, Sonmezgoz E, Karaaslan E, Taskin S, Butun I, et al. Simple markers for subclinical inflammation in patients with Familial Mediterranean Fever. Med Sci Monit 2015;21:298-303.

[8] Dobiasova M, Frohlich J. The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apo B-lipoprotein-depleted plasma. Clin Biochem 2001;34:583-8.

[9] Karepov V, Tolpina G, Kuliczkowski W, Serebruany V. Plasma triglycerides as predictors of platelet responsiveness to aspirin in patients after first ischemic stroke. Cerebrovasc Dis 2008;26:272-6.

[10] Song TJ, Suh SH, Min PK, Kim DJ, Kim BM, Heo JH, et al. The influence of anti-platelet resistance on the development of cerebral ischemic lesion after carotid artery stenting. Yonsei Med J 2013;54:288-94.

[11] Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G. Red blood cell distribution width: A simple parameter with multiple clinical applications. Crit Rev Clin Lab Sci 2015;52:86-105.

[12] Fornal M, Wizner B, Cwynar M, Krolczyk J, Kwater A, Korbut RA, et al. Association of red blood cell distribution width, inflammation markers and morphological as well as rheological erythrocyte parameters with target organ damage in hypertension. Clin Hemorheol Microcirc 2014;56:325-35.

[13] Vaya A, Sarnago A, Fuster O, Alis R, Romagnoli M. Influence of inflammatory and lipidic parameters on red blood cell distribution width in a healthy population. Clin Hemorheol Microcirc 2015;59:379-85.

[14] Mohanty JG, Nagababu E, Rifkind JM. Red blood cell oxidative stress impairs oxygen delivery and induces red blood cell aging. Front Physiol 2014;5:84.

[15] Tresukosol D, Suktitipat B, Hunnangkul S, Kamkaew R, Poldee S, Tassaneetrithep B, et al. Effects of Cytochrome P450 2C19 and Paraoxonase 1 Polymorphisms on antiplatelet response to clopidogrel therapy in patients with coronary artery disease. PLoS One 2014;9:e110188.

[16] Volpi E, Giusti L, Ciregia F, Da Valle Y, Giannaccini G, Berti S, et al. Platelet proteome and clopidogrel response in patients with stable angina undergoing percutaneous coronary intervention. Clin Biochem 2012;45:758-65.

[17] Tziakas D, Chalikias G, Grapsa A, Gioka T, Tentes I, Konstantinides S. Red blood cell distribution width: a strong prognostic marker in cardiovascular disease: is associated with cholesterol content of erythrocyte membrane. Clin Hemorheol Microcirc 2012;51:243-54.

[18] de Freitas MV, de Oliveira MR, dos Santos DF, et al. Influence of the use of statin on the stability of erythrocyte membranes in multiple sclerosis. J Membr Biol 2010;233:127-34.

[19] Koter M, Franiak I, Strychalska K, Broncel M, Chojnowska-Jezierska J. Damage to the structure of erythrocyte plasma membranes in patients with type-2 hypercholesterolemia. Int J Biochem Cell Biol 2004;36:205-15.

[20] Lippi G, Sanchis-Gomar F, Danese E, Montagnana M. Association of red blood cell distribution width with plasma lipids in a general population of unselected outpatients. Kardiol Pol 2013;71:931-6.

[21] Nada AM. Red cell distribution width in type 2 diabetic patients. Diabetes Metab Syndr Obes 2015;30:525-33.

[22] Bhatt DL. Aspirin resistance: more than just a laboratory curiosity. J Am Coll Cardiol 2004;43:1127-9.

[23] Wang TH, Bhatt DL, Topol EJ. Aspirin and clopidogrel resistance: an emerging clinical entity. Eur Heart J 2006;27:647-54.

[24] Sharma RK, Reddy HK, Singh VN, Sharma R, Voelker DJ, Bhatt G. Aspirin and clopidogrel hyporesponsiveness and nonresponsiveness in patients with coronary artery stenting. Vasc Health Risk Manag 2009;5:965-72.

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What is the ideal age of circumcision for wound healing time?

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ABSTRACT

Objective. Circumcision is practiced worldwide. Currently, the effect of age at the time of circumcision on wound healing is not fully known. This study aimed to determine the effect of age at the time of circumcision on wound healing. ***Methods.*** The study included 382 male patients aged ≤16 years that were circumcised between January 2014 and December 2014. Data for 345 patients that were followed-up regularly were evaluated retrospectively. Circumcision was performed using a bipolar diathermic knife. Circumcision wounds were considered healed when the 2 suture lines were observed to be completely apposed. Wound healing time was analyzed according to age at the time of circumcision. ***Results.*** Mean age of the patients was 7.2 years (range; 6 days-16 years). Mean duration of surgery was 327.5 sec and mean healing time was 4.3 days. The patients were classified according to age as group 1 (0-2 years; n=114; 32.9%), group 2 (3-6 years; n=60; 17.3%), and group 3 (7-16 years; n=171; 49.8%). Mean duration of surgery in groups 1-3 were 280.9 sec, 320.2 sec and 356.5 sec; respectively, and healing times were 4.1, 4.2 and 4.5 days; respectively. Healing time was significantly longer in group 3 than in groups 1 and 2 ($p<0.05$). There was no significant difference in healing time between groups 1 and 2 ($p>0.05$). ***Conclusion.*** Wound healing time was shorter in the patients aged 0-6 years than in those aged 7-16 years.

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Keywords: Circumcision; wound healing; age; pediatric; penis

Introduction

Circumcision, which is perceived to step of being a man in Turkey, is among the most commonly performed surgical procedures worldwide. Circumcision is known to protect against urinary tract infections in children and HIV infection in adults. Circumcision is commonly performed in newborns in western countries, whereas it is commonly performed in children in eastern countries and in adults in African

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countries in which sexually transmitted diseases are common [1. However, the ideal age for circumcision remains a matter of debate.

Currently, the effect of age at the time of circumcision on wound healing is not fully elucidated. As such, the present study aimed to determine the effect of age at the time of circumcision on wound.

Methods

The study included 376 male patients aged ≤16 years that were circumcised between January 2014 and December 2014 at Orhangazi State Hospital by a single surgeon. Data for 345 patients that were followed-up regularly were evaluated retrospectively. Circumcision was performed under sedation anesthesia (IV ketamine HCl, 2 mL kg–1) following penile block with prilocaine in patients aged 1-16 years, whereas in those aged <1 year only penile block was used. The prepuce was suspended in the 12 o'clock and 6 o'clock lines by using a clamp after the adherence of prepuce had been released. Excess prepuce was excised using a bipolar diathermic knife over the clamp, while preserving the glans. Excessive tissue on the mucosa and skin was removed using a bipolar knife when necessary. Mucosa and skin were sutured using 4.0 rapid vicryl. Duration of surgery was considered the time from the onset of local anesthesia to the last suture.

Dressing was not applied post-surgery and antibiotic prophylaxis was not given. Patients hospitalized about two hour after the circumcision for controlling any bleeding or side effects of anesthesia. Patients were discharged with prescriptions for an analgesic drug and topical epithelizing cream. Wound healing time was recorded hospital database when patient came to control about one week later. Circumcision wounds were considered healed when the two suture lines were observed to be completely apposed (Figure 1A-D).

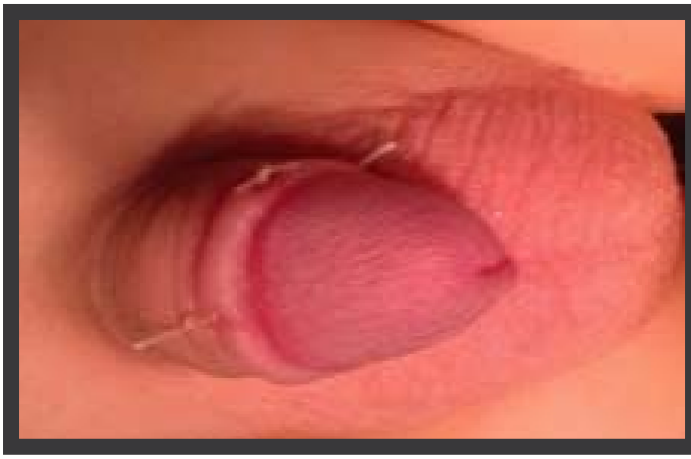

Figure 1A. Postoperative circumcision wound

Figure 1B. Circumcision wound at 2nd day

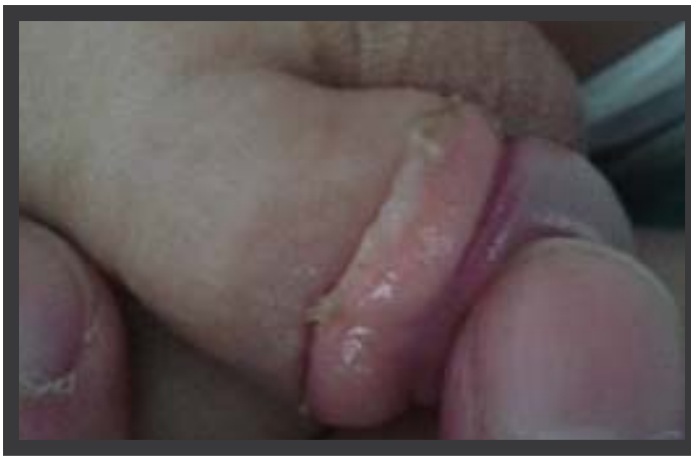

Figure 1C. Circumcision wound at 3rd day

Figure 1D. Wound healing completed at 4th day

Families of the patients were informed about taking daily photograph of circumcision wound area and pictures were checked by surgeon. Written informed consent was obtained from all the patient's families. The study protocol was approved by the local Review Board.

The patients were classified according to age as group 1 (0-2 years), group 2 (3-6 years), and group 3 (6-16 years). Wound healing time was compared between the 3 age groups. Complication rates were also evaluated.

Statistical Analysis

Data were analyzed using IBM SPSS v.20.0 for Windows (IBM Corp., Armonk, NY, USA). Correlation analysis was used to determine the association between variables and the Kruskal-Wallis H test was used for inter-group comparisons. *p* value less than 0.05 was considered as statistically significant.

Results

Mean age of 345 patients was 7.2 years (range; 6 days-16 years). Mean duration of surgery was 327.5±70.1 seconds and mean healing time was 4.3±0.9 days. Groups number of patients, operation time, healing time and statistical results shown in Table 1.

There was a significant and moderate correlation between surgical duration and age at the time of circumcision (p=0.0001); duration of surgery increased with patient age. There was a significant but low degree of correlation between age and recovery time (p=0.003). Healing time was significantly longer in group 3 (p<0.05), whereas as healing time did not differ significantly between groups 1 and 2 (p>0.05). Mild edema 2-3 days in duration was the most common complication and was noted in 82 (24%) patients. In all, 19 (5.6%) patients had edema for >3 days and all had symptomatic recovery following topical steroid treatment. None of the patients had burn, infection or inadequate tissue resection.

Discussion

The ideal age for circumcision remains a contentious issue. The procedure is primarily performed in newborns in Western countries, versus primarily in children in Eastern countries and in adults in African countries in which sexually transmitted diseases are common [1]. Any procedure done to the body of a child during the phallic period (aged 2-6 years) is thought to be potentially perceived as a threat to body integrity and negatively affect a child's psychology; therefore, circumcision is not recommended in this age group unless medically indicated. But time of circumcision decision mostly given by the parents regarding the psychological affects. Sahin *et al.* [2] studied 411 children and reported that age at the time of circumcision in Turkey varies between 2 years and 11 years (mean: 7 years), and that 15% of children undergo circumcision at age <1 year, 8% at age 1-3 years, 35% at age 3-6 years, and 41% at age >6 years. A Turkish study performed by Sivasli *et al.* [3] reported that circumcision before age 1 year was preferred because of rapid recovery and the child is thought to not experience any pain or fear and that circumcision after age 2 years was preferred because of the belief that undergoing circumcision at a younger age may be harmful. In the present study mean age at the time of circumcision was 7.2 years, which is consistent with Sahin *et al.* [2], and 32.9% of the patients were aged 0-2 years (group 1), 17.3% were aged 3-6 years (group 2), and 49.8% were aged 7-16 years (group 3). We think that group 2 was

Table 1. Outcomes of the patients related to operation time and healing time

	Patients (n=345)	Operation time (Seconds)	Healing time (Days)
Group 1 (0-2 years)	114 (32.9%)	280.9±70.1	4.1± 0.9
Group 2 (3-6 years)	60 (17.3%)	320.2±53.8	4.2± 0.8
Group 3 (7-16 years)	171 (49.8%)	356.5±74.0	4.5± 0.9
Kruskall-Wallis H		H=164.04*	H=11.51**

Data are shown as mean±standard deviation or number (percent), * p=0.0001: group 1 vs group 2, group 1 vs group 3 and group 2 vs group 3, ** p=0.003: group 2 vs group 3

proportionally the smallest because of the information we gave.

Researchers have investigated the differences between fetal wound healing and adult wound healing. Inflammation in fetuses was reported to be less severe than in adults [4]. Furthermore, fetal wounds were observed to heal without scarring [4, 5]. Whereas platelet-derived growth factor (PDGF) was not noted in fetal skin tissue, a moderate increase was observed after 12 h and 1 d of the onset of wound healing [5]. It was also reported that hyaluronic acid and platelet growth factor-β3 (PGF-β3) levels are higher in fetal wounds, and that interleukin 6, interleukin 8, PGF-β1, and tumor necrosis factor-alpha (TNF-α) levels are higher in adult wounds [6], indicating that the inflammatory reaction in adults is stronger than that in fetuses. The high levels of these cytokines in adult wounds play a role in scar formation. Additionally, it was reported that an elevation in the PGF-β level leads to granulation tissue formation [7]. The role of hormonal factors in wound healing during the prepubertal period and post-pubertal period has also been investigated [8]. Androgens are known to play a role in pro-inflammatory and anti-inflammatory pathways, both on a systemic level and cellular level [9]. These metabolic differences indicate that wound healing differs according to age. In the present study mean healing time in groups 1-3 was 4.1 days, 4.2 days, and 4.5 days, respectively, and was significantly longer in group 3 than in groups 1 and 2 ($p< 0.05$); healing time increased with age. In our knowledge, this is the first study that evaluate age distribution effects on wound healing time at circumcision

Environmental factors should also be considered when evaluating wound healing after circumcision. A stable penis position associated with diaper use facilitates the integrity of the 2 suture lines post circumcision, whereas the degree and duration of erections can negatively affect apposition of the suture lines. Kelly *et al.* [10] suggested wound dehiscence in adult circumcision patients was caused by penile erection when tissue adhesive was used for wound closure. In the present study the duration of surgery increased significantly as patient age increased, perhaps because the number of sutures required increased along with penile length, which increased with age. In addition, we think surgery was prolonged in some cases due to the need for additional tissue excision associated with inadequate prepuce excision.

The Limitations of the Study

The present study has some limitations due to its retrospective design. Metabolic changes during the wound healing period, and cellular responses and the role of hormones during inflammation were not evaluated. Additionally, the effect of steroid treatment (administered for edema) on wound healing was not evaluated.

Conclusions

The ideal age for circumcision and its effect on wound healing remain unclear. The present findings show that wound healing time following circumcision increased with age. Additional research is required to clearly delineate the ideal age for circumcision (a very common surgical intervention) with regard to its surgical and psychological effects.

Informed consent

Written informed consent were obtained from families of the patients for the publication photographes used in this study.

Conflict of interest

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

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References

[1] World Health Organization. Traditional male circumcision among young people: a public health perspective in the context of HIV prevention. Geneva. 2009. pp:10-5.

[2] Sahin F, Beyazova U, Akturk A. Attitudes and practices regarding circumcision in Turkey. Child Care Health Dev 2003;29:275-80.

[3] Sivasli E, Bozkurt AI, Ceylan H, Coskun Y. [Knowledge, attitude and behavior of parents regarding circumcision in Gaziantep]. Cocuk Sagligi ve Hastaliklari Dergisi 2003;46:114-8. [Article in Turkish]

[4] Ferguson MW, O'Kane S. Scar-free healing: from embryonic mechanisms to adult therapeutic intervention. Philos Trans R Soc Lond B Biol Sci 2004;359:839-50.

[5] Song HF, Chai JK, Lin ZH, Chen ML, Zhao YZ, Chen BJ, et al. A comparative study of PDGF and EGF expression in skin wound healing between human fetal and adult. Zhonghua Zheng

Xing Wai Ke Za Zhi 2003;19:199-202.
[6] Bermudez DM, Canning DA, Liechty KW. Age and pro-inflammatory cytokine production: wound-healing complications for scar-formation and the timing of genital surgery in boys. J Pediatr Urol 2011;7:324-31.
[7] Al-Attar A, Mess S, Thomassen JM, Kauffman CL, Davison SP. Keloid pathogenesis and treatment. Plast Reconstr Surg 2006;117:286-300.
[8] Zouboulis CC, Degitz K. Androgenaction on human skin from basic research to clinical significance. Exp Dermatol 2004;13(Suppl 4):5-10.
[9] Ashcroft GS, Mills SJ. Androgen receptor-mediated inhibition of cutaneous wound healing. J Clin Invest 2002;110:615-24.
[10]. Kelly BD, Lundon DJ, Timlin ME, Sheikh M, Nusrat NB, D'Archy FT, et al. Pediatric sutureless circumcision - an alternative to the standard technique. Pediatr Surg Int 2012;28:305-8.

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Relation of neutrophil/lymphocyte ratio to resistant hypertension

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ABSTRACT

Objectives. Resistant hypertension has unfavourable effects on cardiovascular and other systems. The aim of this study was to investigate the association of neutrophil/lymphocyte (N/L) ratio and resistant hypertension. ***Methods.*** A total of 140 patients were included in the study. Ambulatory 24-hour blood pressure monitoring, transthoracic echocardiography and blood sample analyzing were performed in all patients. There were 60 patients with resistant hypertension group (mean age=55.1±9.7 years) and 80 patients with non-resistant hypertension group (mean age=56.8±14.1 years). ***Results.*** Mean neutrophil levels were significantly higher in resistant hypertension group (71.7±6.1% vs. 65.9±5.4%, $p<0.001$), while lymphocyte levels were significantly higher in non-resistant hypertension group (22±4.7% vs. 17.5±4.1%, $p<0.001$). N/L ratio was significantly higher in resistant hypertension group (4.3±1.2 vs. 3.1±0.9, $p<0.001$). In multivariate analysis, diabetes mellitus (odds ratio [OR]=2.857; 95% confidence interval [CI], 1.349-6.053; $p=0.006$), N/L ratio (OR=2.699; 95% CI, 1.821-4.002; $p<0.001$) and obesity (OR=3.429; 95% CI, 1.675-7.019; $p=0.001$) were independent predictors of resistant hypertension. ***Conclusion.*** The N/L ratio, which is cheaply and easily measurable laboratory data, is independently associated with resistant hypertension.

