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European Journal of Therapeutics (Eur J Ther) is the double-blind peer-reviewed, open access, international publication organ of the Gaziantep University School of Medicine. The journal is a quarterly publication, published on March, June, September, and December. The journal publishes content in English.

European Journal of Therapeutics aims to contribute to the international literature by publishing original clinical and experimental research articles, case reports, review articles, technical notes, and letters to the editor in the fields of medical sciences. The journal's target audience includes researchers, physicians and healthcare professionals who are interested or working in in all medical disciplines.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

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Address: Gaziantep Üniversitesi Tıp Fakültesi, 27310 Şehitkamil, Gaziantep, Turkey
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Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
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Case Report	1000	200	15	No tables	10 or total of 20 images
Technical Note	1500	No abstract	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

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Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

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All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the

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Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

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Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

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Address: Gaziantep Üniversitesi Tıp Fakültesi, 27310 Şehitkamil, Gaziantep, Turkey
Phone: +90 342 360 60 60 / 77751
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E-mail: info@eurjther.com

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Address: Büyükdere Cad. 105/9 34394 Mecidiyeköy, Şişli, İstanbul, Turkey
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Contents

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Review

Management of Type 2 Diabetes Mellitus with Overweight: Focus on SGLT–2 Inhibitors and GLP–1 Receptor Agonists

Sergei V. Jargin

Department of Pharmacology, Peoples' Friendship University of Russia 6, Moscow, Russia

ABSTRACT

GLP-1 receptor agonists (GLP-1RAs) and SGLT-2 inhibitors, along with the widely used metformin, are the drug classes discussed in this mini-review. GLP-1RAs stimulate insulin secretion and slow down gastric emptying, thereby contributing to weight loss. SGLT-2 inhibitors lessen renal glucose reabsorption, lower blood pressure, and contribute to body weight reduction. A similar effect on body weight should be anticipated from the intestinal alpha-glucosidase inhibitor (acarbose), but its efficiency depends on the carbohydrate contents of diet. Notably, the hypoglycemic effects of the two drug classes are unrelated to the stimulation of insulin secretion by beta cells. An exhaustion of beta cells as a result of a prolonged stimulation is regarded as possible. Insulin hypersecretion contributes to an increase in body weight. This indicates that, other things being equal, drugs acting without the stimulation of insulin secretion may be preferable. In conclusion, the goals of glycemic control need to be individualized based on age, prognosis, the presence of macrovascular disease, and the risk of hypoglycemia.

Keywords: Anti-diabetic drugs, glycemic control, type 2 diabetes mellitus

INTRODUCTION

There have been innovations in the management of type 2 diabetes mellitus (T2DM) in the last decades. In this mini-review, only those medications that are not associated with weight gain are discussed. Metformin is the first-line medication for T2DM, but sooner or later, a second-line treatment may be needed (1, 2). It reduces the demand for insulin, thereby improving the sensitivity of peripheral tissues and inhibiting hepatic glucose production. It does not stimulate insulin secretion by pancreatic beta cells, thus not inducing hypoglycemia (3-8). It is not only indicated for the treatment of T2DM with obesity but also benefited patients with a normal body weight. Among the beneficial effect of metformin is appetite suppression, which contributes to weight loss. However, not all studies confirm the weight reduction after a prolonged intake of metformin; some authors classify metformin as neutral with regard to body weight (3, 6, 8). The main contraindication to metformin use is a significant reduction of the glomerular filtration rate because of the risk of lactic acidosis. Further contraindications include conditions associated with hypoxia and the risk of metabolic acidosis, as well as severe liver disease (4). Furthermore, metformin treatment is associated with gastrointestinal side effects, such as diarrhea, nausea, vomiting, bloating, indigestion, abdominal discomfort, or pain, in 20%–30% of patients, whereas approximately 5% of patients have severe symptoms and discontinue the treatment (9, 10). New extended-release metformin preparations have better gastrointestinal tolerability and adherence (11). In case of contraindications or intolerance of metformin, other drugs are administered.

Dipeptidyl peptidase 4 (DPP-4) inhibitors suppress the degradation of glucagon-like peptide 1 (GLP-1), which stimulates insulin secretion and inhibits the synthesis of glucagon. DPP-4 inhibitors do not enhance the risk of hypoglycemia and have no impact on body weight. The hypoglycemic effect of GLP-1 receptor agonists (GLP-1RAs) is more pronounced than that of DPP-4 inhibitors. In addition to the stimulation of insulin secretion, these drugs slow down gastric emptying, suppress appetite, and contribute to weight loss (12, 13). The delayed gastric emptying is associated with eructation and regurgitation (14, 15), which might be disturbing, in particular, for older patients. There are experimental data about an increase in beta cell mass and reduction of their apoptosis under the influence of GLP-1RA; however, direct evidence in humans is lacking (13, 16, 17). At the same time, an exhaustion of beta cells due to excessive stimulation by GLP-1RA is deemed possible (18). Disadvantages include delivery by injection and relatively high costs. An oral preparation of semaglutide (Oral sema; Novo Nordisk, Bagsvaerd, Denmark)

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ORCID ID of the author: S.V.J. 0000–0003–4731–1853

Corresponding Author: Sergei V. Jargin **E–mail:** sjargin@mail.ru

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is currently under evaluation (19). A combination of a GLP-1RA with metformin is efficient, being associated with weight loss and low risk of hypoglycemia (4). The intestinal alpha-glucosidase inhibitor acarbose (Glucobay; Bayer, Leverkusen, Germany) hampers the digestion of carbohydrates, lowers postprandial hyperglycemia and, secondarily, hyperinsulinemia, whereas the risk of hypoglycemia is low. Side effects include meteorism and other intestinal symptoms (20). According to one meta-analysis, acarbose does not influence body weight (21); however, another meta-analysis indicated that it contributes to weight loss especially in patients with T2DM with obesity (22, 23). In experiments, acarbose reduced the body weight of animals (20). The hypoglycemic effect of acarbose depends on the carbohydrate contents of food; therefore; it can be used occasionally during violations of a low-carbohydrate diet. Pramlintide (Symlin; AstraZeneca, Cambridge, United Kingdom), a synthetic amylin analog, lowers the glycated hemoglobin (HbA1c) level in patients with type 1 and 2 diabetes, slows down gastric emptying, reduces appetite, and exerts favorable effects on body weight. It is administered subcutaneously before meals and is comparatively expensive. Adverse effects may include nausea and headache (1).

Sodium glucose co-transporter-2 (SGLT-2) inhibitors reduce the renal reabsorption of glucose. Osmotic diuresis lowers blood pressure, thereby reducing the risk of cardiovascular (CV) complications. Thus, the loss of glucose reduces the potential glucotoxicity and the risk of beta cell failure (24). High levels of glycosuria induced by SGLT-2 inhibitors increase the risk of genital infections, such as vulvovaginitis and balanitis. A slight risk increase of urinary tract infections (UTIs) was reported in some studies; other studies found no statistically significant increase of UTI risk in patients receiving SGLT-2 inhibitors compared with placebo. Usually, these infections are mild to moderate, being successfully treated with standard therapies (25-28).

Clinical and Research Consequences

Owing to their insulin-independent action mechanism, SGLT-2 inhibitors can be combined with other anti-diabetic drugs and insulin (12, 29). In particular, a combination of SGLT-2 inhibitors with metformin or GLP-1RAs was reported to be favorable for patients with T2DM also with obesity and insulin resistance (2, 30, 31). The ketogenic effect of SGLT-2 inhibitors, in consequence of switching from carbohydrates to lipids as a source of energy, should be pointed out (30). A similar effect has low-carbohydrate–high-fat diet (LCHFD), which at a carbohydrate content ≤50 g/day is called ketogenic (32). Under its impact, the amount of glucose absorbed from food does not suffice to maintain glycogen stores, which results in a lowering of glucose and insulin levels in blood, reduction of glycogen stores, and burning of fatty acids with the production of ketones. These ketones are used by the brain and muscles along with glucose as sources of energy. The literature shows that diet studies with LCHFD in patients with T2DM and obesity do induce favorable effects on weight loss, blood glucose, and insulin. However, there is a lack of data supporting the long-term efficacy, safety, and health benefits of LCHFD (32). The LCHFD and SGLT-2 inhibitors act partly in parallel lowering the availability of glucose so that their combination would probably be efficient for the purpose of weight loss. However, caution is needed because of the potential risk of euglycemic ketoacidosis, whose incidence was slightly increased with SGLT-2 inhibitors mainly in type 1 diabetes, sometimes provoked by alcohol excess, surgery, or intercurrent disease (30, 33, 34). A combination of SGLT-2 inhibitors with a strict LCHFD is regarded as a contraindication (35). Notably, the development of mild ketosis has been hypothesized to contribute to the beneficial effects of SGLT-2 inhibition on cardiac and renal outcomes (30). Considering that a prolonged adherence to LCHFD is difficult for patients, a combination of LCHFD with SGLT-2 inhibitors might contribute to the catabolism of fat depots causing less discomfort than a strict LCHFD alone. Such an experimental therapy would require a tight clinical control.

Furthermore, the SGLT-2 inhibitors decrease the risk of heart failure and other CV complications due to their diuretic action with the reduction of blood pressure. Notably, the prevalence of heart failure is increased in patients with T2DM receiving various glucose-lowering agents, such as thiazolidinediones and probably also DPP-4 inhibitors. As for GLP-1RAs, their positive effect on left ventricular ejection fraction, if any, appears to be inconsistent and rather modest in most patients with heart failure (36). In the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial, the rates of nonfatal myocardial infarction and stroke, as well as hospitalization for heart failure, were insignificantly lower in the liraglutide group than in the placebo group, whereas patients in the liraglutide group had lower rates of CV events and death from any cause than those in the placebo group (37). In the ELIXA (Evaluation of Lixisenatide in Acute coronary syndrome) trial, there was no significant difference in the rates of CV events, including heart failure, and of death from any cause, between the lixisenatide and placebo groups of patients with T2DM after a recent acute coronary event (38). The CV protection by GLP-1RA has been hypothesized to act via anti-atherogenic/anti-inflammatory actions (31, 36). However, the mechanisms remain largely unexplained (36). Based on recent trials with SGLT-2 inhibitors, especially the EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) trial, a paradigm shift in the management of T2DM has been proposed. It implies a transition from current algorithms based primarily on glucose and HbA1c control to a strategy additionally focused on the secondary prevention of CV complications using SGLT-2 inhibitors earlier in the management of T2DM. This may be of particular importance for patients with a pre-existing macrovascular disease (39-41).

It appears that the adverse effects of SGLT-2 inhibitors are sometimes exaggerated to promote more expensive drugs. In a previous analysis of nationwide registers from two countries, the use of SGLT-2 inhibitors, as compared with GLP-1RAs, was associated with an increased risk of lower limb amputation and diabetic ketoacidosis (25). This study sounds impressive also for patients if they read the abstract (25). This information has been repeated in Ref. (41). The complication rates of lower limb amputation and diabetic ketoacidosis per 1000 patient-years were 2.7 versus 1.1 and 1.3 versus 0.6, respectively (30), which is a rather low incidence rate. For amputations, these figures are within the usual range (1.5–5.0 per 1000 patient-years) of amputation incidence

in patients with diabetes (42). Ketoacidosis has been discussed above. The reason for the enhanced amputation rate remains speculative; it is unclear whether it concerns all SGLT-2 inhibitors or particular ones (43). Existing records are not sufficient to prove a cause–effect relationship (44, 45). A retrospective cohort study and meta-analysis of four observational databases found no evidence of the increased risk of below-knee lower limb amputations for patients with T2DM treated by SGLT-2 inhibitors, in particular, with canagliflozin (42, 46). The EMPA-REG OUTCOME trial did not report any increased risk of amputation with empagliflozin (46). The putative mechanism of the increased risk of amputation is an intravascular volume depletion due to diuretic effect (25, 41). This is in agreement with studies suggesting that diuretics are generally a risk factor for amputations (47). Therefore, it is essential for patients receiving SGLT-2 inhibitors to maintain adequate hydration. Fortunately, the frequency of more general diabetic foot-related complications was significantly lower in reports for SGLT-2 inhibitors than in those for non-SGLT-2-inhibitor drugs with the diabetes indication, although this difference was tapered after the exclusion of reports listing insulin as a concomitant drug (44). Importantly, the study found no association between the use of SGLT-2 inhibitors and the risk of serious UTIs, venous thromboembolism, acute pancreatitis, and bone fractures, which are adverse events of current concern (25).

The following considerations are sometimes excluded in comparing the GLP-1 RA and SGLT-2 inhibitors. The hypoglycemic effect of the latter is unrelated to the stimulation of insulin secretion. The beta cell failure is a known factor of the T2DM progression (48). A protection from excessive stimulation may arrest the beta cells exhaustion (49, 50). Some experts regard the reduction of beta cell workload to be an effective therapeutic strategy (16). In contrast, e.g., to sulfonylureas, GLP-1RAs potentiate glucose-dependent insulin secretion, but do not stimulate secretion at basal glucose levels (48). GLP-1RAs were reported to induce significant changes of fasting insulin level neither in patients with T2DM nor in healthy volunteers (51, 52); sitagliptin, a DPP-4 inhibitor, did not affect the fasting insulin level in obese prediabetic spontaneously hypertensive rats (53). In addition, there have been reports on the elevation of the fasting serum insulin level and its reduction or modulation under the influence of GLP-1RAs or DPP-4 inhibitors, depending on doses and glucose concentrations (54-56). An exhaustion of beta cells as a result of prolonged stimulation by GLP-1RA is regarded as possible (18). For example, in "humanized mice," a long-term administration of liraglutide resulted in progressive deterioration of glycemic control (57). Further studies, shielded from conflicts of interest, are needed. The elevated insulin level is associated with weight gain, insulin resistance, and mortality risk (50, 58-60). Therefore, other things being equal, drugs acting without the stimulation of insulin secretion appear to be preferable.

CONCLUSION

It is preferable for the treatment of T2DM with overweight to use medications diminishing body weight. Along with the widely used metformin, the following drug classes should be mentioned. The GLP-1RAs stimulate insulin secretion and slow down gastric emptying, thereby contributing to weight loss. The SGLT-2 inhibitors reduce the renal glucose reabsorption, thereby lowering blood pressure and contributing to weight loss. A similar effect on body weight should be anticipated from the intestinal alpha-glucosidase inhibitor (acarbose); however, its efficiency depends on the carbohydrate contents of diet. Importantly, the hypoglycemic effects of the latter two drug classes are unrelated to the stimulation of insulin secretion, which may be an advantage. In conclusion, the management of T2DM and goals of glycemic control need to be individualized considering age, prognosis, the presence of CV disease, hypertension, dyslipidemia, and other risk factors.

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Original Research

Effects of Voluntary and Forced Exercise on Anxiety-Related Behaviours and Motor Activity in Parkinson Mouse Model

Nadide Özkul Doğru, Ramazan Bal

Department of Physiology, Gaziantep University School of Medicine, Gaziantep, Turkey

ABSTRACT

Objective: The aim of this study was to investigate the effect of two different types of exercise, voluntary and forced, on motor activity and anxiety in a neurotoxic parkinsonian mouse model.

Methods: Parkinsonian mice exposed to neurotoxin underwent voluntary exercise (VE) and moderate forced exercise (FE). The motor activity levels were then measured using the rotarod and pole test. Anxiety was assessed using an open-field test (OFT) and elevated plus maze (EPM) test.

Results: Bradykinesia, a motor dysfunction, was assessed using the pole test. The T_{turn} and T_{total} durations were significantly reduced in Parkinson-induced FE ($p<0.001$). The motor activity was assessed with the rotarod test, and the best improvement was in the long-term FE group ($p<0.001$). The time spent on the opened arms in the EPM test or the time spent in the peripheral zone in the OFT is significantly shorter in the Parkinson groups that performed FE than the VE groups. This suggests that the FE group is more anxious.

Conclusion: The study showed that long-term FE was the best exercise to improve the motor function. Moderate-intensity FE provided restorative effects on the motor symptoms of the disease. However, while this type of exercise increases anxiety, the VE has a healing effect on anxiety. Data obtained in this study showed that exercise provided an effective improvement in motor skills and anxiety behaviors. Thus, exercise is an effective and non-invasive way to be safely recommended by clinicians to all patients with Parkinson's disease.

Keywords: Anxiety, forced exercise, motor activity, Parkinson's disease, voluntary exercise

INTRODUCTION

Parkinson's disease (PD) was first described by the British physician James Parkinson in 1817 as the shaking palsy (1). It is a neurodegenerative disease affecting 2%-3% of the population >65 years (2). PD is physiopathologically characterized by the presence of typical eosinophilic cytoplasmic inclusion bodies (Lewy body) and degeneration in pigmented neurons in the substantia nigra. PD has motor and non-motor symptoms (3). Motor symptoms show four basic features: tremor, rigidity, akinesia (or bradykinesia), and postural instability (4). In addition to the well-described motor features, non-motor symptoms including psychiatric symptoms such as olfactory dysfunction, cognitive impairment, anxiety, sleep disorders, autonomic dysfunction, pain, and fatigue form a significant symptomatic burden (5).

An effective pharmacologic treatment to cure the disease completely has not yet been found despite the extensive research on PD. Levodopa is the most effective treatment for motor symptoms (2). However, many studies in the literature report that exercise has a therapeutic effect on motor (6) and non-motor symptoms of PD (7).

Physical activity is defined as any bodily movement produced by the skeletal muscle and causing energy expenditure. Physical activity in daily life can also be divided into occupational, sportive, conditioning, and domestic work activity. Therefore, exercise is a subtype of physical activity that is planned, structured, and routinized (8). On the other hand, physical inactivity, a common risk factor for chronic diseases, is the fourth risk factor leading to death in the world, because it is accounted for 6% of deaths globally.

A lifestyle is determined by various factors such as physical exercise, social interaction, and nutrition. These factors have a positive effect on people's mood. Physical exercise is an effective tool to slow down the physical and cognitive decline caused by illnesses. Regular physical exercise reduces anxiety and increases physical and mental development. It is also recommended as a

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ORCID IDs of the authors: N.Ö.D. 0000-0003-2027-0748; R.B. 0000-0003-3829-8669

Corresponding Author: Nadide Özkul Doğru **E-mail:** nadideozkul@hotmail.com

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complementary treatment for problems such as anxiety, depression, and attention-deficit-accompanying multifactorial diseases like PD or Alzheimer disease. Although the mechanism of the healing effect of regular exercise has not been fully explained due to inadequate studies conducted on humans, data indicate that it is necessary to increase physical activity (9). However, it is still unclear which type of exercise contributes most to these healing effects.

The aim of this study was to investigate the effect of physical exercise types on motor activity and anxiety in an animal model of neurotoxic PD. This model of PD was created by four intraperitoneal injections of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (4×20 mg/kg, at 12 h intervals). Two types of exercise (voluntary exercise [VE] and forced exercise [FE]) were used in the mice. An open-field test and an elevated plus maze (EPM) test were applied to measure anxiety levels. In addition, the mice were subjected to the rotarod and pole test to determine the development of motor activity.

METHODS

Animals
This study was carried out at Gaziantep University Experimental Animal Center laboratories, and C57BL/6 mice (male, weighing 25-30 gr, 6-10 months old) were used. All mice were housed at 23±2°C in a 12-hour ligh-dark cycle with free access to standard rodent food and water.

Groups
The mice were randomly divided into eight experimental groups, as follows: (1) Control (n=10); (2) MPTP (n=10); (3) 4VE+Saline+4VE (n=10); (4) 4FE+Saline+4FE (n=8); (5) MPTP+4VE (n=8); (6) MPTP+4FE (n=8); (7) 4VE+MPTP+4VE (n=8); and (8) 4FE+MPTP+4FE (n=8). Descriptions of the groups are given below (*).

*Control group: Animals were housed in the cage as a sedentary, and no intervention was performed.

MPTP group: MPTP was intraperitoneally injected to mice at the beginning of the experiment, and the mice were housed in the cage as sedantary.

MPTP+4VE group: MPTP was intraperitoneally injected to mice at the beginning of the experiment, and VE was performed for 4 weeks.

MPTP+4FE group: MPTP was intraperitoneally injected to mice at the beginning of the experiment, and FE was performed for 4 weeks.

4VE+Saline+4VE: After VE was performed for 4 weeks, saline was intraperitoneally injected, and VE was performed for 4 weeks again.

4FE+Saline+4FE: After FE was performed for 4 weeks, saline was intraperitoneally injected, and FE was performed for 4 weeks again.

4VE+MPTP+4VE: After VE was performed for 4 weeks, MPTP was intraperitoneally injected, and VE was performed for 4 weeks again.

4FE+MPTP+4FE: After FE was performed for 4 weeks, MPTP was intraperitoneally injected, and FE was performed for 4 weeks again).

Experimental protocol
Body weights were measured once a week by a digital scale.

Experimental Parkinson model
1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) neurotoxin induces dopaminergic neurodegeneration. Thus, it was used to obtain the Parkinson model. MPTP hydrochloride (M-0896, Sigma-Aldrich, St. Louis, Mo, USA) was applied with intraperitoneal injections to all MPTP groups to generate the Parkinson model in animals. MPTP was dissolved in saline (pH 7.4) as 3 mg/mL. To reduce the risk of death, the applied dose was 4×20 mg/kg every 12 hours (10).

Exercise Protocols

Forced exercise
A custom design treadmill system for the FE was produced according to dimensions and specifications, which have been commonly used in the literature. The maximum speed was up to 16 m/min for this treadmill, which had 8 lanes, 38×5×5 cm each (Figure 1) (11).

The animals were run at 10 m/min for 5 days before starting the experiment. If they did not comply with the experimental protocol, they were excluded from the experimental group (12). The exercise protocol was performed at a speed of 15 m/min for 40

Figure 1. Treadmill system for forced exercise

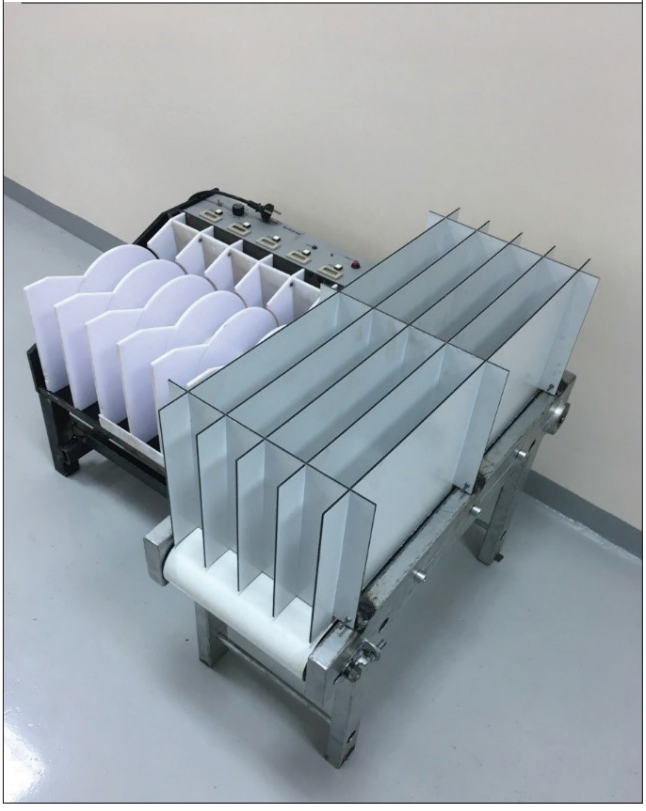
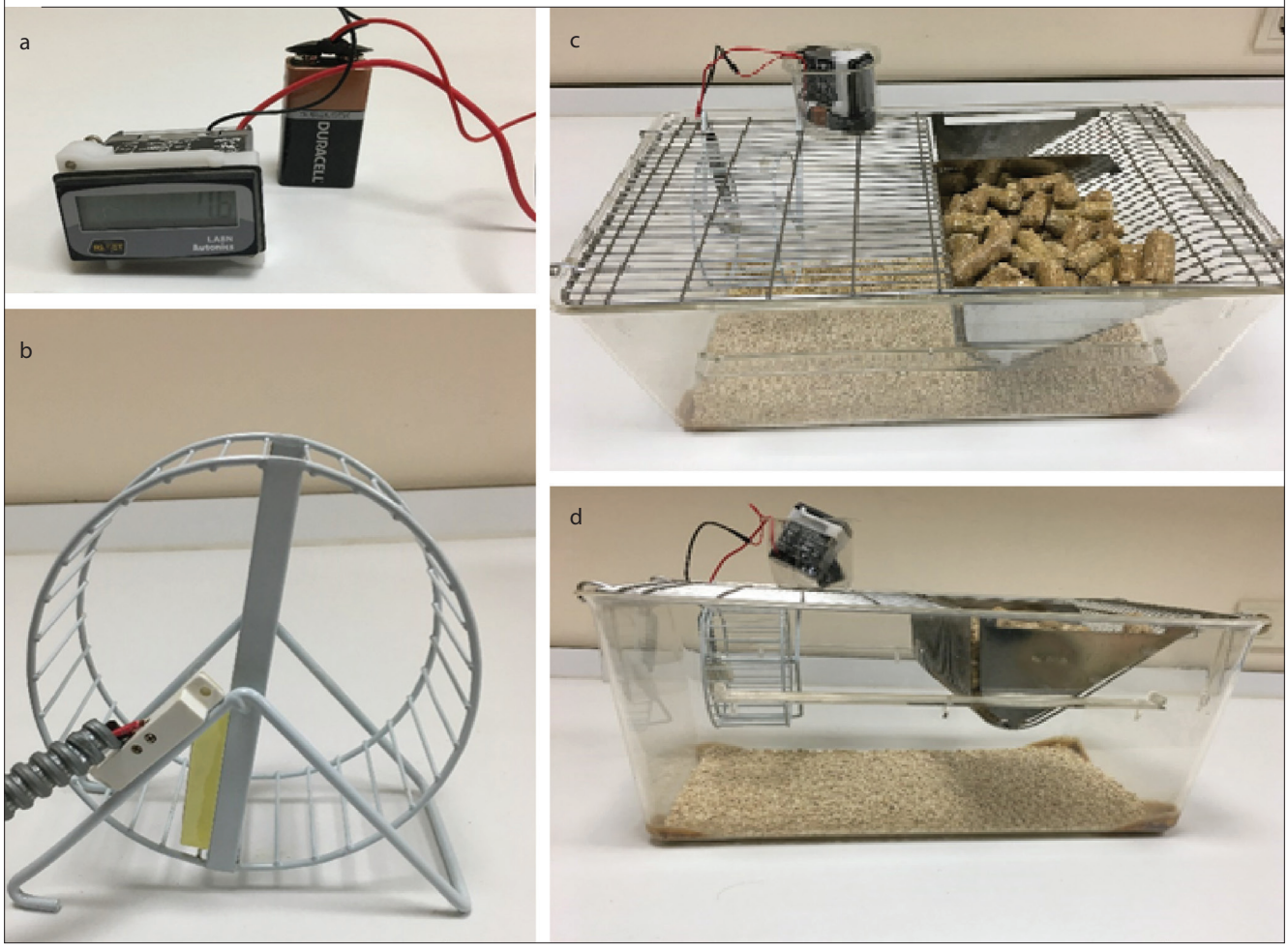


Figure 2. a-d. Wheel-running system for voluntary exercise



minutes per day (6 m/min for 5 min, 9 m/min for 5 min, 12 m/min for 20 min, 15 m/min for 5 min, 12 m/min for 5 min) and 5 days/week with 0° of inclination for the FE groups. Thus, each animal in the FE group run 450 m/day. This exercise is defined as a moderate-intensity exercise in the literature. FE was not applied to the sedentary mice groups; however, they were transported to the training room daily so that they were exposed to the same environmental stress with animals from the exercise group (13).

Voluntary exercise

A wheel-running system, which includes a 5" wheel and a magnetic counter and two electrodes, is produced for each cage as a custom design (Figure 2). Each animal from the VE groups was singly housed. The mice were allowed for 5 days to acclimate before the experiment. The number of wheel rotations was recorded every day at 10 am for each cage (14, 15).

Motor Performance Tests

Pole test

The pole test, performed according to Ogawa et al. (16), is a useful test evaluating the degree of bradykinesia, a typical and basic sign of Parkinsonism. The diameter of the metal bar is 0.8 cm, and the length is 50 cm. Before the experiment, this bar was wrapped with gauze to prevent slipping and make it more suitable for animal. A mouse was placed head upward at the top of the bar. The mouse traveled along the pole freely and came down to the floor (pre-trial). After animals were allowed to get used to the test system with two or three pre-trials, two measurements were taken. T_{turn} is the duration between the time point when the mouse is placed on top of the bar and when it turns the head down. T_{total} is the duration between the time point when the mouse is placed on top of the bar and when it comes down on the ground of the cage. The pole test was applied on the 7th days after the MPTP or saline injection for determining the bradykinesia (10).

Rotarod test

The rotarod test has been accepted widely, and it provides a simple drug-free evaluation of overall motor deficits in rodent models of a disease, such as PD, and it may offer a useful quantitative test to assess the efficacy of therapeutic strategies (17). This test was performed to evaluate motor functions 7th days after the MPTP or saline injection. After mice were placed on the rod (Ugo Basile Mouse Rotarod Cat. No. 47650, Varese, Italy) by hand, the speed was increased gradually from 5 rpm to 40 rpm during 300 seconds. The falling time of the mice from rod was recorded.

The experiment would be terminated for the animal which fell 3 times in 300 seconds. If a mouse never fell down from rod, the time was recorded as 300 seconds, and the experiment was not repeated again for this mouse (6).

Locomotor activity tests

Elevated plus maze test

The EPM test is a widely used test to measure anxiety in mice. The EPM apparatus was composed of four plastic arms (two open and two closed arms), arranged as a cross. The length of each arm is 45 cm and the width is 10 cm (9). Each mouse was placed into the center of the maze, and its behavior (spending time in the closed and open circuit, total distance moved, and velocities of motion and immobility) was recorded by a camera (The Axis M1145-L Network Camera system) for 5 minutes once every 2 weeks. The Etho Vision XT 11.5 was used to analyze the EPM data. The propensity to avoid the open arms is considered as an index of anxiety (18).

Open-field test

The OFT, developed by Hall (19) in 1934, is one of the most commonly used tests to detect changes in the emotional state of an animal before and after any procedure. It consists of a square platform measuring 90×90 cm and a camera system. The Axis M1145-L Network Camera system was used to record behavioral data, and the Etho Vision XT 11.5 was used to analyze the data. All animals were left in the center one by one, and behavioral data (the total distance moved, velocity, spent time at the center and periphery) were recorded for 5 minutes once every 2 weeks. In this test, the preferential exploration of the peripheral area of the open-field was considered an index of anxiety (18).

In both systems, the area was cleaned with 30% ethanol after each animal was tested, and it was waited to dry before the new animal underwent the experiment (20).

Statistical Analysis

Data were presented as the mean±SEM. The Statistical Package for the Social Sciences (SPSS) Statistics 20 (IBM Corp.; Armonk, NY, USA) was used to compare the means of data acquired. Motor performance was measured by using rotarod and pole test. Differences in motor performance among the groups were analyzed using the one-way analysis of variance and followed by the Bonferroni or Tamhane T2. Motor behaviours and anxiety was evaluated by using open field and elevated plus maze tests. Differences in motor behaviour among the groups were analyzed using Kruskal-Wallis test and followed by the "pairwise multiple comparisons" test. A statistically significant difference was considered for $p<0.05$.

RESULTS

Body Weight Changes

There was no significant difference in the body weights of the groups (Data not shown).

Motor Performance

Bradykinesia

The changes in the bradykinesia are presented in Figures 3 and 4. The T_{turn} is reduced in the long-term exercise (4FE+MPTP+4FE) group compared to other MPTP groups (Figure 3). Also, the T_{total} is reduced in all FE groups compared to VE groups and the MPTP group. However, T_{total} was significantly longer in the MPTP, 4VE+Saline+4VE, MPTP+4VE, and 4VE+MPTP+4VE groups than in the control, as shown in Figure 4 ($p<0.001$).

Rotarod

The injection of MPTP impaired the ability of mice to stay on the rotating rod for 5 min. There was a significant difference between

Figure 3. T_{turn} values for determining of bradykinesia by the pole test. Data are the means±SEM. Statistical analysis was conducted using the Kruskal–Wallis, followed by pairwise multiple comparisons against the indicated group

*p<0.001 vs. control002E

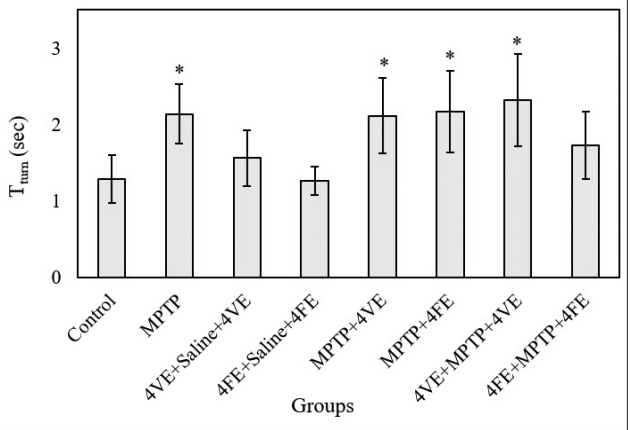


Figure 4. T_{total} values for determining of bradykinesia by the pole test. Data are the means±SEM. Statistical analysis was conducted using the one-way analysis of variance, followed by the Bonferroni test against the indicated group

*p<0.001 vs. control

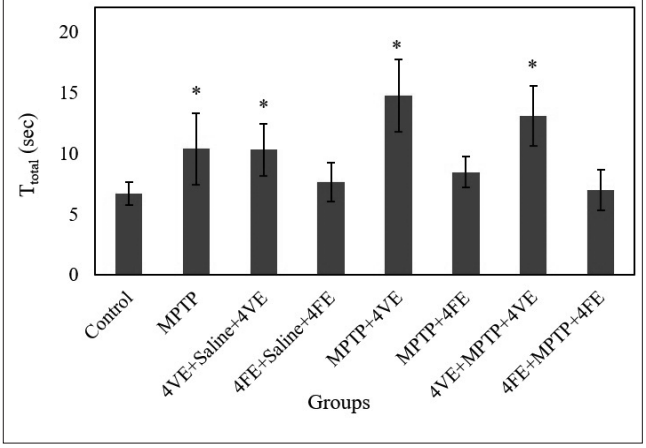


Figure 5. Rotarod performance at 7 days after the MPTP injection. Data are the means±SEM. Statistical analysis was conducted using the one-way analysis of variance, followed by Tamhane's T2 test against the indicated group
*p<0.001 vs. MPTP

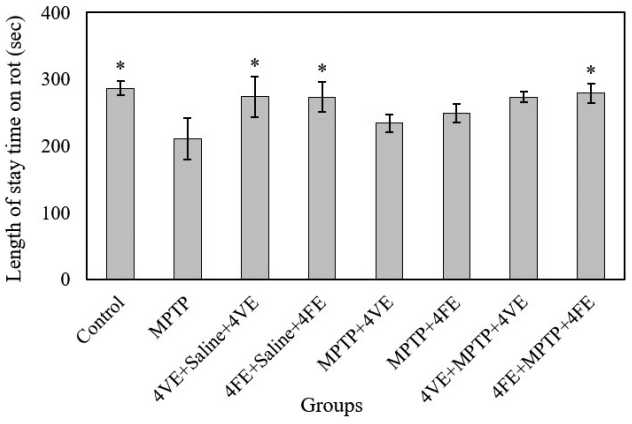
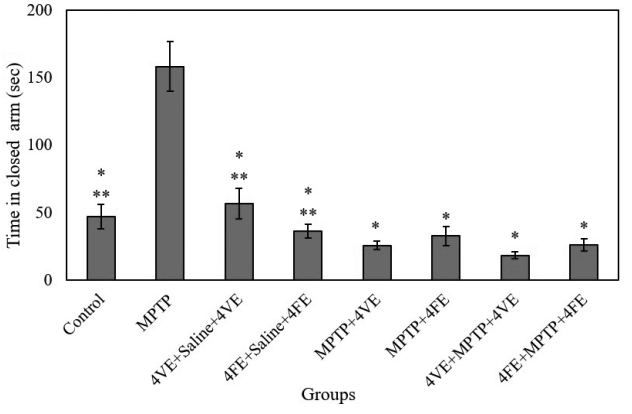


Figure 6. The total time of groups spent in the closed arm of the elevated plus maze test. Data are the means±SEM. Statistical analysis was conducted using the Kruskal–Wallis test, followed by pairwise multiple comparisons against the indicated group
*p<0.001 vs. MPTP; **p<0.001 vs. 4VE+MPTP+4VE
MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; 4VE: Group performed voluntary exercise during 4 weeks; SEM: Standard error of mean



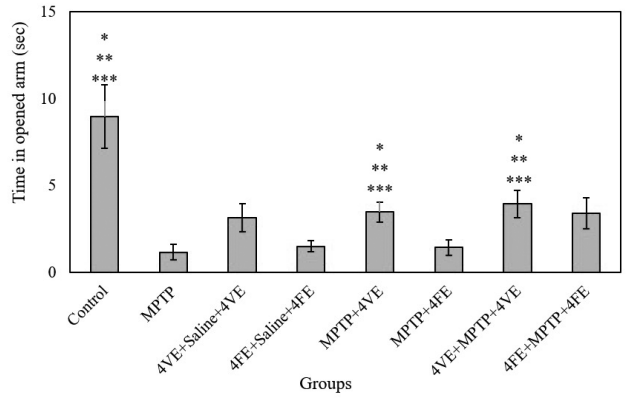
the 4FE+MPTP+4FE and all of the other MPTP groups, as shown in Figure 5 (p<0.001). Long-term FE especially prolonged the duration of the staying on the rod.

Locomotor activity

Elevated plus maze test

Elevated plus maze is one of the most popular tests for evaluating anxiety. The total time spent by animals in the closed arm of the EPM test was shown in Figure 6. Accordingly, there was a significant decrease in the time spent in the closed arm in all groups compared to the MPTP group (p<0.001). Namely, anxiety was reduced in all exercise groups.

Figure 7. The total time of groups spent in the open arm of EPM. the elevated plus maze test. Data are the means±SEM. Statistical analysis was conducted using the Kruskal–Wallis test, followed by pairwise multiple comparisons against the indicated group
*p<0.001 vs. control; **p<0.001 vs. MPTP, ***p<0.001 vs. MPTP+4FE



The time spent in closed arm in the EPM test gives information about animal's anxiety. If the animal is anxious, it stays longer than normal in the closed arm. The spent time in the closed arm in the MPTP group was significantly prolonged compared to the all other groups, as presented in Figure 6. Namely, animals from the MPTP group were more anxious than the others. However, the time spent in the closed arm in the 4VE+MPTP+4VE group was significantly reduced compared to the control, 4VE+Saline+4VE, and 4FE+Saline+4FE groups.

The time spent in the opened arm of the EPM test was reduced in the MPTP, 4FE+Saline+4FE, and MPTP+4FE groups compared to the control (Figure 7). Also, the time spent in the opened arm was reduced in the MPTP and MPTP+4FE groups compared to the MPTP+4VE and 4VE+MPTP+4VE groups.

Open-field test

Mobility decreases when animals are anxious. The total mobility in the MPTP and 4VE+Saline+4VE groups decreased compared to other groups, as shown in Figure 8.

It has been accepted that animals, which spend more time in the central zone, are less anxious, while animals, which spend more time in the peripheral zone, are more anxious. The spent time in the central zone was significantly increased in the control, 4VE+Saline+4VE, 4FE+Saline+4FE, MPTP+4VE and 4VE+MPTP+4VE groups compared to the MPTP groups, as shown in Figure 9.

The time spent in the peripheral zone was increased significantly in the MPTP, 4VE+Saline+4VE, MPTP+4VE, and 4FE+MPTP+4FE groups, compared to control, while it was decreased significantly in the 4VE+Saline+4VE, 4FE+Saline+4FE, MPTP+4FE, and 4VE+MPTP+4VE groups compared to the MPTP group, as presented in Figure 10.

Figure 8. The total mobility of groups in the open-field test. Data are the means±SEM. Statistical analysis was conducted using the Kruskal–Wallis test, followed by pairwise multiple comparisons against the indicated group
*p<0.001 vs. MPTP

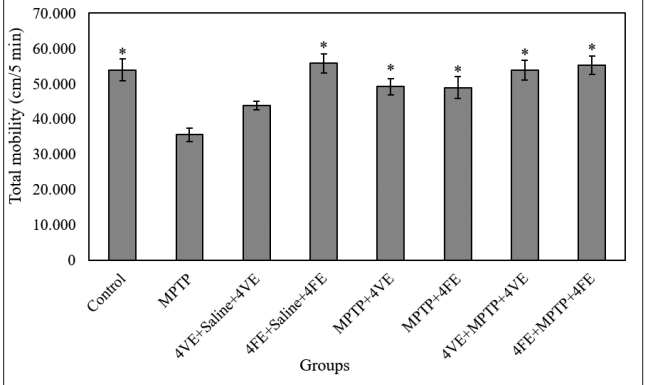


Figure 9. The time spent in the central zone in the open-field test. Data are the means±SEM. Statistical analysis was conducted using the Kruskal–Wallis test, followed by pairwise multiple comparisons against the indicated group
*p<0.001 vs. MPTP

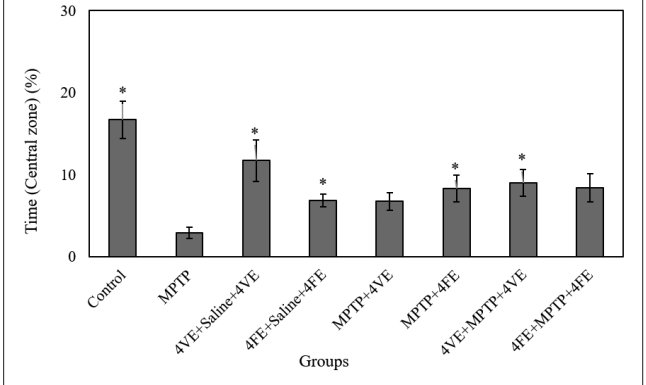
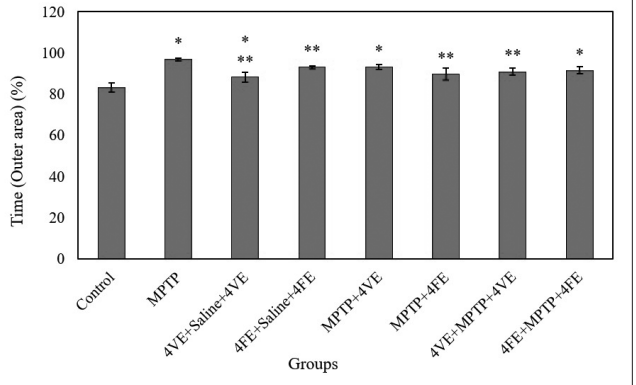


Figure 10. The time spent in the peripheral zone in the open-field test. Data are the means±SEM. Statistical analysis was conducted using the Kruskal–Wallis test, followed by pairwise multiple comparisons against the indicated group
*p<0.001 vs. control; **p<0.001 vs. MPTP



DISCUSSION

The presented study revealed that exercise had a healing effect on motor activity and anxiety. A meta-analysis study showed that exercise can increase the physical functions, quality of life, power, balance, and walking speed of patients with PD (6).

The duration of staying on the rod in the MPTP group was shorter than in other groups in the rotarod test used to evaluate motor performance. However, the duration of staying on the rod in the FE group, performing FE during 8 weeks (4FE+MPTP+4FE), was longer ($p<0.001$). Namely, it was found that performing long-term FE improved motor performance. A study in the United States (2016) reported that FE and anti-parkinson drugs provide similar levels of improvement in the symptoms of the disease. Clinical evaluation of the improvement of upper extremity motor function of patients showed a correlation between the activation fields and the activation scores of FE and anti-Parkinson drugs. These results suggested that FE may be a useful and non-invasive method for the improvement of the PD symptoms (21). Therefore, it was reported that FE is an effective method that partially relieved motor impairment and improved the motor function by reducing loss of dopaminergic neurons and α-synuclein expression in the MPTP animal model in another study (22).

A motor dysfunction, bradykinesia, was assessed by the pole test. Especially FE groups showed significant improvement ($p<0.001$), whereas the results of VE groups were similar to the MPTP group. Particularly long-term FE seems to have contributed significantly to improved motor functions. In a study on PD, rats performed walking and balance exercises after the PD model, and improvements in theirmotor function were examined with neuro-behavioral evaluations. According to this study; both types of exercise were found to improve motor function when assessed on Days 7, 14, 21, and 28 in the pole test (23).

The longer time spent in the closed arm (24) and decreasing in total mobilization (25) indicate that the animal is more anxious during the EPM test. In the presented study, it was determined that there was an improvement in anxiety and depressive behaviors in both types of exercise. Another study reported that exercise improves the cognitive function and reduces symptoms of depression in elderly people (14). The results of this study are consistent with the results obtained in the presented study.

According to the EPM test results, the time spent in the open arms was reduced in the FE groups compared to the VE groups. This result indicates that animals in the FE groups are more anxious. In a study conducted in 2016, it was shown that the corticosterone level, known as stress hormone, was lower in the VE group performed during 10 days than the forced treadmill- or forced wheel-running exercise groups. Researchers noted that VE worked like a reward system and increased motivation, so it did not increase corticosterone levels (26).

More time spent in the peripheral zone than in the middle area indicates anxiety in the OFT (27). In the presented study, the time spent in the central zone was significantly reduced in the long-term VE group, but there was no significant decrease in the long-term FE group. At the end of the OFT test, it was indicated that VE seems to be more beneficial in improving anxiety than FE. This may be due to an anxiety enhancing effect of FE (23).

All the study data showed that the presence of an improvement in motor skills and anxietic behaviors in all exercise types. In addition, long-term FE is more beneficial for ameliorating motor skills. However, long-term VE has a less significant anxietic effect.

CONCLUSION

In conclusion, FE has a positive effect on motor activity when done for a long time. VE has an ameliorative effect on anxiety. Thus, exercise is a non-invasive method that clinicians can safely recommend to all patients with PD.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gazintep University (no: 2017/14, date: 07.06.2017).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - N.Ö.D., R.B.; Design - N.Ö.D.; Supervision - N.Ö.D., R.B.; Resources - N.Ö.D.; Materials - N.Ö.D.; Data Collection and/or Processing - N.Ö.D.; Analysis and/or Interpretation - N.Ö.D., R.B.; Literature Search - N.Ö.D.; Writing Manuscript - N.Ö.D.; Critical Review - N.Ö.D., R.B.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Original Research

The Efficacy of 0.2 Tesla Open Magnetic Resonance Imaging Scanner in the Diagnosis of Anterior Cruciate Ligament Injury

Ayşe Selcan Koç

Clinic of Radiology, University of Health Sciences, Adana Health Practice and Research Center, Adana, Turkey

ABSTRACT

Objective: The aim of the present study was to search the efficiency of low-field (0.2 Tesla) open magnetic resonance scannerin the diagnosis of anterior cruciate ligament injury.

Methods: In the present study, 102 patients (54 males and 48 females; mean age 38.1±14 years) were collected from 562 cases who were referred to the radiology department from the orthopedic clinic due to the preliminary diagnosis of meniscopathy and ligamentous pathology and who had bone contusion on magnetic resonance imaging.

Results: Of the 102 patients, 87 (85.3%) had medial meniscus injury, 41 (40.2%) had lateral meniscus injury, 46 (45.1%) had anterior cruciate ligament injury, 9 (8.8%) had posterior cruciate ligament injury, and 93 (91.2%) had synovial fluid. Patients with anterior cruciate ligament injury were found to have 100% lateral compartment injury, 69% femoral lateral condyle contusion, and 76% tibial lateral plateau contusion.

Conclusion: It was concluded that the low-field (0.2 Tesla) open magnetic resonance scanner may be used efficiently to diagnose anterior cruciate ligament injury, as well as the pathological conditions in the knee.

Keywords: Anterior cruciate ligament injury, bone contusion, open low-field magnetic resonance scanner

INTRODUCTION

The main ligaments of the knee are the anterior and posterior cruciate ligaments and the medial collateral and lateral collateral ligaments. The most injured ligament of the knee is the anterior cruciate ligament. Although physical examination and bilateral direct knee radiography are used for evaluation of anterior cruciate ligament injury, the role of non-invasive imaging methods with high diagnostic value became important for pathologies requiring further examination.

Magnetic resonance imaging (MRI), which is reported with high accuracy rate on the knee joint, is preferred to diagnostic arthroscopy by many orthopedists (1). The quality of images acquired using an MRI has increased with the use of high-field magnets developed over time (≥1.5 Tesla) and advanced computer software, and the examination time has gradually decreased. Despite high-field scanner, as well as some advantages, such as longer scanning duration, low signal noise rate, insufficient number of thin slices, and low resolution (spatial resolution), low-field MRI scanners are most commonly used for diagnosis because of some reasons, such as better magnet homogeneity, relevant cost, and minimize claustrophobia handicap that appeared in closed gantry systems. Different resultshave been reported about the diagnostic accuracy of low-field MRI scanner in anterior cruciate ligament injury.

The aim of the present study was to detect the efficiency of low-field MRI scanner of 0.2 Tesla on anterior cruciate ligament injury in the knee joint and detection of other pathologies of the knee associated with anterior cruciate ligament injury.

METHODS

Overall, 562 cases who were referred from the orthopedics department to the MRI unit within the radiology clinic of our hospital due to the preliminary diagnosis of meniscopathy or ligamentous pathology between September 2007 and March 2009 were examined. A total of 102 (54 male and 48 female) patients who had pathological findings on MRI in the knee joint were included in this retrospective study. The mean age of the patients was 38.1±14 years. The cases were selected from patients without any history of trauma as assessed by an orthopedist in the orthopedics polyclinic and who presented clinical findings reminding meniscopathy or ligamentous pathology. Patients with rheumatoid arthritis, previous knee surgery, cardiac pacemaker, malignancy, and who are not

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ORCID ID of the author: A.S.K. 0000–0003–1973–0719

Corresponding Author: Ayşe Selcan Koç **E–mail:** drayseselcankoc@gmail.com

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Table 1. Demographic data of the patients

	Knee joint pathology (n=102)
Age (years)	38.1±14
Gender (Female/Male)	54/48

Table 2. MRI findings of the patients

Parameter	Knee joint pathology (n=102)
Medial femoral condyle contusion (n, %)	52 (51.0)
Lateral femoral condyle contusion (n, %)	46 (45.1)
Medial tibial plateau contusion (n, %)	65 (63.7)
Lateral tibial plateau contusion (n, %)	54 (52.9)
Medial meniscus injury (n, %)	87 (85.3)
Lateral meniscus injury (n, %)	41 (40.2)
Anterior cruciate ligament injury (n, %)	46 (45.1)
Posterior cruciate ligament injury (n, %)	9 (8.8)
Synovial fluid (n, %)	93 (91.2)
Medial collateral ligament injury (n, %)	7 (6.9)
Lateral collateral ligament injury (n, %)	9 (8.8)
Baker's cyst	14 (13.7)
Osteoarthritis (n, %)	13 (12.7)

MRI: magnetic resonance imaging

technically eligible for MRI were excluded from the study. The patients were informed about the procedure and possible complications (claustrophobia and possible consequences due to magnetic field in case of existence of any metallic instrument in the body). Informed consent was obtained from the patients. MRI examinations were performed in a 0.2 T low fieldstrength open MRI scanner (Hitachi Airis Mate, Hitachi Corp., Japan).

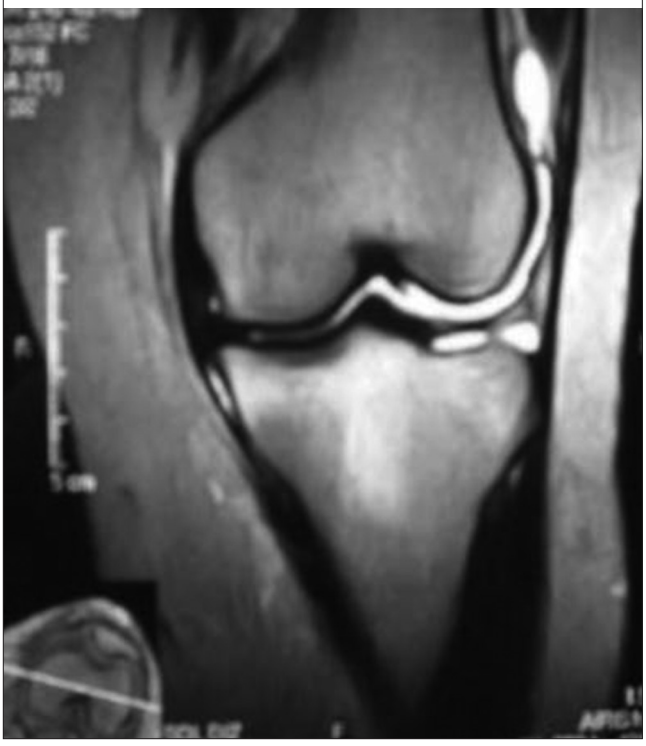
Two-dimensional gradient echo (GRE) axial images were obtained from the patients first for localization. In such imaging procedures, the parameters were as follows: repetition time, 100; echo time, 12; flip angle, 30°; slice thickness, 8 mm; slice interval, 9 mm; number of signal averages, 2(1); and matrix, 224×128. In MRI images, plan was first made through axial section for sagittal examination. Spin echo (SE) T1A, PDA, and fast spin echo (FSE) T2A slices on sagittal plane and then SE T1A, PDA and FSE T2A slices on coronal plane were obtained. Furthermore, axial and sagittal GRE images were added. The evaluation was performed by one radiologist both on the computer screen.

Statistical Analysis

All analyses were performed using Statistical Package for the Social Sciences 15.0 statistical software package (SPSS Inc.; Chicago, IL, USA). Continuous variables in the group data were expressed as mean±standard deviation. Categorical variables were presented as number and percentage. Comparison t test and variance analysis were used for parametric tests of univariate analysis, and Mann–Whitney U test and Kruskal–Wallis test were used for non-parametric tests according to the distribution of continuous variables in independent groups. Chi-square test was used for comparison of categorical variables. Multivariate logistic regression analysis was performed for significant changes as a result of univariate analyses for determination of the factors affecting anterior cruciate ligament injury. As a result of such analysis, an increase or a decrease of significant variables was presented as odds ratio according to the unit increase. A p value <0.05 was accepted as statistically significant.

Figure 1. MRI T2A coronal image shows a tibial medial plateau contusion

MRI: magnetic resonance imaging



RESULTS

The average age of 102 patients enrolled was 38.1±14 years including similar number of males and females (Table 1). In comparison with the pathological findings detected by MRI and age, as well as gender, patients with femur lateral condylar contusion were younger (33.6±12.8 and 41.7±13.9, p=0.003) and generally male (30 males and 16 females, p=0.001); there was no any significant association detected between other findings (p>0.05).

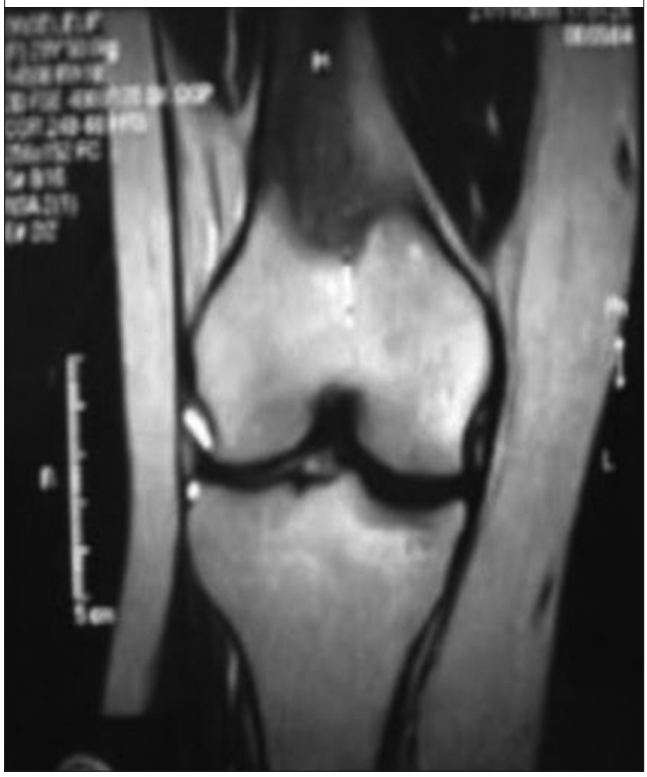
When patients with pathological MRI findings were evaluated, the most common pathological findings were synovial fluid and medial meniscus injury; and the least common pathological findings were medial collateral ligament, lateral collateral ligament, and posterior cruciate ligament injury. The number of patients with anterior cruciate ligament injury was 46 (45.1%) (Table 2).

Table 3. MRI findings associated with anterior cruciate ligament

		Anterior cruciate ligament injury			
Parameter		**No (56)**	**Yes (46)**	**kappa**	**p**
Medial femoral condyle contusion	None(50)	15	35	—0.487	<0.001
	Yes (52)	41	11		
Lateral femoral condyle contusion	None(56)	42	14	0,446	<0.001
	Yes (46)	14	32		
Medial tibial plateau contusion	None (37)	15	22	—0.203	0.028
	Yes (65)	41	24		
Lateral tibial plateau contusion	None (48)	37	11	0,415	<0.001
	Yes (54)	19	35		
Medial meniscus injury	None (15)	6	9	—0.082	0.209
	Yes (87)	50	37		
Lateral meniscus injury	None (61)	41	20	0.300	0.002
	Yes (41)	15	26		
Synovial fluid	None (9)	4	5	—0.034	0.509
	Yes (93)	52	41		

MRI: magnetic resonance imaging

Figure 2. MRI T2A coronal image shows tibial medial plateau and femoral medial condyle contusion
MRI: magnetic resonance imaging



Anterior cruciate ligament injury was found to be positively associated with medial femoral condyle contusion and medial tibial plateau contusion and negatively associated with lateral tibial plateau contusion and lateral meniscus injury (Table 3) (Figures 1–4).