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Keywords: Resistant hypertension; ambulatory blood pressure monitoring, neutrophil/lymphocyte ratio

Introduction

Hypertension is the most common condition seen in primary care and leads to myocardial infarction, stroke, renal failure, and death if not treated appropriately [1]. Resistant hypertension has more unfavorable effects on cardiovascular and other systems when compared with non-resistant hypertension. Several risk factors including obesity, excessive alcohol consumption, high sodium intake,

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obstructive sleep apnea and undetected secondary forms of hypertension have been demonstrated for resistant hypertension [2].

Resistant hypertension is defined as persistent elevation of blood pressure above goal despite concurrent use of three antihypertensive drugs, each of unique class with a diuretic included among the treatment regimen, and with all drugs at target dose [2]. The main pathophysiological mechanisms of resistant hypertension have not been clearly understood. For many years, researchers have focused to determine the underlying pathophysiological mechanisms for better understanding the resistant hypertension and to produce new therapeutic targets to reduce the mortality and morbidity from cardiovascular disorders.

Cardiovascular disorders are the most important reason for death around the world [3, 4]. Recent years, with the growing understanding of the role of inflammation in cardiovascular disorders, studies have focused on to investigate the relation of inflammatory markers and cardiovascular outcomes.

Neutrophil/lymphocyte (N/L) ratio is the sign of balance between neutrophil and lymphocyte levels in the body and an indicator of systemic inflammation [3, 4]. The N/L ratio has been associated with poor outcomes in cardiovascular disorders [5-8]. Little is known, however, regarding the association of N/L ratio levels with resistant hypertension. The goal of this study was to evaluate the association of the N/L ratio with resistant hypertension.

Methods

Patients

This is a multicenter, cross-sectional study from four different outpatient clinics. We use official and ambulatuar blood pressure monitoring to diagnose resistant hypertension. Five hundred and eighty-two patients with hypertension for this study were screened between January and December 2015. The study population included 60 patients with resistant hypertension (21 female; mean age=55.1±9.7 years) and 80 patients with non-resistant hypertension as control group (26 female; mean age=56.8±14.1 years). Patients included in the study were older than 18 years and had both non-resistant hypertension and resistant hypertension. Age, gender, body mass index, risk factors, current therapy and biochemical measurements, fasting blood glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride levels were recorded.

The exclusion criteria were cardiovascular disease including coronary artery disease, congestive heart failure, congenital heart disease, moderate and severe valvular heart disease, peripheral vascular disease, established chronic renal failure or serum creatinine levels >1.5 mg/dl (132 μmol/l), chronic obstructive pulmonary disease, thyroid dysfunction, known malignancy, known inflammatory disease, hematological disease, autoimmune disease, acute infection, pregnancy, anticoagulant agent use, white blood cell count >12 000 cells per μL or <4000 cells per μL, and high body temperature >37.3 ^{0}C, anemia, other medication that would affect blood pressure such as nasal decongestants. Fifty-eight patients including 22 patients with coronary artery disease, 13 patients with congestive heart failure, 2 patients with chronic renal failure and 21 patients refused to participate were excluded from the study.

The class of antihypertensive drugs were thiazide diuretics, calcium channel blockers, ACE inhibitors, angiotensin II receptor antagonists (ARB), beta blockers and alfa adrenergic receptor antagonists. There were hundred and ninety-eight patients taking one or more drugs including diuretics.

A 12-lead electrocardiography and transthoracic echocardiography (TTE) were performed for each patient. This study complied with the Declaration of Helsinki, informed consent was obtained from all patients and the protocol was approved by our local ethics committee.

Echocardiographic study

TTE was performed by two independent echocardiographers with a 2.5-MHz transducer and harmonic imaging in the cardiology department according to the recommendations of the American Society of Echocardiography. Left ventricular systolic and diastolic diameters were measured by M-mode echocardiography. The left ventricular ejection fraction (LVEF) was assessed using with Teichholz method [9]. Additionally, diameter of the left atrium, abnormal blood flows due to valve insufficiency, and if present, the degree of valvular stenosis were evaluated with 2D, M-mode, Doppler, and tissue Doppler studies. Systolic pulmonary artery pressure was calculated by adding the estimated right atrial pressure to the right ventricle systolic pressure obtained from the tricuspid insufficiency peak velocity.

Blood Pressure Monitoring

Clinical blood pressure was measured 3 times in the seated position by a cardiologist using a mercury sphygmomanometer after 10 minutes resting. The average of the 3 measurements was used for the representative examination value. Proper cuff size was determined based on arm circumference. The measurement was performed under controlled condition in a quiet room.

Twenty-four hours ambulatory blood pressure monitoring was performed for all subjects with Space-Labs 90207 (Redmond, WA USA). The cuff was mounted on the non-dominant arm between 8 and 9 AM and removed 24 h later. Cuff size was chosen according to arm circumference. Device was programmed to register blood pressure at 30-min intervals in day-time and one hour intervals in night-time for the 24-h period. The majority of records were performed on working days. Subjects were instructed to maintain their usual activities and keep their arm immobile at the time of each cuff inflation. Valid records had to fulfill a series of pre-established criteria, including at least 80% of systolic blood pressure and diastolic blood pressure successful recordings during the day-time and night-time periods, 24-h duration, and at least one blood pressure measurement per hour. Evaluation was performed taking the mean values of day and night blood pressures into account. Subjects were classified as hypertensive if the day-time value of systolic blood pressure >135 mmHg or diastolic blood pressure >85 mmHg, or night-time value of systolic blood pressure >120 mmHg or diastolic BP>70 mmHg on ambulatory blood pressure monitoring according to recommendations for the management of hypertension in the European guidelines [10]. Resistant hypertension is defined as resistance to treatment when a therapeutic strategy that includes lifestyle modification plus a diuretic and two different classes of antihypertensive drugs at adequate doses fails to control systolic and diastolic blood pressure (10). Each reading was edited by the computer and manually, and outliers (systolic blood pressure <80 mm Hg or >260 mm Hg; or diastolic blood pressure <40 mmHg or >150 mmHg; and heart rate <40 or >150 beats/min) were deleted.

Blood Samples

In all patients, antecubital venous blood samples for the laboratory analysis were drawn on admission in the hospital. The blood samples were drawn in the morning. Common blood counting parameters were stored in citrate-based anticoagulated tubes and measured by Sysmex K-1000 auto analyzer within 5 minutes of sampling. Hematology tests are essential for determining the number of blood cells that are responsible for oxygen transport or hemostasis. Reference counts were obtained by a standardized Sysmex K-1000 auto analyzer (Sysmex Corporation, Kobe, Japan). Comparisons between HemoCue white blood cell and the reference analyser were assessed in several groups, namely white blood cell below normal, within normal range, above normal range, and at borderline between normal and abnormal. Glucose, creatinine, blood urea nitrogen, lipid profile (total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol, triglyceride were determined by standard methods.

Statistical Analysis

Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. We report continuous data as mean and standard deviation or median. We compared continuous variables using Student t-test or Mann-Whitney U test between groups. Categorical variables were summarized as percentages and compared with the Chi-square test. The effects of different variables on resistant hypertension were calculated in univariate analysis for each. The variables for which the unadjusted p value was <0.10 in logistic regression analysis were identified as potential risk markers and included in the full model. We reduced the model by using backward elimination multivariate logistic regression analyses and we eliminated potential risk markers by using likelihood ratio tests. A two tailed p value <0.05 was considered significant and confidence interval was 95%. All statistical analyses were performed with the SPSS version 21 (SPSS Inc., Chicago, Illinois).

Results

The baseline demographic, biochemical characteristics, history of medicine use of patients in both groups are shown in Table 1. Age, gender, biochemical parameters, smoking, hypercholesterolemia were similar between groups. With respect to baseline laboratory status, fasting glucose, cholesterol parameters, blood urea nitrogen levels were not significantly different between groups (Table 1). The presence of diabetes mellitus, obesity and creatinine levels were significantly higher in the

Table 1. Baseline characteristics of patients in groups

Variable	*Non-resistant Hypertension (n=80)*	*Resistant Hypertension (n=60)*	*p*
Age, years	56.8±14.1	55.1±9.7	0.41
Gender, female/male	26/54	21/39	0.75
Body mass index, kg/m^2	25.2±4.1	27.9±4.1	<0.001
Obesity, n (%)	20 (25)	32 (53.3)	0.001
Smoking, n (%)	21 (26.3)	20 (33.3)	0.36
Hypercholesterolemia, n (%)	28 (35)	27 (45)	0.23
Diabetes mellitus, n (%)	16 (20)	25 (41.7)	0.005
Mean Official Blood Pressure			
Systolic (mmHg)	119.4±10.5	161.6±14.5	<0.001
Diastolic (mmHg)	70.7±7.8	108.9±11.8	<0.001
Heart rate, beats/min	74.3±9.3	75.3±9.8	0.54
Biochemical parameters			
Total cholesterol, mg/dl	184±39.7	173.5±38.5	0.11
High density lypoprotein, mg/dl	36.2±6.3	35.8±6.2	0.72
Low density lypoprotein, mg/dl	128.3±28.5	122.3±29.3	0.23
Plasma triglycerides, mg/dl	120.1±40	123.5±49.4	0.66
Fasting glucose, mg/dL	111.3±46.5	128.4±44.8	0.03
Blood urea nitrogen, mg/dL	23.4±7.5	23.8±7.3	0.93
Creatinine, mg/dL	1.15±0.26	1.35±0.35	<0.001
hs-CRP (mg/L)	3.9±2.2	7.5±4.2	<0.001
Current therapy			
Treated with 3 drugs, n (%)	19 (23.8)	47 (78.3)	<0.001
Treated with 4 drugs, n (%)	0	9 (15)	<0.001
Treated with 5 drugs, n (%)	0	4 (2.9)	0.02

Data are expressed as mean ± standart deviation. hs-CRP=high-sensitivity C-reactive protein

resistant hypertension group when compared to the other group (p=0.005, p=0.001, p<0.001, respectively). The mean systolic and diastolic blood pressures were significantly higher in resistant hypertension group (161.6±14.5 vs. 119.4±10.5, p<0.001; 108.9±11.8 vs. 70.7±7.8, p<0.001, respectively) (Table 1). High-sensitivity C-reactive protein (hs-CRP) levels were significantly higher in resistant hypertension group than in non-resistant hypertension group (7.5±4.2 vs. 3.9±2.2, p<0.001).

The ambulatory blood pressure monitoring and echocardiographic parameters for each group are shown in Table 2. Patients with resistant hypertension had significantly higher 24-h, day-time and night-time mean blood pressure levels. The mean LVEF was similar between groups (55.6±6.7 vs. 54.2±5.0, p=0.16).

Hemoglobin, white blood cell, platelet count and mean platelet volume were similar between groups. With respect to white blood cell distribution, mean neutrophil levels were significantly higher in resistant hypertension group (71.7±6.1% vs. 65.9±5.4%, p<0.001), while lymphocyte levels were significantly higher in non-resistant hypertension group (22±4.7% vs. 17.5±4.1%, p<0.001). N/L ratio was also significantly higher in resistant hypertension group (4.3±1.2 vs. 3.1±0.9, p<0.001) (Table 3). There were positive correlations between the N/L ratio and day-time systolic ambulatory blood pressure (r : 0.328, p<0.001) and night-time systolic ambulatory blood pressure (r : 0.427, p<0.001).

In the groups, some of variables that can be effective on resistant hypertension were significantly different between groups. Thus, the effects of multiple variables on the resistant hypertension analyzed with univariate and multivariate logistic regression analyses. The variables for which the unadjusted p value was <0.10 in univariate analysis were identified as potential risk markers for resistant hypertension and included in the full model. In multivariate logistic

Table 2. Comparison of ambulatory blood pressure monitoring and echocardiographic parameters of patients in groups

Variable	Non-resistant Hypertension (n=80)	Resistant Hypertension (n=60)	*p*
Mean 24-hour systolic ABP (mmHg)	118.2±10.9	146.5±14.9	<0.001
Mean 24-hour diastolic ABP (mmHg)	73.8±8.4	82±12.9	<0.001
Mean 24-hour heart rate	76±9.8	78.±9.7	0.24
Mean day-time systolic ABP (mmHg)	118.4±10.4	148.1±13.8	<0.001
Mean day-time diastolic ABP (mmHg)	71.9±7.2	83.7±14.9	<0.001
Mean night-time systolic ABP (mmHg)	107.6±11.3	140.6±11.2	<0.001
Mean night-time diastolic ABP (mmHg)	65.2±8.9	81.9±11.9	<0.001
Mean night/day systolic BP	0.91±0.09	0.95±0.11	0.001
Mean night/day diastolic BP	0.88±0.14	0.81±0.09	<0.001
Conventional echocardiography			
LVEDD, mm	50.5 ± 4.5	49.2 ± 4.5	0.09
LVESD, mm	32.5 ± 3.8	30.9 ± 4.5	0.02
IVS thickness, mm	12 ± 1.6	12.6 ± 1.5	0.04
PW thickness, mm	11.9 ± 1.4	12.2 ± 1.4	0.20
LVEF, %	55.6 ± 6.7	54.2 ± 5.0	0.16

Data are expressed as mean ± standard deviation. ABP=ambulatory blood pressure, BP=blood pressure, IVS=interventricular septum, LVEDD=left ventricular end-diastolic diameter, LVEF=left ventricular ejection fraction, LVESD=left ventricular end-systolic diameter, PW=posterior wall

regression analysis, diabetes mellitus (odds ratio [OR]=2.857; 95% confidence interval [CI], 1.349-6.053; *p*=0.006), N/L ratio (OR=2.699; 95% CI, 1.821-4.002; *p*<0.001) and obesity (OR=3.429; 95% CI, 1.675-7.019; *p*=0.001) were independent predictors of resistant hypertension (Table 4).

Discussion

In the present study, we hypothesized that N/L ratio as a marker of inflammatory status in the body could be associated with resistant hypertension and a widely available predictor for resistant hypertension in hypertensive patients. We found that N/L ratio was significantly higher in resistant hypertensive patients than in non-resistant hypertensive patients. Additionally, N/L ratio is independent predictor of resistant hypertension.

Hypertension is the most common condition seen

Table 3. Common blood counting parameters of patients

Variable	*Non-resistant Hypertension (n=80)*	*Resistant Hypertension (n=60)*	*p*
Hemoglobin, g/dL	12.4±1.6	12.5±1.5	0.57
White blood cell count, x 10^9/L	6.9±2.3	7.3±2.0	0.27
Platelet count, x 10^9/L	270±70	286.5±79.3	0.20
Red blood cell count, x 10^6/mL	4.7±0.8	4.8±0.9	0.98
Mean corpuscular volume, fl	84±5.4	85.3±5.7	0.20
Mean platelet volume, fl	8.8±0.8	8.9±0.9	0.64
White cell distribution			
Neutrophil, %	65.9±5.4	71.7±6.1	<0.001
Lymphocyte, %	22±4.7	17.5±4.1	<0.001
Eosinophils, %	2.2±0.5	2.1±0.7	0.47
Monocytes, %	6.8±1.4	6.4±1.4	0.11
Neutrophil/lymphocyte ratio	3.1±0.9	4.3±1.2	<0.001

Data are expressed as mean ± standard deviation

Table 4. Effects of various variables on resistant hypertension in logistic regression analyses

Variables	Univariate			Multivariate		
	Unadjusted OR	95% CI	*p*	Adjusted OR*	95% CI	*p*
Age	0.994	0.958 - 1.030	0.729			
Gender	1.337	0.522 – 3.424	0.545			
Diabetes mellitus	2.798	1.141 – 6.864	0.025	2.857	1.349 – 6.053	0.006
Smoking	1.737	0.690 – 4.376	0.241			
Hypercholesterolemia	1.637	0.690 – 3.887	0.264			
Obesity	3.934	1.643 – 9.419	0.002	3.429	1.675 – 7.019	0.001
Hemoglobin	1.075	0.836 – 1.383	0.571			
Neutrophil/lymphocyte ratio	2.878	1.872 – 4.426	0.046	2.699	1.821 – 4.002	<0.001

*Adjusted for, age, gender, diabetes mellitus, smoking, hypercholesterolemia, hemoglobin and neutrophil/lymphocyte.
OR= odds ratio, CI= confidence interval

in primary care and leads to myocardial infarction, stroke, renal failure, and death if not treated appropriately [1]. During last 20 years clinical investigations have demonstrated an important correlation between ambulatory blood pressure monitoring readings and prevalence and extent of cardiovascular events [11].

Resistant hypertension is defined as resistance to treatment when a therapeutic strategy that includes lifestyle modification plus a diuretic and two different classes of antihypertensive drugs at adequate doses fails to lower systolic value to 140 mmHg and diastolic blood pressure value to 90 mmHg [10]. Resistant hypertension has more unfavorable effects on cardiovascular and other systems when compared with non-resistant hypertension. Several risk factors have been demonstrated for resistant hypertension. Obesity, excessive alcohol consumption, high sodium intake, obstructive sleep apnea and undetected secondary forms of hypertension have been well established causes of resistant hypertension [2]. According to current literature, association between inflammatory status and hypertension has been demonstrated. Previous studies have suggested that there is a relation between hypertension and systemic inflammation [12]. The relationship between circulating subtype of white blood cell and hypertension has also been well documented [13, 14]. In a large cohort with a long follow-up period, Tatsukawa *et al.* [13] aimed to investigate the relationship between white blood cell count, including differential white blood cell count, and the incidence of hypertension over a 40-year period in 9,383 subjects who did not have hypertension at baseline. They concluded that the neutrophil and total white blood cell counts are significantly associated with the incidence of hypertension. Tian *et al.* [14] showed in their study that increased neutrophils and decreased lymphocytes are significantly correlated with the regulation of blood pressure and the development of hypertension. However, inflammatory status and resistant hypertension has not been fully elucidated. The purpose of the present study is to examine this relation. According to this study, inflammation has also been implicated in the development and the progression of resistant hypertension.

The effects of neutrophils on the development of hypertension may follow from their role in inflammation. Recent evidences suggest that the pro-inflammatory cytokines, especially IL-6 and IL-8, are associated with obesity [15, 16], diabetes mellitus [17], and cardiovascular disease [18]. IL-8 is also the main cytokine that responsible for neutrophil recruitment and activation [19]. Activated neutrophils adhere to vascular endothelium with higher affinity, which may result in capillary increased vascular resistance [20]. Activated neutrophils also release reactive oxygen specifies which contribute to oxidative stress [21, 22], and impair the endothelium-dependent vasorelaxation [23].