A logistic regression analysis was performed for usability of MRI findings to detect the anterior cruciate ligament injury. When the parameters associated with anterior cruciate ligament injury were included in the analysis, there was an independent association between anterior cruciate ligament and contusion of lateral femoral condyle, medial femoral condyle, and lateral tibial plateau (Table 4).

DISCUSSION

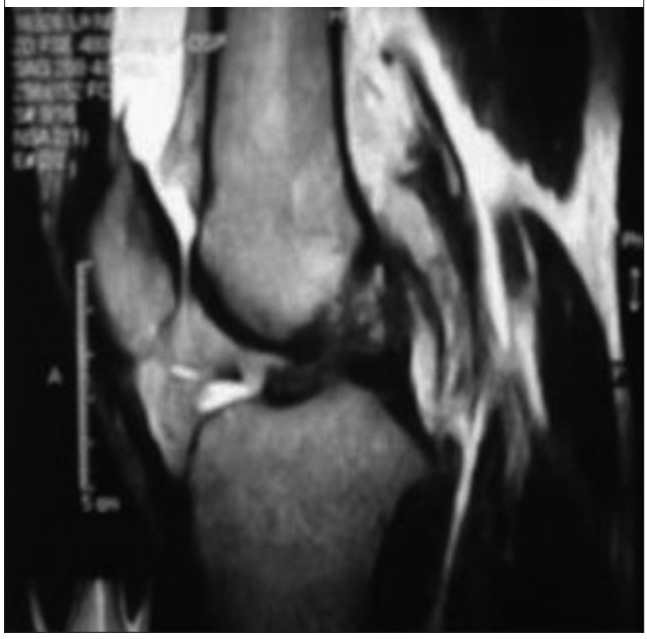
The main finding of the present study was that low-field (0.2 Tesla) open magnetic resonance scanner may be used efficiently to diagnose anterior cruciate ligament injury and the pathological conditions in the knee.

Among knee pathologies, anterior cruciate ligament injury, which is the second most common knee pathology, was detected in 46 (45.1%) patients in our study. MRI is the most valuable method to show anterior cruciate ligament directly, better non-invasive imaging of other soft tissues, and also for preoperative evaluation of an injured knee (2). The cruciate ligaments are stabilizers of the knee; and their evaluation has a specific importance. Anterior cruciate ligament is the most commonly affected ligament in knee traumas. Injury develops as secondary to large

Table 4. Regression analysis associated with anterior cruciate ligament injury

Parameter	Odds ratio	95% CI	p
Medial femoral condyle contusion	19.510	4.401–86.495	<0.001
Lateral femoral condyle contusion	0.054	0.012 – 0.242	<0.001
Lateral tibial plateau contusion	0.174	0.046 – 0.657	0.010

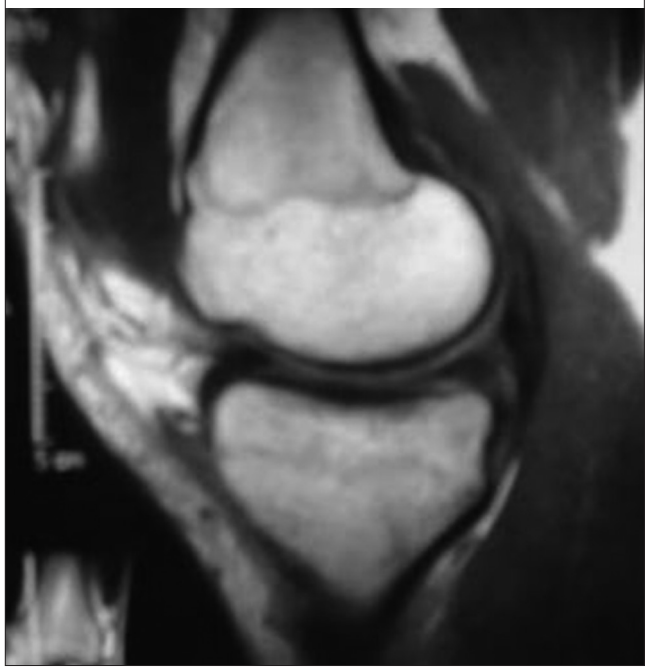
Figure 3. MRI T2A sagittal image shows anterior cruciate ligament injury
MRI: magnetic resonance imaging



traumas, and meniscus lacerations may accompany such injuries (3). If edema of soft tissue is added to diffuse or focal discontinuity of the ligament, anterior cruciate ligament rupture may be diagnosed. Anterior cruciate ligament injuries (ruptures on intraligamentary, femoral, and tibial connection sites) may be detected by MRI with an accuracy rate >80% (4). It was shown that anterior cruciate ligament injury is detected less in young patients, especially in children because of ligament laxity; and these patients may develop bone contusion only without any anterior cruciate ligament injury (5). In our study, there was no any difference with regard to age and gender between those with and without anterior cruciate ligament injury; and anterior cruciate ligament injury was detected independently from age. The possible cause for that may be the average age of the patients, which is 38 years in the present study.

The bone contusion in anterior cruciate ligament injury is detected at the posterior-lateral side of the tibial plateau and on the lateral femoral condyle just over the anterior horn of the lateral meniscus. Johnson et al. (6) showed that 80% of cases with anterior cruciate ligament injury have contusion of the lateral compartment. Furthermore, lateral tibial plateau contusion was detected on the lateral femoral condyle by 50% and on the lateral tibial plateau by 50%; contusion finding was detected on multiple zones in 30% of these patients (6). Similar to the previous study, Papalia et al. (7) showed contusion of lateral compartment by 70% in patients with anterior cruciate ligament injury. The same study detected that contusions of terminal sulcus on the lateral femoral condyle more specifically determine the anterior cruciate ligament injury. In the studies performed, the association between anterior cruciate ligament injury and contusion of the lateral femoral condyle and lateral tibial plateau was commonly connected to the mechanism creating lateral tibial rotation, as well as femoral medial rotation during flexion of the knee, namely, valgus stress. Such maneuver causes injury of the anterior cruciate ligament; frontal subluxation on the tibia relative to the femur and contusion of the terminal sulcus located on the posterior side of the lateral tibial plateau and medial part of the lateral femoral condyle (6 ,8). Snearly et al. (9) investigated bone contusion findings of adult patients without anterior cruciate ligament injury and detected bone contusion without anterior cruciate ligament injury in 28% of the patients. Similar to the previous study, in the present study, contusion finding on the lateral compartment was detected in 26% of patients without anterior cruciate ligament injury. In our study, lateral compartment injury was detected in 100% of patients with anterior cruciate ligament injury; contusion on the femoral lateral condyle and lateral tibial plateau was detected in 69% and 76%, respectively. Similarly, 100% ratio on bone contusion was shown in the study conducted by Kaplan et al. (10); lateral compartment contusion

Figure 4. MRI T2A sagittal image shows medial meniscus posterior horn injury
MRI: magnetic resonance imaging



was detected in all of 200 MRIs of patients with anterior cruciate ligament injury. Furthermore, the development of contusion on the lateral femoral condyle and lateral tibial plateau was shown as an independent indicator to detect the anterior cruciate ligament injury.

In addition, similar to the study conducted by Papalia et al. (7), contusion of the lateral femoral condyle specifically determined the anterior cruciate ligament injury. Another study supporting the findings of the present study was conducted by Spindler et al. (11), and they found a close association between anterior cruciate ligament injury and contusion of the lateral femoral condyle. In the present study, contusion on the femoral lateral condyle and lateral tibial plateau was detected in 69% and 76%, respectively. Although contusion of the lateral tibial plateau is more common in patients with anterior cruciate ligament injury, the statistical examination detected that contusion of the lateral femoral condyle is more associated with anterior cruciate ligament injury.

The present study has some limitations. Our study is a small-scale study for knee pathologies. Studies with larger patient series would provide more clear results. More objective findings might have been obtained if patients who had arthroscopy were included in the present study. Zeiss et al. (12) divided patients with anterior cruciate ligament injury according to partial and whole layer injury; lateral tibial plateau contusion was detected in 12% of patients with partial injury and 72% of patients with whole layer injury. Another study reported that the most common contusion detected in the anterior cruciate ligament injury was on the lateral tibial condyle by 82% (13). However, there was no any differentiation as partial or complete layer injury of the anterior cruciate ligament in the present study; all anterior cruciate ligament injuries were compared with contusion findings. Our study has shown that even 0.2 Tesla MRI examination in patients with claustrophobia and knee pathology may be useful in the evaluation of knee pathologies. However, owing to the fact that our study was performed between 2007 and 2009, a low Tesla MRI device was used. For this purpose, currently, open MRI with higher Tesla is used. Therefore, in our study, higher Tesla MRI could be used.

CONCLUSION

Low-field (0.2 Tesla) open magnetic resonance scanner may be used efficiently to diagnose anterior cruciate ligament injury, as well as the pathological conditions in the knee. Low-field (0.2 Tesla) open magnetic resonance scanner should be considered as a possible alternative for patients who cannot have high Tesla MRI because of claustrophobia.

Ethics Committee Approval: Author declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Informed Consent: Informed consent was not received because data analysis for the study was made retrospectively.

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The author has no conflicts of interest to declare.

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Original Research

The Efficacy of Pneumatic Compression Devices in the Treatment of Patients with Lymphedema after Mastectomy

Tomris Duymaz

Department of Physiotherapy and Rehabilitation, İstanbul Bilgi University Faculty of Health Sciences, İstanbul, Turkey

ABSTRACT

Objective: The aim of the present study was to compare the efficacy of compression bandage and compression device in the treatment of patients with breast cancer with mild to moderate upper extremity secondary mastectomy with secondary lymphedema.

Methods: The present study was conducted on 80 female patients with unilateral upper extremity lymphadenopathy diagnosed postoperatively in women with breast cancer who underwent mastectomy. Only bandage was applied to the control group (n=40); intermittent pneumatic compression (IPC) and bandage (n=40) were applied to the treatment group. All patients received treatment for a total of 15 sessions for 5 weeks, 3 days/week. After all the patients' age and body mass index (BMI) were recorded, the shoulder joint range of motions (ROMs) were measured by goniometer, circumferential measurements were measured by tape measure 4 times and on days 5, 10, and 15, and the Q-DASH functional disability scale was evaluated. The SPSS 22.0 package program was used for statistical analyzes. A p value <0.05 was accepted as statistically significant.

Results: The average age of the patients was 54.80±10.36 years, and BMI was 28.78±4.65 kg/m^2. When the circumferential and ROM measurements of the patients were examined, improvement was observed in both groups, but only the bandaged group was better than the IPC group (p=0.030, 0.019, 0.044, < 0.001, and < 0.001). In case of functional status assessments, improvement was observed only in patients who received bandages (p<0.001).

Conclusion: As a result of the present study, there was no significant difference between compression bandage and intermittent compression device applications in the treatment of patients with lymphedema after mastectomy. Even in some measurements, it was seen that there was more improvement in patients who had only bandages applied.

Keywords: Lymphedema, mastectomy, pneumatic compression

INTRODUCTION

Breast cancer is one of the most common types of cancer among women and can lead to high morbidity and mortality rates. Surgeries performed as part of breast cancer treatment include mastectomies and conservative surgeries. Independently of what type of surgery is performed, these techniques can be accompanied by axillary lymph node drainage, which may cause upper limb lymphedema (1). Lymphedema affects up to 50% of all breast cancer survivors. It is a condition resulting from lymphatic dysfunction in which persistent swelling exists due to an abnormal accumulation of protein-rich fluid in an extremity or other body region and is accompanied by marked subcutaneous and skin changes as the condition worsens (2). The incidence of breast cancer-related lymphedema increases dramatically from 3% to 15% after sentinel node biopsy, 10% to 20% after complete axillary dissection, and 30% to 50% with subsequent radiotherapy (3-5). As a part of treatment, physiotherapy plays a role in postoperative physical rehabilitation, prevention and treatment of complications, such as lymphedema, decrease movement range of upper limb joints, correction of postural misalignment, and sensitive alterations, thus promoting functional recovery and a better quality of life (6).

Complex decongestive therapy (CDT) is a method that combines manual lymphatic drainage (MLD), compression bandages, myolymphokinetic exercises, skin care, and precautions during daily activities. MLD alone is not effective for lymphedema treatment either, and the best results are achieved when associated with compression. Moreover, according to recent studies, compression bandages have been reported to be more effective in reducing edema than MLD (7). Compressive bandaging not only maintains but also increases lymphatic absorption, thereby stim-

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ORCID ID of the author: T.D. 0000-0003-0917-2098

Corresponding Author: Tomris Duymaz **E-mail:** tomrisduymaz@gmail.com

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ulating lymphatic functioning. Compression bandages act by modifying the capillary dynamics of veins, lymph vessels, and tissues. They can be applied through functional compressive bandaging or elastic containment (sleeve). They promote increased interstitial pressure and increased efficacy of muscle and joint pumping (8).

Pressure therapy is a technique that consists of compressed air pumps, aimed at pressuring the limb with edema. Pneumatic compression (PC) devices utilize an air compressor unit that attaches to a garment or series of garments. It is composed of different forms of air chambers (gloves or boots). Basically, two types of compression pump exist: segmental, also called sequential or dynamic, and static or nonsegmental. Static PC involves the affected limb with a single continuous high-pressure chamber, which compresses the entire limb at once. This form of compression is out of use as it promotes the collapse of lymph vessels and impairs the venous system (9). Dynamic pressure therapy contains a number of individually regulable compartments or not. Usually, there are at least three compartments that fill up separately, producing a pressure level that goes from distal to proximal, turning fluid drainage more efficient. PC can lead to complications if the upper lymph conduits have not been emptied and stimulated first. Lymphatic capillaries are small and fragile, with possible injuries and breakdown due to high pneumatic pressure. In case of insufficient deep drainage, the body region above the pneumatic chamber becomes congested, which can cause a new lymphedema area and reduce lymph collection capacity even further (10).

The aim of the present study was to compare the efficacy of compression bandage and compression device in the treatment of patients with breast cancer with mild to moderate upper extremity secondary mastectomy with secondary lymphedema.

METHODS

The present study was conducted on 80 female patients with unilateral upper extremity lymphadenopathy diagnosed postoperatively in women with breast cancer who underwent mastectomy operation in the Department of Physiotherapy and Rehabilitation of Florence Nightingale Hospital. The study was approved by the ethics committee of İstanbul Bilgi University (no: 2017-40016-18, date: 07.11.2017), and voluntary approvals were received from the patients. Oral and written consents were obtained from the patients prior to treatment. Inclusion criteria are woman between 40 and 70 years old, at least 6 months after breast cancer treatment, lymphedema for a maximum of 8 years, unilateral lymphedema, and at least 2 cm diameter difference in at least one region in arm–hand circumference measurements compared with the normal side. Exclusion criteria are male patients, local or distant relapse due to breast cancer, active infection or deep venous occlusion, additional disease or psychiatric disorder affecting the study, and having undergone bilateral mastectomy. Patients were divided into 2 groups of 40 people. Only bandage was applied to the control group, and intermittent pneumatic compression (IPC) (40 minute) and bandage were applied to the treatment group. All patients received treatment for a total of 15 sessions for 5 weeks, 3 days/week. After all the patients' age, height, weight, and body mass index (BMI) were recorded, the shoulder joint range of motions (ROMs) (flexion, extension, and abduction) were measured by a goniometer, circumferential measurements (wrist circumference and 4, 12, 20, 28, 36, and 44 cm above the wrist) were measured by tape measure 4 times and on days 5, 10, and 15 after the treatment, and the short form—arm–shoulder–hand disability questionnaire (Q-DASH) functional disability scale was evaluated.

It has taught the essentials to be aware of in all sick skin care. When compression bandage is applied, care is taken to ensure that the skin is slightly moist. Then, the patient was first wrapped in multilayered cotton on a sock prepared for the appropriate length for the arm, and the latest rigid compression bandage was wrapped from the distal to the proximal using the spiral winding technique. This pressure is reduced to 75%, 50%, and 25% by increasing the proximal pressure to 100% pressure from the distal side of the bandage to make the edema better. There was no overpressure when passing through the elbow, and the dressing was performed when the elbow was in the semi-flex position. At the end of the band under the arm, the winding was finished with a pressure of approximately 0% so that the lymph flow was not blocked.

The other group was IPC therapy with Jobs Phalebo Press (Lympha Press) 701-E serial no. 01451 PC device with 40–60 mmHg pressure four-chamber sleeve for 40 min. Thereafter, multilevel lymphedema bandage was applied to this group. The inflation/deflation cycle for each chamber is 1–3 s in duration.

Upper limb edema was investigated by measuring the circumference of both upper limbs at 7 areas with a retractable, fiberglass, 150 cm measuring tape and calculating the difference. Measurements were made at the wrist joint and 4, 12, 20, 28, 36, and 44 cm above the wrist. All measurements were made by the same investigator (a physiotherapist) who used the same procedure at all times.

The range of flexion, extension, and abduction in the affected shoulder joint was measured by a standard goniometer (based on degree) by the same researcher in all women. Flexion, extension, and abduction were measured with the patient in the standing position to ensure accuracy.

Upper extremity functional assessment was performed with a Q-DASH scale. Q-DASH is a regional outcome measure that includes a sports and musician module that evaluates the entire upper extremity function developed for upper extremity musculoskeletal system disorders and includes 11 questions. At least 10 out of 11 questions are required to calculate the scoring scale reported to be used in place of DASH, and it must be answered. Each question is scored on a 5-point scale, and the total score is calculated from 0 (no disability) to 100 (severe disability). The scale has validity and reliability in Turkish. Completion time is approximately 3–4 min, and the ease of scoring is medium. Higher scores show more disability. Reasons for selection of the Q-DASH questionnaire in our study are the Turkish cultural adaptation of the questionnaire, the measurement of the characteristics of

Table 1. Demographic characteristics of the patients

	IPC + bandage group (n=40) Mean±SD	Bandage group (n=40) Mean±SD	z	p
Age (year)	57.00±10.62	52.60±10.15	−0.908	0.364
BMI (kg/m^2)	28.04±3.95	29.51±5.37	−0.454	0.650
Time since mastectomy (month)	11.00±3.16	11.55±2.40	−0.467	0.640

Mann–Whitney U test
IPC: intermittent pneumatic compression; BMI: body mass index; SD: standard deviation

the test, the fact that it is a questionnaire on the upper limb, and the idea of the entire upper extremity functioning. The questionnaire's score is obtained by dividing the total score of the marked items by the number of marked items and subtracting 1 and multiplying the resulting score by 25. It is normal between 0 and 20 points, mild between 21 and 40 points, moderate between 41 and 60 points, and severe disability between 61 and 80 points. Q-DASH's business model questionnaire also contains four questions to assess the difficulties that one has on his/her way while doing his/her job. The difficulty level is scored between 1 and 5. The total score of the items marked in the scoring is calculated by dividing by 4, subtracting by 1, and multiplying by 25 (11).

Statistical Analysis

Statistical Package for the Social Sciences 22.0 program (SPSS IBM Corp.; Armonk, NY, USA) was used for data analysis. Descriptive statistic variables were recorded. Mann–Whitney U test was used for comparison of nonparametric data between the two groups. Kruskal–Wallis test was used for comparison of nonparametric data between >2 groups. Friedman K test was used for pretreatment and posttreatment comparisons. A p value <0.05 was considered significant.

RESULTS

The demographic characteristics of the patients are shown in Table 1. There was no statistically significant difference between the groups with regard to age, BMI, and lymphedema development (p>0.05) (Table 1). Of all 80 patients, 80% have developed lymphedema in the right arm.

Compared with the patients' environmental measurements, there was a significant improvement in all the measurement levels of all patients (p<0.001 and <0.001), whereas the wrist circumference was 4 cm above the wrist, and the circumference above 44 cm showed more improvement in the control group (p=0.030, 0.019, 0.044, and <0.001) (Table 2).

When the shoulder joint ROM measurements were compared, there was a statistically significant improvement in shoulder flexion and abduction of the IPC therapy group (p=0.023 and 0.046); there was a statistically significant improvement in the control group in shoulder flexion, extension, and abduction at the end of the treatment (p<0.001, 0.032, and <0.001) (Table 3).

When the functional status of the patients was compared, there was a mild to moderate functional disability in all patients before the treatment, and there was no improvement observed in the IPC therapy group at the end of treatment (p=0.753 and p=0.014). There was a statistically significant improvement in the control group at 10 and 15 seasons of treatment for intergroup comparisons (p=0.43 and 0.019) (Table 3).

DISCUSSION

Lymphedema is a debilitating condition manifesting in excess lymphatic fluid and swelling of subcutaneous tissues due to obstruction, destruction, or hypoplasia of lymphatic vessels and is one of the great challenges in plastic surgery, where a satisfactory solution has not yet been found (12). As a result of the present study, there was no significant difference between compression bandage and intermittent compression device applications in the treatment of patients with lymphedema after mastectomy. The PC device has not shown any additional benefit in improving edema.

Compression therapy (1) reduces effective ultrafiltration pressure, (2) increases venous and lymphatic drainage, (3) improves venous pump function, (4) helps maintain therapeutic results, and (5) loosens tissues with fibrotic changes. Compression therapy can be performed with compression bandages, compression stockings or clothing, compression pads, PC devices, or special compression garments (13). IPC has been used in lymphedema reduction treatment, and it was concluded that no difference in reduction occurred in comparison with the control group.

After mastectomy, the damaged lymph nodes cannot carry enough lymph fluid, the fluid accumulation in the lymphatic vessels as a pressure increases in the opposite direction to the periphery, and the deterioration of the working mechanism of the valves that provide different directional circulation in the lymph vessels causes lymphedema to develop. Although the flow direction of the lymph fluid in the lymphatic vessels progresses from the periphery to the center, it acts as a circulant to not follow a fixed straight path. However, the lymphatic vessels immediately run superficially in the subcutaneous tissue and have an extremely slow flow rate. Therefore, by exerting pressure exerted externally through the lymphatic intravascular pressure, fast, constant pressure in the same direction, it can cause the veins in the veins to be ponded especially in the joint regions. The compression applied to provide drainage of the edema must be precisely adjustable according to edema density and amount. For this reason, the compression device can be applied mechanically and constantly, which can be explained as the reason for not pro-

Table 2. Comparison of intergroup and intragroup circumferential measurements of the patients

	IPC + bandage group (n=40) Mean±SD	Bandage group (n=40) Mean±SD	p
Wrist 1	19.25±3.33	17.85±1.81	0.158[k]
Wrist 2	17.85±1.39	16.95±1.27	0.108[k]
Wrist 3	17.75±1.20	16.55±1.25	0.030[k*]
Wrist 4	17.45±1.06	16.20±1.05	0.019[k*]
p	0.002[f**]	< 0.001[f**]	
Above 4 cm 1	20.70±1.76	20.25±1.94	0.542[k]
Above 4 cm 2	20.90±1.30	19.4 ±1.60	0.044[k*]
Above 4 cm 3	20.35±1.22	19.20±1.51	0.068[k]
Above 4 cm 4	19.95±1.03	18.90±1.55	0.067[k]
p	< 0.001[f**]	< 0.001[f**]	
Above 12 cm 1	23.00±3.37	22.80±1.41	0.565[k]
Above 12 cm 2	23.80±5.73	21.80±1.65	0.403[k]
Above 12 cm 3	22.20±2.86	21.10±2.07	0.403[k]
Above 12 cm 4	21.80±2.35	20.80±2.13	0.424[k]
p	< 0.001[f**]	< 0.001[f**]	
Above 20 cm 1	23.25±3.89	22.80±3.02	0.623[k]
Above 20 cm 2	22.50±3.53	21.40±2.68	0.448[k]
Above 20 cm 3	22.10±3.50	20.75±2.31	0.324[k]
Above 20 cm 4	21.20±3.11	20.00±2.54	0.303[k]
p	< 0.001[f**]	< 0.001[f**]	
Above 28 cm 1	27.85±3.49	28.90±3.68	0.448[k]
Above 28 cm 2	27.20±3.62	27.35±3.39	0.820[k]
Above 28 cm 3	26.60±3.45	26.55±3.60	0.879[k]
Above 28 cm 4	25.60±3.05	25.20±3.78	0.649[k]
p	< 0.001[f**]	< 0.001[f**]	
Above 36 cm 1	30.55±3.50	30.80±3.93	1.000[k]
Above 36 cm 2	29.50±3.05	29.75±3.52	0.970[k]
Above 36 cm 3	28.95±3.26	28.95±3.26	0.790[k]
Above 36 cm 4	28.10±3.20	28.10±3.20	0.703[k]
p	< 0.001[f**]	< 0.001[f**]	
Above 44 cm 1	33.70±3.95	33.70±3.95	0.382[k]
Above 44 cm 2	32.50±3.43	32.50±3.43	0.649[k]
Above 44 cm 3	31.55±3.33	31.55±3.33	0.733[k]
Above 44 cm 4	30.50±3.24	30.50±3.24	< 0.001[k**]
p	< 0.001[f**]	< 0.001[f**]	

**p<0.001; *p<0.05
[k]Kruskal–Wallis test; [f]Friedman K test
1: Pretreatment; 2: 5th session of treatment; 3: 10th session of treatment; 4: post–treatment
IPC: intermittent pneumatic compression; Q–DASH: short form—arm–shoulder–hand disability questionnaire; SD: standard deviation

Table 3. Comparison of intergroup and intragroup joint range of motion and functional status of the patients

	IPC + bandage group (n=40) Mean±SD	Bandage group (n=40) Mean±SD	p
Shoulder flexion 1	143.50±11.55	140.50±11.65	0.560[k]
Shoulder flexion 2	148.00±11.83	155.50±7.97	0.129[k]
Shoulder flexion 3	153.00±12.73	163.50±12.03	0.071[k]
Shoulder flexion 4	157.50±10.86	170.50±12.12	0.023[k*]
p	< 0.001[f**]	< 0.001[f**]	
Shoulder extension 1	15.00±5.00	10.00±5.00	0.261[k]
Shoulder extension 2	16.33±3.21	16.67±7.63	1.000[k]
Shoulder extension 3	17.00±2.64	23.33±10.40	0.500[k]
Shoulder extension 4	18.00±2.00	38.33±2.88	0.046[k*]
p	0.120	0.032[f*]	
Shoulder abduction 1	148.50±8.51	135.50±14.99	0.051[k]
Shoulder abduction 2	154.00±9.06	151.50±10.01	0.640[k]
Shoulder abduction 3	158.50±9.44	160.00±12.01	0.565[k]
Shoulder abduction 4	162.50±9.50	167.50±15.50	0.120[k]
p	< 0.001[f**]	< 0.001[f**]	
Q–DASH 1	18.29±8.63	17.21±11.60	1.000[k]
Q–DASH 2	19.14±7.52	12.38±6.31	0.237[k]
Q–DASH 3	18.42±8.66	6.64±5.38	0.043[k*]
Q–DASH 4	14.78±4.48	3.41±4.35	0.019[k*]
p	0.753[f]	0.014[f*]	

**p<0.001; *p<0.05
[k]Kruskal–Wallis test; [f]Friedman K test
1: Pretreatment; 2: 5th session of treatment; 3: 10th session of treatment; 4: post–treatment
IPC: intermittent pneumatic compression; Q–DASH: short form—arm–shoulder–hand disability questionnaire; SD: standard deviation

viding additional benefit in treatment. Since the lymphatic vessels have a very sensitive flow, manual therapy methods that are much slower, softer, and more applicable to the flow of lymphatic valves may be more beneficial (14, 15). Some studies associated components of CDT with PC (16, 17). There are contradictory ideas in the literature. Some studies report that PC devices are useful, but some studies also mention that they do not provide any additional benefit. In a systematic review, treatment methods applied to 172 patients with lymphedema after mastectomy were compared. Only patients treated with IPC after 4 weeks of treatment showed a recovery of 37.7%, whereas patients treated with electrotherapy and magnetotherapy with IPC reported an improvement of 76.3% (18). Therefore, these results should be interpreted with caution. IPC lacks the ability to be a standalone

therapy since it only stimulates the lymphatic drainage in working collectors. Therefore, IPC has a limited effect on the resorption of interstitial edema fluid. In a review study, a group of 24 women with lymphadenopathy performed MLD with only IPC, other group with only IPC and 75 mL reduction in patients with IPC + MLD when only 25 mL of edema volume was observed in patients in the IPC group (19). Ridner et al. (20) performed IPC for 40 min on 42 women with post-mastectomy lymphedema and found no improvement.

According to the results from randomized controlled trials, IPC effect sizes from the pre to post designed studies showed no benefit on volume reduction. Especially for IPC, the results demonstrated a very low effect size, confirming that IPC is not a standalone therapy (21-23). A randomized study involving 23 patients with lymphedema without previous treatment compared 2 interventions: CDT + PC and CDT alone. In this group, greater climb volume reduction was achieved when applying PC, and this result continued on further evaluations. In the same study, PC was combined with self-massage and sleeve use in 27 previously treated patients with chronic lymphedema, and volume reduction occurred in this group, as opposed to the group that was not submitted to PC (24). In this study, it can be considered that PC is applied to decrease edema due to the addition of the group of self-drainage techniques. In this study, IPC was not used alone, suggesting that improvement was observed in patients when applied with MLD and bandage.