In respect to role of lymphocytes in hypertension, there is controversial data in the literature. Low grade activated immune system with lymphocyte subtypes cause the renal damage with tubulointerstitial area via maintaining the autoimmune reactivity [24]. After the oxidative stress-induced renal vasoconstriction, modified oxidative proteins can serve as autoantigens that aggravate auto-inflammatory response [25] and result with tubulointerstitial infiltration of lymphocytes and macrophages [26]. However, the association of lymphocytes infiltration and circulating lymphocytes has not been explained. In a previous

study, Guzik *et al.* [27] showed that in genetically altered mice lacking B and T cells do not develop hypertension or vascular damage. When they transferred T cells, then hypertension was occurred. This evidence supports that lymphocytes have a pivotal role and a positive association in the pathogenesis of hypertension. In another aspect, normally functional T-lymphocytes are required for the genesis of hypertension. However, in the pathological process with activated autoimmune system, auto-antibodies attacked to lypmphocytes [28]. Lymphocyte destruction may release ROS with the activation of NADPH oxidase activity and Ang II via the AT1 receptors [27]. With the inflammatory process, more chemotactic cytokines and intracellular adhesion molecules were produced which could attract more lymphocytes into tissue including the kidneys. Consequently, circulating lymphocytes decrease with the destruction and infiltration to tubulointerstitiel area [26]. In the present study, neutrophil count was significantly higher while lymphocyte count was significantly lower in resistant hypertensive patients suggest that more inflammation cause more uncontrolled hypertension.

Obesity is a very common feature of patients with resistant hypertension. The mechanisms by which obesity contributes to blood pressure elevation and interferes with blood pressure control are complex. Insulin resistance and hyperinsulinemia, impaired sodium excretion, increased sympathetic nervous system activity, increases in aldosterone sensitivity related to visceral adiposity, and obstructive sleep apnea have all been implicated as potential reasons [29]. The patients with resistant hypertension had higher albuminuria, lower eGFR and higher prevalence of any chronic kidney disease and advanced diabetic retinopathy than non-resistant hypertension patients. Also, these variables were independently associated with resistant hypertension versus non-resistant hypertension, and resistant hypertension was twice more prevalent in patients with than in those without chronic kidney disease. This is the first evidence on an association between diabetic retinopathy and resistant hypertension, though it is in keeping with the high frequency of retinal lesions in nondiabetic patients with resistant hypertension [30].

The Limitations of the Study

The major limitations of the present study may be represented by the small number of patients. The hematological parameters may vary depending on body mass index, hs-CRP levels, presence of diabetes mellitus, and the medication history affecting white blood cell count such as steroid, or other medical history of physical or emotional stress status. However, our population contain homogeneous unselected patients with resistant hypertension, therefore mirroring the real world scenario. Finally, these conclusions may not extend to the general population; therefore, the results of this study need confirmation in larger studies.

Conclusions

In the light of these evidences, in the present study we aimed to investigate the role of inflammation in resistant hypertension. We used an index that N/L ratio to reflect the inflammatory status of the body. We showed that N/L ratio is significantly higher in resistant hypertensive patients and a significant predictor of resistant hypertension even after multivariate model. We suggest that in addition to previously described factors inflammatory status should be considered in the underlying mechanisms of resistant hypertension. Therefore, for treatment of resistant hypertension, it might be more accurate to target of inflammation.

Conflict of interest

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

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References

[1] James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507-20.

[2] Parati G, Lombardi C, Hedner J, Bonsignore MR, Grote L, Tkacova R, et al. Position paper on the management of patients with obstructive sleep apnea and hypertension: joint recommendations by the European Society of Hypertension, by the European Respiratory Society and by the members of European COST (Co-operation in Scientific and Technological research) ACTION B26 on obstructive sleep apnea. J Hypertens 2012;30:633-46.

[3] Akpek M, Kaya MG, Lam YY, Sahin O, Elcik D, Celik T, et al. Relation of neutrophil/lymphocyte ratio to coronary flow to in-hospital major adverse cardiac events in patients with ST-elevated myocardial infarction undergoing primary coronary intervention. Am J Cardiol 2012;110:621-7.
[4] Kaya MG, Akpek M, Elcik D, Kalay N, Yarlioglues M, Koc F, et al. Relation of left atrial spontaneous echocardiographic contrast in patients with mitral stenosis to inflammatory markers. Am J Cardiol 2012;109:851-5.
[5] Horne BD, Anderson JL, John JM, Weaver A, Bair TL, Jensen KR, et al. Which white blood cell subtypes predict increased cardiovascular risk? J Am Coll Cardiol 2005;45:1638-43.
[6] Turak O, Ozcan F, Isleyen A, Tok D, Sokmen E, Buyukkaya E, et al. Usefulness of the neutrophil-to-lymphocyte ratio to predict bare-metal stent restenosis. Am J Cardiol 2012;110:1405-10.
[7] Yildiz A, Kaya H, Ertas F, Oylumlu M, Bilik MZ, Yuksel M, et al. Association between neutrophil to lymphocyte ratio and pulmonary arterial hypertension. Arch Turk Soc Cardiol 2013;41:604-9.
[8] Kalay N, Dogdu O, Koc F, Yarlioglues M, Ardic I, Akpek M, et al. Hematologic parameters and angiographic progression of coronary atherosclerosis. Angiology 2012;63:213-7.
[9] Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al; American Society of Echocardiography's Nomenclature and Standards Committee; Task Force on Chamber Quantification; American College of Cardiology Echocardiography Committee; American Heart Association; European Association of Echocardiography, European Society of Cardiology. Recommendations for chamber quantification. Eur J Echocardiogr 2006;7:79-108.
[10] Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013;34:2159-219.
[11] Kurtul A, Yarlioglues M, Murat SN, Ergun G, Duran M, Kasapkara HA, et al. Usefulness of the platelet-to-lymphocyte ratio in predicting angiographic reflow after primary percutaneous coronary intervention in patients with acute ST-segment elevation myocardial infarction. Am J Cardiol 2014;114:342-7.
[12] Pauletto P, Rattazzi M. Inflammation and hypertension: the search for a link. Nephrol Dial Transplant 2006;21:850-3.
[13] Tatsukawa Y, Hsu WL, Yamada M, Cologne JB, Suzuki G, Yamamoto H, et al. White blood cell count, especially neutrophil count, as a predictor of hypertension in a Japanese population. Hypertens Res 2008;31:1391-7.
[14] Tian N, Penman AD, Mawson AR, Manning RD, Flessner MF. Association between circulating specific leukocyte types and blood pressure: the atherosclerosis risk in communities (ARIC) study. J Am Soc Hypertens 2010;4:272-83.
[15] Trayhurn P, Wood IS. Adipokines: inflammation and the pleiotropic role of white adipose tissue. Br J Nutr 2004;92:347-55.
[16] Straczkowski M, Dzienis-Straczkowska S, Stepien A, Kowalska I, Szelachowska M, Kinalska I. Plasma interleukin-8 concentrations are increased in obese subjects and related to fat mass and tumor necrosis factor-α system. J Clin Endocrinol Metab 2002;87:4602-6.
[17] Herder C, Haastert B, Muller-Scholze S, Koenig W, Thorand B, Holle R, et al. Association of systemic chemokine concentrations with impaired glucose tolerance and type 2 diabetes: results from the Cooperative Health Research in the Region of Augsburg Survey S4 (KORA S4). Diabetes 2005;54:S11-7.
[18] Boekholdt SM, Peters RJ, Hack CE, Day NE, Luben R, Bingham SA, et al. IL-8 plasma concentrations and the risk of future coronary artery disease in apparently healthy men and women: the EPIC-Norfolk prospective population study. Arterioscler Thromb Vasc Biol 2004;24:1503-8.
[19] Baggiolini M, Dewald B, Moser B. Interleukin-8 and related chemotactic cytokines-CXC and CC chemokines. Adv Immunol 1994;55:97-179.
[20] Mugge A, Lopez JA. Do leukocytes have a role in hypertension? Hypertension 1991;17:331-3.
[21] Smedly LA, Tonnesen MG, Sandhaus RA, Haslett C, Guthrie LA, Johnston RB, et al. Neutrophil-mediated injury to endothelial cells. Enhancement by endotoxin and essential role of neutrophil elastase. J Clin Invest 1986;77:1233-43.
[22] Weiss SJ. Tissue destruction by neutrophils. N Engl J Med 1989;320:365-76.
[23] Griendling KK, FitzGerald GA. Oxidative stress and cardiovascular injury. Part II: Animal and human studies. Circulation 2003;108:2034-40.
[24] Caetano EP, Zatz R, Praxedes JN. The clinical diagnosis of hypertensive nephrosclerosis—how reliable is it? Nephrol Dial Transplant 1999;14:288-90.
[25] Harrison DG, Guzik TJ, Goronzy J, Weyand C. Is hypertension an immunologic disease? Curr Cardiol Rep 2008;10:464-9.
[26] Rodriguez-Iturbe B, Quiroz Y, Herrera-Acosta J, Johnson RJ, Pons HA. The role of immune cells infiltrating the kidney in the pathogenesis of salt-sensitive hypertension. J Hypertens 2002;20:S9-14.
[27] Guzik TJ, Hoch NE, Brown KA, McCann LA, Rahman A, Dikalov S, et al. Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. J Exp Med 2007;204:2449-60.
[28] Takeichi N, Ba D, Kobayashi H. Natural cytotoxic autoantibody against thymocytes in spontaneously hypertensive rats. Cell Immunol 1981;60:181-90.
[29] Bramlage P, Pittrow D, Wittchen HU, Kirch W, Boehler S, Lehnert H, et al. Hypertension in overweight and obese primary care patients is highly prevalent and poorly controlled. Am J Hypertens 2004;17:904-10.
[30] Solini A, Zoppini G, Orsi E, Fondelli C, Trevisan R, Vedovato M, et al; Renal Insufficiency And Cardiovascular Events (RIACE) Study Group. Resistant hypertension in patients with type 2 diabetes: clinical correlates and association with complications. J Hypertens 2014;32:2401-10.

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Transapical transcatheter aortic valve implantation in a high-risk patient with aortic and mitral regurgitation: usage of the JenaValve™ system

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ABSTRACT

JenaValve™ system is a second-generation transcatheter heart valve that provides a successful deployment not only in calcified stenotic aortic valves but also in non-calcified, severe regurgitant aortic valves. We performed a transapical transcatheter aortic valve implantation procedure using this system without any procedure-related complications in a 75-year-old woman with multiple co-morbidity factors, who had both mitral and aortic regurgitation, and low ejection fraction.

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Keywords: Aortic regurgitation; mitral regurgitation; transcatheter aortic valve implantation; transapical; JenaValve™ system

Introduction

Indication criteria of transcatheter aortic valve implantation (TAVI) in patients with severe aortic stenosis and the contraindications or risk profile for open heart surgery have been determined but treatment of regurgitation of both mitral and aortic valves in a high risk patient with very low ejection fraction is a surgical challenge. Regurgitation in aortic valve without stenosis presents a subject of debate for TAVI and increases the risk of dislocation depending on the lack of the calcifications needed for perfect deployment of transcatheter heart valves. In addition to existing co morbidities, the combination of afterload mismatch and decreased ejection fraction following the relief of mitral regurgitation may increase the perioperative mortality and morbidity. An ejection fraction lower than 30% is accepted as an inoperability criterion in patients with mitral regurgitation by some authors. Severe aortic regurgitation related with left ventricle (LV) volume overload and resultant LV dilatation may contribute to the development of mitral regurgitation and relief of aortic insufficiency via a less invasive way may decrease the mitral regurgitation by decompression and reverse remodeling of the dilated LV. The JenaValve™ is the only TAVI system approved for both aortic regurgitation and stenosis because the JenaValve™ prosthesis represents a clip fixation on the native aortic valve cusps providing perfect

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deployment for the transcatheter heart valves even in the lack of calcifications [1, 2].

Case Presentation

A 75 year-old woman with orthopnea was admitted to our institution with symptomatic severe aortic and moderate-severe mitral regurgitation (Figure 1). She had a functional class of NYHA IV. In addition to co-morbidities like diabetes, chronic renal failure, chronic obstructive pulmonary disease and history of stroke; she had an ejection fraction of 30%, a dilated LV (LV end-diastolic diameter: 6.5 cm) and an elevated systolic pulmonary artery pressure of 70 mmHg with a logistic EUROSCORE of 38%. Those factors made us think an open surgical repair of both valves would be too risky and a palliative approach with the relief of aortic regurgitation alone could be a better option with a TAVI procedure.

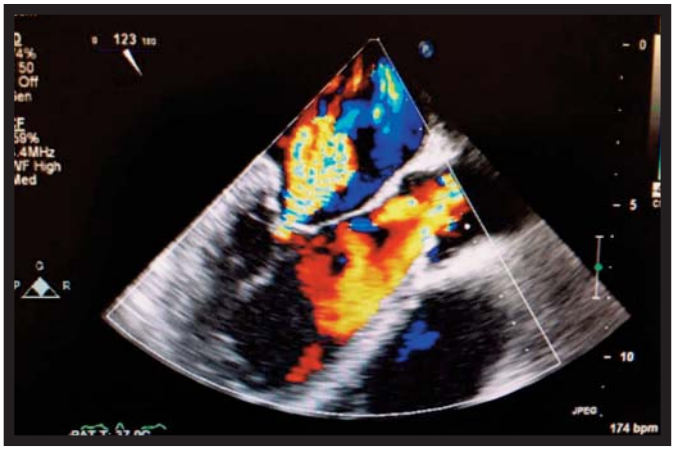

Figure 1. Preoperative echocardiographic view of the regurgitant aortic and mitral valves

The JenaValve™ implantation was performed under general anesthesia by a multidisciplinary approach team including cardiac surgeons, cardiologists and anesthesiologists. Transapical access was performed via a left anterolateral minithoracotomy and purse-string sutures were carried out to the left ventricular apex. A 27 mm JenaValve™ (JenaValve Technology GmbH, Munich, Germany) was implanted and the patient tolerated the procedure well (Figures 2 and 3). No adverse events existed related with the procedure and postoperative period of the patient was uneventful.

Her immediate and postoperative 2nd month echocardiography studies depicted a reduction in the level of mitral regurgitation, the size of LV (end-diastolic diameter from 6.5 to 5.8 cm) and systolic pulmonary artery pressure (from 70 mmHg to 45 mmHg) in addition to improvement of her functional class from NYHA IV to II. Postoperative VARC 2 (Valve Academic Research Consortium) endpoints were evaluated and there were no symptoms or signs of the complications defined [3].

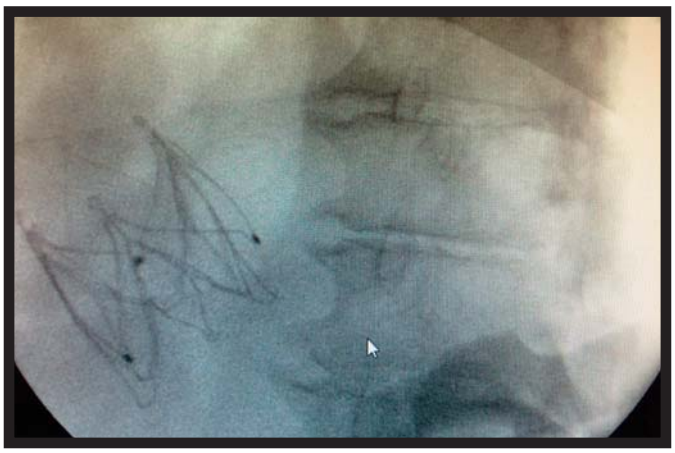

Figure 2. Intraoperative image of the completed transapical TAVI procedure by JenaValve™

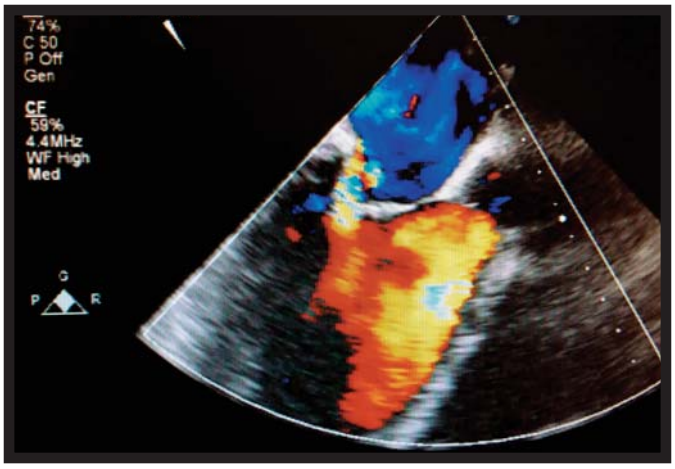

Figure 3. Postoperative echocardiographic view

Discussion

In respect of the guidelines on the management of valvular heart disease; aortic valve surgery is advised to be performed (Class IB) in severe aortic regurgitation for symptomatic patients and in the presence of ejection fraction <50%, LVEDD>70mm, LVESD>50mm as the prognostic signs of impaired LV [1].

In our case, symptoms and signs of operable severe aortic regurgitation were present but unfortunately, she could not be an optimal candidate

for an open surgical procedure because of having multiple major co-morbidity factors additionally to severe non-calcified aortic regurgitation concomitant with mitral regurgitation. Non calcified, severe aortic regurgitation was accepted as a relative contraindication for TAVI before, because both Medtronic Core Valve and Edwards Sapien transcatheter heart valves could offer only a limited success in the treatment of non-calcified aortic regurgitation with a serious risk of annular rupture, incomplete valve expansion, insufficient anchoring, valve embolization or residual paravalvular regurgitation because either of the transcatheter heart valves were produced to be implanted on a calcified aortic annulus safely via radial force of the prosthesis [2].

The JenaValve™ system is a second-generation transcatheter heart valves that provides a successful deployment not only in calcified, stenotic aortic valves but also in non-calcified, severely regurgitant aortic valves by its feeler guided positioning and secure clip fixation mechanism to the native aortic valve cusps. Calcium spots occurring on regurgitant aortic valve may complicate the procedure by causing an incomplete stent expansion because the JenaValve™ system carries less radial force than a balloon-expandable transcatheter heart valves [3].

In our patient, existence of severe aortic regurgitation was accompanying with moderate-severe mitral regurgitation. We consulted that severe aortic regurgitation might have contributed to severity of mitral regurgitation. As a result; due to the presence of multiple co-morbidities in this case, we considered that amelioration of aortic regurgitation alone and eventual decompression of distended LV might attenuate the level of mitral regurgitation and the patient could have tolerated a TAVI procedure by a second-generation transcatheter heart valve JenaValve™ system better than a surgical repair/replacement for both aortic and mitral valve pathologies.

We also chose to perform the TAVI procedure using JenaValve™ system for the advantages about the complications seen less than the other TAVI procedures, such as thromboembolic and cerebrovascular events, conduction disturbances, annular dilation or rupture by the exclusion of oversizing and valvuloplasty as well as cancelling rapid ventricular pacing during the deployment of the valve. The procedure can be performed while heart is beating and this makes the procedure safer than the others especially in patients with low cardiac output as our patient [3].

Conclusion

In high risk setting of combined aortic and mitral valve regurgitations and low ejection fraction, a suboptimal treatment option with a transapical TAVI procedure by a second-generation transcatheter heart valves, the JenaValve™ system alone may be a more reasonable and safer option than open surgical repair/replacement of both regurgitant valves.