Shao et al. (25) conducted a systematic review and meta-analysis and showed no significant differences in the percent of volume reduction and subjective symptoms (heaviness, pain, paresthesia, or tension) between decongestive lymphatic therapy (DLT) (also known as CPT + IPC) and DLT groups. Li et al. (26) thought that IPC may also not be associated with the addition of effectiveness to CPT. In our study, we found a decrease in the environmental measures of the patients in each of the two groups, but this improvement was more in the bandage only group. Haghighat et al. (27) concluded that compression bandage alone or in combination with compression pumping reduces the limb volume significantly, but compression bandage alone exhibits better results. Moattari et al. (28) found that a group of 21 patients with upper limb lymphedema have only one group of CDTs and the other group only has IPCs, and that arm circumference and shoulder ROMs have more improvement in the CDT group after treatment. In our study, we found that patients who underwent IPC improved 9.79% in shoulder flexion and 9.45% in shoulder abduction and who had only bandage improved 21.42% in shoulder flexion, 23.70% in shoulder abduction, and 62% in shoulder abduction in patients. Therefore, it was determined that there was more improvement only in patients in the bandage-treated group.

Johansson performed IPC at 40–60 mmHg pressure for 2 h and reported that patients do not benefit from edema quantities and arm use in daily living activities (29). Uzkeser et al. (30) have applied CDT to a portion of 31 patients who developed lymphedema after mastectomy and IPC in addition to the other part. They reported that the administration of IPC in the environment, volume measurements, and functionality do not contribute to healing in addition to the treatment they were given for 5 days/week for 3 weeks. When we examined the upper extremity functionalities of the patients, we found that patients treated with IPC improved 22.23%, and only 82.36% of patients treated with bandage had improvement. Although mild to moderate functional impairment in both groups of patients continued with mild deficits in patients with IPC prior to treatment, there was a near improvement in functional status of only bandaged patients. The fact that PC devices do not provide additional benefit in treatment can be attributed to the constant pressure of the patient giving a constant pressure without distinguishing the amount of skin and edema. Concurrently, treatments, such as radiotherapy, can lead to skin lesions when applied in sensitive areas after treatment.

CONCLUSION

The present study contributes to the clarification of ideas on the effectiveness of PC devices by contributing to the unclear information in the literature. Compression bandage and compression bandage together with the PC device showed that the healing was the same in all patients, but in some of the measurements, only better bandage patients were treated. Thus, PC devices were found to have no additional benefit on lymphocyte reduction. Therefore, it is considered that the use of treatment devices in the treatment programs will not have benefit because the compression devices applied to the disease will cause time and societal cost loss, as well as the loss of time and the increase of the patients' edemas, as well as the decrease in their functional activities.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul Bilgi University (no: 2017-40016-18, date: 07.11.2017).

Informed Consent: Written and verbal informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The author has no conflicts of interest to declare.

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Original Research

Comparison of Success Rates of Pleurodesis with Talc, and Holmium–YAG Laser in the Patients with Malignant Pleural Effusion

Ahmet Uluşan[1], Maruf Şanlı[1], Ersin Arslan[2], Ahmet Feridun Işık[1], Bülent Tunçözgür[3], Seval Kul[4], Öner Dikensoy[5], Levent Elbeyli[6]

[1]Department of Thoracic Surgery, Gaziantep University School of Medicine, Gaziantep, Turkey

[2]Clinic of Thoracic Surgery, Dr. Ersin Arslan State Hospital, Gaziantep, Turkey

[3]Clinic of Thoracic Surgery, Ankara Güven Hospital, Ankara, Turkey

[4]Department of Biostatistics, Gaziantep University School of Medicine, Gaziantep, Turkey

[5]Clinic of Chest Diseases, Acibadem Taksim Hospital, İstanbul, Turkey

[6]Clinic of Thoracic Surgery, Medicalpark Hospital, Gaziantep, Turkey

ABSTRACT

Objective: We aimed to investigate the efficacy of Holmium-yttrium aluminum garnet (Ho-YAG) laser using video assisted thoracoscopic surgery (VATS) and compare it with the talcslurry pleurodesis in patients with malignant pleural effusion (MPE).

Methods: A total of 51 patients with MPE were included. Patients were divided into two groups. In the laser group, pleurodesis was attempted using Ho-YAG laser through auniportal VATS in 30 patients; in the talc group, pleurodesis was attempted using talc slurry through a small bore chest tube in 21 patients. The success rate of pleurodesis was evaluated using chest X-ray and/or thorax computed tomography obtained at the second month following pleurodesis and was graded as total success, partial success, or failure.

Results: In the laser group, pleurodesis was a total success in 19 (63%) patients and partial in 7 (23%) patients. The volume of pleural effusion drained postoperatively was significantly different between the success subgroups (total success subgroup vs. failure subgroup, p=0.000; partial success subgroup vs. failure subgroup, p=0.001). In the talc group, pleurodesis was a total success in 11 (52%) patients and partial in 6 (29%) patients. The success rates of pleurodesis between the talc and laser groups showed no significant difference (p=0.725).

Conclusion: The use of Ho-YAG laser through VATS is a safe and effective option for pleurodesis in the management of MPE. However, there is no difference between Ho-YAG laser and talc slurry pleurodesis in terms of procedure success rates.

Keywords: Holmium-YAG lasers, malignant, pleural effusion, pleurodesis, talc

INTRODUCTION

One of the most substantial reasons for exudative pleural effusions is malignancy (1) and lung cancer is the most common cause of malignant pleural effusions (MPEs); however, any cancer can spread to the pleura (2). MPE indicates an advanced disease and a limited life expectancy in most cases (3, 4). Most MPEs are resistant to primary cancer treatment and the recurrence rate is high. Also, MPE causes significant dyspnea and deterioration in the quality of life. Therefore, effective management of MPE to improve the quality of life in these patients is crucial. The most common methods used in the management of MPEs are chemical/mechanical pleurodesis followed by the drainage of the pleural fluid using indwelling catheters (5). To date, as there is no consensus on the optimal method for pleurodesis, the attempt to find the optimal method continues.

It has been suggested that interventions performed under general anesthesia through uniportal video-assisted thoracoscopic surgery (VATS) provide certain advantages, such as the total elimination of pleural adhesions, direct observation of lung expansion, and performance of more effective pleurodesis (6). However, data on the role of video-thoracoscopic laser applications for pleurodesis are limited, and most of these studies have been conducted in patients with pneumothorax (7, 8). The holmiumyttrium aluminum garnet (Ho-YAG) laser has a broad range of potential applications; it was used initially for arthroscopic

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ORCID IDs of the authors: A.U. 0000–0003–3068–408X; M.Ş. 0000–0001–5097–0775; E.A. 0000–0001–6378–3215; A.F.I. 0000–0002–8687–3819; B.T. 0000–0001–6554–535X; S.K. 0000–0002–4716–9554; Ö.D. 0000–0003–1161–6225; L.E. 0000–0002–3405–079X

Corresponding Author: Ahmet Uluşan **E–mail:** draulusan@gmail.com

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surgery. Today, it is commonly used in many surgical areas, including general surgery, urology, laparoscopy, neurosurgery, lithotripsy, angioplasty, orthopedic surgery, and dental surgery (9). To our knowledge, this is the first study using VATS through Ho-YAG laser applications for pleurodesis in patients with MPE. The aim of this study was to determine the efficacy of Ho-YAG laser through a uniportal VATS and compare it with talc slurry pleurodesis in patients with MPE.

METHODS

Study Design

This was a prospective non-randomized controlled study approved by the local institutional ethics committee of the Gaziantep University (Project No: TF.08.22). The inclusion criteria were as follows: presence of MPE, no contraindications for general anesthesia and/or talc pleurodesis, total expansion of the lung, and improvement of dyspnea following the drainage of the fluid. Patients not willing to participate and those with a life expectancy of less than 1month were excluded.

Patients and Procedures for Pleurodesis

Laser group

A total of 30 patients with MPE between January 2008 and March 2011who provided informed consent were included. Laser pleurodesis was performed using Ho-YAG laser through uniportal VATS. The Ho-YAG laser system (Stone Light®; San Jose, California, USA) used for pleurodesis had a wavelength of 2.1 µm, maximum power of 15 watts, and maximum energy/pulse of 1.5 J maximum (invisible radiation in the mid-infrared portion of the spectrum). The pulse duration was 350 µsec. The output of the Ho-YAG laser was focused into a 550 µm core diameter, low OH quartz fiber optics. The same Ho-YAG laser apparatus was used in all patients. The procedure, lasting about 20-30 minutes on an average, was performed under general anesthesia using doublelumen intubation to allow ventilation of a single lung. Uniportal VATS was performed using a 10 mm thoracoport introduced through a 1-1.5 cm long incision in the sixth or seventh intercostal space on the anterior axillary line, followed by introducing an operative Hopkins telescope (Karl Storz Hopkins®; Tuttlingen, Germany) into the pleural space. After the pleural adhesions were separated, pleural effusion was aspirated, and the expansion capacity of the lung was observed. In patients without a confirmed preoperative diagnosis, MPE was confirmed by the examination of frozen section specimens collected during the operation. The sterile fiber of the Ho-YAG laser was connected to the outside of the thoracoscopic aspirator using sterile drapes, having the tip 3 mm ahead on an average; this combined unit was introduced into the pleural space through the channel of the thoracoscope (Figure 1a) before a pleural abrasion was initiated. The Ho-YAG laser energy was directly guided to the parietal pleura to generate an effective abrasion on the surface. The parietal pleura was abraded with the continuous use of pulses of 15W/1.5 J of energy each (Figure 1b). The number of required laser pulses changed depending on the thickness of the parietal pleura. The laser procedure was continued until the surgeon was satisfied with the level of burning that had occurred at the localization of the parietal pleura. A second port entry was not needed in most cases.

If a sufficient abrasion surface was obtained on the pleura following the placement of the chest tube from the port entry hole, a suction of 15 cm H_2O was maintained to aid there-expansion of the lung. During the postoperative follow-up, the chest tube was removed and drainage was discontinued when daily drainage was below 100 mL. The total delivered energy ranged from 3,375 J to 16,899 J.

Talc group

A total of 21 patients with MPE between April 2011 and February 2013who provided informed consent were included. Under local anesthesia, a smallbore catheter (8-10 French, Pleuracan®; Braun, Melsungen, Germany) was placed through the sixth or seventh intercostal space on the posterior axillary line. The lung re-expansion was confirmed in a chest X-ray following the catheter placement. Talc pleurodesis was performed by applying

Figure 1. a, b. (a) Entry of the Ho-YAG laser fiber using athoracoscopic aspirator as a combined unit into the intrapleural space from within the telescope. (b) Areas of abrasion on the parietal pleura formed by the laser

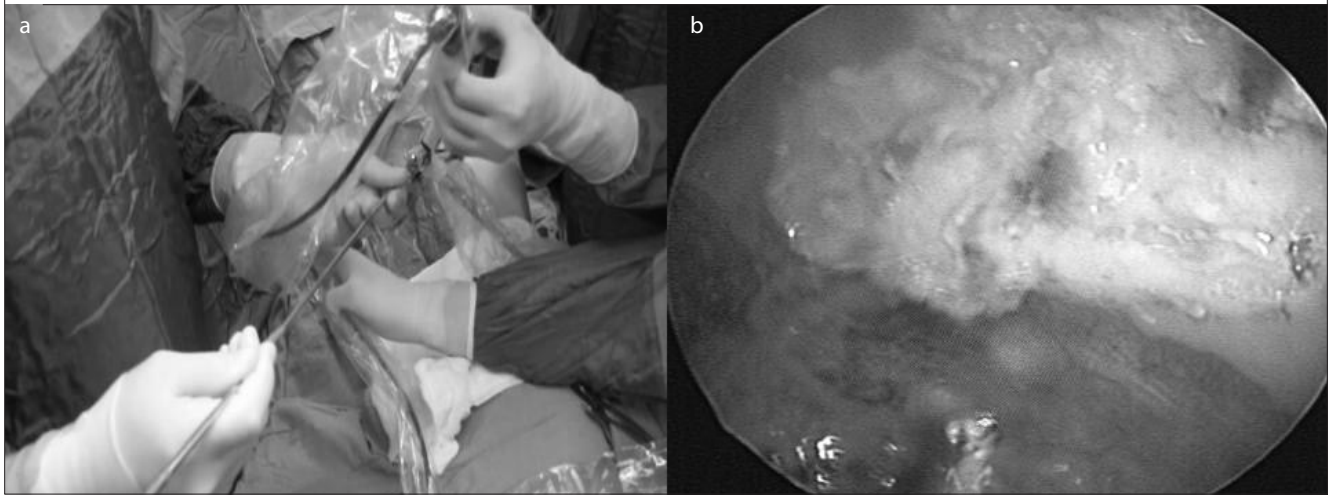


Table 1. Distribution of cases with reference to primary pathology in the laser and talcgroups

Primary pathology	Laser group, N	Talc group, N
Lung carcinoma	7	5
Breast cancer	7	10
Unknown primary etiology	3	2
Other malignancies	13	4

Table 2. Evaluation of pleurodesis success in the laser and talcgroups

Subgroups	Laser group N (%)	Talcgroup N (%)
Total success (0%)	19 (63.3%)	11 (52.4%)
Partial success (<50%)	7 (23.3%)	6 (28.6%)
Failure (>50%)	4 (13.3%)	4 (19%)
Total	30 (100%)	21 (100%)

Table 3. Volume of postoperative drainage based on success subgroups in the laserand talc groups

	Laser group		Talc group	
Subgroups	Mean (mL)	Standard deviation	Mean (mL)	Standard deviation
Total success (0%)	492*	175	255	195
Partial success (<50%)	478†	143	317	232
Failure (>50%)	1337	1012	200	100
Total	601	464	262	197

*: p=0.000 vs. failure subgroup; †:p=0.001 vs. failure subgroup

talc slurry prepared as 4g talc (Steritalc®; Novatech, France) in 100 mL saline through the smallbore catheter. The catheter was clamped for 2 h for keeping talc inside and was subsequently opened. A negative suction was not applied postoperatively to the chest drain. The drained volume of the pleural effusion was monitored daily. When the volume of drained effusion was below 100 mL per day, the catheter was removed and drainage was discontinued.

Outcome Measures

Follow-ups were continued with serial chest X-rays or computed tomography (CT) and quartz fiberoptics of the thorax obtained at the first week, second week, first month, and second month after the surgery. The success rate was defined as total if no re-accumulation of pleural effusion was observed in the postoperative chest X-ray and/or thorax CT at the second month following pleurodesis. The success rate was defined as partial if the volume of pleural effusion in the postoperative chest X-ray and/or thorax CT at the second month following pleurodesis was <50% compared to the preoperative imaging studies. Conditions other than these were evaluated as failures.

Statistical Analyses

For continuous variables, the Student's t-tests was used to compare two implementation groups or the Mann-Whitney U test was used for two-group comparisons; ANOVA or the Kruskal-Wallis test was used for more than three group comparisons. The relationship between categorical variables was determined using the Chi-square test. Descriptive statistics and frequencies were given as mean ± standard deviation (SD). Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS®) for Windows, version 11.5, (SPSS Inc.; Chicago, IL, USA). The statistical analyses were accepted as significant when the p value was <0.05.

RESULTS

Laser Group

Of the 30 patients included, 13 were males and 17 were females, with a mean age of 56.4 years (range, 25-77 years). Dyspnea, cough, and chest pain were the most common complaints at admission. The primary origins of the MPEs are shown in Table 1. The pleural effusions were exudates in all patients. Uniportal VATS was performed on the left side in 18 patients and on the right in 12 patients.

The mean±SD duration of drainage following pleurodesis was 4.4±1.3 days, while the total length of hospital stay was 5.6±1.3 days.

The success rates were as follows: totally successful pleurodesis was observed in 63.3% (n=19) of the patients, partially successful pleurodesis in 23.3% (n=7) of the patients, and failure was observed in 13.3% (n=4) of the patients (p=0.001; Table 2). Two-group comparisons showed that the success rates were significantly different between the total and partial response groups (p=0.004, Figure 2).

Total success rate was achieved in all the breast cancer patients (100%, n=7) and in 85.7% (n=6) of the lung cancer patients.

The mean volumes of pleural effusion drained during the postoperative period were 492.1±175.8, 478.6±143.9, and 1,337.5±1,012.7 mL in the total success subgroup, partial success subgroup, and failed pleurodesis subgroup, respectively, (p=0.001; Table 3).

Pleurodesis was performed with 2.250-11.266 laser pulses. The number of pulses was not statistically different in the subgroups (p=0.717).

There were no differences in gender, chemotherapy, and/or radiotherapy used for the treatment of primary cancer between the subgroups (p=0.568, p=0.893, p=0.104, respectively).

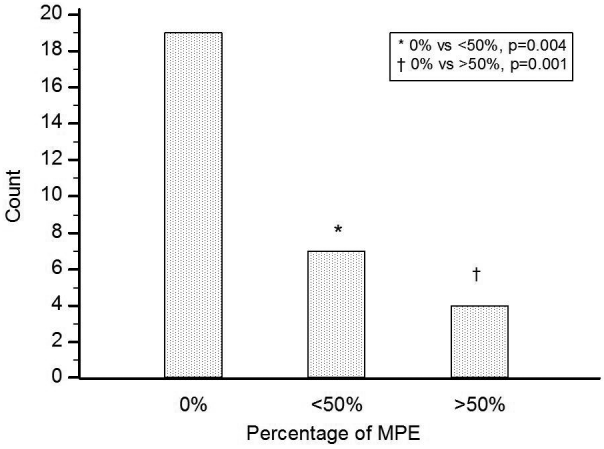
Complications following the procedure were pneumonia in 2 cases, wound site infection in 1 patient, respiratory failure in 1 patient, and arrhythmia in 1 patient. No postoperative mortality was observed.

Table 4. Comparison between laser and talc groups for different parameters

Variable	Talc group (n=21)	Laser group (n=30)	p
Age (years)	54.6±16.6	56.4±13.4	0.669
Initial drainagea (mL)	2785.7±1353.9	3086.6±1415.8	0.451
Mean drainageb (mL)	261.9±201.8	601.6±464.5	0.001
Duration of drainage (days)	4.24±2.42	4.40±1.30	0.759
Duration of hospital stay (days)	4.90±1.99	5.57±1.27	0.156

[a]drainage before pleurodesis procedure; [b]drainage after pleurodesis procedure

Figure 2. Distribution of cases and correlation of the subgroups in the laser group, based on the amount of fluid evaluated radiologically atthesecond postoperative month



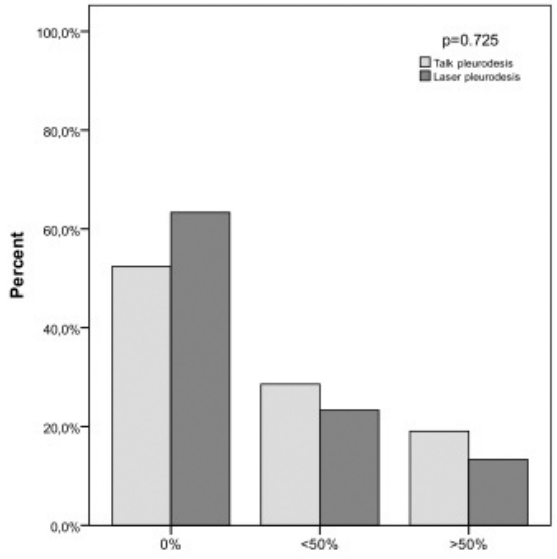
Talc group

Of the 21 patients included, 6 were males and 15 were females, with a mean age of 54.6 years (range, 26-78 years). Dyspnea, cough, and chest pain were the most common complaints. The primary etiology was breast and lung cancer in 48% and 28% of patients, respectively. Pleural fluid was exudates in all cases. Chest tube placement was performed on the left in 7 patients and on the right in 14 patients.

The mean duration before removal of the chest tube was 4.2±2.4 days, while the length of hospital stay was 4.9±2 days.

Eleven patients (52.4%) were accepted to have totally successful pleurodesis without any recurrences. Partial success was achieved in 6 patients (28.6%), while the pleurodesis was failed in 4 patients (19%). The 4 patients who had pleurodesis failure underwent repeated drainage and re-talc pleurodesis. Comparison of the three subgroups showed that the success rates almost achieved the point of statistical significance (p=0.053).

Figure 3. Comparing laser and talc groups according to success subgroups



There was no significant difference in the volumes of the drained pleural fluid, either initially or following the pleurodesis, between the subgroups of different success rates (p=0.259, p=0.639, respectively).

Gender, chemotherapy, and radiotherapy used for the treatment of the primary pathology did not seem to have any influence on the success rates of pleurodesis (p=0.102, p=0.046, p=0.819, respectively).

Complications following the procedure were respiratory failure in 2 patients. No mortality was observed.

Comparison of the Laser and Talc Groups

Both laser and talc groups were found to be normally distributed in terms of age and gender. The two groups showed no difference between the following variables: age, drainage before pleurodesis procedure, duration of drainage, and duration of hospital stay (p=0.669, p=0.451, p=0.759, p=0.156, respectively). However, the difference between the drained volumes of pleural effusion following pleurodesis was statistically significant (p=0.001; Table 4). The success rates of pleurodesis between the talc group and the laser group showed no significant difference (p=0.725; Figure 3).

DISCUSSION

The most common causes of MPE are lung cancer (30%) and breast cancer followed by ovarian and gastric cancer (10, 11). Particularly, for those with primary lung cancer, MPE indicates limited survival of around 6 months. Furthermore, MPE due to lung cancer causes a significant decrease in the quality of life due to dyspnea and respiratory distress (12). The re-accumulation of the effusion occurs rapidly following the drainage in this condition. Therefore, pleurodesis is performed very often in these patients.

The most suitable method of pleurodesis in patients with MPE is not definitely known (13). The frequently used methods worldwide for the management of MPE are talc pleurodesis and placement of indwelling catheters. Talc pleurodesis can be performed either during the uniportal VATS or through a chest tube; these two methods of talc pleurodesis (VATS vs. chest tube) showed conflicting results (13-15). In our experience, the best method of talc pleurodesis should be decided on a casebycase basis. The results of this study showed no difference in the success rates between talc pleurodesis performed through a smallbore chest tube and Ho-YAG laser performed through uniportal VATS. The only difference observed between the two treatment groups was in the total volumes of pleural effusion drained following pleurodesis. In contrast, both methods were found to be more efficient in patients with breast cancer, followed by lung cancers, compared to patients with a primary cancer of other organs.

Videoassisted thoracoscopic surgery (VATS) is safe with low complication rates. VATS has certain advantages, such as the possibility to obtain biopsy under direct visualization, elimination of pleural adhesions, drainage of loculated fluids, direct observation of lung expansion, and the ability to perform pleurodesis during the same procedure (16, 17). We preferred VATS, particularly for releasing loculations and evaluating the maximum expansion of the lungs. In 8 of our patients, the diagnosis of malignancy was obtained during VATS, and pleurodesis was performed during the same session.

Endoscopic applications have been reported since the development of lasers that can be introduced using thin quartz filaments. The application of <30W power in laser provides coagulation, while using around 50W provides vaporization efficacy. In our study, we used the 15W/1.5 J Ho-YAG laser system. The Ho-YAG laser can be easily applied endoscopically through the operative channel of the thoracoscope. If laser energy is to be applied directly to the parietal pleura, a large pleural abrasion and permanent pleurodesis can be obtained. Previous reports have mentioned the use of different types of laser for achieving pleurodesis. However, there were no reports stating the use of Ho-YAG laser for obtaining pleurodesis in MPE cases. In 1993, Bresticker et al. (18) conducted a study on dogs with the aim of studying the efficacy of different pleurodesis methods, and in the evaluation period of 30±2 days, they rated the efficacy of pleurodesis from 0 to 4 (0 corresponds to total absence of pleural adhesions and 4 corresponds to adhesions of the mediastinum inmore than one lobe). They found that the least effective method for pleurodesis was neodymium-doped-YAG laser. They did not recommend using laser techniques for pleurodesis. However, Torre et al. (8) performed pleurodesis on 85 pneumothorax patients using Nd-YAG laser and did not observe any recurrences. In the present study, we had success in 26 patients (86.7%) in the laser group. The pleurodesis was deemed to have failed in 4 patients.

The volume of drained pleural fluid before uniportal VATS and laser pleurodesis was not related to the success rate of pleurodesis (p=0.185); however, there was a statistically significant difference in the volume of postoperatively drained pleural fluid between the subgroups with different success rates (complete success group vs. failure group, p=0.000; partial success vs. failure group, p=0.001). In other words, we suggest that having increased fluid drainage after pleurodesis with Ho-YAG laser predicts the increased risk of failure in pleurodesis. There were no similar differences in the talc group.

Previously, the success rate of talc pleurodesis has been reported to be over 90% in selected patients (19-21). In the present study, the success rate of pleurodesis with talc slurry through a smallbore chest tube was found to be 81% (17 of 21 cases; complete success in 11 patients and partial success in 6 patients). In the laser group, the success rate of pleurodesis was found to be 86.7% (26 of 30 cases; complete success in 19 patients and partial success in 9 patients). The success rates of pleurodesis between the talc and laser groups showed no significant difference (p=0.725). We recommend that laser pleurodesis canbe used as an alternative to talc pleurodesis in selected cases where appropriate equipment and experienced staff are available.

Videoassisted thoracoscopic surgery (VATS) is a safe and well-tolerated method with low operative mortality and complication (22-24). A recent meta-analysis reported no mortality associated with thoracoscopy and that the major complication rate of mini-thoracotomy (MT) was 1.5% and the minor rate was 10.5% (25). The most commonly encountered major complication was acute respiratory failure due to empyema, infection, or re-expansion pulmonary edema in MT (23, 26, 27). In the laser group, 2 of our cases developed pneumonia, 2 had wound site infections, 1 had respiratory failure, and 1 experienced arrhythmia. In the talc group, only 2 patients had respiratory failure. The talc group had fewer complications compared to laser group, Although this difference was not statistically significant (p=0.31).

The drawback of the present study should however be emphasized, considering the limited number of enrolled patients to study and comparing two series of cases in consecutive periods of time.

CONCLUSION

Although the most common methods used worldwide for the management of MPE are talc pleurodesis and placement of indwelling catheters, pleurodesis performed using Ho-YAG laser through a uniportal VATS seems an alternative to talc slurry using a small-bore chest tube. Ho-YAG laser via uniportal VATS can be used safely inappropriately selected patients owing to the low morbidity and mortality. Increased fluid drainage after pleurodesis using Ho-YAG laser could be used as a predictive criterion for pleurodesis failure.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University (No: TF.08.22).

Informed Consent: Written and verbal informed consent was obtained from patients who participated in this study.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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Original Research

Evaluation the Effects of RME on Turkish Vowels: A Pilot Study

Ayşegül Güleç[1], Güzin Bilgin Büyüknacar[2], Merve Göymen[1]

[1]Department of Orthodontics, Gaziantep University School of Dentistry, Gaziantep, Turkey

[2]Private Practice, Orthodontist, Gaziantep, Turkey

ABSTRACT

Objective: Any possible change on the quality of voice of the patient after rapid maxillary expansion (RME) treatment should be clarified at pre-treatment counseling of patients and guardians. The aim of the present study was to assess the impact of RME on the spelling of eight Turkish vowels.

Methods: Six patients whose treatment plan was approved as RME and going to wear acrylic cap-type hyrax were recruited for the study. The recordings of eight Turkish vowels (/a/, /ɛ/, /ω/, /i/, /ɔ/, /œ/, /u/, and /y/) were pronounced one by one by the patients. Acoustical analysis was performed using PRAAT analysis tools. Fundamental frequencies (F0), formant frequencies of F1, F2, F3, and F4, and vowel durations for Turkish vowels were measured before (T0) and after (T1) the RME.

Results: A significant difference in the mean of F2 /i/ and F3 /i/ (p=0.001 and p=0.002, respectively) and F3 /ω/ was found at T0 and T1 (p=0.022). There was no statistically significant difference between the changes in F0 values for both gender and vowel durations at T0 and T1 (p>0.05). There was no statistically significant difference in any of the other formants of F1, F2, F3, and F4 for vowels /a/, /ɛ/, /ɔ/, /œ/, /u/, and /y/.

Conclusion: Subject to the small sample size limitation of the present study, the spelling of vowels /i/ and /ω/ is lowered after maxillary expansion. The possibility of voice change after RME should be informed to the patient before treatment.

Keywords: Acoustic analyses, rapid maxillary expansion, Turkish vowels

INTRODUCTION

Rapid maxillary expansion (RME) is a widely used treatment in orthodontics that not only provides progress in patients with arch length discrepancies or crossbites but also decreases nasal resistance that in fact relieves mouth breathers. It can increase palatal volume in a statistically significant fashion (1). Any modification in the palatal morphology can affect speech by altering the area of the articulation of the tongue on the palate and change the oral resonance mechanism by enlarging the oral cavity (2).

Phonation is a complex process that involves different parts of the body, such as diaphragm, chest, lungs, larynx, vocal cords, nose, nasal passages, maxilla, teeth, and lips. Any changes at the vocal apparatus may have effects on speech whether it modifies the morphology of the resonating cavities or stiffness and other possible mechanical properties of the related tissues (3). In the literature, there are some studies investigating patients with cleft palate suffering from speech impairment primarily due to velopharyngeal insufficiency (4). In addition, articles investigating the impacts of orthognathic surgery on voice reported that surgery has effects on voice (3, 5). All this information reinforces the hypothesis that RME may have an effect on voice.

In the literature, there are orthodontic-related phonetics studies focused on the alterations caused by the RME. Stevens et al. (6) investigated the speech disturbance and adaptation of the patients wearing RME appliances with the idea of initial discomfort together with functional obstacles related with an intraoral orthodontic appliance may have impacts on patient's compliance that can be resulted with an unsuccessful result Biondi et al. (2) compared the effects of two different types of banded RME appliances on both the possible changes and/or device-related impairments in phonetic habits. In a recent study, Yurttadur et al. (7) evaluated the effects of RME on vocal function in patients with bilateral maxillary crossbite using the acoustic analysis of the /a/ vowel. To the best of our knowledge, there are no studies investigating the influence of RME on the acoustic quality of Turkish vowels. The objective of this prospective pilot study was to assess the impact of RME on the spelling of eight Turkish vowels, namely, /a/ (/a/), /ɛ/ (/e/), /ɯ/ (/ı/), /i/ (/i/), /ɔ/ (/o/), /œ/ (/ö/), /u/ (/u/), and /y/ (/ü/). It is thought that consonant sounds are influenced by dental irregularities, whereas vowels are affected by skeletal discrepancies (8, 9). Within phonetic sounds, vowels can be analyzed more simply acoustically. Owing to these two important findings, Turkish vowels were preferred for investigation

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ORCID IDs of the authors: A.G. 0000–0001–8838–1546; G.B.B. 0000–0002–8845–1193; M.G. 0000–0003–1044–277X.

Corresponding Author: Merve Göymen **E–mail:** mervegoymen@gmail.com

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in the present study. Formants are the major acoustic features of vowels (10). Although there are five formants for each vowel, as performed previously (11), the first four formants (F1, F2, F3, and F4) of the vowels were investigated in the present study. Any possible change on the quality of voice of the patient after RME treatment should be clarified at pre-treatment counseling of patients and guardians.

METHODS

Six patients whose treatment was planned as RME in the Orthodontic Department of Gaziantep University Dentistry Faculty were recruited for the study. The study included 4 female and 2 male patients. The mean age of the patients was 12-16 (13.68±1.4) years. All of the patients were Turkish native speakers. None of the patients have a history of speech therapy or hearing disorders. The study was approved by the ethics committee of the Sanko University (29.03.2018/15). Informed consent was obtained from all patients and their guardians.

All six RME appliances (acrylic cap-type hyrax) were made by the same laboratory technician. Appliances were fabricated with a central jackscrew and were activated as described before (2) with a less difference (0.25 mm/day). The patients wore only RME appliance throughout the study.

Speech recordings were performed at a 44-100 Hz sampling rate and 16-bit resolution. A condenser microphone (RODE NT1-A) on a laptop computer (Intel core i5 863 Mhz, 512 MB of RAM) was used. Speech samples were recorded in a quiet room in the same department. The microphone was fixed at a 10 cm distance from the mouth of the patient. The recordings of eight Turkish vowels (/a/, /ɛ/, /ɯ/, /i/, /ɔ/, /œ/, /u/, and /y/) were pronounced one by one by the patients. Patients were asked to phonate these vowels just before the insertion of the RME device and after the removal of the RME device in approximately 2 weeks.

Acoustical analysis was performed using PRAAT (version 5.3.57; Paul Boersma and David Weenink; www.praat.org) analysis tools. Fundamental frequencies (F0), formant frequencies of F1, F2, F3, and F4, and vowel durations for Turkish vowels were measured before (T0) and after (T1) the RME.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences version 24 for Windows (SPSS IBM Corp.; Armonk, NY, USA). All descriptive statistics were expressed as mean±SD. Shapiro-Wilk test was used for normally distributed continuous variables. For each subject, the F1, F2, F3, and F4 and mean vowel duration were collected before and after treatment, and paired sample t-test was conducted. Wilcoxon signed-rank test was used for fundamental frequencies stratified by gender before and after treatment. A p value <0.05 was accepted as statistically significant.

RESULTS

A significant difference in the mean of F2 /i/ and F3 /i/ (p=0.001 and p=0.002, respectively) and F3 /ɯ/ was found at T0 and T1 (p=0.022) (Figures 1-3).

Figure 1. F2 /i/ before and after RME in subjects 1–6
RME: rapid maxillary expansion

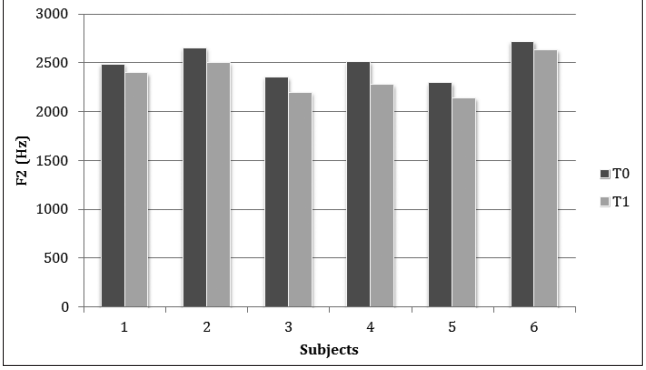

Figure 2. F3 /i/ before and after RME in subjects 1–6
RME: rapid maxillary expansion

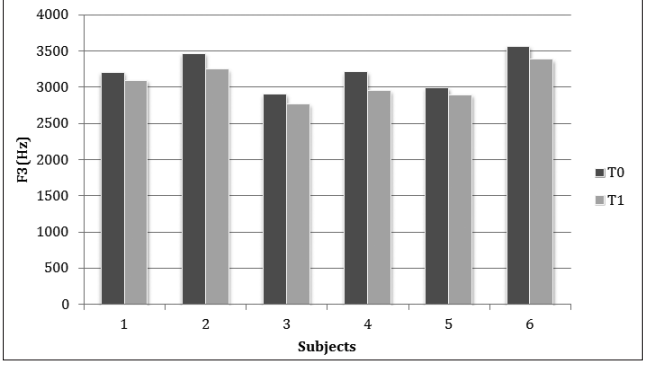

Figure 3. F3 /ɯ/ before and after RME in subjects 1–6
RME: rapid maxillary expansion

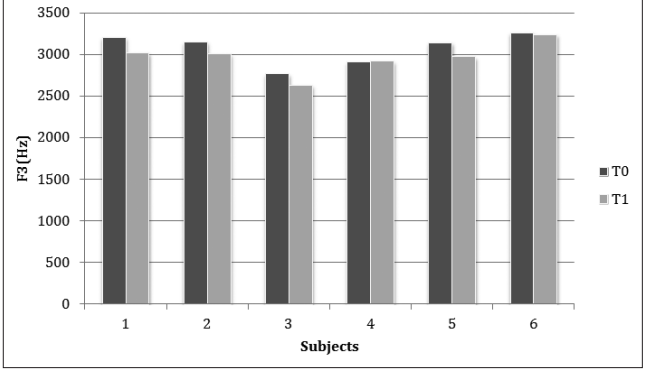

Table 1. Acoustic parameters before and after treatment

Variables (N=6)	T0 Mean (SD)	T1 Mean (SD)	p
Fundamental frequencies (Hz)	224.4 (58)	222.1 (55)	>0.05
Vowel durations (ms)	335.5 (73)	322.39 (67)	>0.05

*Wilcoxon Signed Rank Test, significant if p<0.05
T0: before expansion; T1: after expansion
SD: standart deviation

Table 2. Mean values and 95% Confidence Intervals of parameters at T0 and T1 for F1, F2, F3 and F4 frequencies (Hz) and significance values of differences (T0–T1)

Vowels	T0 Mean (SD) (N=6)	95% CI Lower – Upper Bound	T1 Mean (SD) (N=6)	95% CI Lower – Upper Bound	p
Formant 1 (Hz)					
/a/	763.8 (59)	610 – 917.6	788.8 (65)	619.5 – 958.1	>0.05
/ɛ/	586.1 (24)	522.1 – 650.1	610.3 (39)	508.6 – 712	>0.05
/ɯ/	483.6 (27)	413.1 – 554.1	502.8 (42)	392.3 – 613.2	>0.05
/i/	433.3 (32)	349.1 – 517.4	440.3 (45)	322.6 – 557.9	>0.05
/ɔ/	564.3 (31)	482.6 – 646	562.1 (64)	395.7 – 728.5	>0.05
/œ/	550.5 (19)	500.0 – 600.9	569.6 (53)	433.1 – 706.2	>0.05
/u/	467 (29)	391.6 – 542.3	455.8 (43)	344.1 – 567.5	>0.05
/y/	465.3 (29)	390.7 – 539.9	461.5 (28)	389.3 – 533.6	>0.05
Formant 2 (Hz)					
/a/	1260.1 (37)	1164.2 – 1356	1239.8 (54)	1099.9 – 1379.7	>0.05
/ɛ/	1612.6 (191)	1120.4 – 2104.8	2051.1 (71)	1867.3 – 2234.9	>0.05
/ɯ/	1324.3 (38)	1224.7 – 1423.9	1356.8 (68)	1180.7 – 1532.8	>0.05
/i/	2504 (67)	2331.1 – 2676.8	2359 (76)	2161.7 – 2556.2	*0.001
/ɔ/	1048.5 (44)	935.2 – 1161.7	1060.8 (45)	942.9 – 1178.6	>0.05
/œ/	1541.16 (90)	1307.5 – 1774.7	164 (60)	1486.8 – 1799.1	>0.05
/u/	936 (51)	804.5 – 1067.4	1227.8 (113)	937.2 – 1518.4	>0.05
/y/	1868.1 (118)	1563.2 – 2173	1772.3 (42)	1662.4 – 1882.2	>0.05
Formant 3 (Hz)					
/a/	2954.3 (210)	2412 – 3496.5	2928.5 (147)	2548.7 – 3308.2	>0.05
/ɛ/	2857.3 (125)	2534.3 – 3180.3	2922.5 (128)	2591.2 – 3253.7	>0.05
/ɯ/	3071.1 (78)	2869.1 – 3273.2	2962.3 (80)	2755.2 – 3169.4	*0.022
/i/	3220.8 (104)	2952 – 3489.6	3056 (93)	2814.9 – 3297	*0.002
/ɔ/	3106.8 (102)	2843.1 – 3370.4	3068.8 (117)	2767 – 3370.6	>0.05
/œ/	2801.5 (128)	2471.5 – 3131.4	2873.3 (68)	2698.2 – 3048.3	>0.05
/u/	3108.5 (73)	2920.1 – 3296.8	2925.1 (89)	2695.6 – 3154.6	>0.05
/y/	2811.6 (63)	2647.3 – 2976	2875 (83)	2659.2 – 3090.7	>0.05
Formant 4 (Hz)					
/a/	4036.6 (202)	3516.9 – 4556.3	3796.5 (177)	3340.6 – 4252.3	>0.05
/ɛ/	3955.1 (148)	3574.2 – 4336	3922 (246)	3289.4 – 4554.5	>0.05
/ɯ/	3901.6 (148)	3519 – 4284.2	3832.1 (99)	3575.8 – 4088.4	>0.05
/i/	4113.6 (143)	3745.6 – 4481.6	4039.1 (141)	3675.8 – 4402.5	>0.05
/ɔ/	3837.5 (128)	3507.7 – 4167.2	3851 (116)	3552.3 – 4149.6	>0.05
/œ/	3630.3 (92)	3393.6 – 3867	3854.6 (103)	3588 – 4121.2	>0.05
/u/	3964.3 (146)	3588.2 – 4340.4	3968.3 (96)	3720.1 – 4216.5	>0.05
/y/	3837 (149)	3451.9 – 4222	3954.3 (148)	3573.4 – 4335.2	>0.05

*Paired Sample t Test, significant if p<0.05
T0: before expansion; T1: after expansion
SD: standart deviation

There was no statistically significant difference between the changes in F0 values and vowel durations at T0 and T1 (p>0.05) (Table 1).

There was no significant difference in any of the other formants of F1, F2, F3, and F4 for vowels /a/, /ɛ/, /ɔ/, /œ/, /u/, and /y/ (Table 2).

DISCUSSION

Anatomical changes in the vocal tract may affect speech production in case of any change of the resonating cavities (12). RME may affect formant frequencies due to the altered and anteriorly replaced tongue after RME. Niemi et al. (3) reported that the facial skeleton burdens direct limitations on the morphology of the resonating vocal tract cavities and is therefore very relevant to speech acoustics or articulation. As a result of the present study, differences in the mean values of F2 /i/, F3 /i/, and F3 /ɯ/ were found to be statistically significant between T0 and T1. Vowel /i/ showed a statistically significant decrease in F2 and F3 values from T0 to T1. Although there are studies reporting no effect of RME on vowel /i/ (11), our finding is in accordance with the result of a previous study that investigated the impact of RME appliance on speech. The authors evaluated only F1 and F2 formants of the /i/ vowel and reported a centralization of the vowel by looking at the increase in F1 and the decrease in F2 (6). In another study, in contrast to our findings, vowel /i/ displayed a decrease of the F1 and an increase in the F2 and F3 (2). Meanwhile, a study investigating the effects of surgically assisted RME on voice quality reported a lowered F2 frequency and linked this finding enlargement of the size of the anterior oral cavity after surgery. Vowel /i/ is a high front vowel, meaning the position of the tongue is just behind the upper incisors, in the anterior oral cavity, during pronunciation. In case of maxillary constriction, since the tongue was unable to access the anterior oral cavity, it is not unreasonable to expect a perturbation of this vowel. In addition, the investigation of this susceptible vowel when conducting speech evaluation is recommended in a very recent study (13).

Vowel /ɯ/ is a very specific Turkish sound; it was not evaluated before except one research with no significant difference before and after surgically assisted RME (10). This difference mainly emerges from the fact that the previous researchers only investigate the F1 and F2 not F3 frequencies. Vowel /ɯ/ is also a high front vowel that can be affected by the size of the anterior oral cavity.

The changes in fundamental frequencies for both females and males before and after RME treatment demonstrated no statistically significant difference as previously reported (10, 11).

The results of this preliminary study show that no statistically significant difference was seen in the remaining Turkish vowels. For vowel /a/, our findings corroborate with other studies (7, 10). Only Macari et al. (11) reported a lowering of the F1 and F2 values of the /a/ vowel and advised that patients with narrowed maxilla who underwent RME should be aware of the possible change in speech quality.

In the present study, rather than a perceptual investigation, acoustic analysis was used to investigate speech errors just before the insertion of RME appliance and after the removal of RME. Acoustic analysis provides a more objective and reliable measurement, which may be difficult to reliably document perceptually and may not be noticeable perceptually. In the present study, acoustic analysis was performed by the PRAAT program. PRAAT program, which was also used in previous studies (2, 14), is a completely free software often used for acoustical analysis.

CONCLUSION

Despite to the small sample size limitation of the present study, it may be concluded that RME has an effect on voice acoustics. The spelling of high front vowels of /i/ and /ɯ/ is lowered after maxillary expansion. The possibility of voice change after RME should be discussed before treatment decision of patients. A larger sample of RME subjects is needed to substantiate this conclusion.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Sanko University (29.03.2018/15).

Informed Consent: Written informed consent was obtained from patients and patients' parents who participated in this study.

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Original Research

Effect of Different Colors of Resin Cement and Stainability on the Final Color of CAD/CAM Materials

Nermin Demirkol[1], Özge Parlar Öz[1], Funda Soysal[1], Derya Sürmelioğlu[2]

[1]Department of Prosthodontics, Gaziantep University School of Dentistry, Gaziantep, Turkey

[2]Department of Restorative Dentistry, Gaziantep University School of Dentistry, Gaziantep, Turkey

ABSTRACT

Objective: A computer-aided design/computer-aided manufacturing (CAD/CAM) system is the most popular technology that produces ceramics and has gained increasing popularity in dentistry. In the present study, we aimed to investigate the effect of four colors of resin cements and the stainability effect of hot coffee on the final color of glass ceramic (GC) CAD/CAM blocks.

Methods: Two colors of a CAD/CAM restorative material of 1 mm thickness with four colors of a dual–curing resin cement of 0.5 mm thickness were tested in this study (n=5). After cementation, the specimens were divided into two groups for thermocycling one half of them with coffee and the remaining without coffee. The first spectrophotometric measurement was applied after cementation and the second after thermocycling. Data were analyzed using the Statistical Package for Social Sciences software (SPSS®), and a p value of <0.05 was accepted as significant.

Results: The color of resin cement did not significantly affect the restoration of the final color of the GC. Statistically significant differences were found in white, transparent, and yellow colors of the resin cement after thermocycling with/without hot coffee.

Conclusion: The esthetic achievement of porcelain laminates can be affected by the color of the resin cements. The GC of 1 mm thickness was not affected by the resin cement color after cementation. The color of resin cement can change in the duration of its usage.

Keywords: Computer-aided design/computer-aided manufacturing, stainability, color change

INTRODUCTION

Modern healthcare has progressed due to developments in science and technology. A computer-aided design/computer-aided manufacturing (CAD/CAM) system is the most popular technology used for producing ceramics and has gained increasing popularity in the area of dentistry (1). There are many CAD/CAM blocks with advantages, such as biocompatibility; durability; esthetics; fewer clinical stages; rapid production, cost effectiveness; different contents; and physical properties, such as lithium disilicate glass ceramic (GCs), leucite-reinforced GCs, feldspathic GCs, aluminum-oxide, and yttrium tetragonal zirconia polycrystal (2).

GCs are the commonly used materials in dental prostheses, and CAD/CAM blocks provide thinner restorative materials with increased translucency, producing more conservative and esthetic restorations as laminate veneers. The surface texture, production steps of porcelain, and underlying resin cement could influence the optical properties of ceramics (3, 4). GC incontent of crystalline component has high light transmission and mechanical properties. Feldspathic porcelains (CEREC Blocs PC, Sirona) are fabricated using fine-grained powders to produce a nearly pore-free ceramic with fine crystals, which results in improved polish ability and decreased enamel wear (5). The polychromatic feature gives feldspathic ceramic a natural appearance in the anterior teeth with several layers of color.

Color evaluation can be performed using two basic methods: objective and subjective. Subjective measurement methods using porcelain or acrylic resin shade guides have some limitations, which affect the color perception lie. The color perception can be changed according to the lighting terms, age, conditions, experiences, and human eye strain (6). Spectrophotometry as an objective practice is more reliable and sensitive than the visual scale. A color difference (ΔE) between two measurements can be calculated within the CIELAB color system. The mechanism of a spectrophotometer is based on the CIELAB system, which has three axes: L* axis (from 0 to 100; black–white) representing clearness and a* and b* representing the redness–greenness and yellowness–blueness axis, respectively (7). Calculations are based on the following equation:

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ORCID IDs of the authors: N.D. 0000–0002–2415–5977; Ö.P.Ö. 0000–0002–8927–3448; F.S.0000–0001–7701–6156.

Corresponding Author: Nermin Demirkol **E–mail:** dt_nerminhamdemirci@hotmail.com

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Table 1. Materials tested in the study and distribution of specimens

Resin cement		Glass ceramic		Termocycling			
Variolink N, base	Variolink N, catalist	A1	A2	A1 with coffee/without coffee		A2 with coffee/without coffee	
Bleach xl	Transparent low viscosity	n=10	n=10	n=5	n=5	n=5	n=5
White a1	Transparent low viscosity	n=10	n=10	n=5	n=5	n=5	n=5
Yellow a3	Transparent low viscosity	n=10	n=10	n=5	n=5	n=5	n=5
Transparant	Transparent low viscosity	n=10	n=10	n=5	n=5	n=5	n=5

Figure 1. Preparing for cementation of GC specimens in silicon mold
GC: glass ceramic

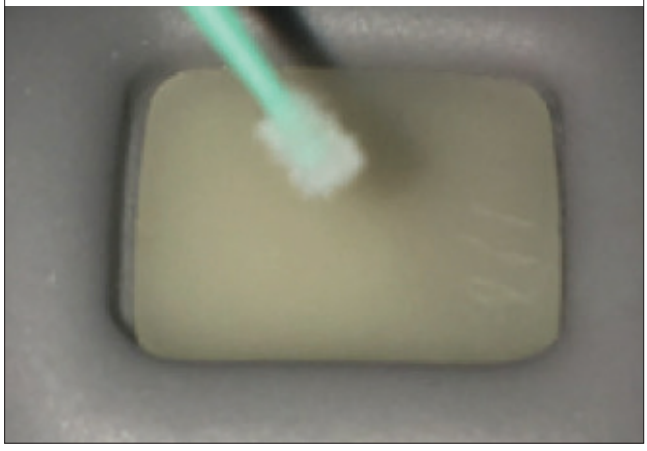
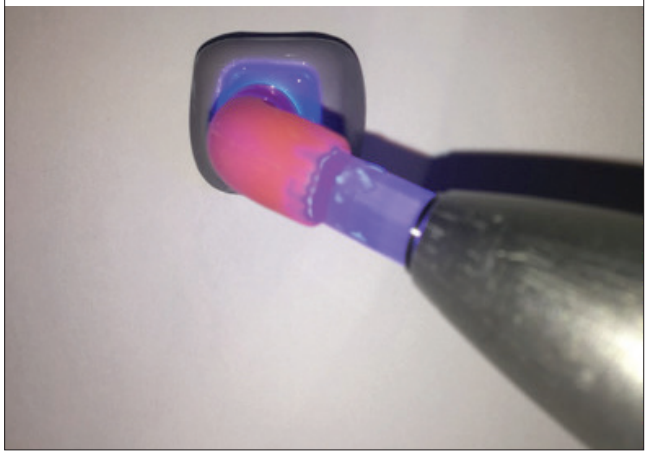


Figure 2. Light curing of GC specimens
GC: glass ceramic



ΔE (L,a,b)=[(L1−L2)2+(a1−a2)2+(b1−b2)2]1/2 (8).

The cement color, ceramic layer thickness, and tooth structure color identify the final color of ceramic veneer restorations (9, 10). Several studies that analyzed the effect of resin cement shades on veneer restorations have found that a variation in the thickness of the ceramic material and different shades of cement can lead to perceptible color differences in veneer restorations (9). The restoration of the final color is affected by the cement color; however, it seems to have less influence on the overall color of the definitive restoration compared to the other variables (3, 11).

The color stability of a material is important, as the mechanical features and many factors are related to the color change of the dental materials in the mouth (12, 13). Clinical usage may affect the color durability of restorations. The longevity of dental materials has been evaluated by artificial aging in many in-vitro studies. The null hypothesis of the present study was that different colors of the same resin cement do not affect the dyeability of the GC, and thermocycling with or without coffee does not affect the measured color change. The purpose of current study was to investigate the effect of four colors of resin cement and stainability of hot coffee on the final color of GC CAD/CAM blocks after thermocycling.

METHODS

Two colors of a CAD/CAM restorative material (CEREC Blocs PC, Sirona) with four colors of a dual–curing resin cement (Variolink N; Ivoclar Vivadent) were tested in this study (Table 1). Two groups of GC specimens (N=40/group), A1 and A2, were prepared using a slow-speed diamond blade (Buehler® Wafering Blades, series 15 LC diamond; Microstructural Analyses Division) and a cutting machine (Vari/cut VC-50; LECO Corp.) into rectangular plate slices of 1 mm in thickness (n=5). The GC samples were polished using 600, 800, and 1200 grit silicon carbide abrasive papers (3 M ESPE, St. Paul, MN, USA) for 15 s using a 170-rev/min grinding machine (Minitech 233; Presi, Grenoble, France) under running water. The GCs were then ultrasonically cleaned for 3 min in ethanol and deionized water and air-dried. The final thicknesses of each specimen was measured using a digital micrometer. Before the cementation and aging procedure, the color values of ceramic groups were measured under the standard illuminant D65 on a white background (14).

Cementation of Glass Ceramic with Resin Cement

Only one GC specimen was prepared with 1.0 mm thickness. The specimen was placed on a smooth plane and boxed with putty silicon (Zetaplus-Zhermack). A glass slab was placed on the specimen until the impression material solidified. A silicon rim was obtained with a height of 1.5 mm. The GC specimen surfaces were placed in the silicon box, and cement was applied in a standard condition by the rim (Figure 1). Therefore, the cement thickness was adjusted 0.5 mm.

Table 2. ΔE values, standard deviatians (SD) and mean values

Ceramic	Resin cement		Subdivision		p
			Coffee Mean±SD	Without coffee Mean±SD	
A1	Bleach XL	ΔE 1	6.84±0.67	5.67±1.11	0.087
		ΔE 2	6.74±1.00	6.52±1.25	0.750
		ΔE difference	2.34±0.80	1.74±0.66	0.238
	White A1	ΔE 1	9.48±0.84	11.00±1.57	0.106
		ΔE 2	9.23±0.68	9.29±2.49	0.964
		ΔE difference	3.40±1.02	5.83±0.72	0.011*
	Yellow A3	ΔE 1	13.66±0.48	13.47±1.93	0.838
		ΔE 2	13.26±1.40	11.44±1.51	0.123
		ΔE difference	4.61±2.28	7.63±1.15	0.086
	Transparant	ΔE 1	9.20±0.80	8.81±2.15	0.729
		ΔE 2	9.43±2.04	6.38±0.71	0.055
		ΔE difference	5.65±0.62	6.38 ± 1.19	0.338
A2	Bleach XL	ΔE 1	5.81±0.62	5.80±0.45	0.973
		ΔE 2	6.66±1.35	4.50±0.92	0.072
		ΔE difference	2.75±1.06	3.00±0.85	0.677
	White A1	ΔE 1	8.66±1.14	8.39±2.02	0.797
		ΔE 2	8.48±2.56	2.90±1.49	0.025*
		ΔE difference	4.28±0.83	6.75±2.49	0.176
	Yellow A3	ΔE 1	12.08±1.21	10.16±1.66	0.091
		ΔE 2	10.58±1.77	7.53±1.48	0.029*
		ΔE difference	4.13±1.12	5.57±1.61	0.171
	Transparant	ΔE 1	8.98±1.17	8.84±1.42	0.842
		ΔE 2	9.72±1.72	5.77±1.42	0.009*
		ΔE difference	5.20±1.50	3.82±0.36	0.130

ΔE: Color change; *: p<0.05

On each specimen, a hydrophilic acid (porcelain etch and silane, Ultradent, USA) was applied and rinsed for 20 s. After drying, bonding (monobond, Variolink N; Ivoclar Vivadent) was applied on each specimen. Four different shades of resin cement (yellow, white, transparent, bleach XL, base and transparent low viscosity catalyst) was applied in two groups of GC (A1 and A2) and cured for 20 s (Figure 2). After removing the mold, light polymerization was repeated for 40 s for both surfaces to ensure complete light curing. The measurement of color was performed using a color spectrophotometer for consistent and objective results for all specimens (15, 16).

Thermocycling

A coffee solution was prepared according to the manufacturer's instructions: 60 g coffee in 1 L of water placed in a hot tank. The coffee in the hot tank was refreshed every 8 hours. One-half of the cemented specimens from each group were subjected to 5,000 thermocycles (SD Mechatronik Thermocycler) between two water baths of 5°C and 55°C with a dwell time of 30 s at each temperature extreme in coffee and the remaining specimens were subjected to thermocycling in a bath without coffee water bath. After thermocycling, the specimens were washed and brushed with toothpaste 10 times and dried with paper (12). The samples were measured using a spectrophotometer after mechanical cycling with and without coffee. Thus, the color measurement was performed the second time in the same conditions of a white background because this is considered more suitable for the posterior teeth (17).

Color Measurement of Ceramic Specimens

A contact spectrophotometer (Vita Easyshade®, Vita-Zanhnfabrik®, Bad Säckingen, Germany) was used for measuring the color. The baseline color values were L*, a* and b*, in which L* represents the value from 0 (black) to 100 (white) and a* and b* represent the shade, where a* is the measurement along the red–green axis and b* is the measurement along the yellow–blue axis. The samples were placed in a 37.8°C water bath in dark for 24 h.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS®) software (SPSS, IBM Corp.; Armonk, NY, USA) was used for the analysis, and a p value of <0.05 was accepted as significant. The normality of the data distribution was tested using the Shapiro–Wilk test. Analysis of variance and the least significant difference (LSD) test were used to compare normally distributed data, which were reported as mean±standard deviation. The General Linear Model (Univariate) test was used for comparison of independent variables. Fisher's LSD and Bonferroni tests were used for post hoc analysis.

RESULTS

The mean and standard deviations of the color difference values between before (initial measurements) and after aging (with/without coffee; final measurements) are represented in Table 2. The statistical analysis of ΔE values is also shown (for each column), which corresponds to a comparison between the materials in each staining solution.

None of the resin cement colors affected the restoration of the final color. Statistically significant differences were found between the groups of A1 ceramic cemented with transparent resin and coffee thermocycling and A2 ceramic cemented with yellow resin and coffee thermocycling. Also, A1 and A2 ceramic cemented with white resin showed statistically significant difference between with and without coffee thermocycling.

DISCUSSION

In the present study, the effect of the resin cement color and two types of thermocycling (with and without coffee) on the final restoration of color were evaluated. Eight materials were tested: two colors of CAD/CAM GC blocks and four colors of resin cement. The GC blocks included a feldspathic ceramic incontent of the crystalline component (CEREC Blocs PC, Sirona). The monomer matrix of Variolink N resin cement is composed of bisphenol A-glycidyl methacrylate (BisGMA), urethane dimethacrylate, and triethylene glycol dimethacrylate. A spectrophotometer was preferred as an objective criterion instead of a visual examination (4).