Informed consent

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

Conflict of interest

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

References

[1] Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC); European Association for Cardio-Thoracic Surgery (EACTS), Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, et al. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J 2012;33:2451-96.

[2] Holmes DR Jr, Mack MJ, Kaul S, Agnihotri A, Alexander KP, Bailey SR, et al. 2012 ACCF/ AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement. J Am Coll Cardiol 2012;59:1200-54.

[3] Seiffert M, Bader R, Kappert U, Rastan A, Krapf S, Bleiziffer S, et al. Initial German experience with transapical implantation of a second-generation transcatheter heart valve for the treatment of aortic regurgitation. JACC Cardiovasc Interv 2014;7:1168-74.

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Giant cervical myoma associated with actinomycosis: a rare cause of uremia

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ABSTRACT

Myomas are commonly seen benign tumors of the uterus; they may cause a great variety of symptoms depending on the location. Herein, we presented an unusual case of giant cervical myoma with associated actinomycosis resulting in bilateral hydronephrosis and uremia. A 42-year-old woman was admitted to emergency service with anuria and confusion. She had an intra-abdominal mass extending 4-5 cm above the level of umbilicus. The hemoglobin level was 5.1 g/dl and creatinine level was 5.2 mg/dl. Magnetic resonance imaging revealed enlarged uterus with intrauterine device which was displaced up above the level of umbilicus due to a large cervical mass measuring 16.5x11.5x12 cm, tortuous hydroureters on both sites and left tuba ovarian abscess. A huge cervical lobulated mass which was pressing both ureters and filling the lower abdomen, and left tuba ovarian abscess with dense adhesions which was created by actinomycotic infection were detected on explorative laparotomy. Uremia was normalized gradually following hysterectomy, and the patient was discharged with penicillin treatment. Although myomas are the benign tumors, they may mimic the genital malignancy, and may cause life-threatening complications such as renal failure and uremia.

Eur Res J 2016;2(3):222-224

Keywords: Myoma; uremia; actinomycosis

Introduction

Uterine myoma is a benign genital tract tumor affecting approximately 50% of the women over 35 years of age [1]. It originates from smooth muscle of the uterus and may rarely reach to giant sizes. The clinical symptoms vary according to localization of the tumor and can adversely affect the quality of life, and may cause compressive effect on vital organs such as lungs and heart [2]. Urinary symptoms, like increased frequency of micturition or intermittent urination were frequently seen especially in women with big myomas [2]. We could only detect one case of myoma causing uremia in our literature search [3].

Herein, we presented an unusual case of giant cervical myoma with associated actinomycosis resulting in bilateral hydronephrosis and uremia.

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Case Presentation

A 42-year-old pre-menopausal woman was admitted to emergency service with anuria and confusion. Physical examination revealed an intra-abdominal mass extending 4-5 cm above the level of umbilicus. The cervical os could not be visualized due to compressive effect of the mass on pelvic exam. The hemoglobin level was 5.1 g/dl and leukocyte count was 30,950/mm^3 with neutrophil predominance. Heavy menstruation lasting 7-8 days and 20 to 25 days apart were noticeable in medical history of the patient. Serum creatinine level was 2.59 mg/dl on admission, and increased progressively to 5.2 mg/dl on the next day. Carcinoembryonic antigen, cancer antigen 125, and alpha-fetoprotein levels were within normal limits. A giant mass extending 4-5 cm above the umbilicus was detected on sonographic exam. Magnetic resonance imaging (MRI) revealed enlarged uterus with intrauterine device which was displaced up above the level of umbilicus due to a large cervical mass measuring 16.5x11.5x12 cm, tortuous hydroureters on both sites and left tuba-ovarian abscess (Figure 1). There was no regional nodal or distant metastasis detected on MRI.

Blood transfusion and hemodialysis were performed to improve general condition of the patient. Explorative laparotomy revealed enlarged, lobulated cervical mass occupying the whole lower abdomen and compressing the ureters with left tuba-ovarian abscess (Figure 2). Ureters were encircling the outer surface of the myoma on both sites. Both ureters and dense adhesions were dissected from the myoma and total hysterectomy and bilateral salphingo-oophorectomy were performed. Pathologic exam revealed 16.5x11.5x12 cm cervical myoma weighing 1,620 g, distorting the uterine shape and left tuba-ovarian abscess infiltrated with actinomycosis colonies. Histologic signs of malignancy were not found microscopically.

Penicillin treatment was started in the postoperative period. The patient was completely free of symptoms and had normal serum creatinine levels within two weeks.

Discussion

Our case is important to show that a benign condition such as myoma may result in a life-threatening condition. The size and location determine the presence and degree of the symptoms [2]. Many cases of uterine leiomyoma causing intra-abdominal compression have been reported previously, but only one case of uremia developed secondary to ureteral compression of myoma was seen in our literature search [2]. Renal failure due to ureteral obstruction may be seen in advanced cervical cancer [4]. However, renal failure due to cervical myoma is not an expected situation, because myomas usually give symptoms such as bleeding, pain or problems of urination before reaching to this stage [1]. Our patient had deep anemia, confusion, and uremia on admission. Probably due to low socio-cultural level, she did not

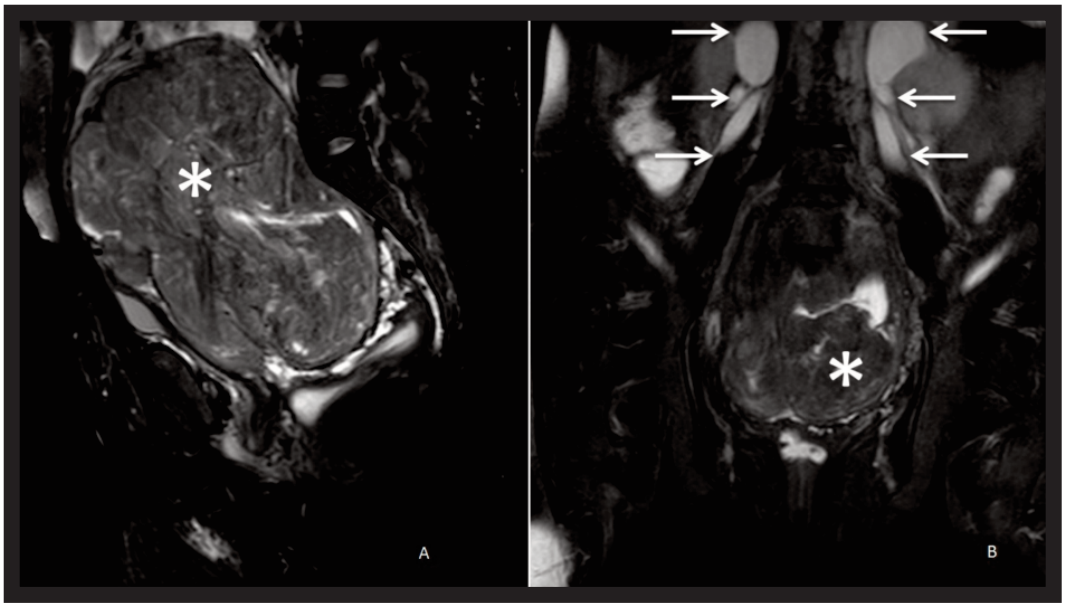

Figure 1. Sagittal (A) and coronal (B) magnetic resonance images show multilobulated huge cervical mass (*asterisks*) filling the pelvis and causing bilateral hydroureteronephrosis (*arrows*).

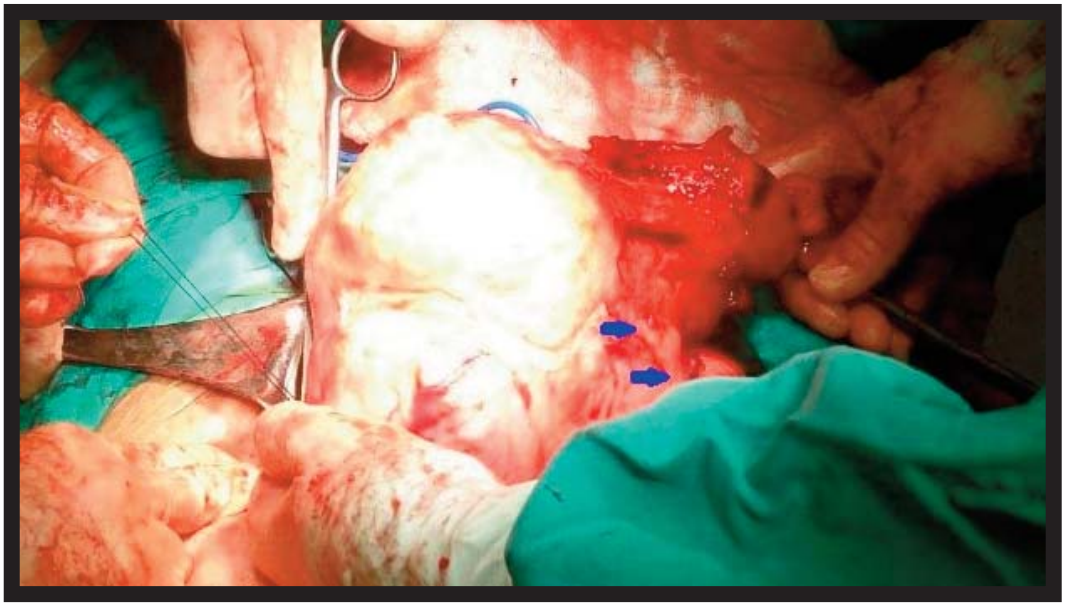

Figure 2. Intraoperative appearance of the uterine mass. Blue arrows show the pathway of left ureter.

admitted previously and chronic anemia was developed progressively which causes depressed cognitive functions. The cervical myoma enlarged and extended into the parametrium. As time goes on, obstructed ureters led to hydroureteronephrosis, and eventually renal failure. Increased uremia further deteriorated the situation and resulted in confusion.

Although, we detected actinomycotic infection which may cause fibrosis in retroperitoneal area, tubal area was moved upwards due to large myoma, and myoma itself was the reason for the ureteral compression. Actinomycotic infection was known to be associated with the presence of foreign body, and most often with use of intra-uterine contraceptive device. It may cause abscess formation and creates dense adhesions [5]. There was left tuba-ovarian abscess in our case. Fever is usually not observed despite elevated leucocytes with neutrophil predominance. Similarly we observed no fever in clinical follow-up, but leukocyte count was highly elevated with neutrophil predominance. Antibiotic treatment should be dictated by the clinical setting.

Conclusion

In conclusion, although myomas are benign tumors of the uterus, they may cause life-threatening complications, and mimic genital malignancy. Presence of actinomycotic infection may further complicate the situation by causing tuba-ovarian abscess formation. Imaging modalities are helpful to visualize myoma and its compressive effects in such complicated cases.

Informed Consent

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

Conflict of interest

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

Acknowledgement

The article was presented as P-101 poster in TJOD 13th Congress, May 11-15, 2015, Antalya, Turkey

References

[1] Hoffman B. Pelvic mass. In: Williams gynecology. Schorge J, editor. Dallas, Texas: McGraw-Hill Companies, 2008, p.197.
[2] Inaba F, Maekawa I, Inaba N. Giant myomas of the uterus. Int J Gynaecol Obstet 2005;88:325-6.
[3] Heimer G, Axelsson O, Johnson P. Uterine myoma causing uremia in a 15-year-old girl. Gynecol Obstet Invest 1991;32:247-8.
[4] Plesinac-Karapandzic V, Masulovic D, Markovic B, Djuric-Stefanovic A, Plesinac S, Vucicevic D, et al. Percutaneous nephrostomy in the management of advanced and terminal-stage gynecologic malignancies: outcome and complications. Eur J Gynaecol Oncol 2010;31:645-50.
[5] Valour F, Senechal A, Dupieux C, Karsenty J, Lustig S, Breton P, et al. Actinomycosis: etiology, clinical features, diagnosis, treatment, and management. Infect Drug Resist 2014;7:183-97.

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Left atrial appendage tear due to blunt chest trauma: off-pump repair

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ABSTRACT

Left atrial appendage tear due to blunt trauma is a very rare clinical entity with high mortality rates. Traumatized patients may have no symptoms, or be in a cardiogenic shock state. For diagnosis, it is crucial to determine hemopericardium by echocardiography. Herein, we report a 28-year-old male patient who developed left atrial appendage tear following a fall from a higher distance. He underwent successful off-pump repair of the tear through a median sternotomy.

Eur Res J 2016;2(3):225-227

Keywords: Left atrial appendage tear; blunt chest trauma; off-pump; surgery

Introduction

Cardiac rupture dependent on blunt trauma is related to high mortality. The incidence varies between 0.16% and 2%, and is considerably rare [1]. A significant number of the patients are lost, due to late initial intervention, insufficiency at transportation, and delay of operation. In this case presentation, a patient who developed left atrial appendage rupture after falling from a high distance was reported.

Case Presentation

A 28-year-old male patient was taken to the emergency room because of falling from a walnut tree with a height of approximately 6 meters. He was conscious, oriented, and cooperated. His complaint was dyspnea. At the physical examination, he had no major finding, except scratches on the left part of his face. His respiratory rate was 24 breaths per minute, blood pressure was 70/50 mmHg, and heart rate was 124 beats per minute. In his chest x-ray, enlargement of the cardiac silhouette was observed. His hemoglobin value was 9 g/dl, and hematocrit value was 27%. Hemopericardium was observed at the thoracoabdominal computed tomography (Figure 1). Aorta and major vessels were intact. Echocardiograhy showed pericardial effusion, which was causing a pressure of approximately 2 cm. The patient was taken to the operation room instantly without losing time, with placing a required vascular access for blood and volume transfusion.

Following median sternotomy, the pericardium

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was explored and approximately 1400 cc fresh blood was aspirated; though, active bleeding still existed. No bleeding focus was observed at aorta, right atrium, right ventricle and caval veins, and the surface of the back of the heart was checked. A rupture and active bleeding was detected at the right side of the left atrial appendix (Figure 2).

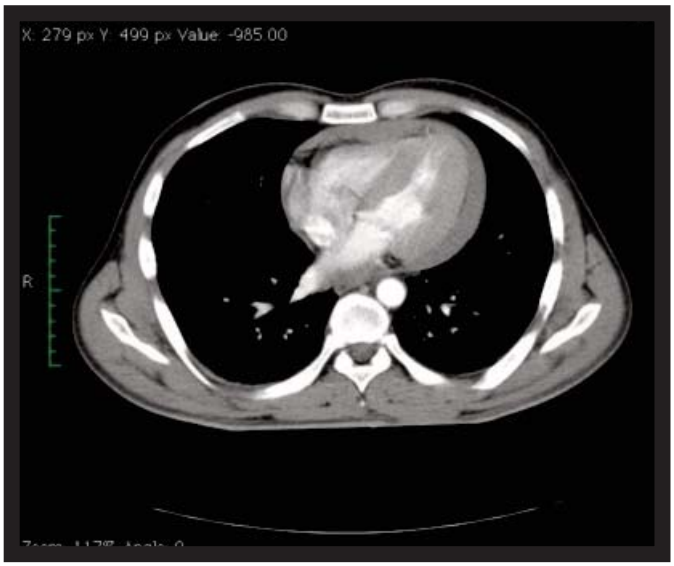

Figure 1. Thoracoabdominal computed tomography shows hemopericardium

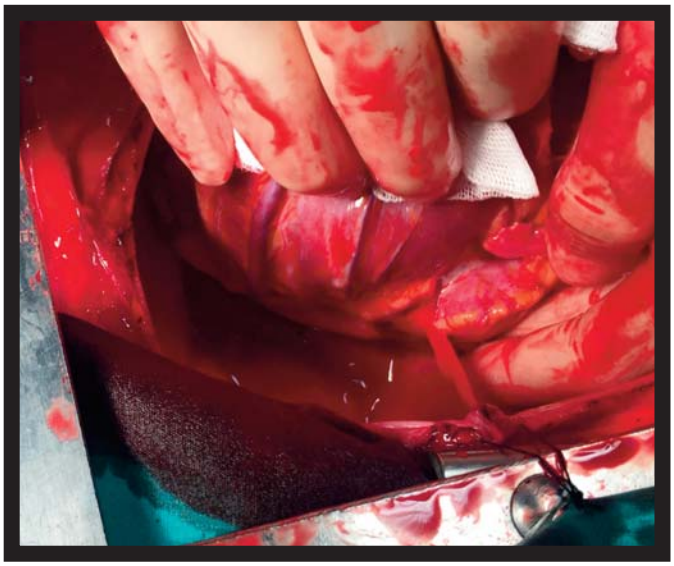

Figure 2. Intraoperative view of the left atrial appendage tear

The defect was repaired with pledgeted 4-0 polypropylene sutures using off-pump approach (on a beating heart), and the bleeding was stopped (Figure 3). The sternum was closed after the last controls, when we were sure that there was no bleeding, and the patient was taken to the intensive care. The patient who had no problem at the postoperative period was discharged at the 4th day.

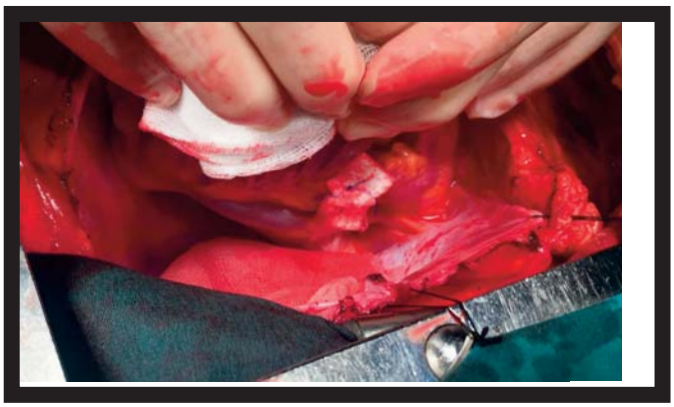

Figure 3. The view of the tear repaired with pledgeted sutures

Discussion

Approximately 25% of deaths occur due to a chest injury caused by blunt trauma. Cardiac injuries due to blunt chest trauma can cause hemothorax and tamponade and are at high risk of mortality. Blunt chest trauma can be traced from a simple rib fracture to cardiovascular rupture [2]. The incidence of injury of heart and major vessels with blunt chest traumas varies between 4% and 1%5 [3]. Cardiac rupture is a rare complication which occurs in 1 of 2400 blunt truma patients [4]. In 160 autopsies in trauma, where the cause is blunt mechanisms, cardiac rupture was found in 96.9% [5].

The rapid deceleration with disruption of the atria from their connections to the vena cava and pulmonary veins is the most popular theory of cardiac rupture following blunt thoracic trauma [6]. The chamber tear is related to a high rate of mortality. Because of the low-pressure chamber, unlike ventricle ruptures, immediate death is delayed in atrial rupture [7]. National trauma data bank reports that the chamber tears make the 0.041% of all trauma cases and there is a mortality rate of 89.2% [4].