Many methods, such as visual inspection using a standard shade guide, for evaluating the color effect are subjective, while objective methods include spectrophotometry, colorimetry, and analysis software usage. A spectrophotometer was used in the current study for calculating the differences in L*, a*, b* values and resulting color differences DE values because we decided to prefer well-known DE values as color measurement (15). Also, the background effect of color perception is controversial and white background has been used widely as a standard background, as in our study (16).

A ΔE value >3.7 is a clinically unacceptable color change. High ΔE values in this study may be based on the optical properties of the material, which is described as high translucency material due to the optical combination of a glass matrix that reduces internal scattering of the light as it passes through the material. Medium or high opacity that are designated for the fabrication of core structures might be a resolution for this situation (17). In the current study, resin cements did not affect the restoration of color in all the groups before the aging procedure. However, after aging, different color changes were observed. The water absorption of the composite resin can be a sign of color change when absorbing colored liquids in line with a study by Bagheri et al. (18). In the present study, the color change of materials was evaluated with/without coffee thermocycling.

The different shades of resin cement did not influence the overall color of porcelain veneer alone and may be related to the limited thickness and translucency of resin cement under the cemented veneers (19). The resin cement tested in the current study contains Bis-GMA, which is a monomer having chemical structure groups. The chemical groups are prone to hydrolysis and/or hydrogen bridging with water due to the hydroxyl in Bis-GMA. Hydrolytic degradation and hygroscopic effects of the materials are signs of color variation in resin-based materials (20). The present study supported the agreement that different resin cement colors do not affect the restoration of the final color but only the aging with coffee affects A1 ceramic cemented transparent and white resin cements, and A2 ceramic cemented yellow and white resin cements of specimens.

The thin layer of the agents bonded to ceramic disks with no dental structure involved limited the study, thereby lacking simulation to a clinical situation.

CONCLUSION

The esthetic achievement of porcelain laminates can be affected by the color of the resin cements. A GC of 1 mm thickness did not affect only resin cement color after cementation. The color of resin cements can change during its usage. The current results indicate that resin cements aging with coffee affect the final color of restoration for transparent, yellow, and white colors. The influence of abutment tooth color should be considered in future studies.

Ethics Committee Approval: Ethics committee approval was not taken due to in vitro design of the study.

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

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Original Research

Data Analysis of 1811 Major Trauma Patients Admitted to the Emergency Departments of Thirteen Hospitals

Demet Yaldız[1], Gökhan Akbulut[2], Murat Anıl[3], Mustafa Onur Öztan[4], Sadık Yaldız[1]

[1]Department of Thoracic Surgery, Manisa Celal Bayar University School of Medicine, Manisa, Turkey

[2]Clinic of General Surgery, Tepecik Training and Research Hospital, İzmir, Turkey

[3]Clinic of Pediatrics, Tepecik Training and Research Hospital, İzmir, Turkey

[4]Division of Pediatric Surgery, Katip Çelebi University School of Medicine, İzmir, Turkey

ABSTRACT

Objective: Our objective was to determine metrics and measure the trauma-related emergency care quality.

Methods: Patients with majortrauma admitted to emergency departments of 13 hospitals in the north region of İzmir between January 01, 2014, and December 31, 2014, were included in this study. For the definition of major trauma, guideline of Centers for Disease Control (CDC) for field triage of injured patients version 2011 was used. Age, time passed in emergency, first order timing, number of consultations and amount of time taken by the consultations, number of deaths in emergency departments and intensive care units, number of radiological tests applied to patients, total score of interventional applications, and total billing were recorded.

Results: In one-year period, 2,415,361 patients applied to selected hospitals' emergency departments, and 1811 patients (0.07%) were accepted as major trauma. The mean age of the patients was 29.4 years. The meantime passed in emergency was 28.3 h. The mean number of consultations and amount of time taken by consultations were 1.6 and 26.2 h, respectively. The number and mean X-ray, ultrasound, computerized tomography, and magnetic resonance imaging numbers were 3910 and2.16; 518 and0.29; 2805 and1.55; 114 and0.06, respectively. The total mortality rate was 1.04% (19 patients).

Conclusion: This is a preliminary study presenting the data obtained from different level hospitals in the region, and indicators in such a high number of patient group were evaluated for the first time. We believe that as national emergency care is built and strengthened with data, management of care for patients with trauma will improve.

Keywords: Data, emergency department, major trauma

INTRODUCTION

The increasing burden of trauma has emphasized the need for effective emergency care to alleviate the morbidity and mortality. About 1.25 million people died from traffic injuries in 2013 (1). One of the most important causes of deaths in the first four decades of life is trauma, which also leads to serious disabilities. According to estimations, if the number of injuries continue to increase at this rate, trauma will settle in the third place among all the causes of deaths in 2020 (2). Every trauma that results in death in the United Kingdom means 45 hospitalizations, 630 consultations, and 5000-6000 minor traumas to the hospital (3). Annually, 50 million people become permanently disabled because of trauma. The number of cases with all known causes of death is 280,531 in our country according to the 2009 data. Four percent of the deaths (approximately 11,000 people) is caused by traumatic events. Although trauma affects all age groups, it is primarily seen in young population. Medical, social, and economic consequences of trauma have led to structural changes in the treatment of these patients. As a result, understanding the pathophysiology of trauma-related medical conditions and improvement of patient care in prehospital and emergency services, imaging systems, trauma surgery, and intensive care unit have favorably altered the prognosis of patients with major trauma. However, if the necessary medical interventions are not carried out adequately on time, the efficacy of the treatment will diminish despite all the developments (4). In Turkey, some study groups are working on trauma, aiming to establish the national trauma systems (5). Little has been reported about the metrics

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ORCID IDs of the authors: D.Y. 0000–0002–5698–3056; G.A. 0000–0002–3924–5342; M.A. 0000–0002–2596–4944; O.Ö. 0000–0003–3696–4090; S.Y. 0000–0001–6521–6185

Corresponding Author: Demet Yaldız **E-mail:** demetyaldiz@gmail.com

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Table 1. Major trauma criteria

1. Patients with vital signs abnormality after trauma
Blood pressure <90/60 mmHg, heart rate>100 beats/min, respiratory rate>20/min, O^2 saturation <90%
2. Glasgow coma score <14
3. Patients who require permanent airway for any reason
4. Patients with penetrative, incisive tool injury to the body / gunshot wounds or suspected gunshot wounds
5. Epidural hematoma, subdural hematoma, traumatic subarachnoid hemorrhage, deplase head fracture, head base fracture, or suspected ones
6. Patients with major burn criteria
7. Two or more proximal long bone fractures
8. Complete or almost complete amputations proximal to the wrist and ankle
9. To be involved in a fatal traffic accident in the same vehicle
10. Falling down >2 flats/>5 m (more than three times of the children height)
11. An extremity injury without a distal pulse
12. Pelvic fracture or suspected fracture
13. Flail chest
14.Thrown from a car, stuck in a vehicle, motorcycle accident, bike–vehicle collision
15. Deep neck incisions (incision below M. sternocliculo mastoid), enlarging neck hematoma, post–traumatic hoarseness, active bleeding
16. Active bleeding from the injuries proximal to elbow and knee
17. Risky patients who do not fulfill the above criteria (>20 weeks of gestation, advanced respiratory failure, chronic dialysis program, coumadin treatment, age over 65 years)

and measures of the patients with major trauma admitted to hospitals in our country. As global emergency care is built and strengthened with data, regulations of the emergency medicine departments and management of care for patients with trauma will improve. This paper aims to contribute to the eliminate this deficiency.

METHODS

Study Design

This study analyzed the patients with major trauma who applied to the emergency departments of 13 hospitals in the north region of İzmir, two of which are training and research type. A module named "major trauma patient collection card" was structured in the hospital information management system (HBYS). Through this module, all patients who applied with a trauma diagnosis between January 2014 and December 2014 were prospectively evaluated by the "2011 Guidelines for Field Triage of Injured Patients," and among them, patients with major trauma were selected for the study (6). Major trauma criteria are shown in Table 1. Trauma indicators were determined before the study and collected as prospective data during the hospitalization of patients with major trauma (Table 2). As far as we know, the indicators used in this study were first to be prospectively evaluated in such a large group of patients in our country.

Study Duration

Between January 2014 and December 2014, the data of the patients with major trauma who applied to the emergency departments of 13 hospitals, two of which are training and research type, were included in this study.

This is a retrospective analysis of data within the knowledge of hospital administrations. Therefore, no ethics committee was consulted. Since this was a retrospective study performed only with screening of medical records no informed consent was obtained from the patients. The study was conformed in accordance with the ethical issues as outlined in the Declaration of Helsinki.

RESULTS

During the study period, 2,415,361 cases were applied to the emergency services of 13 hospitals; and a total of 1811 patients were identified as major trauma in our database. Among them, 1255 patients (69.3%) were male, and 556 (30.7%) were female. The mean age of patients was 29.4±23.4 years. As evident from Table 2, the median waiting periods for the first order and clinical intervention were 42 min and 47 min, respectively. The average number of consultations required was 1.6. The mean time to complete the consultations and the duration of emergency stay were 26.2 h and 28.3 h, respectively. A total of 3910 X-ray

Table 2. Major trauma indicators

Total number of emergency department admissions	2,415,361
Number of major trauma patients (% ratio)	1811 (0.07%)
Mean age (years)	29.4
Mean emergency department length of stay (h)	28.3
Mean duration for first order (min)	42.8
Mean consultation number (per patient)	1.6
Mean duration for finalization of consultation (h)	26.2
Number of exitus in emergency department (% ratio)	6 (0.33%)
Number of emergency department dispatch (% ratio)	71 (3.92%)
Number of hospitalization to ICU (% ratio)	199 (11%)
Mean ICU stay (days)	11.4
Total hospitalization number in surgical clinics (% ratio)	846 (46.7%)
Mean hospital stay (days)	6.2
Total exitus number (% ratio)	19 (1.04%)
Mean invoice cost per patient (Turkish Lira)	650.1
Mean invasive procedure score	343.9
X–ray number/mean	3910/2.16
Ultrasound number/mean	518/0.29
CT number/mean	2805/1.55
MR number/mean	114/0.06

h: hour; ICU: intensive care unit; CT: computed tomography; MR: magnetic resonance

(mean 2.16), 518 ultrasound (mean 0.29), 2805 computerized tomography (mean 1.55), and 114 magnetic resonance imaging (mean 0.06) were performed to 1811 patients with major trauma. A total of 199 patients (11%) were treated in the intensive care unit, and 846 patients (46.7%) were treated in the surgical clinics. Six patients died in the emergency room, nine in the intensive care unit, and four were already dead when they arrived to emergency department. Total mortality was 1.04%. The duration of average hospitalization was 6.2 days, and the average cost per patient was 650.1 Turkish Lira.

DISCUSSION

In this study, patients with major trauma among emergency department attendances were found to be 0.07%. Even though this ratio is low, 1811 patients with major trauma affect the emergency department process both in healthcare empowerment, medical procedures, and costs. Rapid, accurate, and privileged medical intervention is needed to save lives. The mean age of the patients was29.4 years. Since this population is socially and economically active, the loss of empowerment is highly dramatic. The mean length of stay and time passed until first order in emergency department was 28.3 hand 42 min, respectively. The mean consultation number was 1.6, and the mean duration for completion of consultations was 26.2 h. These data are important to show the burden of patients with major trauma in emergency departments. But unfortunately, comparison of these data is not possible in our country because of lack of studies in this regard.

It is very important to make quick decisions and administer the correct interventions in major trauma cases. In our study, the median time passed until first physician order and first clinical intervention were 42minand 47 min, respectively. Since that time range includes the radiological assessments, it is considered acceptable. The mean emergency department length of stay was found to be long (28.3 h) in our study. Rathlev et al. (7) reported 232 min of emergency department length of stay (3.8 h).

Our study results showed lower mortality rate than the results of studies conducted in other countries. In our study, the total mortality rate was 1.04% (19 patients). Harnod et al. (8) showed a mortality rate of 12.5% for severely injured patients (ISS>15) and Leung et al. (9) showed 31.6% for such patients. In Turkey, most of the patients with trauma are carried to the nearest hospitals by ambulance. Once the patients enter the nearest hospitals, their medical records are out of sight; and patients who died from injury outside the hospitals are also not recorded in our database. This could be

one of the reasons explaining the lower mortality rate in our research. Nineteen deaths were included in this study. Six of them occurred in emergency department, nine in the intensive care unit, and four of them were already dead when they arrived to emergency department. This shows that effective and rapid treatment is necessary for this patient group. We suggest that all patients with major trauma should be sent to trauma centers or most convenient hospitals than the closest one. These centers have more staff to manage such patients and a greater chance of providing on-time operations for them. Thus, patients with major trauma may have better survival rates in such hospitals.

Each emergency department needs measured metrics that they have used. This will provide them to plan how the patients will be coordinated at the emergency care. Avoiding waits and sometimes harmful delays can only be achieved in this way (10). To improve the management of patients with trauma, future work is needed to analyze outcome-based measures.

In addition, there is no information about how much money is annually spent on patients with trauma in Turkey. It was found to be 650 Turkish Liras per patient in our study.

A few limitations of our study need to be recognized. Although the injury severity score (ISS) should serve as a considerable adjustment, we adjusted our major trauma criteria only depending on the "Guidelines for field triage of injured patients: recommendations of the National Expert Panel on Field Triage, 2011," and we did notevaluate the mortality rates of patients who were transferred from one hospital to another.

CONCLUSION

Major trauma remains a significant medical concern, leading 11,000 deaths annually in Turkey. Trauma metrics and measurements improve the outcomes in different countries. In Turkey, we also urgently need the data for regulations of the emergency medicine departments and management of care for patients with trauma.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Since this was a retrospective study performed only with screening of medical records no informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

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Original Research

Biophysical Properties of ERG Channels in Octopus Neurons of Ventral Cochlear Nucleus

Caner Yıldırım, Ramazan Bal

Department of Physiology, Gaziantep University School of Medicine, Gaziantep, Turkey

ABSTRACT

Objective: ERG (Ether a go go related gene) channels (Kv 11) are the members of the voltage-dependent potassium channel family, which have three subtypes as ERG1 (Kv 11.1), ERG2 (Kv 11.2), ERG3 (Kv 11.3). Electrophysiological, biophysical properties of ERG channels and their functions are not known in the cochlear nucleus (CN) neurons, which is the first relay station of auditory pathway. For that reason, we aimed to study pharmacological and biophysical properties and their functions in the octopus neurons of the ventral cochlear nucleus (VCN).

Methods: A total of 70 mice at 14-17 day-old were used for this study. Electrophysiological characterization of ERG channels was performed using patch clamp technique in CN slices.

Results: In current clamp, application of ERG channel blockers, terfenadine (10 μM) and E-4031 (10 μM), significantly increased input resistance in all the cells ($p<0.05$). Also, in octopus cells, it was found that terfenadine (10 μM) and E-4031 (10 μM) significantly reduced threshold for induction of action potentials (AP) with square current pulses ($p<0.05$). Tail ERG currents were measured under voltage-clamp. Steady state activation curve for ERG tail current was determined, yielding a half-activation voltage (V0.5) and slope factor (k factor). Steady state activation curve for ERG tail current was determined with a half-activation voltage in Octopus cell V0.5 -50.72±0.32 with a slope factor of 6.04±0.23 mV (n=3). The quasy steady-state inactivation curve for chord conductances gave for Octopus cell V0.5 value of -74.34±0.46 and the slope of 7.89±0.32 (n=3).

Conclusion: In conclusion, the findings obtained in the present study suggest that Octopus neurons express ERG channels and appear to threshold for AP induction and, possibly, resting membrane potentials in this cells.

Keywords: Auditory pathway, cochlear nucleus, electrophysiology, ERG channels, patch clamp

INTRODUCTION

ERG "ether-a-go-go-related gene" channels were named "ether-a-go-go" in 1969 because of the similarity to the leg movements of flies that were anesthetized with ether and resembled "the go-go" dance that was popular at that time (1). ERG channels, a subgroup of the voltage-gated potassium channel family, have been widely expressed both in the central nervous system (CNS) and the heart. There is not much information concerning the functional roles and electrophysiological properties of these channel currents, which were first isolated from the hippocampus area in the brain in the neuronal system (2). It was seen that studies on ERG channels were generally focused on the heart rather than the brain. Although ERG channels are expressed in many tissues, their physiological roles were best revealed in cardiac ventricular cells (3).

There are many studies that aim to understand the biophysical, pharmacological and electrophysiological properties and determine the functions of ion channels in the cochlear nucleus. These studies have described three different neuron groups that have completely different biophysical and functional properties from the morphological and electrophysiological aspect. Many ion channels in these neuron groups have been physiologically, pharmacologically and biophysically characterized, wherein their function in the relevant nucleus and the extent of their contribution to signal formation and transmission were defined (4, 5).

In all mammals, octopus nerve cells are located in the caudal and dorsal part of the Posterior Ventral Cochlear Nucleus (PVCN) in an area with clearly visible margins. It was found that other cell types are not found in this area, especially in humans (4). Each octopus nerve cell receives inputs from many auditory nerve fibers via synapses located both on their soma and dendrites. Mice have nearly 200 octopus nerve cells in each cochlear nucleus located in this area (6).

It is reported that octopus nerve cells found in mammalian PVCN detect the firing of auditory nerve fibers with excellent temporal precision and transmit this information to the upper auditory nuclei in the brain. It is known that octopus nerve cells respond with exceptionally well-timed action potential to "click" stimuli,

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ORCID IDs of the authors: C.Y. 0000–0003–0091–9925; R.B. 0000–0003–3829–8669

Corresponding Author: Caner Yıldırım **E–mail:** caneryildirim27@gmail.com

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the beginning of sounds with a pure tone (stimulus by a sound that consists of one frequency) and periodic sounds (4) .

A study on whether ERG channels contribute to the action potential of voices has not been found in the literature. In this study, we aimed to investigate whether ERG channels had a physiological contribution in the process of transformation of auditory signals into action potential. With this purpose, we first investigated how ERG channels affected cell excitability in octopus cells characterized in the ventral cochlear nucleus using the Current Clamp technique. ERG channel currents were then isolated as tail current with the help of specific ion channel antagonist chemical agents (terfenadine and E-4031) using the Voltage Clamping technique. The activation, inactivation and deactivation kinetics and biophysical properties of these channels in the relevant cochlear nucleus neurons were determined for the first time by analyzing these currents.

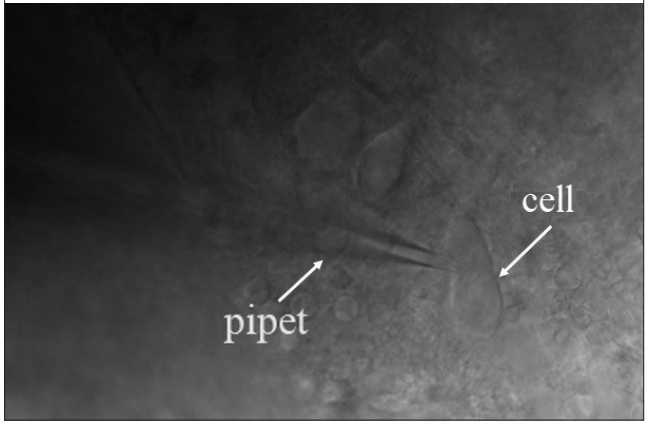
METHODS

The Electrophysiological Patch Clamp technique was used to characterize ERG channels in cochlear nucleus tissue. ERG channels were characterized by using Current Clamp and Voltage Clamp configurations. All data from the cells were obtained by whole cell configuration. An example of the whole cell configuration is shown in Figure 1.

Preparation of Brain Sections

The study began after obtaining the approval of the ethics committee of Gaziantep University Experimental Animals Studies Unit (protocol no: 06.01.2016 / 03). Animals were decapitated under anesthesia (halothane) followed by dissection without creating any physical damage and especially without stretching the cranial nerves emerging from the brain stem after placing the animal's head in continuously oxygenated normal artificial cerebrospinal fluid (aCSF). After the brain was completely taken out of the skull, it was incised coronally at an angle of approximately 60º at the inferior colliculus-superior colliculus level. The part that contains the brainstem was glued onto a Teflon block with the inferior colliculus facing down using a cyanoacrylate adhesive and then placed in a vibratome that contains the continuously oxygenated normal aCSF. Coronal sections of 175-200 µm thickness were taken with a vibrating vibratome. The obtained sections were incubated in continuously an oxygenated normal aCSF solution for approximately 15-30 minutes and then moved to a 0.3 mL volume recording chamber and through which fresh oxygenated normal aCSF solution was perfused at a speed of 4-5 mL/min for intracellular recording purposes. The temperature of the perfused aCSF solution was consistently maintained at 33ºC with a thermoregulator with a negative feedback circuit component probe at the part where the perfusion system opens to the recording chamber.

Figure 1. View of the cell with a pipette under a microscope in whole cell configuration



Solutions

Pipette solution

The constituents of the pipette solution were as follows (in mM): 108 potassium gluconate, 9 HEPES, 9 EGTA, 4.5 $MgCl_2$, 14 phosphocreatinine (tris salt), 4 ATP (Na-salt) and 0.3 GTP (tris salt). The pH of the solution was set to 7.40 with potassium hydroxide (KOH). The pipette solution was prepared as a stock solution to be used before each experiment and stored at -40ºC.

Perfusion solution

"Normal aCSF" was used as a perfusion solution in the Current Clamping. The constituents of aCSF solution were as follows: 138 mM sodium chloride (NaCl) (Merck), 4.2 mM potassium chloride (KCl) (Merck), 2.4 mM calcium chloride ($CaCl_2$) (Fluka), 1.3 mM magnesium sulfate ($MgSO_4$) (Merck), 10 mM HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (Merck), 10 mM glucose (Sigma Aldrich). This solution was continuously oxygenated with carbogen gas (95% O_2 + 5% CO_2) throughout the experiment starting at least 30 minutes prior to obtaining the brain slices. The pH of the solution was set between 7.35-7.40 using 1 M sodium hydroxide (NaOH) (7, 8).

Two types of perfusion solutions were used in the Voltage Clamping. One of these was a solution with high K^+ concentration (40 mM) in order to increase the amplitude of ERG channel currents. This solution did not contain Ca^{+2} in order to prevent Ca^{+2} -activated K^+ currents. Osmolarity of the solution was kept constant at 295-305 mOsm/L by increasing the potassium concentration from 4.2 mM to 40 mM while decreasing NaCl at the same ratio. The constituents of this solution were as follows (in mM): 102 NaCl, 40 KCl, 3.7 $MgSO_4$, 10 HEPES and 10 glucose. To this solution, 1 µM tetradotoxin (TTX) (Alexis Biochemicals (USA)) was added to block sodium currents, 1mM 4-aminopyridine (4-AP) (Sigma Aldrich), 1mM tetraethyl ammonium (TEA) (Fluka) to block I_{KDR} and I_A currents, respectively, as well as 2 mM cesium (Cs) (Sigma Aldrich) to block nonspecific cation channel currents (I_h) activated by hyperpolarization. In addition, 5 µM 6.7-Dinitroquinoxaline-2.3-dione (DNQX), 10 µM 2-amino-5-phosphonopentanoic acid (APV-5) and 1 µM strychnine were added to the solution in order to block the synaptic activities due to glutamate, GABA and glycinergic receptors, respectively. This solution was called "control aCSF".

In addition to; 10 µM 1-[2-(6-methyl-2-piridyl)ethyl]-4-(4-methylsulfonyl-aminobenzoyl) piperidine (E-4031) (Alemon lab-Israel)

was added to the "control aCSF" solution as the specific blocker in order to isolate ERG currents and a third solution called "control aCSF containing E-4031" was prepared.

Among the employed chemical agents, E-4031, terfenadine, APV-5 and Cs were dissolved in dimethyl sulfoxide (DMSO) such that the final concentration would not exceed 1/1000. It was not desired to use a higher concentration of DMSO as it could have a toxic effect on the cells. All the other chemical agents were dissolved in aCSF solution. The pH and osmolarity values were taken into account while preparing the solutions. The pH values of the perfusion solution and pipette solution were set to 7.4 and 7.35, respectively. The osmolarity of both solutions were maintained between 295-310 mOsm. Test solutions that contained a pharmacological agent were applied to the recording chamber with the perfusion system that consists of pipes and valves.

Statistical Analysis

Statistical evaluation was performed using the Statistical Package for Social Science version 23.0 (SPSS, IBM Corp.; Armonk, NY, USA). Records obtained before applying ERG channel antagonists were used as the "control", and records obtained after applying these antagonists were used as the "test group". Normal distribution of the groups were analyzed in order to statistically evaluate the difference between the two groups before and after applying ERG channel antagonists. Regression analysis was performed to analyze the current-voltage curve of the cells. Descriptive statistics for numerical variables were expressed as group mean ± standard error (SE) (n indicates the number of animals used in the experiment). Statistical evaluation was performed using the parametric Student's t test for groups that had a normal distribution and $p<0.05$ was considered statistically significant.

RESULTS

Current Clamping Studies

Specific ERG channel antagonists, E- 4031 and terfenadine, were applied on octopus cells in the slices obtained from cochlear nuclei of 14-17 days old mice during Current Clamp recording. Resting membrane potential, input resistance and firing threshold values of cells were compared for both antagonists before and after the application. Recording periods ranged between 15 and 120 minutes. Cells were identified by considering their anatomical localizations, electrophysiological and intrinsic properties. The typical voltage response of octopus cells to the depolarizing current (Figure 2) and hyperpolarizing current (Figure 3) are provided in Figure 2 and Figure 3, respectively.

Effect of ERG Currents on Octopus Type Neurons

Effects on resting membrane potential

Effects of E-4031 and terfenadine were investigated on 6 and 10 cells respectively, in which stable intracellular recording was performed. The resting membrane potential under control conditions and after terfenadine application was measured as -61.84 mV±2.05 and -61.54 mV±1.90 (n=10), respectively in the cells on which terfenadine was applied ($p>0.05$). The resting membrane potential under control conditions and after E-4031 application was measured as -62.1 mV±1.34 and -61.7 mV±1.69 (n=6), respectively in the cells on which E-4031 was applied ($p>0.05$). There was no effect of E-4031 and terfenadine on resting membrane potential.

Effects on input resistance

Input resistance of the cells before and after terfenadine application were measured as 3.64 MΩ±0.25 and 6.38 MΩ±0.47 (n=8), respectively ($p<0.01$). Input resistance of the cells before and after E-4031 application were measured as 3.61 MΩ±0.56 and 5.24 MΩ±0.56 (n=8), respectively. The increase in input resistance as a result of blocking ERG currents with the two blockers was found to be statistically significant ($p<0.05$).

Effects on threshold value and excitability

The effect of E-4031 on threshold value and excitability was investigated in octopus type neurons. Experiments have shown that cells were stimulated by a current that was 180 pA lower in comparison to the control conditions in order to create action potential in 9 out of 14 cells ($p<0.05$) (Figure 4).

Voltage Clamping Studies

Figure 5 shows the recording samples obtained from cells perfused with the control solution in octopus type neurons in the Aa graph and in the presence of a solution that contains a pharmacological agent in the Ab graph. Ac graph, which shows ERG channel currents and currents blocked by E-4031, was obtained by subtracting Ab graph from Aa graph. Traces on the right side of the graph are large-scale presentations of tail currents in order to see and understand the currents better.

Current/voltage curves from the records obtained from octopus cells are provided in Figure 6. The steady state curve was used to generate the current/voltage curves. In the obtained tail current records, the activation curve of each cell was normalized in order to calculate the mean value and obtain a single curve. Then, it was fitted with the Boltzmann function in order to obtain the half-activation voltage value ($V_{0.5}$) of ERG channels and the slope factor (k) of the curve. After being fitted with the Boltzmann function, $V_{0.5}$ value was found to be -50.72±0.32 and the slope of the curve (k factor) was found to be 6.04±0.23 (n=3). Analysis of this curve revealed that ERG channel current activation took place at more depolarized values in comparison to -60 mV in octopus type neurons.

Voltage-dependent inactivation kinetics

Figure 7 shows the recording samples obtained from cells perfused with the control solution in octopus type neurons in the Aa graph and in the presence of a solution that contains a pharmacological agent in the Ab graph. Ac graph, which shows ERG channel currents and currents blocked by E-4031, was obtained by subtracting Ab graph from Aa graph. Traces on the right side of the graph are large-scale presentations of tail currents in order to see and understand the currents better.