Due to the anatomical localization of cardiac injuries, the most affected chamber is right ventricle, and than left ventricle is the second one [8]. Brathwaite *et al.* [9] reported that left atrial injury occurs in the 25% of the cases with cardiac rupture, and atrial appendage and pulmonary vein-atrial junction are the most affected sides. In a study that reported the anatomical distribution of 42 injuries; the number of patients have affected chambers are; 21 patients (50%) in right atrium, 7 patients (17%) in right ventricle, 10 patients (24%) in left atrium, and 4 patients in left ventricle [10]. Tanoue *et al.* [11] reported a case that they operated because of the

rupture of left atrial appendage due to the blunt trauma. Akar *et al.* [12] reported the case of a 33-year-old man with a rupture of the left atrium after blunt thoracic trauma.

It is usually difficult to diagnose cardiac tear in falling from high levels which doesn't have a clinical sign. The clinical signs may vary from no symptoms to cardiogenic shock. In the early stage typical symptoms of tamponade (hypotension, elevation of central venous pressure, decreased heart sounds and tachycardia) are not available in all patients, so if the patients have minimal thoracic injury and vitable signs, the results of injury may be overlooked. In cardiac injuries, the hemopericardium that is shown with echocardiograhy at emergency room is very important and helpful for the diagnosis. In our patient, the prominent pericardial effusion showed by echocardiograhy was also helpful in the detection of the cardiac injury.

The required fluid replacement and urgent surgery should be performed to patients at the time of diagnosis. The tamponade should be relieved quickly in heart injuries. In our case as well, the blood pressure increased to 130/70 mmHg from 80/50 mmHg, following the drainage of blood after the pericardium was opened, resulting from the heart's contractions turning into normal state and the cardiac functions were normalized.

In these cases, there is no consensus on approaching with median sternotomy or thoracotomy. As the median sternotomy provides advantage for cardiopulmonary bypass when needed, by exploring the whole heart and the aorta and because we didn't know the type of the injury we would have faced with, we chose median sternotomy in this case. In addition, because a considerable amount of active bleeding was continuing, we didn't want to lose time with cardiopulmonary bypass and we decided that we could repair the injury site by suturing; so we elevated the heart and performed an off-pump (on a beating heart) repair.

Conclusion

As a result, cardiac rupture, especially the left atrial appendage tear due to blunt trauma is a condition that is a rare entity with a high rate of mortality. In these patients, it is life-saving to diagnose quickly and to repair the heart by off-pump or on-pump surgical approach.

Informed consent

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

Conflict of interest

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

References

[1] Schultz JM, Trunkey DD. Blunt cardiac injury. Crit Care Clin 2004;20:57-70.
[2] Turk F, Ozcan V, Yuncu G, Ekinci Y, Girgin S. [An isolated right auricular rupture following blunt chest trauma causing massive hemothorax]. Turk Gogus Kalp Dama 2014;22:410-3. [Article in Turkish]
[3] Adalia R, Sabater L, Azqueta M, Muntanya X, Real MI, Riambau V, et al. Combined left ventricular aneurysm and thoracic aortic pseudoaneurysm caused by blunt chest trauma. J Thorac Cardiovasc Surg 1999;117:1219-21.
[4] Teixeira PG, Inaba K, Oncel D, DuBose J, Chan L, Rhee P, et al. Blunt cardiac rupture: a 5-year NTDB analysis. J Trauma 2009; 67:788-91.
[5] Fedakar R, Turkmen N, Durak D, Gundogmus UN. Fatal traumatic heart wounds: review of 160 autopsy cases. Isr Med Assoc J 2005;7:498-501.
[6] Nan YY, Lu MS, Liu KS, Huang YK, Tsai FC, Chu JJ, et al. Blunt traumatic cardiac rupture: therapeutic options and outcomes. Injury 2009;40:938-45.
[7] Alameddine AK, Alimov VK, Alvarez C, Rousou JA. Unexpected traumatic rupture of left atrium mimicking aortic rupture. J Emerg Trauma Shock 2014;7:310-2.
[8] Ata Y, Turk T, Yalcin M, Selimoglu O, Ozyazicioglu A, Yavuz S. [Heart Injuries]. IU Kardiyol Enst Derg 2009;8:16-9. [Article in Turkish]
[9] Braithwaite CE, Rodriguez A, Turney SZ, Dunham CM, Cowley R. Blunt traumatic cardiac rupture: a 5-year experience. Ann Surg 1990; 212:701-4.
[10] Ryu DW, Lee SY, Lee MK. Rupture of the left atrial roof due to blunt trauma. Interact Cardiovasc Thorac Surg 2013;17:912-3.
[11] Tanoue K, Sata N, Moriyama Y, Miyahara K. Rupture of the left atrial 'basal' appendage due to blunt trauma in an elderly patient. Eur J Cardiothorac Surg 2008;34:1118-9.
[12] Akar I, Ince I, Aslan C, Ceber M, Kaya I. Left atrial rupture due to blunt thoracic trauma. Ulus Travma Acil Cerrahi Derg 2015;21:303-5.

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Bilateral acute myopia and angle-closure glaucoma in a migraine patient receiving topiramate: a case report

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ABSTRACT

We present a case of topiramate-induced angle-closure glaucoma that was treated with cycloplegia. A 40-year-old woman with a history of migraine presented with bilateral acute onset of blurred vision and headache. She had been prescribed 50 mg of oral topiramate bid for migraine prophylaxis 10 days prior to her presentation. On her ocular examination visual acuity was 20/20 with a myopic correction of -4.0 diopters in both eyes. Biomicroscopic examination revealed bilateral shallow peripheral anterior chambers. Intraocular pressures were 37 OD and 36 OS. On gonioscopic examination bilateral 360 degrees of angle closure was seen. B-scan ultrasonography showed peripheral choroidal effusions. The mainstay of the treatment for topiramate induced secondary angle closure is cyloplegia. Whenever a case of bilateral acute angle-closure glaucoma associated with myopia and shallow anterior chambers is encountered, ciliochoroidal effusion syndrome induced by drugs should be considered in the differential diagnosis.

Eur Res J 2016;2(3):228-232

Keywords: Acute myopia; glaucoma; migraine; topiramate

Introduction

In this case report we present a case of topiramate-induced angle-closure glaucoma (TiACG) that was treated with cycloplegia. This case emphasizes the importance of interrogating use of medications that may cause angle closure as a side effect, in diagnosis and management of acute angle closure glaucoma patients.

Case Presentation

A 40-year-old woman applied to our emergency department with bilateral acute onset of blurred vision and headache. She had no history of hypertension, diabetes or glaucoma. She also did not have history of excessive reading, or psychiatric disorder. She had a history of migraine and had been prescribed 50 mg of oral topiramate twice a day for migraine prophylaxis 10 days prior to her presentation.

On her ocular examination visual acuity was 20/40, which improved to 20/20 with a myopic

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correction of -4.0 diopters in both eyes. The patient declared that she had no refractive problems previously. Bio-microscopic examination revealed bilateral mild conjunctival hyperemia and shallow peripheral anterior chambers. Pupil reactions were normal, the lenses were clear, and any sign of pupillary block in either eyes was not observed. Intraocular pressures (IOPs) were 37 mmHg, OD, and 36 mmHg, OS, by Goldmann applanation tonometry. On gonioscopic examination bilateral 360 degrees of angle closure was seen. Fundus examination revealed normal appearance of retina and optic discs in both eyes. These findings suggested bilateral acute onset of myopia with angle-closure glaucoma.

B-scan ultrasonography (USG) was performed which showed peripheral choroidal effusions, bilaterally (Figure 1). Baseline anterior chamber depth measurements were also recorded as 2.04 mm, OD, and 2.03 mm, OS.

Regarding this information, topiramate-induced angle-closure glaucoma and acute myopia secondary to ciliochoroidal effusion was suspected. The patient was asked to discontinue topiramate, 450 ml of intravenous mannitol 20% was given, and topical anti-glaucoma medications (i.e.; a combination of brimonidin tartarat 0.2% and timolol maleat 0.5%), and a topical steroid (dexamethasone %0.1) were prescribed. Two hours later IOPs were 36 mmHg, OD, and 35 mmHg, OS. The patient refused to be hospitalized and was sent to home with topical treatment. The next morning her IOPs were 37 mmHg in both eyes. Her refractive error remained unchanged. One drop of a cycloplegic agent (cyclopentolate 1%) was administered on both eyes and IOPs were decreased to 25 mmHg, OD, and 26 mmHg, OS in one hour with significant deepening of the anterior chambers (Figure 2 and 3). Two hours later, her IOPs were 18 mmHg, OD, and 19 mm Hg, OS. Ciliary

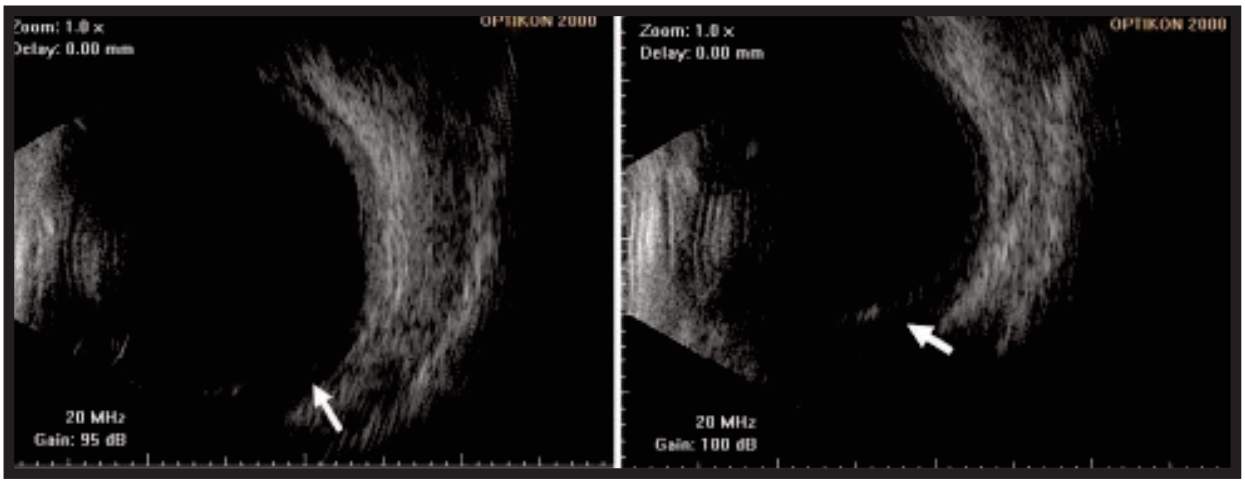

Figure 1. B-scan ultrasonography suggested bilateral mild peripheral choroidal effusions

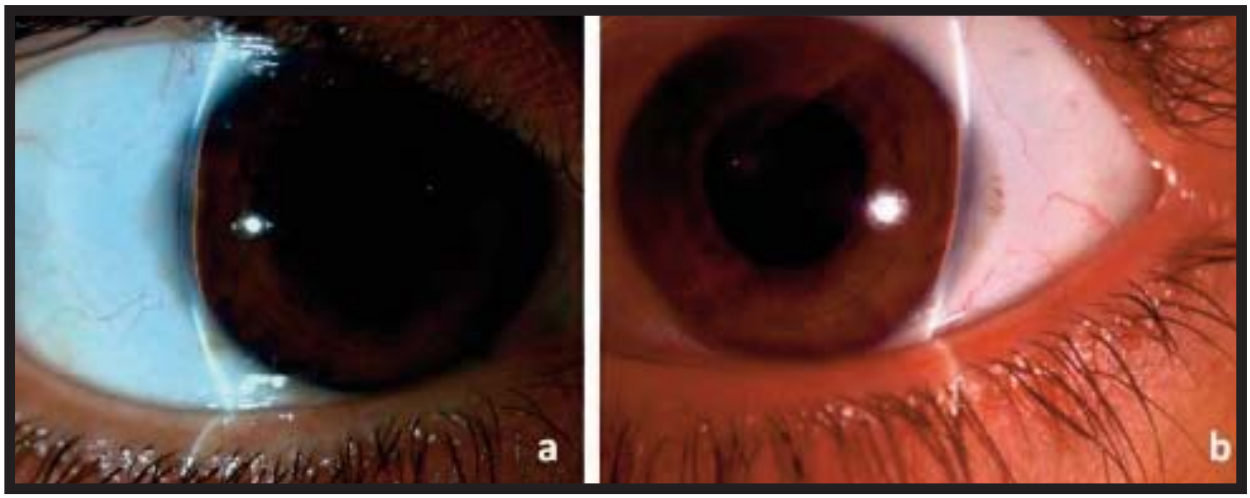

Figure 2. Bilateral shallow peripheral anterior chambers

edema was observed through the angle mirror of the Goldmann's three mirror contact lens (Figure 4).

Cyclopentolate three times a day was added to the topical regimen. On the third day her refractive errors appeared to regress. Her vision was 20/20 with -2.25 D in the right eye, and was 20/20 with -2.75 D in the left eye, while IOPs were 17 mmHg and 16 mmHg, respectively. Her optical coherence tomography scans were also obtained and no pathological finding was observed, central foveal thickness measurements were within normal limits bilaterally. The next day IOPs were measured as 14 mm Hg, with -1.0 D myopia in both eyes. On the fifth day, her refractive status was normalized, intraocular pressures were 11 mm Hg in both eyes and gonioscopy revealed bilateral open angles. Anterior chamber depths were 3.06 mm, OD, and 3.11 mm, OS. All topical medications were discontinued on the tenth day and her examinations remained uneventful thereafter.

Discussion

Topiramate (Topamax ®) is a sulfamate-substituted anticonvulsant drug which is primarily used for the control of seizures and the prophylaxis of migraine attacks. Ocular side effects related to topiramate use are: abnormal vision, acute myopia, supra-choroidal effusions, and acute secondary angle closure glaucoma [1]. The main intraocular effect of

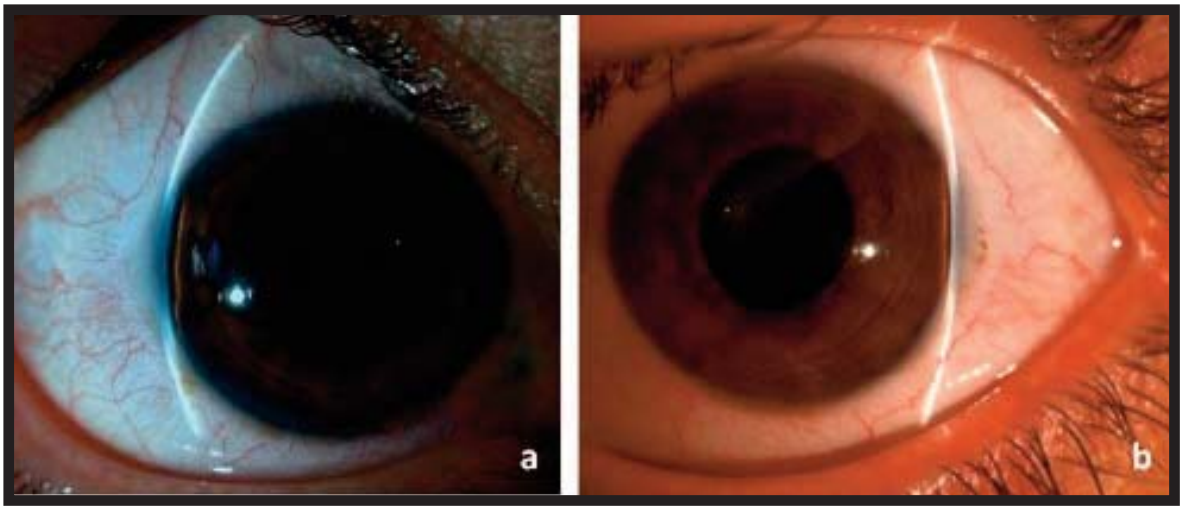

Figure 3. Bilateral peripheral anterior chambers widened after cycloplegic treatment.

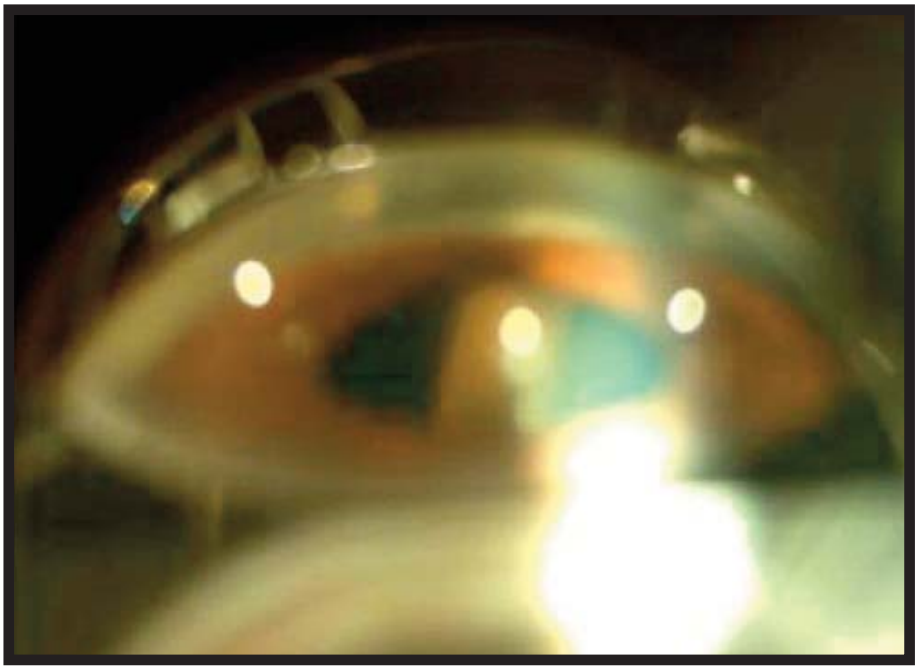

Figure 4. Ciliary edema is seen through Goldman 3 mirror lens. Angle closure is also observed.

topiramate is ciliochoroidal effusion which develops due to weak carbonic anhydrase activity and prostaglandin mediated effect [2, 3]. Ciliochoroidal effusion and/or ciliary edema leads to forward rotation of the ciliary body and anterior displacement of the iris-lens diaphragm. This results in myopia and consequent secondary angle closure. These mechanisms seem to be involved in our case in which myopia and angle closure as ciliary edema was observed through the angle mirror of the Goldmann's three mirror contact lens.

Cycloplegia relaxes the ciliary body and tightens the zonulas, restoring the position of the iris-lens diaphragm. Therefore, it is the mainstay of the treatment for TiACG. Topical corticosteroids have also been reported to help resolve the ciliary edema. Systemic corticosteroids and hyperosmolar agents are also suggested to mediate faster recovery and to avoid the need for surgical intervention in severe cases [4]. In our case, initial topical anti-glaucoma treatment turned out to be ineffective until the initiation of cycloplegia. Ten days of topical treatment with cessation of topiramate resulted in complete resolution of the symptoms.