Current/voltage curves created from the records obtained from octopus cells using the steady state curve are provided in Figure 8. In

Figure 2. Electrophysiological responses of the octopus cell to depolarizing current injections

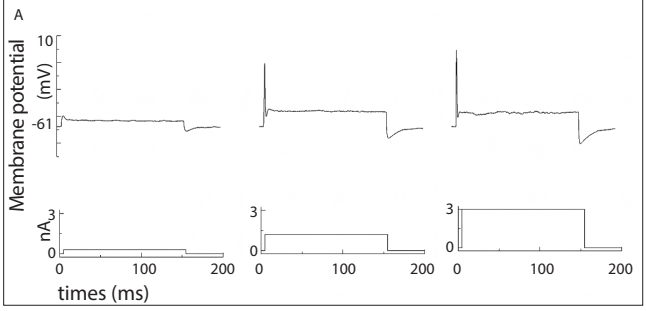


Figure 3. a, b. Electrophysiological responses of the octopus cell to hyperpolarizing current injections, (a) hyperpolarizing responses in the octopus cell, and (b) current/voltage curve of the octopus cell

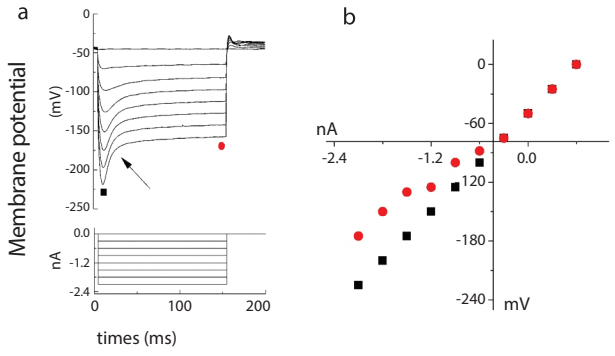
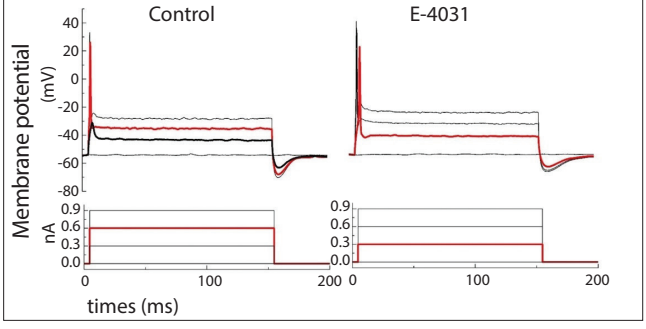


Figure 4. Effect of E-4031 on excitability in octopus cells. The cell created the first action potential with 0.6 nA under control conditions and with 0.3 nA in the presence of E-4031. Therefore, ERG channel antagonists decrease the threshold value



the obtained tail current records, the activation curve of each cell was normalized in order to calculate the mean value and obtain a single curve. Then, it was fitted with the Boltzmann function in order to obtain the half-inactivation voltage value ($V_{0.5}$) of ERG channels and the slope factor (k) of the curve. After being fitted with the Boltzmann function, $V_{0.5}$ value was found to be -74.34±0.46 and the slope of the curve (k factor) as 7.89± 0.32 (n=3).

Figure 5. Voltage-dependent activation records of octopus-type cells

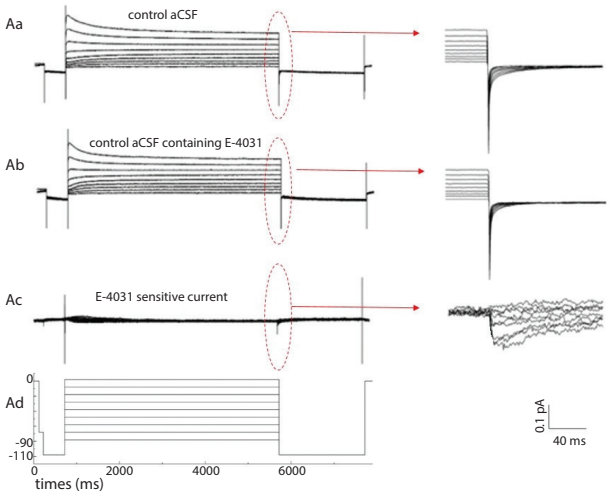
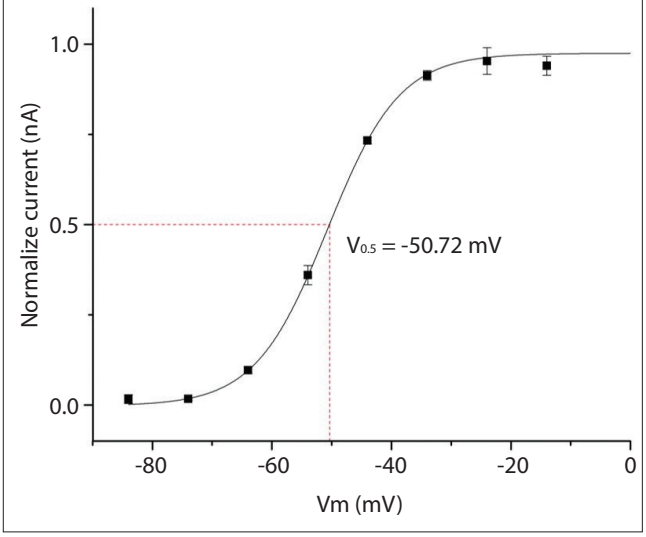


Figure 6. Steady state activation curve of octopus cells



Deactivation kinetics of octopus type cells were determined using the same protocol. The time constant was measured to be 17 ms at a membrane potential of -120 mV and 196 ms at a membrane potential of -80 mV. Accordingly, it was found that the deactivation speed was increased as the resting potential moved towards negative values in octopus cells (Figure 9).

DISCUSSION

It was found that both terfenadine and E-4031 as ERG channel blockers increased input resistance as compared to the control conditions in octopus cells. This means that some ion channels are blocked by these specific blockers. The input resistance of a neuron is associated with the amount of open ion channels on the membrane. Neurons with low input resistance have high conductance and this indicates that there are many open ion

Figure 7. Voltage-dependent inactivation records of octopus-type cells

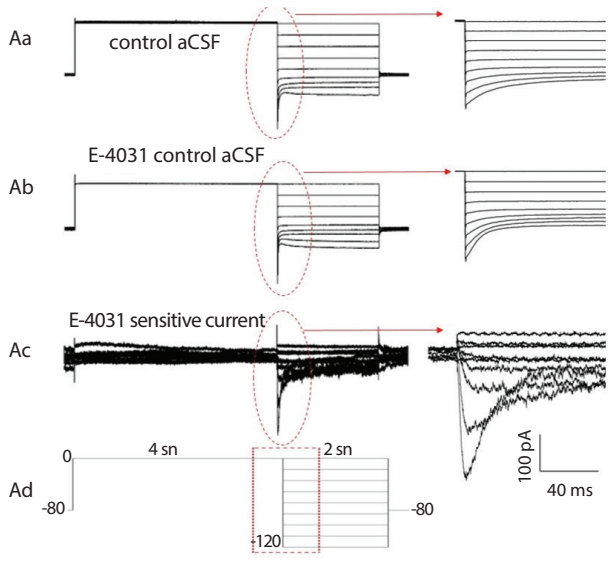
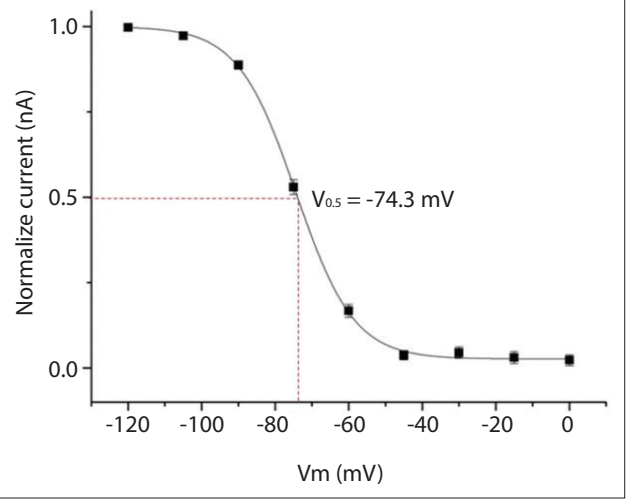


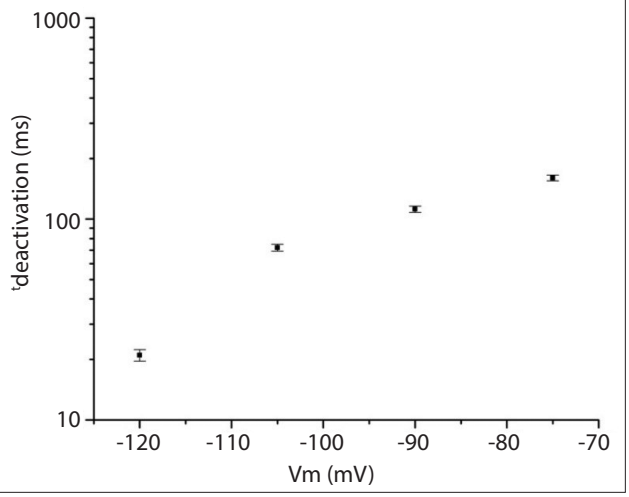
Figure 8. Steady state inactivation curve of octopus cells



channels in the membrane. On the other hand, neurons with high input resistance have low conductance and this indicates that many ion channels in the membrane are blocked. It was also shown in previous studies that both terfenadine and E-4031 specifically blocked ERG channels strongly and selectively (9).

It was found that the resting membrane potential exhibited a slight depolarization as a result of the specific blocking of ERG channels by both terfenadine and E-4031. The amount of this depolarization is approximately 0.20 mV in octopus type neurons. However, this depolarizing effect was not at a statistically significant level. In studies by Pessia et al. (10) on medial vestibular nucleus neurons, by Hardman and Forsythe (9) on medial nucleus neurons of the trapezoid body, and by Sacco et al. (11) and Niculescu et al. (12) on cerebellar purkinje neurons, it was reported that cells were depolarized in a mean value interval of approximately 0.30-2.50 mV with the inhibition of ERG channels by specific blockers but this effect was not statistically significant. In this respect, our study is similar to the aforementioned studies.

Figure 9. Deactivation kinetics of octopus cells



The current passing through ERG channels, known as inward rectifiers, in Voltage Clamping studies is directly related to the extracellular K^+ ion concentration. Therefore, the K^+ ion concentration in aCSF was raised to 40 mM in order to increase ERG channel currents and to better analyze voltage-dependent activation and inactivation kinetics. It was reported that the amplitude of ERG tail currents were increased by doing so(13). This is because the equilibrium potential, according to the Nernst equation, was calculated to be -83.4 mV for the potassium ion when K^+ concentration in aCSF ($[K^+]_o$) was 4.2 mM, whereas the same was calculated to be -25.4 mV when K^+ ion concentration was increased to 40 mM. Accordingly, the amplitude of the ERG tail current will be increased as the concentration gradient for the ERG current that enters the cell from ERG channels will increase at voltages close to the resting membrane potential (9, 11, 12).

Activation kinetics of ERG channels

As a result of the Voltage Clamping studies, it was observed that the activation threshold value of ERG channels was close to the resting membrane potential. Analyzing the steady state activation curves, it was found that the activation ratio of ERG channels was nearly 32% at the resting membrane potential (-61.1 mV) of octopus-type neurons. In other words, it was found that ERG channels were activated at higher rates at more positive values in comparison to the resting membrane potential. However, it was understood that this activation took place following a depolarization wave. This depolarization can take place physiologically under *in vivo* conditions in EPSP states as well as during action potentials that can develop spontaneously.

According to the steady state activation curve, $V_{0.5}$ was -50.7 and k factor was 6.0 in octopus type neurons. This indicates that the channels have completed their activation at 50% around -50 mV. Niculescu et al. (12) conducted studies on cerebellar purkinje

cells and reported that they measured the activation value of ERG channels at levels around $V_{0.5=}$ -44,1 mV. Hardman and Forsythe (9) conducted studies on the neurons in medial nucleus of the trapezoid body (MNTB) and reported $V_{0.5}$ values of -58 and -56 mV in postnatal 12 and 25 day old mice, respectively in analyses of voltage-dependent activation kinetics. Although age-dependent $V_{0.5}$ values were similar, the most striking difference was reported in the slope values of the curve. The k factor of the curve was 3.28 in 12 day-old mice, whereas the same increased to 8.61 in 25 day-old mice. In a study by Sacco et al. (11) it was reported that $V_{0.5}$ value was around -50,7 mV in purkinje cells. It was found that ERG channel activation values in cochlear nucleus neurons were similar to the activation values in cerebellar purkinje cells and MNTB neurons.

It should be emphasized that the data from cochlear nucleus was obtained using aCSF that does not contain Ca as in the studies conducted by Sacco et al. (11) and Niculescu et al. (12) On the other hand, Hardman and Forsythe (9) used 0.5 mM calcium chloride in their study. The k factor, i.e. the slope of the activation curve, found in the study conducted by Hardman and Forsythe (9) was much lower than the k factor values obtained in this study and other studies mentioned above. This might stem from the calcium contained in aCSF.

Inactivation kinetics of ERG channels

Analyzing the steady state inactivation curves, it was found that 34% of the tail current of ERG channels was free from inactivation (recovery state) at the resting membrane potential of octopus-type neurons (-61.1 mV). According to the voltage-dependent steady state inactivation curve of the cells, $V_{0.5}$ was -78.34 and k factor was 7.89.

Sacco et al. (11) found a $V_{0.5}$ value of -70 mV in their study on purkinje cells, whereas Shoeb et al. (14) found more depolarized values (-36 mV), and Smith et al. (15) found higher negative values (-102 mV and -90 mV, respectively) in heterologous expression studies. Hardman and Forsythe (9) conducted studies on MNTB neurons and reported $V_{0.5}$ values of -76.17 and -70.77 mV in postnatal 12 and 25 day old mice, respectively in analyses of voltage-dependent inactivation kinetics. In all studies, the slope of the inactivation curves, k ranged between 10-20 mV. For instance, Hardman and Forsythe (9) found k=17 mV in MNTB neurons. This value was lower in our study (9-10 mV). This could possibly stem from the fact that aCSF did not contain calcium in our study.

Deactivation kinetics of ERG channels

Deactivation kinetics were obtained from tail currents and measured to be 17 ms at -120 mV and 217 ms at -60 mV for octopus-type neurons. Accordingly, it was found that deactivation kinetics was faster as the membrane potential of the cells moved towards negative values. In this case, the tail current will be rapidly reset to zero, as opposed to the negativity of the cell membrane potential. Thus, the contribution to the action potential repolarization phase will be more limited. The time constants of the cell tail currents were most suitably fitted with the single exponential function at potentials between -60 and 100 mV, whereas they were fitted with a double exponential at potentials between -100 and 120 mV. In comparison to the study by Ohya et al. (16) it is apparent that deactivation time constants obtained in our study were faster (lower). This indicates that ERG channels are mostly constituted by the ERG-3 subtype, because it has been reported that the deactivation kinetics of the ERG-3 subtype was the fastest (lowest) among ERG channel subtypes (16).

CONCLUSION

Consequently, although the physiological roles of ERG channels have been defined in studies conducted on the heart and other excitable cells, it is thought that the density of these currents are considerably lower in comparison to cochlear nucleus neurons and these currents have a minimal effect on the levels of the resting membrane potential. In the light of all this information, even though it is possible to say that ERG channels were electrophysiologically detected in cochlear nucleus neurons, immunohistochemical studies and PCR studies should also be conducted to show the existence of these channels both at the protein and gene levels. In addition, advanced imaging techniques (confocal imaging) should be used as a support to reveal the spatial localizations of the channel in each cell type (somatic?, axonic? or dendritic?), the expression levels of ERG subtype channels (ERG1, ERG2, ERG3) and how much these channels contribute to total ERG currents.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University (protocol no: 06.01.2016 / 03).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - C.Y.; Design - C.Y., R.B.; Supervision - R.B.; Data Collection and/or Processing - C.Y., R.B.; Analysis and/or Interpretation - R.B., C.Y.; Literature Search - R.B., C.Y.; Writing Manuscript - C.Y.; Critical Review - R.B., C.Y.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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Case Report

Treatment of High-Output Thoracic Chylous Fistula with Transabdominal Embolization of Cisterna Chyli: A Case Report and Review of the Literature

Osman Nuri Dilek[1], Oğuzhan Özşay[1], Ömür Ballı[2], Selda Gücek Hacıyanlı[1], Volkan Çakır[2], Emine Özlem Gür[1], Mehmet Hacıyanlı[1]

[1]Clinic of Surgery, İzmir Katip Çelebi University, Atatürk Training and Research Hospital, İzmir, Turkey

[2]Clinic of Radiology, İzmir Katip Çelebi University, Atatürk Training and Research Hospital, İzmir, Turkey

ABSTRACT

Postoperative thoracic chylous fistula is an infrequent complication after esophageal surgery. It represents a difficult management problem due to the serious mechanical, nutritional, and immunological consequences of the constant loss of protein and lymphocytes. A 55-year-old woman sequentially developed a high-output (2500 mL/day) thoracic chylous fistula and right-sided chylothorax, after a transhiatal total esophagectomy for adenocarcinoma of the distal esophagus. In this study, we discuss the case and treatment modalities in view of the literature. Multimodal procedures including low-triglyceride diet, sclerosing agents, repeated thoracentesis, and closed thoracostomy tube drainage were applied for treatment within two months after surgery. Finally, embolization of the cisterna chyli with liquid embolic agents produced rapid clinical and radiographic improvement. The procedure of opacification, catheterization, and embolization of the cisterna chyli was successful. Percutaneous transabdominal duct embolization is a safe, effective, and minimally invasive option to treat chylous fistula.

Keywords: Chyle fistula, embolization, esophagus, lymphangiography, surgery

INTRODUCTION

Chylous fistula is an uncommon form of ascites. It is defined as the leakage of the lipid-rich lymph into the peritoneal cavity. Damage or obstruction to the lymphatic system or one of its tributaries produces ascites with an opaque or milky appearance from the high-triglyceride content (1). Although the incidence of chyle fistula post surgery is low (1%-4%), this complication can present significant challenges including fluid and electrolyte abnormalities, malnutrition, and overwhelming infections, including peritonitis and empyema (2, 3).

Here in, we described and discussed a successful case of image-guided percutaneous embolization of cisterna chyli as a treatment modality for chylous fistula after failed conservative treatment modalities in an adult.

CASE PRESENTATION

A 55-year-old woman sequentially developed a high-output thoracic chylous fistula after a transhiatal total esophagectomy for adenocarcinoma of the distal esophagus. The mean daily drainage was 800 mL/day (range: 250-2500 mL/day). The mean concentration of triglycerides of 135 mg/dL in drainage fluid was accepted as chylous fistula. First right-sided and then left-sided chylothorax (bilateral) developed that lasted two and one month, respectively (Figures 1, 2). Multimodal procedures including low-triglyceride diet, sclerosing agents, repeated thoracentesis, and repeated closed thoracostomy tube drainage (bilateral) were applied for treatment within two months after surgery.

The cisterna chyli and lymph nodes were successfully embolized in the first intervention, but there was continuation of the chylothoraxes through development of collateral lymphatic ducts seen leaking into both hemithorax. Then, our radiology team tried second image-guided percutaneous cannulation and embolization of cisterna chyli (Figures 3, 4). Finally, embolization of the cisterna chyli with liquid embolic agents (Lipiodol Ultra-Fluide; Guerbet, France) produced rapid clinical and radiographic improvement (Figure 5). The patients remained recurrence-free for 24 months. As a formal procedure, the patient signed the informed consent form before treatment, interventive procedures, and publication.

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ORCID IDs of the authors: O.N.D. 0000-0002-6313-3818; O.Ö. 0000-0001-6291-2652; Ö.B. 0000-0001-6593-649X; S.G.H. 0000-0002-5956-8421; V.Ç. 0000-0003-4032-3288; E.Ö.G. 0000-0003-2749-2220; M.H. 0000-0002-0512-1405.

Corresponding Author: Osman Nuri Dilek **E-mail:** osmannuridilek@gmail.com

Received: 20.12.2017 • **Accepted:** 19.02.2018

Figure 1. Chest X-ray; first left-sided chylothorax developed

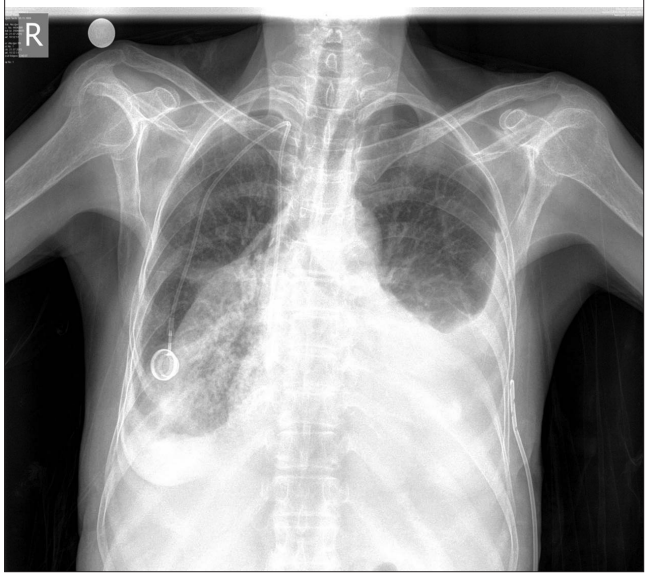
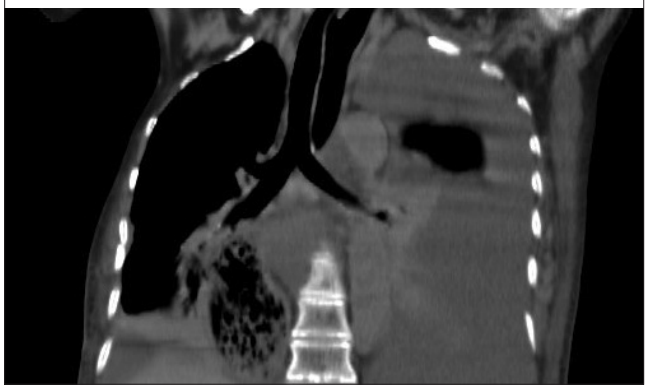


Figure 2. CT thorax demonstrating bilateral chylothorax
CT: computed tomography



DISCUSSION

Damaged lymphatics most often heal spontaneously or direct lymph centrally via rich interconnected lymphatic collaterals, without any significant morbidity (1). High-output thoracic chyle fistula is a rare but potentially devastating and morbid condition.

Conservative approaches including fasting, dietary modification with low fat medium, thoracentesis, tube drainage, and octreotide administration are generally used as first treatment. It is well known that fasting and the administration of low fat medium chain triglycerides by mouth resolves approximately 50% of traumatic chylous fistulas (1, 2). The healing rate of nonoperative treatment modalities enormously varies; the maximum success rate in series is 70% (3).

In cases refractory to treatment, malnutrition, infection, immunologic complications, and high mortality rate of up to 50% have been reported. Several authors recommend interventional or surgical approaches (thoracic duct ligation, pleurodesis, and pleuroperitoneal shunt) in such cases (3, 4).

Figure 3. Fluoroscopic image shows 25 G needle in the inguinal lymph node (arrowheads) and opacification of the lymphatic vessels (arrows)

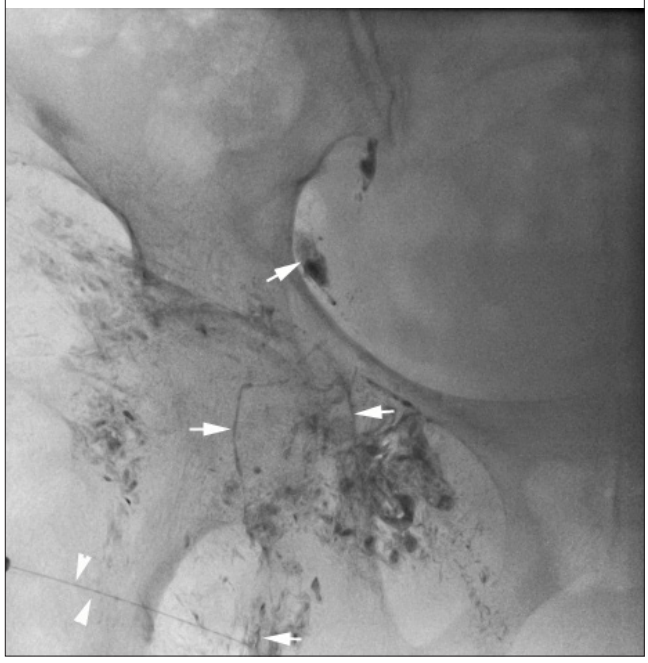
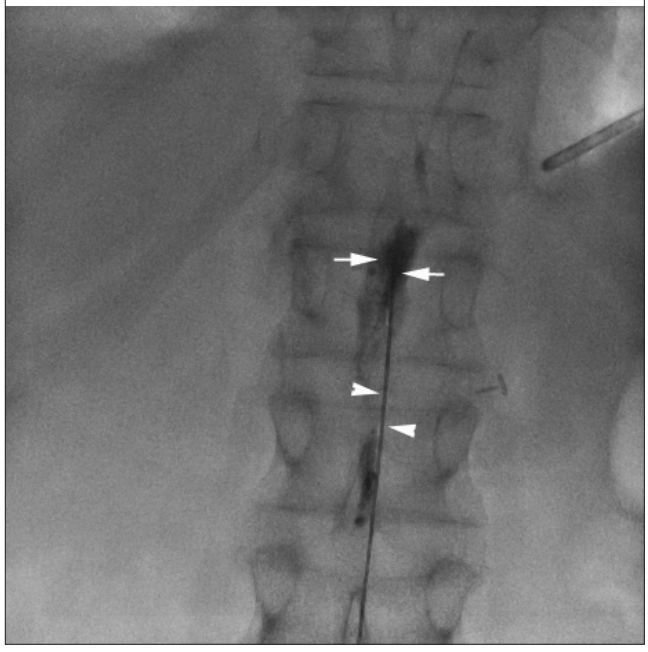
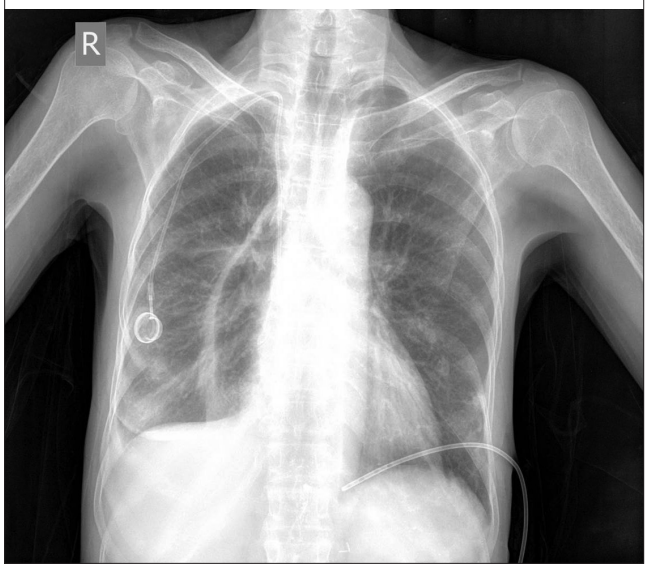


Figure 4. Fluoroscopic image shows 22 G needle (arrowheads) in the opacified cisterna chyli (arrows)



Pleurodesis, defined as promotion of adhesions between pleura and lung, may be a good option for the treatment of chylous fistula. It is reported that pleurodesis may be successful in 73%-

Figure 5. Chest X-ray; last condition



83% of cases with chylous fistula (3, 4). Also, there are many reports on intrapleural instillation of octreotide, concentrated glucose solution, tetracycline, streptokinase, or fibrin glue therapy (5-7). Huang (7) recommended pleurodesis using via continuous intrapleural irrigation with minocycline instead of conventional intermittent pleurodesis. There are new reports related with using orlistat and etilefrine for medical treatment (6). Picibanil (OK-432) is a lyophilized mixture of *Streptococcus pyogenes* with antineoplastic activity. It has capacity to produce a selective fibrosis of lymphoid tissue (7). Shimizu et al. (4) reported that OK-432 injection of into the thoracic cavity is effective and safe in the management of postoperative chylous fistula, and they revealed a success rate of 87%.

Sziklavari et al. (5) reported that the combination of radiotherapy and dietary restriction in the treatment of postoperative thoracic chylous fistula is more rapid response, safe, and successful. They recommend that radiotherapy should be indicated if the daily chylous drainage exceeds 450 mL after cessation of oral food intake. The major restriction to using radiation therapy for thoracic chylous fistula is the probability of acute and long-term side effects.

Cope reported that two-thirds of the patients with life-threatening thoracic chylous fistula can be safely treated with percutaneous transabdominal embolization of the thoracic duct (8). Matsumoto et al. (9) reported that lymphangiography is effective not only for differential diagnosis but also for treatment of chylous leakages. Schoellnast et al. (10) reported that the needle interruption of the cisterna chyli with subsequent resolution of the chylous fistula is successful in 50% of cases. In our case, our radiology team performed twice image-guided percutaneous cannulation and embolization of cisterna chyli. On the second attempt, embolization of the cisterna chyli with liquid embolic agents (Lipiodol Ultra-Fluide, France) was successfully performed, and it then produced rapid clinical and radiographic improvement.