The differential diagnoses include primary angle closure and accommodative spasm. Accommodative spasm is defined as an involuntary accommodative response that is greater than normal for a given accommodative stimulus and it is commonly associated with pupillary miosis and convergence spasm [5]. It may be seen after sustained near work, in head trauma and emotional problems [6, 7]. The patient becomes artificially myopic with asthenopic complaints. However, angle closure or IOP rise are not typical components of this clinical situation. Our patient who declared no previous refractive problems admitted with bilateral myopia of 4 diopters. She did not report any preexisting period of prolonged reading or other near work either. Additionally, neither angle closure, nor glaucoma has not been reported in accommodative spasm cases.

Differential diagnosis of TiACG and acute angle closure glaucoma (AACG) might be a challenging issue. TiACG does not respond to standard topical treatment of AACG with pilocarpine and aqueous suppressants. Pilocarpine may even worsen the clinical course by causing further anterior displacement of the iris-lens diaphragm. Our patient's young age and acute myopia was not quite compatible with primary angle closure. Young age, progressive myopic refractive status and ciliochoriodal effusions on B-scan USG are the features which may help to differentiate TiACG from primary angle closure [8].

Any drug use should be questioned in history of angle closure glaucoma cases. Many drugs have been reported to cause a forward shift of the iris-lens diaphragm; the most important group being sulfonamide derivatives including acetazolamide, indapamide, and topiramate [8]. Ophthalmologists will probably be the first to see these patients and they should be aware of this potential side effect. Whenever a case of bilateral acute angle-closure glaucoma associated with myopia and shallow anterior chambers is encountered, ciliochoroidal effusion syndrome induced by drugs should be considered in the differential diagnosis. Pediatric or mentally retarded patients on topiramate should be monitored for this potential side effect during the first 2 weeks of treatment because angle-closure is particularly seen in this period [8]. This information is consistent with our case, who was under topiramate prophylaxis for 10 days before she became symptomatic.

Conclusion

Bilateral acute angle-closure glaucoma associated with myopia and a shallow anterior chambers should suggest ciliochoroidal effusion syndrome and systemic medications should be considered in the etiology and differential diagnosis. Cycloplegia should be started as the first step in the treatment of TiACG, in contrast to primary angle closure glaucoma. Additionally, patients or relatives in charge should be warned about this potential side effect and its clinical presentation when prescribing sulfonamide derivatives.

Informed Consent

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

Conflict of interest

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

References

[1] Banta JT, Hoffman K, Budenz DL, Ceballos E, Greenfield DS. Presumed topiramateinduced bilateral acute angle-closure glaucoma. Am J Ophthalmol 2001;132:112-4.

[2] Fraunfelder FW, Fraunfelder FT, Keates EU. Topiramate associated acute, bilateral, secondary angle closure glaucoma. Ophthalmology 2004;111:109-11.
[3] Spaccapelo L, Leschiutta S, Aurea C, Ferrari A. Topiramate-associated acute glaucoma in a migraine patient receiving concomitant citalopram therapy: A case-report. Cases J 2009;2:87.
[4] Rhee DJ, Ramos-Esteban JC, Nipper KS. Rapid resolution of topiramate induced angle-closure glaucoma with methylprednisolone and mannitol. Am J Ophthalmol 2006;141:1133-4.
[5] Rutstein RP, Daum KM, Amos JF. Accommodative spasm: A study of 17 cases. J Am Optom Assoc 1988;59:527-38.
[6] London R, Wick B. Kirschen D. Post-traumatic pseudomyopia. Optometry 2003;74:111-20.
[7] Moore S, Stockbridge L. Another approach to treatment of accommodative spasm. Am Orthopt J 1973;23:71-2.
[8] Lee GC, Tam CP, Danesh-Meyer HV, Myers JS, Katz LJ. Bilateral angle closure glaucoma induced by sulphonamide-derived medications. Clin Experiment Ophthalmol 2007;35:55-8.

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Mitral valve myxoma associated with intracranial tumor: a case report

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ABSTRACT

Primary tumors of the heart are rare, and among them, cardiac myxoma is the most prevalent primary cardiac neoplasm in adult patients. Astrocytoma is the most common glioma and can occur in most parts of the brain and occasionally in the spinal cord. There is a little knowledge about coexistence of cardiac myxoma and astrocytoma in the literature. Cardiac myxoma associated with intracranial tumor is a very rare entity. We presented a case of cardiac myxoma originating mitral anterior valve associated with astrocytoma. The patient underwent the operation for intracranial tumor 2 months before cardiac surgery. Mitral valve myxoma was successfully treated with surgical resection without mitral valve replacement.

Eur Res J 2016;2(3):233-235

Keywords: Cardiac myxoma; mitral valve myxoma; intracranial tumor; astrocytoma

Introduction

Primary tumors of the heart are rare, and cardiac myxoma represents the most common type of primary cardiac tumor. About 80% of primary cardiac tumors are benign, and of these more than half are myxomas. Myxomas occur in all age groups, but are especially frequent 30-60 years, with a female predilection [1]. About 75% of these tumors arise from the left atrium and 20-25% from the right atrium. Tumors originate from atypical sites such as left and right ventricle and valves are very rare, and have occasionally been found in all four cardiac chambers [2]. Astrocytomas are a type of cancer of the brain. They originate in a particular kind of glial cells, star-shaped brain cells in the cerebrum called astrocytes. Association of astrocytoma and cardiac myxoma is very rare.

Case Presentation

A 66-year-old man was admitted to our hospital for a routine cardiac examination. In past medical history, he had undergone surgery for intracranial tumor 2 months ago. Pathological analysis of this tumor was consistent with low-grade, World Health Organization grade II astrocytoma.

He had no history of cardiac symptoms, syncope or fever. On examination vital signs were as follows: blood pressure 120/80 mmHg, pulse 76 beats/min. Blood biochemistry was revealed to be normal. The electrocardiogram demonstrated regular sinus rhythm and the chest x-ray was normal. Transthoracic echocardiography revealed a mobile mass, 31×20 mm, attached to the ventricular surface of the anterior mitral leaflet. There was mild mitral regurgitation. The

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left ventricular function was normal.

The patient was scheduled for cardiac surgery. Standard aortic and bi-caval cannulation was performed. Myocardial protection was provided by means of antegrade cardioplegic solution with topical and mild systemic cooling. The left atrium was approached through the interatrial groove. Myxoma was attached to the atrial surface of the anterior mitral leaflet. Appearance of this tumor was yellowish translucent jelly and shiny (Figure 1a). Tumor was excised preserving the structure of mitral valve (Figure 1b). After excision, minimal mitral regurgitation was observed. On pathological examination, tumor was identified as myxoma.

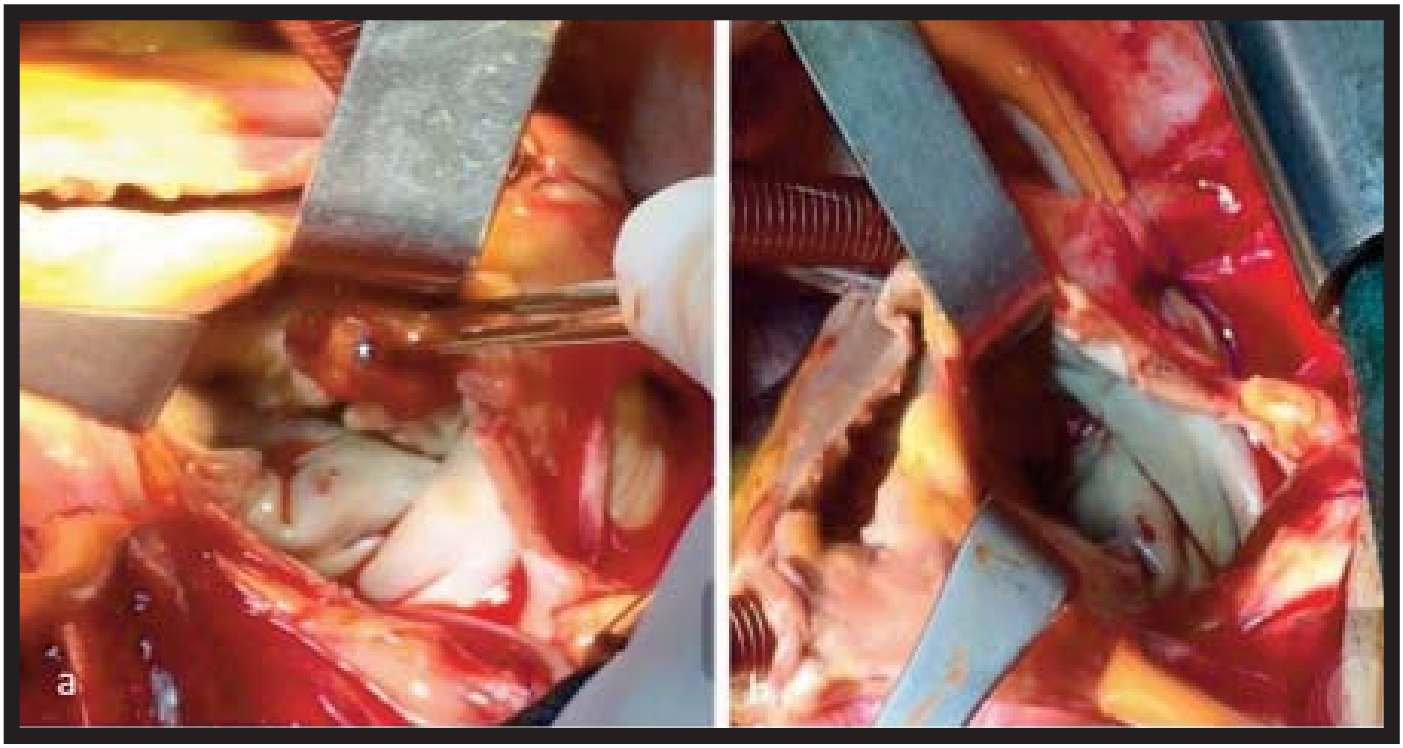

Figure 1. (a) Intraoperative appearance of the myxoma (asterisk). (b) The myxoma was excised preserving the structure of mitral valve.

Discussion

Myxoma is the most prevalent primary cardiac tumor. Myxomas can be originated in atypical locations, arising from the posterior or anterior left atrial wall, and arising from the mitral valve. Mitral valve myxomas is very rare. When the mitral valve is involved, the myxoma is frequently located on the atrial side with equal distribution between the anterior and the posterior leaflets [3-5]. The exact incidence of myxomas originating from the mitral valve is not clear.

Cardiac myxomas can be found along with other tumoral formation in the body. Complex cardiac myxomas are a classification of familial tumours, and occur as a syndromic presentation, requiring the presence of a cardiac myxoma with any two or more of the following concurrent conditions; skin myxomas, cutaneous lentiginosis, myxoid fibromas of the breast, pituitary adenoma, primary adrenocortical micronodular dysplasia with Cushing's syndrome, testicular tumours [6]. There are few reports in the literature about the association of glial tumors and cardiac myxoma [7]. This association is probably coincidental and there is no familial property.

Cardiac myxomas may restrict valve opening, causing functional mitral stenosis. In this patient, the tumor led to annular dilation and destruction of the valve, resulting in mitral insufficiency [8]. Clinical manifestations of myxoma are determined by the location, size, mobility, and friability, and can be divided into 3 general categories: systemic symptoms, embolism, and intracardiac obstruction. Echocardiography is most important diagnostic modality available for imaging cardiac tumors; it is noninvasive and does not pose the risk of tumor embolization. Echocardiography easily defines the size, location, shape, morphological characteristics, and relations of mass with intracardiac components [9, 10].

The manifestations of mitral valve myxoma may be cerebral or peripheral embolism. When located on

the mitral valve, they usually occur on the atrial surface of the valve and the anterior and posterior leaflets are involved with equal frequency. The treatment of choice for myxoma is surgical removal, and complete excision is the goal. Immediate postoperative mortality ranges from 0% to 3.6% [10]. Arrhythmia is a common postoperative complication, which may require long-term medication.

All mitral valve myxomas require surgical resection because of their potential to obstruct the valve orifice, dilate the annulus, embolism, or cause rhythm disturbances. The debate for uniatrial and biatrial approach continues. Most authors think that a uni-atrial approach, especially for the left atrial myxoma is adequate [11]. However, a large series reported from Texas Heart Institute advocates an aggressive approach and that the bi-atrial approach may help the surgeon to handle the tissues more gently [2, 5, 10-12]. We used left atriotomy. Thinking of the benign nature of the myxomas, a more conservative approach may prevail.

Cardiac surgery in patients with malignant diseases remains a problem. Although most malignant diseases are curable, surgeons are usually reluctant to perform open heart surgery in patients with advanced tumors and a short life expectancy. Among patients undergoing open heart surgery, the incidence of malignancy is 1.2% [13]. Due to the risk of intracranial hemorrhage which our patient had previously intracranial tumor operation, we choose myxoma excision. The preferred surgical technique is excision without valve resection if possible. Resultant varying degrees of mitral valve insufficiency can be treated by primary or patch repair of the valve or replacement with a prosthesis [3]. Myxomas should be completely resected to avoid recurrence. In Garatti *et al*.'s [1] study, freedom from tumor recurrence was 92%, 91%, and 86% at 10, 20, and 30 years, respectively. Younger age, smaller tumor dimension, and tumor localized to the ventricles were predictors of recurrence. It is not known whether replacement of mitral valve reduces the recurrence of mitral valve myxoma. Recurrences are usually managed by re-excision.

Conclusion

Although myxomas rarely can be seen with intracranial tumors, other possible concomitant intracranial tumors should be investigated in the presence of myxoma.

Informed consent

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

Conflict of interest

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

References

[1] Garatti A, Nano G, Canziani A, Gagliardotto P, Mossuto E, Frigiola A, et al. Surgical excision of cardiac myxomas: twenty years' experience at a single institution. Ann Thorac Surg 2012;93:825-31.
[2] Samanidisa G, Perreasa K, Kalogrisa P, Dimitrioua S, Balanikab M, Amanatidisa G, et al. Surgical treatment of primary intracardiac myxoma: 19 years of experience. Interact Cardiovasc Thorac Surg 2011;13:597-600.
[3] Yavuz S, Celkan A, Ata Y, Mavi M, Turk,T, Eris C, et al. Mitral valve myxoma. Asian Cardiovasc Thorac Ann 2000;8: 64-6.
[4] Arruda MV, Braile DM, Joaquim MR, Soares MJ, Alves RH. Resection of left ventricular myxoma after embolic stroke. Rev Bras Cir Cardiovasc 2008;23:578-80.
[5] Choi BW, Ryu SJ, Chang BC, Choe KO. Myxoma attached to both atrial and ventricular sides of the mitral valve: report of a case and review of 31 cases of mitral myxoma. Int J Cardiovasc Imaging 2001;17:411-6.
[6] Raith EP. Heart: cardiac myxoma. Atlas Genet Cytogenet Oncol Haematol 2010;14:164-8.
[7] Chozick BS, Ambler MW, Stoll J Jr. Malignant astrocytoma six years after the resection of a cerebral metastatic cardiac myxoma: case report. Neurosurgery 1992;30:923-6; discussion 926-7.
[8] Kaya M, Ersoy B, Yeniterzi M. Mitral valve regurgitation due to annular dilatation caused by a huge and floating left atrial myxoma. Kardiochir Torakochirurgia Pol 2015;12:248-50.
[9] Lobo A, Lewis JF, Conti CR. Intracardiac masses detected by echocardiography: case presentations and review of the literature. Clin Cardiol 2000;23:702-8.
[10] Ipek G, Erentug V, Bozbuga N, Polat A, Guler M, Kirali K, et al. Surgical management of cardiac myxoma. J Card Surg 2005; 20:300-4.
[11] Seub BKH. Surgical considerations in the treatment of cardiac myxoma. J Thorac Cardiovasc Surg 1984;87:251-9.
[12] Yilman M, Kolbakir F, Keceligil HT, Keyik T, Erk MK. Myxoma originated from mitral annulus. Turk Gogus Kalp Dama 1994;2:159-61.
[13] Narin C, Ege E, Onoglu R, Yazici M, Sarigul A. Surgery of left atrial myxoma as a second primary tumor in a patient previously treated for breast cancer. Turk Gogus Kalp Dama 2012;20:133-5.

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Spontaneous intracranial hypotension in Graves' disease

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ABSTRACT

Autoimmune thyroid disorders such as hyperthyroidism and hypothyroidism are rare causes of intracranial pressure alterations. We present a case of spontaneous intracranial hypotension associated with Graves' disease which was not reported previously in the literature. A 42-year-old woman was admitted to our institution because of a sudden developed headache, neck pain, nausea and vomiting. The headache was severe during standing and walking but improved within 15 to 30 minutes after lying down. Thyroid gland was grade 1b diffuse palpable and other physical examinations were normal. Autoimmune hyperthyroidism was diagnosed according to laboratory results. Gadolinium-enhanced magnetic resonance imaging revealed a hyperintensity that is consistent with thickened dura and subdural effusion. The patient was managed with bed rest, hydration, methimazole, methyl-prednisolone 16 mg/day of three days and then tapered gradually. After these medications the headache resolved. It should be kept in mind that encephalopathy associated autoimmune thyroid disease may be related with spontaneous intracranial hypotension.

Eur Res J 2016;2(3):236-239

Keywords: Intracranial hypotension, autoimmune thyroiditis, thyrotoxicosis

Introduction

Spontaneous intracranial hypotension (SIH) develops due to spontaneous spinal cerebrospinal fluid (CSF) leaks. Diagnostic criteria for headache disorders are described by an international classification [1]. It is clinically characterized by an acute or gradual onset of severe orthostatic headache which is relieved with supine position and may be co-exist with tinnitus, diplopia, photophobia, nausea, vomiting, vertigo, neck stiffness, local back pain, facial numbness or weakness [2].

Extra thyroidal manifestations of Graves' disease include thyroid ophtalmopathy, dermopathy and acropachy. In addition autoimmune thyroid diseases may be associated with neurological diseases. Key clinical features of "encephalopathy associated autoimmune thyroid disease" include alterations in

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consciousness, stroke-like events, seizures, tremor, and myoclonus [3]. Albeit rare, endocrine dysfunction (hyperthyroidism or hypothyroidism) is an established cause of benign intracranial hypertension. Reversible benign intracranial hypertension in a patient with autoimmune hyperthyroidism has been reported by Merkenschlager *et al.* [4]. To the best of our knowledge, we report herein the first case in the literature presenting an association between Graves' disease and SIH.

Case Presentation

A 42-year-old woman was admitted to our institution due to sudden-onset headache, neck pain, nausea and vomiting. The headache was severe as long as the patient stands and walks but improved within 15 to 30 minutes provided the patient remained in lying position. There was no loss of vision or photophobia. She was afebrile without any history of spinal trauma, lumbar puncture, surgery, vigorous exercise or sneezing and straining. Based on the obtained anamnesis, she was diagnosed with Graves' disease two years ago which has been in remission state achieved eight months ago.

Blood pressure (125/75 mmHg) and pulse (84/min) were in normal limits. Skin was thin and moist. Thyroid gland was grade 1b diffuse palpable. Other physical examinations, including respiratory, cardiovascular, abdominal, and neuromuscular examinations were all normal. Optic fundus examination was normal.

The laboratory findings were as follows: serum freeT3 >32.2 ng/dL (1.80-4.60 ng/dL), free T4 >7.74 ng/dL (0.93-1.70 ng/dL), thyroid-stimulating hormone <0.01 μIU/mL (0.27-4.20 μIU/mL), TSH receptor antibody 219.94 U/L (14-100 U/L), anti-thyroid microsomal antibody 600 IU/mL (≤34 IU/mL) and thyroglobulin antibody 193.1 IU/mL (≤115 IU/mL). All other laboratory values were in normal range.

Gadolinium-enhanced magnetic resonance imaging (MRI) showed a hyperintensity suggesting thickened dura and subdural effusion. Imaging findings were in countenance with SIH (Figure 1).

Management of the patient involved bed rest, hydration, methyl-prednisolone 16 mg/day for three days which tapered gradually and the headache subsequently resolved. In addition to methimazole for thyrotoxicosis, radioactive iodine (I-131) treatment was also planned.

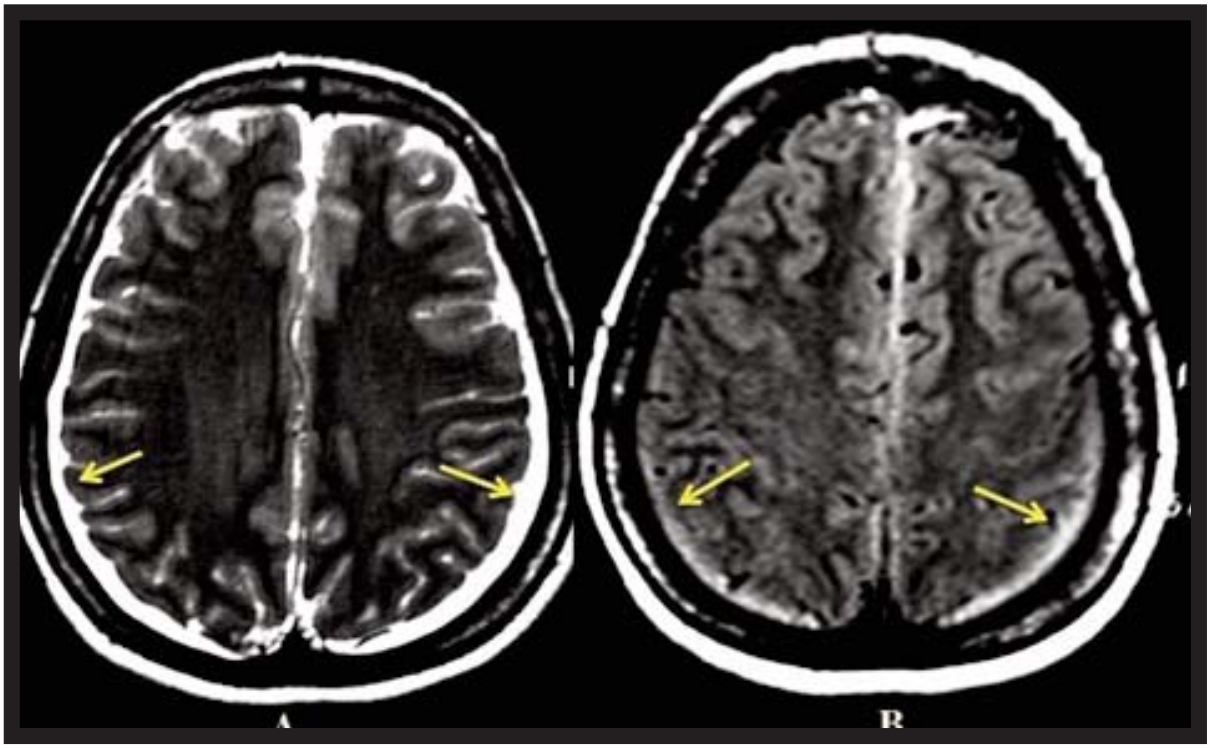

Figure 1. T2-weighted (A) and FLAIR (B) transverse images show hyperintensity of thickened dura and subdural effusion on both hemispheres (arrows).

Discussion

Intracranial hypotension is a clinical syndrome in which orthostatic headache is induced by low volume of CSF. Severe cases may provoke nausea, vomiting, photophobia, and decreased level of consciousness. Most probably, downward displacement of the brain exerting traction on the richly innervated dura causes orthostatic headache in SIH. A majority of the orthostatic headache cases exhibit a gradual onset with a range of severity from mild to debilitating. The headache of our patient was severe when she stood upright or walked but improved within 15 to 30 minutes after she rested in lying position [5]. Characteristics of the headache of our patient were compatible with SIH. Along with the postural headache, secondary symptoms such as posterior neck pain, nausea and vomiting, are common and attributable to meningeal irritation in approximately half of the patients, as in our patient. According to the 2004 International Classification of Headache Disorders at least one of the above-mentioned secondary symptoms, in addition to orthostatic headache, must be present in order to make the diagnosis of headache due to SIH [1]. SIH has an incidence of 5 per 100.000 of the population with a higher occurrence in women and mostly diagnosed in 4th to 6th decade of life [5].

Most often a leakage of CSF through a dural defect leads to SIH, which actually could be primary (idiopathic) or secondary. When it arises in secondary fashion cranial or spinal surgery, head or spine trauma and lumbar puncture may be the underlying reason. The reason of primary SIH is unknown but possible mechanisms include sagging of the brain, dilation of intracranial veins, and activation of adenosine receptors [5]. In 1938, Schaltenbrand [6] described a condition of low or negative CSF pressure with associated orthostatic headache, and postulated three possible causes as follows: low CSF production, high rate of CSF absorption, and CSF leakage. Typical MRI findings of pachymeningeal enhancement should suggest the benign SIH condition. Diffuse meningeal enhancement as detected by imaging studies in relation to intracranial hypotension was first highlighted as a phenomenon in an abstract from Mokri *et al.* [7] in 1991. The MRI changes include a marked degree of diffuse, smooth, contiguous dural thickening (2-8 mm) and enhancement, involving the supratentorial, infratentorial and cervical pachymeninges with no skip areas [8]. In our patient characteristic MRI findings for SIH were noted.

Therapeutic approach recommends strict bed rest and use of epidural blood patch to seal the CSF leakage. Reports indicate positive outcomes attained by corticosteroid treatment and epidural saline infusion [2, 5]. Management in our case employed bed rest, hydration, methyl prednisolone (16 mg/day) for three days which was gradually tapered and the headache subsequently resolved. Methimazole treatment was initiated against thyrotoxicosis.

The likely association of autoimmune thyroid diseases (mostly Hashimoto and lesser Graves' disease) with neurologic diseases was mentioned in a systematic review published in 2006 [9]. Diagnosis of a neurologic disorder associated with thyroid autoimmunity is made upon the event of neuropsychiatric symptoms emerge in a patient with elevated anti-thyroid antibody levels in serum. Until now, no clinical, laboratory or neuroimaging findings that are specific for this entity could be defined. Key clinical features of "encephalopathy associated with autoimmune thyroid disease" are changes in consciousness, stroke-like events, seizures, tremor, and myoclonus [10]. The clinical picture of our patient, however, was not similar to any of these conditions.

A possible condition that might interfere with SIH is pseudotumor cerebri (PTC). PTC is characterized by an elevated intracranial pressure while CSF analysis is preserved as normal and cerebral MRI scans excludes any structural abnormalities. Neurological symptoms are headache, temporary visual disturbances, nausea and vomiting, as well as SIH and papilledema are expected common findings in adults. Reports have pointed out autoimmune thyroid disorders, hypothyroidism and hyperthyroidism causes of PTC [11, 12]. Our patient had neither papilledema nor features of intracranial hypertension on MRI images. Therefore, we did not think intracranial hypertension.

Conclusion

We aimed to present a case with concurrent SIH and Graves' disease. To the best of our knowledge, it is the first case in the literature presenting an association between Graves' disease and SIH. The likelihood of SIH contribution should not be

overlooked in case of encephalopathy associated with autoimmune thyroid disease. Further studies must be planned for explaining the possible relationship between these two conditions.

Informed consent

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

Conflict of interest

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

References

[1] Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. Cephalalgia. 2004;24 Suppl 1:9-160.
[2] Schievink WI, Meyer FB, Atkinson JL, Mokri B. Spontaneous spinal cerebrospinal fluid leaks and intracranial hypotension. J Neurosurg 1996;84:598-605.
[3] Tamagno G, Celik Y, Simo R, Dihne M, Kimura K, Gelosa G, et al. Encephalopathy associated with autoimmune thyroid disease in patients with Graves' disease: clinical manifestations, follow-up, and outcomes. BMC Neurol 2010;10:27.
[4] Merkenschlager A, Ehrt O, Muller-Felber W, Schmidt H, Bernhard MK. Reversible benign intracranial hypertension in a child with hyperthyroidism. J Pediatr Endocrinol Metab 2008;21:1099-101.
[5] Schievink WI. Spontaneous spinal cerebrospinal fluid leaks. Cephalalgia 2008;28:1345-56.
[6] Schaltenbrand G. [Neure anschauungen zur pathophyiologie der liquorzirkulation]. Zentrablbl Neurochir 1938;3:290-300. [Article in German]
[7] Mokri B, Krueger BR, Miller GM, Piepgras DG. Meningeal gadolinium enhancement in low-pressure headaches. J Neuroimaging 1993;3:11-5.
[8] Meltzer CC, Fukui MB, Kanal E, Smirniotopoulos JG. MR imaging of the meninges. Part I. Normal anatomic features and nonneoplastic disease. Radiology 1996;201:297-308.
[9] Ferracci F, Carnevale A. The neurological disorder associated with thyroid autoimmunity. J Neurol 2006;253:975-84.
[10] Castillo P, Woodruff B, Caselli R, Vernino S, Lucchinetti C, Swanson J, et al. Steroid-responsive encephalopathy associated with autoimmune thyroiditis. Arch Neurol 2006;63:197-202.
[11] Kumar A, Kilaikode S, Saenger P. Pseudotumor cerebri caused by uncontrolled Graves' disease in an adolescent. Int J Case Rep Images 2013;4:702-4.
[12] Coutinho E, Silva AM, Freitas C, Santos E. Graves' disease presenting as pseudotumor cerebri: a case report. J Med Case Rep 2011;5:68.

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Left-sided malignant pleural mesothelioma presenting with recurrent pneumothorax 7 years after the right pleuropneumonectomy

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ABSTRACT

Malignant pleural mesothelioma (MPM) is an extremely aggressive tumor arising from the pleura with a median survival of approximately 9–12 months. It can rarely present as a spontaneous pneumothorax. We herein reported a 65-year-old female patient with the left-sided MPM presenting with episodes of recurrent spontaneous pneumothorax. She had undergone the right pleuropneumonectomy due to the right-side MPM 7 years ago. She admitted to our clinic with diagnosis of left pleural effusion. The patient underwent pleural biopsy and talc pleurodesis by thoracoscopy. Histologic study showed the epithelial subtype of MPM. She received chemotherapy nine times. Seven years after pleuropneumonectomy, she had recurrent left-sided spontaneous pneumothorax four times that was treated one by one with tube thoracostomy. We did not perform surgical treatment because of the unsuitable status of the patient. It should be kept in mind that, when pneumothorax develops in the remaining lung after a single-sided pneumonectomy, this may be due to the tumor.

Eur Res J 2016;2(3):240-243

Keywords: Recurrent pneumothorax; pleuropneumonectomy; malignant pleural mesothelioma

Introduction

Malignant pleural mesothelioma (MPM) is almost always a fatal disease, its prognosis being affected by oncologic treatments to a limited extent [1]. Moreover, the diagnosis of MPM is usually delayed because its symptoms and findings are not specific [2]. Additionally, there are various difficulties in the pathological diagnosis of MPM [1-3]. MPM continues being a disease that challenges modern medicine in all aspects. We present here a case with MPM, an example of which is not available in the literature due to its unique clinical progress and treatment difficulties.

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Case Presentation

A 65-year-old female patient admitted to the thoracic clinic with the complaints of chest pain and shortness of breath in another center 10 years ago. She did not have any exposure to asbestos in her personal history and she did not smoke. She also did not have any serious disease. Right hydrothorax was seen in lung x-ray. Computerized tomography (CT) showed a pleural thickening of nodular type on the right side (Figure 1). CT findings did not involve any pulmonary parenchymal invasion or any other important sign.

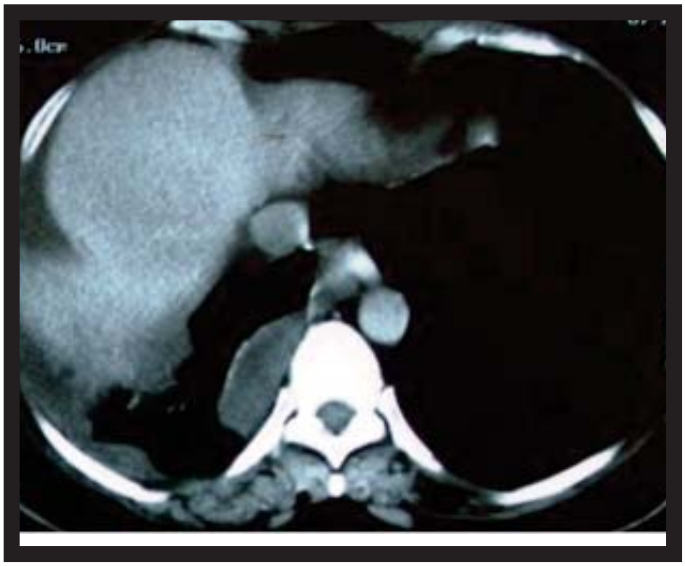

Figure 1. A pleural thickening of nodular type on the right side before extrapleural pneumonectomy operation

Pleural fluid was of exudative type and a videothoracoscopic pleural biopsy was performed. Pathology resulted in an epithelial subtype of MPM.

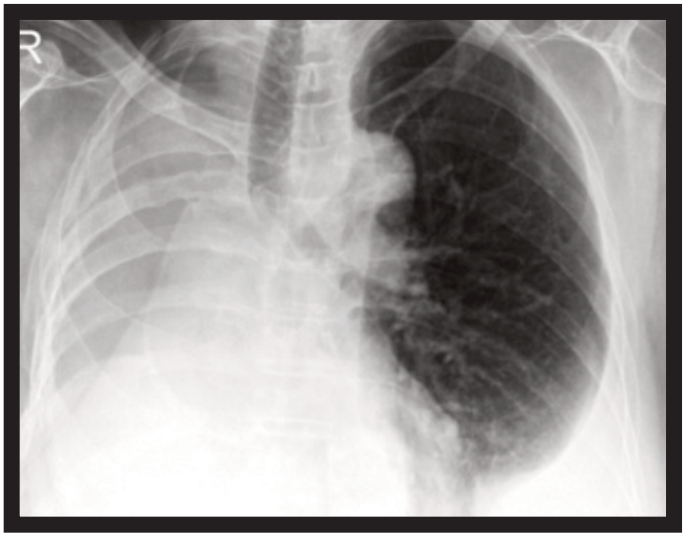

Figure 2. A left side pleurisy

Thoracic magnetic resonance imaging and upper abdominal ultrasound did not show any invasion to the underneath of diaphragm. She had undergone a pleurectomy, but a year later she developed a local relapse and then she underwent an extrapleural pneumonectomy operation. The patient was operated once more 5 years after the extrapleural pneumonectomy due to mucinous ovarian carcinoma and 6 months after this operation she had a left side pleurisy (Figure 2).

The patient was referred to our clinic. With the initial diagnosis of malignant pleural effusion, a pleural biopsy through a left thoracoscopy under local anesthesia was performed and she underwent a chemical pleurodesis through a sterile talk insufflation. The histolologic and immunohistochemical analysis of the pleural biopsy showed an epithelial subtype of MPM (Figures 3 and 4). She was administered 9 cycles of chemotherapy due to left side pleural mesothelioma.

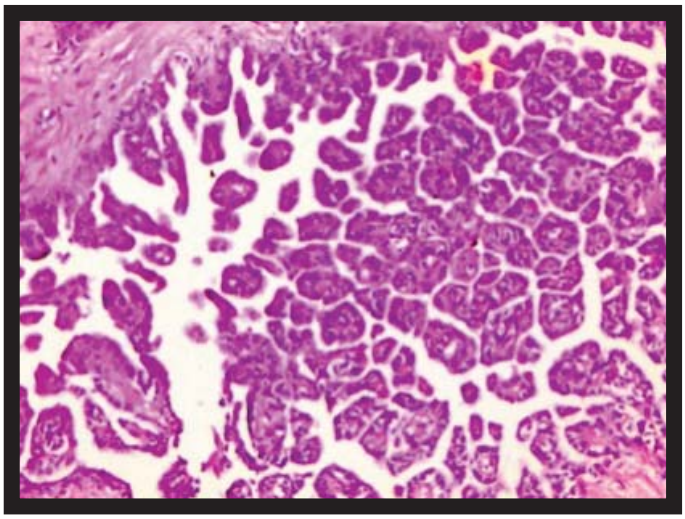

Figure 3. Malignant tumor consisting of papillary proliferation of prominent eosinophilic cytoplasm, vesicular nuclei, prominent nucleoli epithelioid cells. X20, H&E

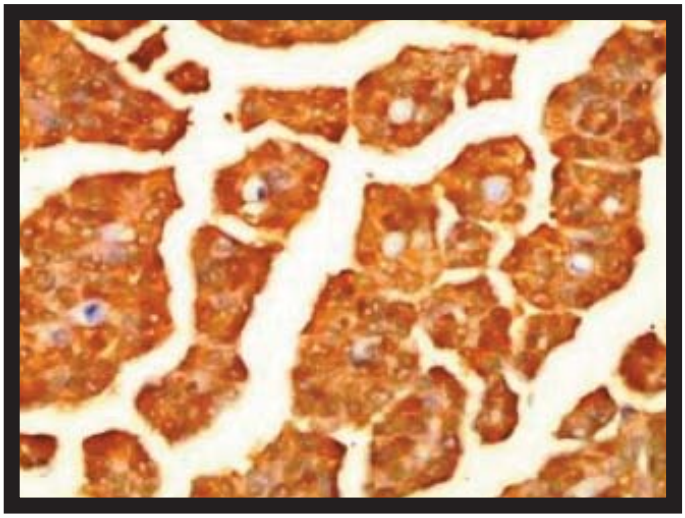

Figure 4. Positivity of calretinin for immunohistochemical X20, IHK.

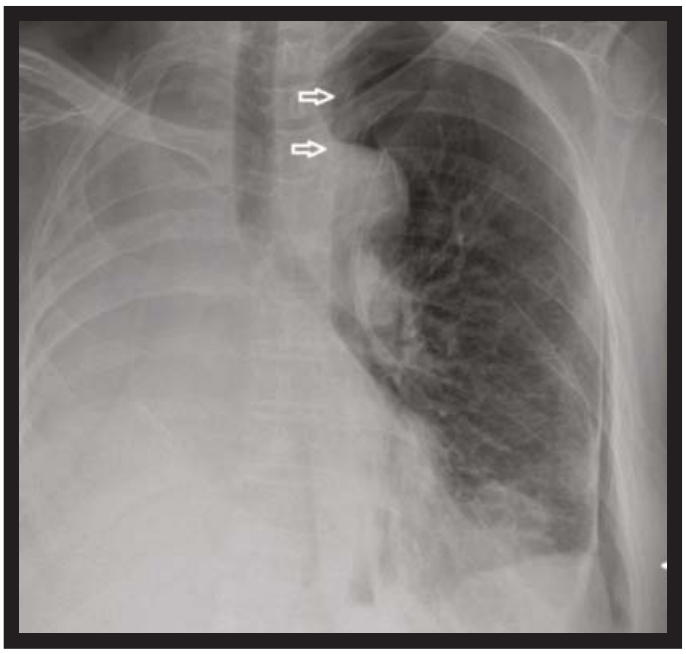

Figure 5. A spontaneous pneumothorax (arrows) attack

She had a spontaneous pneumothorax attack 7 years after the right pleuropnemonectomy even though a chemical pleurodesis had been administered to the left side (Figure 5). During the following 2 years, she had 4 spontaneous pneumothorax attacks, which were treated with a tube thoracotomy each. The last pneumothorax attack lasted 23 days and had an ambulatory treatment with a Heimlich valve. The general condition of the patient was not suitable for a surgical intervention.

The patient is still alive in the 11th year of her first diagnosis and she has MPM in her left hemithorax and mucinous ovarian carcinoma-related metastases in her abdomen.

Discussion

According to many authors, MPM is inevitably fatal [4]. There is no randomized study where a neoadjuvant or adjuvant chemotherapy treatment approach is tested for MPM and the relative contributions of chemotherapy and/or radiotherapy given before or after a cytoreductive surgery are not very well known [1]. Sugarbaker *et al.* [5] have shown that the extrapleural lymph node involvement, surgical margin and cell type are associated with survival after an extrapleural pneumonectomy. Nakas and Walker [4] have reported that survival is good in those who had no nodal involvements, who were at stage T1-2, and who had epithelioid cells. Our patient had good prognostic criteria as previously defined.

Bilateral MPM does not seen very often. Okten *et al.* [2] have reported the rate of bilateral MPM of 1.9%. A bilateral MPM may occur if the tumor directly spreads into the contralateral hemithorax along the mediastinum [6]. In our patient, a left side MPM was found 8 years after the first diagnosis of the right side and there was no recurrence at that time. This situation can be considered as a distant metastasis through the blood; it could also be a second primary MPM since it occurred 8 years after the treatment of the first tumor. Nevertheless, there are many markers, both clinical and biological, of prognosis in MPM [7]. The MPM in our patient seemed to be a very slow progressing biological subtype and with the advancement of the first MPM, the disease in the left hemithorax may be occurred.

The mechanism of pneumothorax is not clear in patients with MPM, but it has been argued that it can develop as a result of the rupture of necrotic tumor nodules [8]. There are very few MPM cases presented with pneumothorax in the literature [7, 8]. This is the first case report involving a patient who had a MPM-related recurrent pneumothorax that developed in the remaining lung years after the EPP of the other side. Our patient, who had 4 recurrences in 2 years despite the pleurodesis she went through, was finally treated with tube thoracostomy.

Conclusion

In conclusion, we presented here an interesting patient who is still alive 11 years after her first diagnosis and who had recurrent pneumothorax attacks in her other lung following an extrapleural pneumonectomy. It should be kept in mind that when pneumothorax develops in the remaining lung after a single side pneumonectomy, this may be due to the tumor. The treatment of patients who develop a tumor-related pneumothorax after a pneumonectomy is difficult to handle.

Informed Consent

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

Conflict of interest

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

References

[1] van Zandwijk N, Clarke C, Henderson D, Musk AW, Fong K, Nowak A, et al. Guidelines for the diagnosis and treatment of malignant pleural mesothelioma. J Thorac Dis 2013;5:E254-307.
[2] Okten F, Koksal D, Onal M, Ozcan A, Simsek C, Erturk H. Computed tomography findings in 66 patients with malignant pleural mesothelioma due to environmental exposure to asbestos. Clin Imaging 2006;30:177-80.
[3] Henderson DW, Shilkin KB, Whitaker D. Reactive mesothelial hyperplasia vs mesothelioma, including mesothelioma in situ: a brief review. Am J Clin Pathol 1998;110:397-404.
[4] Nakas A, Waller D. Predictors of long-term survival following radical surgery for malignant pleural mesothelioma. Eur J Cardiothorac Surg 2014;46:380-5; discussion 385.
[5] Sugarbaker DJ, Flores RM, Jaklitsch MT, Richards WG, Strauss GM, Corson JM, et al. Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients. J Thorac Cardiovasc Surg 1999;117:54-63; discussion 63-5.
[6] Aziz F. Radiological findings in a case of advance staged mesothelioma. J Thorac Dis 2009;1:46-7.
[7] Prasad A, Olsen D, Sriram PS. Malignant mesothelioma presenting as a gradually enlarging pneumothorax. Case Rep Pulmonol 2013;2013:374960.
[8] Saleh HZ, Fontaine E, Elsayed H. Malignant pleural mesothelioma presenting with a spontaneous hydropneumothorax: a report of 2 cases. Rev Port Pneumol 2012;18:93-5.

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Case Report

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Anomalous origin of the left anterior descending coronary artery from the right coronary artery with an interarterial and intramyocardial course: a long-term follow-up

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ABSTRACT

The left anterior descending coronary artery (LAD) originating from the proximal part of the right coronary artery (RCA) is a rare anomaly. An interarterial course for this anomaly is accepted as a 'malign course' and surgical treatment is recommended. In a 66-year-old male patient, coronary angiography showed that the LAD originated from the proximal part of the RCA. Coronary computed tomographic angiography revealed that the LAD had an interarterial and intramyocardial course. The patient refused surgical treatment and has been followed-up without symptoms for the last 4 years with medical treatment. We wanted to contribute to the literature by reporting the long-term results of the medical treatment option for this anomaly with a malign course.

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Keywords: Coronary anomaly; coronary angiography; coronary computed tomographic angiography; interarterial course

Introduction

The angiographic incidence of a left anterior descending coronary artery (LAD) developing from the proximal part of the right coronary artery (RCA) has been reported as 0.05% [1]. A malign intramural course is associated with myocardial ischemic syndromes and sudden death, making surgical repair mandatory [2]. We presented our case who had ischemia on scintigraphy and an interarterial and intramyocardial course on coronary computed tomographic angiography (CTA) but who refused surgical treatment and who has been followed up without symptoms for the last 4 years on medical treatment.

Case Presentation

A 66-year-old male presented with shortness of

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breath on exertion and easy fatigue. Electrocardiography revealed anterior T negativity. Echocardiography showed normal left ventricle systolic functions with no wall motion abnormality. Coronary angiography showed that the circumflex (CX) and RCA had plaques while the LAD originated from the RCA (Figure 1). CTA was performed to demonstrate the LAD course and its relationship with the heart and large vessels and revealed that the LAD originated from the proximal part of the RCA and then advanced between the aorta and the pulmonary artery (interarterial), passing the interventricular septum obliquely (intramyocardial) to reach the anterior interventricular sulcus (Figure 2). The scintigraphy showed ischemia of the left ventricle apical section. The patient did not accept surgery and has been followed up without symptoms for the last 4 years on medical treatment (beta-blocker, nitrate, acetylsalicylic acid).

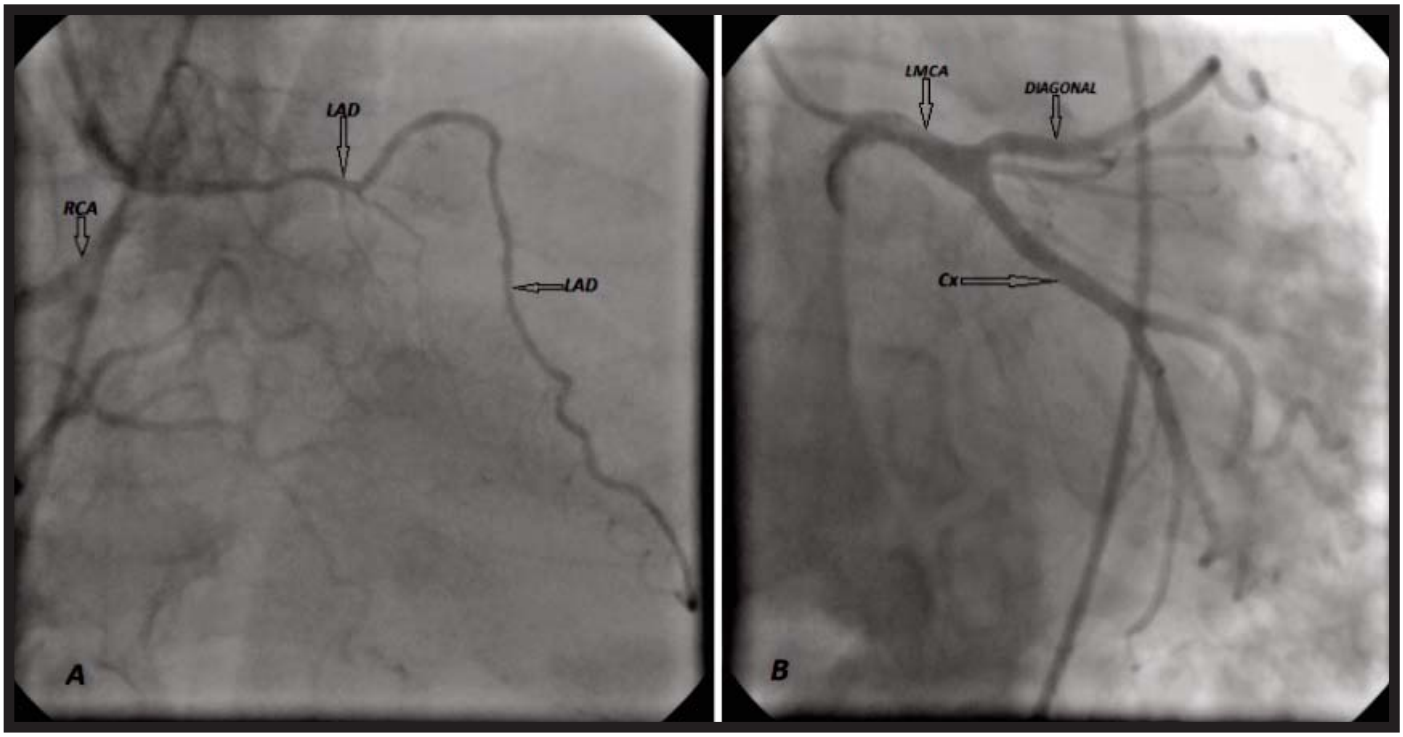

Figure 1. Angiographic view of the LAD. The LAD originated from the RCA.
LAD=left anterior descending coronary artery, RCA=right coronary artery, LMCA=left main coronary artery, Cx=circumflex coronary artery

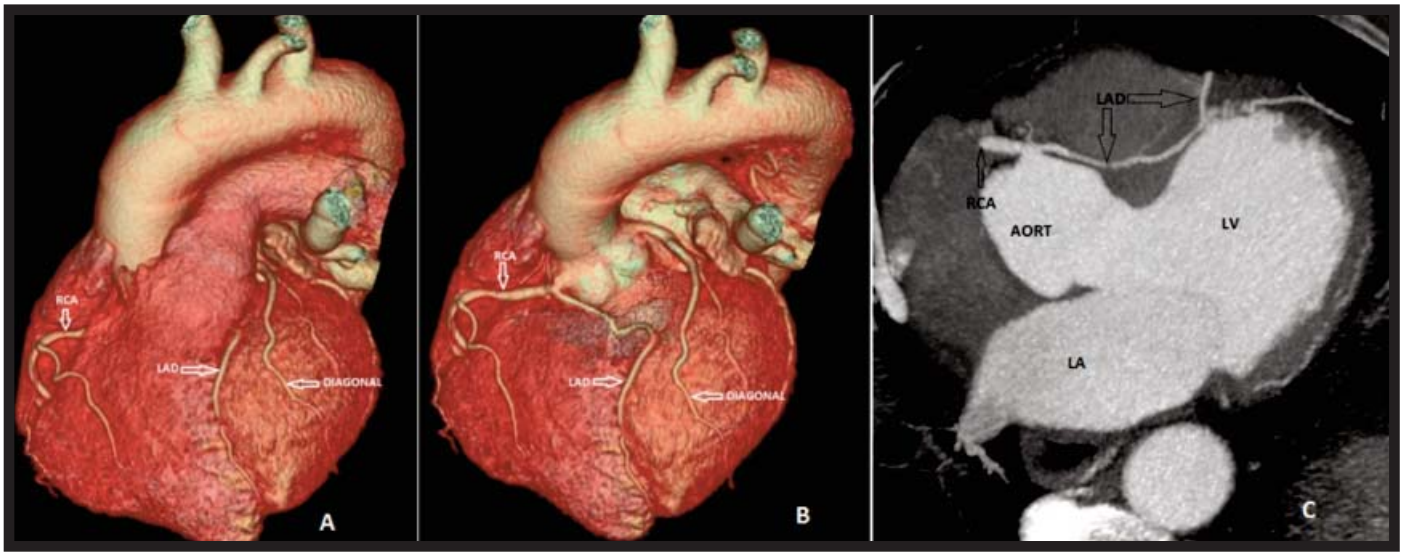

Figure 2. Heart surface rendering (A, B) and curve (C) reconstructions demonstrating the LAD developing from the proximal portion of the RCA with inter-arterial and intra-myocardial course.
LAD=left anterior descending coronary artery, RCA=right coronary artery, LA=left atrium, LV=left ventricle

Discussion

Hemodynamically significant abnormalities include coronary artery atresia, coronary artery originating from the pulmonary artery, a coronary artery with an interarterial course between the aorta and the pulmonary artery, and coronary artery fistulae [3]. The passage of a coronary artery between the aorta and pulmonary artery is named as an interarterial course and can lead to cardiac signs and symptoms such as chest pain, shortness of breath, syncope, arrhythmia, sudden cardiac death (SCD), myocardial infarction and heart failure. SCD is the most important preventable and unexpected event of coronary anomaly. The association between an interarterial course and SCD is ischemia and fatal arrhythmias as a result of compression of great arteries to the anomalous coronary artery [4]. In addition, intramural coronary course of the coronary anomaly may lead to ischemia. Angelini *et al.* [5] demonstrated that an interarterial course is associated with intramural course which is defined as the proximal segment of the coronary artery runs within the aortic wall using intravascular ultrasound. Slit-like lumen [6], ostial occlusion due to aortic expansion during exercise [7], additional anomalies such as myocardial bridging may contribute to myocardial ischemia. Conventional angiography still plays an important role in the definition of cardiac anomalies. However, the recent advances in CTA technology have enabled high sensitivity. The possibility of 3D evaluation and determining the relationship of coronary vessels with the heart and large vessels with CTA make it superior to conventional angiography. CTA is considered the gold standard in the preoperative evaluation of coronary anomalies [8].

Surgery is generally recommended for coronary anomalies with a malign course despite the lack of a consensus [9, 10]. Most of the patients with clinical features similar to ours in the literature have undergone surgery [8, 10]. The guidelines recommend implantable cardioverter defibrillator (ICD) implantation in patients with SCD secondary to ventricular arrhythmias [11]. In addition, ICD implantation may be useful for the primary prevention of SCD in patients with coronary anomaly. Non-invasive and invasive tests may be helpful for the selection of the patients who refuse the surgical therapy. There is no information on the long-term follow-up of these patients and our case report is therefore a first. Although most of the sudden death patients are asymptomatic at the time of unexpected death, long-term results of the medical treatment option can be valuable in part for this anomaly with a malign course. Our 66-year-old male patient with a malign course anomaly has remained without symptoms with medical treatment throughout the continuing follow-up and is currently 70 years old.

Conclusion

Should we insist on surgery for coronary anomaly patients with a malign course or follow-up with medical treatment? We believe that one must evaluate the medical treatment option as well after considering the patient's age, clinical picture and expectations.

Informed consent

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

Conflict of interest

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

References

[1] Sohrabi B, Habibzadeh A, Abbasov E. The incidence and pattern of coronary artery anomalies in the north-west of Iran: a coronary arteriographic study. Korean Circ J 2012;42:753-60.

[2] Van der Mieren G, Van Kerrebroeck C, Gutermann H, Dion R. Surgical angioplasty and unroofing technique for intramural coronary anomaly. Interact Cardiovasc Thorac Surg 2011;13:424-6.

[3] Shriki JE, Shinbane JS, Rashid MA, Hindoyan A, Withey JG, DeFrance A, et al. Identifying, characterizing, and classifying congenital anomalies of the coronary arteries. Radiographics 2012;32:453-68.

[4] Grollman JH Jr, Mao SS, Weinstein SR. Arteriographic demonstration of both kinking at the origin and compression between the great vessels of an anomalous right coronary artery arising in common with a left coronary artery from above the left sinus of Valsalva. Catheter Cardiovasc Diagn 1992;25:46-51.

[5] Angelini P, Velasco JA, Ott D, Khoshnevis GR. Anomalous coronary artery arising from the opposite sinus: descriptive features and pathophysiologic mechanisms, as documented by intravascular ultrasonography. J Invasive Cardiol 2003;15:507-14.

[6] Dogan SM, Gursurer M, Aydin M, Gocer H, Cabuk M, Dursun A. Myocardial ischemia caused by a coronary anomaly left anterior descending coronary artery arising from right sinus of Valsalva. Int J Cardiol 2006;112:e57-9.

[7] Frescura C, Basso C, Thiene G, Corrado D, Pennelli T,

Angelini A, et al. Anomalous origin of coronary arteries and risk of sudden death: a study based on an autopsy population of congenital heart disease. Hum Pathol 1998;29:689-95.
[8] Angelini P. Anomalous origin of the left coronary artery from the opposite sinus of Valsalva: typical and atypical features. Tex Heart Inst J 2009;36:313-5.
[9] Roberts WC, Siegel RJ, Zipes DP. Origin of the right coronary artery from the left sinus of valsalva and its functional consequences: analysis of 10 necropsy patients. Am J Cardiol 1982;49:863-8.
[10] Erol C, Seker M. Coronary artery anomalies: the prevalence of origination, course, and termination anomalies of coronary arteries detected by 64-detector computed tomography coronary angiography. J Comput Assist Tomogr 2011;35:618-24.
[11] Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, et al. ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). Circulation 2008;118:e714-833.

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