Radical dissections increase the incidence of chylous fistulas more than in functional dissections and leads to prolonged hospital stay. It is reported that chylous fistula during the initial operation can be prevented by performing protective dissection and ligating lymphatic vessels, particularly in the posterior mediastinum. Surgical treatment of chylous fistula usually involves ligation of the thoracic duct. Repeated surgical procedures because of complications with postoperative chylous fistula have to be underwent up to 11% of the patients, and 9% experienced recurrence of their chylous fistula (2). Furthermore, surgical treatment also includes pleurodesis and decortication, resection and overlapping of leaking lymphatics, microsurgical or surgical repair of chylous fistula, video-assisted thoracoscopic surgery, closing with locoregional flaps, thoracotomy, pleura-venous or pleura-peritoneal shunts, and pericardial "window" (2). Shimizu et al. (4) found that surgical procedures give better results than conservative treatment modalities when the daily chyle flow exceeds 500 mL/day in adults. Zabeck et al. (2) reported that repeat surgery should be performed as soon as possible in postoperative chylous fistula with a high flow of >900 mL/day, because conservative treatment does not lead to an improved chyle flow. The success rate of the ligation of thoracic duct was reported to be 70%-90% in the largest clinical series (1, 10).

CONCLUSION

Currently, the morbidity and mortality associated with chylous fistula have been better with more energetic management strategies. In cases refractory to conservative treatment, transabdominal embolization may be a good treatment option. It is not only a possible first-line treatment in selected cases but also a primary diagnostic and therapeutic procedure in patients with massive chylous fistula.

Informed Consent: Written consent was obtained from the patient to reproduce information and photographs appearing in this case.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - O.N.D., V.Ç.; Design - O.N.D.; Supervision - M.H.; Resources - S.G.H., E.Ö.G., Ö.B.; Materials - O.Ö.; Data Collection and/or Processing - O.N.D., O.Ö.; Analysis and/or Interpretation - O.N.D., M.H.; Literature Search - O.N.D.; Writing Manuscript - E.Ö.G., O.N.D.; Critical Review - M.H., Ö.B.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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Case Report

Radiological Findings of the Primary Female Urethral Malignant Melanoma: A Rare Case Report

Serkan Öner[1], Gülnur Erdem[2], Zeynep Maraş Özdemir[2], Ali Güneş[3], Serkan Ünlü[2]

[1]Department of Radiology, Karabük University School of Medicine, Karabük, Turkey

[2]Department of Radiology, İnönü University School of Medicine, Malatya, Turkey

[3]Department of Urology, İnönü University School of Medicine, Malatya, Turkey

ABSTRACT

Primary malignant melanomas of the female urethra are rare tumors with poor prognosis. Biopsy of the detected urethral mass was performed in a 71-year-old woman who presented with hematuria and voiding dysfunction. No other localized lesions were detected. The patient was diagnosed with primary malignant melanoma of the urethra according to the histopathologic and immunohistochemical findings. Immunohistochemical staining revealed that the tumor cells were immunoreactive for vimentin, HMB-45, S-100, and Melan-A. The present study aimed to present radiological findings of very rare primary urethral malign melanoma with histopathologic correlation and to review the relevant literature.

Keywords: Female urethra, radiological findings, urethral malignant melanoma

INTRODUCTION

Primary urethral malignant melanoma (MM) is an extremely rare tumor, accounting for 0.2% of all MMs and 4% of urethral cancers (1). Urethral MM is most common in the distal urethra and approximately 20% of them are located at the proximal urethra (2). The incidence of MM is three folds more common in women than that in men, which is similar to the incidence of other malignant urethral tumors such as urothelial carcinomas. Despite the fact that most MMs are diagnosed after 50 years of age, some cases of MMs have been reported in younger patients (3, 4). The symptoms of urethral MM include palpable mass, hematuria, dysuria, vaginal bleeding, incontinence, and pain (5). The clinical presentation of urethral MM is similar to that of urothelial carcinoma; however, the diagnosis of urethral MM is often delayed, and MM has poor prognosis than urethral carcinoma (4). Several studies, including case reports and literature review, have described the clinical and histopathologic features of urethral MM (2-6). However, knowledge about the radiological findings of this tumor is limited.

The aim of this case report was to present ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) findings of very rare primary urethral MM with histopathologic correlation and to review literature.

CASE PRESENTATION

A 71-year-old woman presented at our hospital with hematuria and voiding dysfunction since 3 months. Family history, smoking, and various occupational exposures were negative, with no comorbidities. After routine physical examination, cystourethroscopy was performed with the pre-diagnosis of urethral caruncle. Biopsy of polypoid, brownish mass involving the proximal urethra was obtained, and histopathological diagnosis reported MM. Immunohistochemical staining revealed that the tumor cells were immunoreactive for vimentin, HMB-45, S-100, and Melan-A. Pancytokeratin, LCA, CK7, CK20, and uroplakin were negative. In histochemical studies, hemosiderin and occasionally melanin-pigmented staining in Prussian blue and Masson-Fontana was observed at different foci (Figures 1, 2).

A well-circumscribed mass with heterogeneous echogenicity due to its cystic and solid components was viewed adjacent to the inferior base of the bladder on ultrasound examination. Color Doppler ultrasound has revealed that the mass had predominantly peripheral vascularization (Figure 3).

A heterogeneous hypodense mass with cystic-necrotic components located on the proximal urethra with dimensions of

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ORCID IDs of the authors: S.Ö. 0000–0002–7802–880X; G.E. 0000–0003–2200–8620; Z.M.Ö. 0000–0003–1085–8978; A.G. 0000–0002–2343–6056; S.Ü. 0000–0001–7535–0812

Corresponding Author: Serkan Öner **E–mail:** serkanoner@karabuk.edu.tr

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Figure 1. The presence of melanin pigment on histochemical staining with Masson–Fontana (×200)

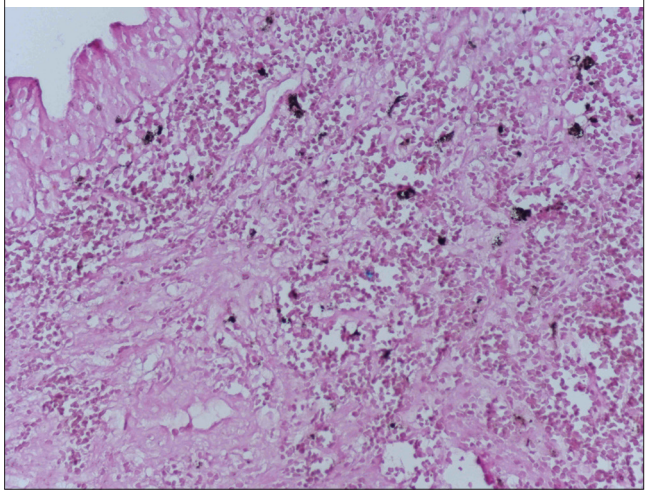


Figure 2. Strong staining of the tumor on immunohistochemical staining with HMB-45 (×200)

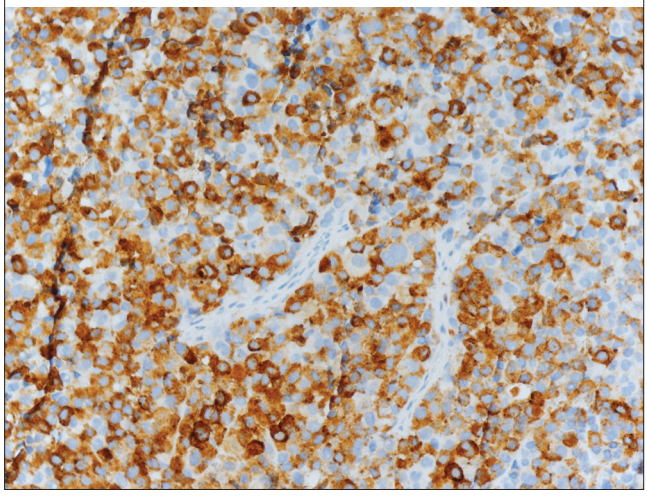


Figure 3. Color Doppler US view of the urethral mass located at the postero-inferior of bladder

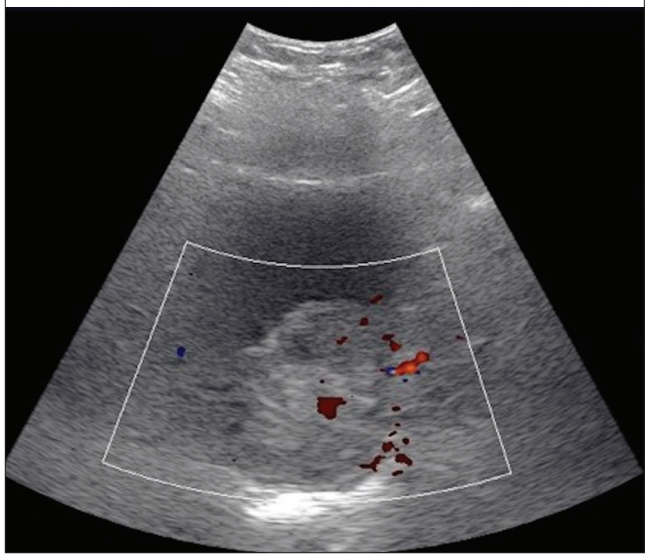
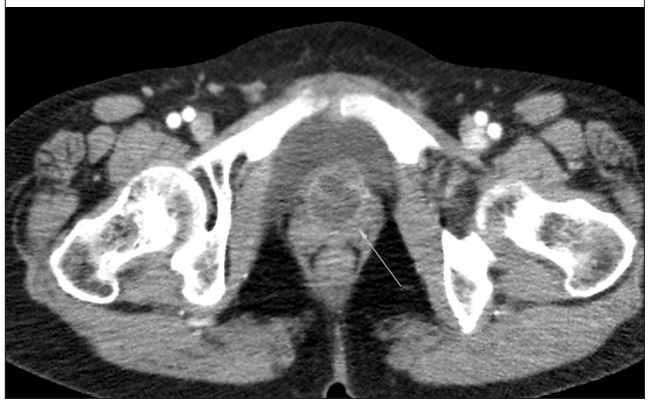


Figure 4. Axial contrast enhancement CT revealed mainly peripheral enhancing mass with cystic-necrotic components between the bladder and cervix uteri



3.3×3.5×5.3 cm (anteroposterior×transverse×craniocaudal) was detected on contrast-enhanced CT images. The mass was indenting towards the base of the bladder. The surrounding fat planes of mass were obliterated. The mass revealed peripheral-weighted contrast enhancement (Figure 4).

Forming indentation at the base of the bladder, with dimensions of 4.2×4.7×5.7 cm (anteroposterior×transverse×craniocaudal), T2W hypointense with a thin capsule, septated multiloculated mainly cystic, well-defined mass was observed on contrast-enhanced abdominopelvic MRI. A 2-cm solid component in the antero-inferior part of the lesion was detected (Figures 5, 6). Solid parts of the mass revealed contrast enhancement and diffusion restriction on DWI (Figures 7, 8).

Thorax and abdominal CT were performed for screening metastasis. No metastasis or pathological lymph nodes were detected elsewhere. We decided to perform surgery for total resection of mass before chemotherapy and immunotherapy.

DISCUSSION

Urethral MMs are frequently polypoid mass and may be clinically confused with urethral polyps, caruncle, mucosal prolapse, chancre, or other common malignant tumors (6). Metastatic melanoma formation is more common than primary MM. Thus it should be determined whether there is any other lesion before primary MM is diagnosed (3, 7). In this case report, although urethral caruncle was considered as a preliminary diagnosis, radiologic examinations revealed that the tumor had malignant features. Radiological findings, especially MRI findings, are important in the diagnosis of urethral MM. The heterogeneous cystic structure of tumors, diffusion restriction in solid parts, and hypointense thin capsules in T2W images may provide differentiation of urethral MM from urethral carcinomas.

Figure 5. Coronal T2W fat-suppressed image revealed a septated, multiloculated, mainly cystic, well-defined mass forming indentation at the base of the bladder

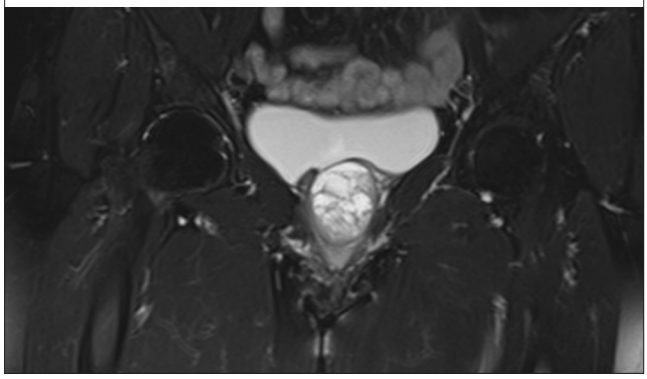


Figure 6. Sagittal T2W image revealed proximal urethral mass anterior to the cervix–vagina with solid component (*)

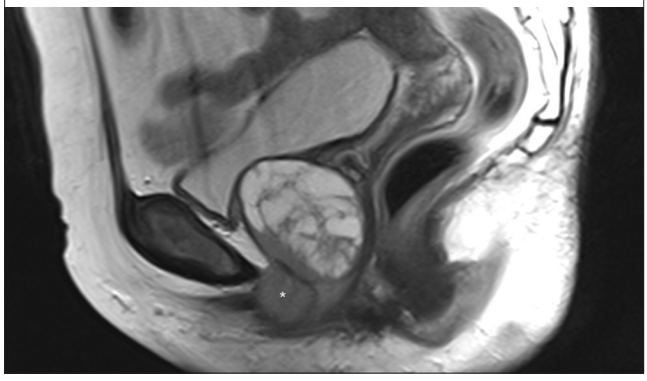


Figure 7. Postcontrast sagittal fat-suppressed T1W image revealed septal and peripheral enhancing heterogeneous mass and 2-cm sized enhancing solid component in the antero-inferior part of the mass (*)

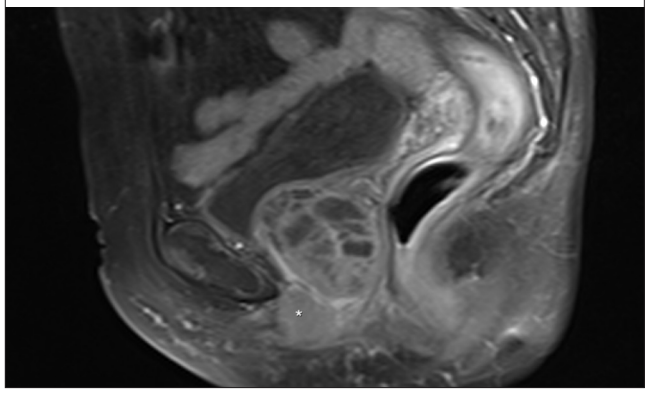
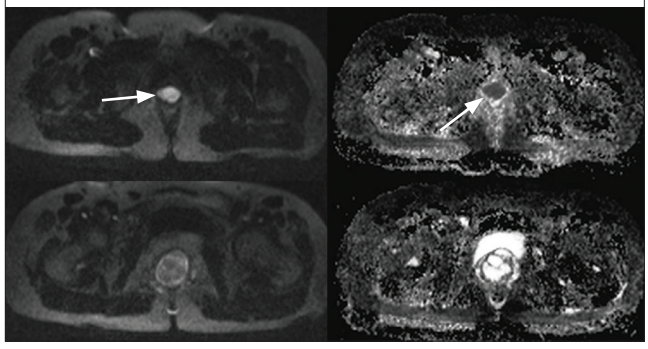


Figure 8. Diffusion and ADC images revealed diffusion restriction of the solid parts



This diagnosis was supported by immunohistochemical staining with a specific marker for melanoma (S-100, HMB-45, and Melan-A) (8). Therefore, these stains were used for immunohistochemical examination in our study, and positive results were obtained.

The urethral MM has a worse prognosis than that of cutaneous melanoma possibly because of the vertical growth phase of the tumor, lymph node metastasis at the time of initial diagnosis, and diagnostic delay (9).

Considering that the number of cases of urethral MM is limited, no clinical studies on the subject, and recommendations for treatment are based on small case series. Although experiences in treatment are reportedly limited, radical surgery is recommended after chemotherapy and immunotherapy (7).

Several articles have been published, mainly including case reports and literature reviews, describing the clinical and histopathologic features of urethral MM (5-9). However, knowledge regarding the radiological findings of this tumor is limited. These tumors may be easily misdiagnosed with clinical findings.

CONCLUSION

Consideration of this tumor in the differential diagnosis in patients with urethral mass provides correct diagnosis without progress in disease. The radiological features of urethral MM such as heterogeneous view, T2W hypointensity and diffusion restriction on DWI can contribute to the differential diagnosis.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.Ö.; Design - S.Ö., S.Ü.; Data Collection and/or Processing - Z.M.Ö., A.G.; Literature Search - G.E.; Writing Manuscript - S.Ö., G.E.; Critical Review - A.G., S.Ü.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Case Report

Diagnosis and Treatment of Bronchocentric Granulomatosis: A Rare Case Report

Mustafa Kuzucuoğlu[1], Yeşim Alpay[2], Figen Aslan[3], Derya Aydın[4]

[1]Department of Thoracic Surgery, Balıkesir University School of Medicine, Balıkesir, Turkey

[2]Department of Infectious Diseases, Balıkesir University School of Medicine, Balıkesir, Turkey

[3]Department of Pathology, Balıkesir University School of Medicine, Balıkesir, Turkey

[4]Clinic of Chest Diseases, Balıkesir Atatürk City Hospital, Balıkesir, Turkey

ABSTRACT

Bronchocentric granulomatosis is a necrotizing granulomatous lesion of the bronchi and bronchioles and a rare disease, which is not associated with any clinical or radiological findings. It usually affects adults and is often incidentally diagnosed on chest X-ray. The diagnosis is confirmed by histopathological evaluations of the lung biopsy specimens. The present study reports the case of a 58-year-old male patient with pulmonary nodules observed on chest X-ray performed as part of general screening. Thoracic computed tomography confirmed the presence of multiple nodular lesions. Both invasive and non-invasive methods failed to remove the masses, and an open lung biopsy was performed. The histopathological diagnosis reported bronchocentric granulomatosis. This case has been presented to highlight the importance of multidisciplinary management of all conditions, which helps in the accurate detection of rare diseases, such as bronchocentric granulomatosis.

Keywords: Aspergillosis, granuloma, necrotizing, resection

INTRODUCTION

Bronchocentric granulomatosis (BG), which was first described by Liebow in 1973 (1), is a destructive granulomatous lesion, which forms in response to airway damage to the bronchi and bronchioles. It is a rare condition that is not associated with any specific clinical or radiological findings, and its diagnosis can be only confirmed histopathologically. Some general clinical manifestations include fever, cough, wheezing, and respiratory insufficiency. Laboratory findings primarily include eosinophilia. In radiological imaging, non-specific signs, such as nodular lesions, consolidations, and atelectasis can be observed (2, 3).

Katzenstein et al. (4) classified BG cases into two groups: those with asthma-like symptoms and those without asthmatic symptoms. Approximately half of the cases are associated with asthmatic findings and bronchopulmonary aspergillosis. These cases are usually observed in young men who present with clinical signs of fever, cough, and respiratory failure. Patients without asthmatic symptoms are usually older and present with non-specific findings, such as fatigue (2).

Herein, we report a case of BG in a 58-year-old male patient and its treatment in the light of the previously recorded scientific literature.

CASE PRESENTATION

A 58-year-old male patient underwent a screening X-ray of the chest and presented with nodular lesions that were incidentally discovered on the radiographic images (Figure 1). He complained about exertional dyspnea and intermittent chest pain. His medical history revealed a 40-pack-per-year smoking history without previous tuberculosis. Complete blood count and biochemical analysis results were normal. Thoracic computed tomography (CT) revealed bilateral, peripheral, mostly calcified, nodular lesions with smooth margins, the largest being 1.5 cm (Figure 2). Pulmonary function test results supported the diagnosis of asthma. Bronchoscopy revealed no endobronchial lesions. Acid-resistant bacilli were not detected in the bronchoalveolar lavage fluid, and the cytology was evaluated as benign. Positron emission tomography (PET/CT), which was performed to rule out secondary malignancies, did not reveal a metastatic disease in any part of the body.

Wedge resection was performed with mini-thoracotomy for diagnostic purposes. Pathological examination of the lung mass revealed necrotic granulomas separated by distinctive fibrous tissues. Positive-stained fungal hyphae on periodic acid-schiff (PAS) staining were observed in the field of necrosis. Mucus, neu-

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ORCID IDs of the authors: M.K. 0000–0001–9889–0061; Y.A. 0000–0003–2298–7531; F.A. 0000–0002–4817–1904; D.A. 0000–0003–1534–8280.

Corresponding Author: Mustafa Kuzucuoğlu **E–mail:** mustafakuzucuoglu@hotmail.com

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trophils, eosinophils, and lymphoplasmacytic cells infiltrating the bronchiolar wall were detected in the lumen (Figure 3). The reproduction of *Aspergillus niger* was detected in the sputum culture. As a result of these definitive findings, the patient was diagnosed with BG.

The treatment of the disease was initiated by administering oral itraconazole with inhaled corticosteroids and bronchodilators. However, the patient was unable to tolerate oral itraconazole and was switched to intravenous (IV) amphotericin B (50 mg daily). After 14 days of therapy, oral itraconazole was re-initiated but could not be used effectively because the patient was non-compliant with the treatment. Subsequently, IV caspofungin was initiated (50 mg daily) because the patient was clinically and radiologically unresponsive and his blood urea and creatinine levels had increased during the amphotericin B treatment. Clinical recovery was achieved after the 14-day therapy, and the patient was discharged with the maintenance treatment of oral itraconazole. The patient did not exhibit any radiological response during the follow-up, and his clinical symptoms had markedly regressed.

Figure 1. Chest X-ray for screening

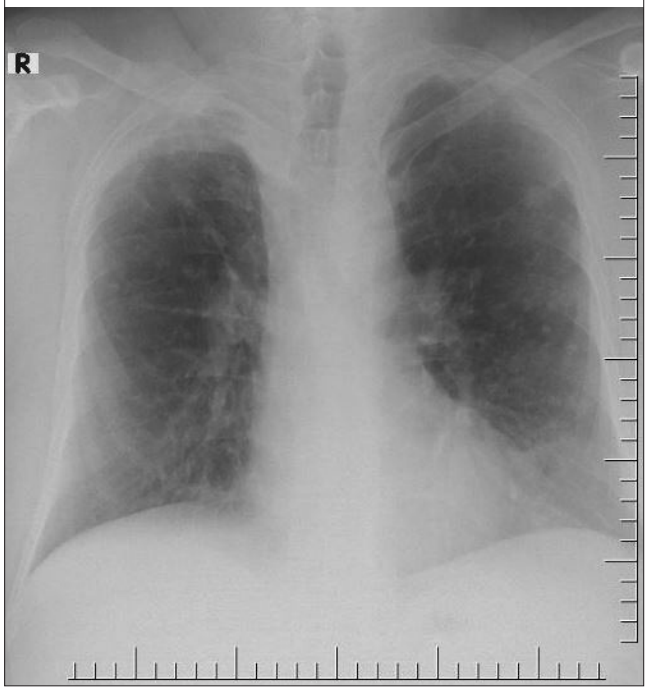
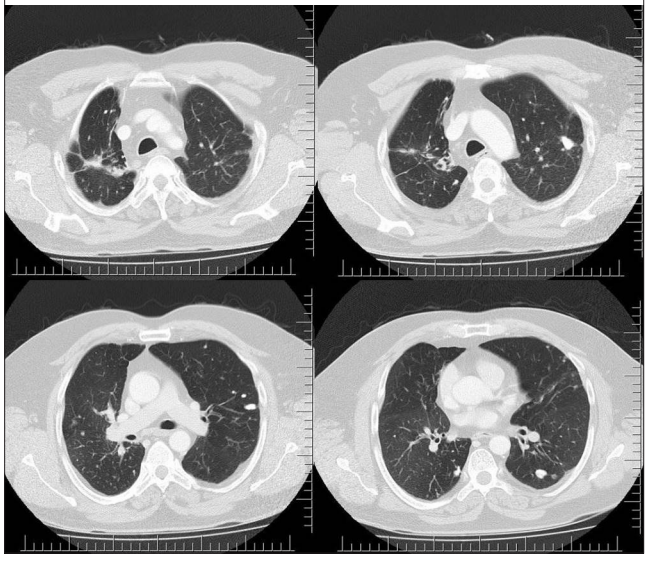


Figure 2. Bilateral, multiple pulmonary nodules on thoracic computed tomography



Written informed consent was obtained from the patient before the commencement of the procedure.

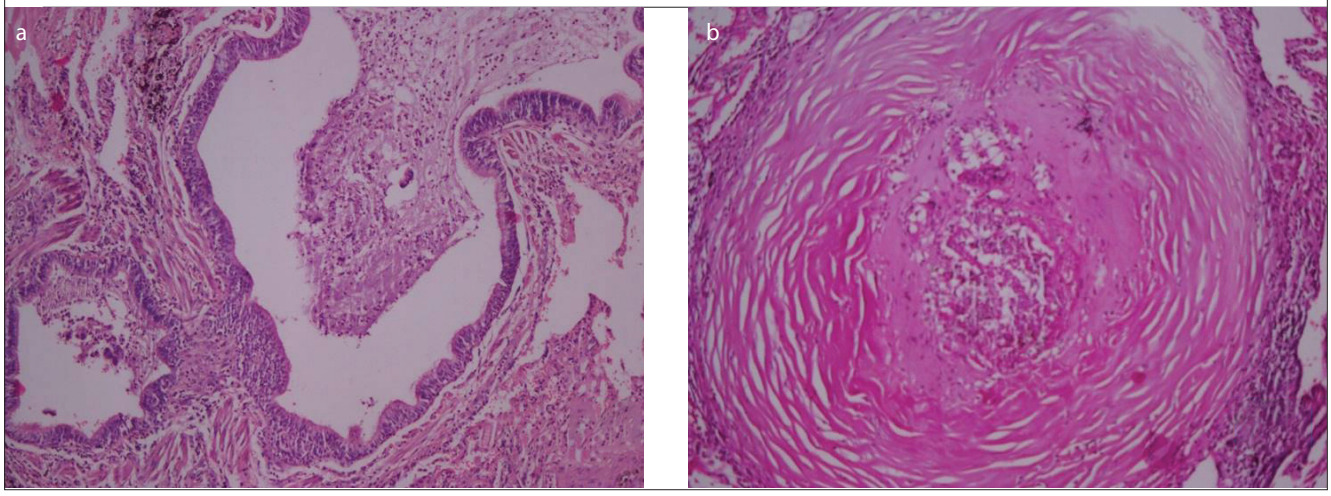
DISCUSSION

According to the BG classification system proposed by Katzenstein et al. (4), patients with asthmatic symptoms are often accompanied with bronchopulmonary aspergillosis; however, the underlying cause of non-asthmatic cases is often unknown. The non-asthmatic condition has been associated with chronic granulomatous diseases, glomerulonephritis, influenza virus, mycobacterial infections, and bronchogenic carcinoma. Patients with asthma-like symptoms are usually younger males aged 20-40 years, whereas those without asthmatic symptoms are relatively older (2, 5). In the present case, asthmatic symptoms such as cough, exertional dyspnea, and asthma were not detected, while the respiratory function test results were suggestive of asthma.

Radiological evaluations reveal no specific finding of BG; however, the findings are frequently observed unilaterally and located in the upper lobes. The disease usually presents with nodular lesions and may also manifest as atelectasis or pneumonic consolidation (2, 6). Thoracic CT of idiopathic BG were reported by Umezawa et al. (7) and Li et al. (3) in a 17-year-old male and a 43-year-old female patient, respectively. In these case reports, consolidation and segmental atelectasis were detected. However, in a report published by Kılıçgün et al. (2), multiple parenchymal nodules were observed at the forefront in the radiographs of both a 37-and 58-year-old male patients.

Seçik et al. (8) presented a case of a 40-year-old patient, in whom radiological examination revealed a 3-cm lesion in the right lung, although there were no significant clinical symptoms of the disease. The diagnosis of this patient was not confirmed by bronchoscopy or needle biopsy, instead BG was confirmed by wedge resection with thoracotomy. Because BG has no specific clinical, immunological, and radiological findings, the definite diagnosis can be made only by performing a histopathological examination of the biopsy specimens (9). Radiological imaging, biochemical and immunological tests, bronchoscopy, and sputum and bronchoalveolar lavage cultures have also been performed in previous studies in the literature; however, the final diagnosis was always established by histopathological examination of the open lung biopsy specimens (2, 3, 5, 7). In the previous studies, necrotizing granulomas and eosinophilia in the bronchial wall were detected histopathologically, and fungal elements were detected in some of them. In our case, we performed wedge resection with mini-thoracotomy, and the presence of necrotic

Figure 3. a, b. Histopathologic examination (Hematoxylin and eosin staining, 100×). (a) Lung biopsy specimen showing a small bronchus filled with mucinous material and inflammatory cells. (b) Respiratory epithelium is replaced by granulomatous inflammation and luminal debris containing fungal hyphal fragments



granulomas, eosinophilia, and fungal hyphae in the lumen observed in the histopathological examination confirmed the diagnosis of BG. The reproduction of *A. niger* was also detected in the sputum culture.

Although there is no established consensus for the treatment of BG, several studies have shown that corticosteroid therapy alone is sufficient to effectively treat this disease in non-asthmatic cases without fungal elements (3). However, antifungal therapy should be added to corticosteroids when fungal elements are detected in the histopathological evaluation or sputum culture (2, 3, 7). In the present case, we performed antifungal treatment combined with inhaled corticosteroid therapy because our patient was diagnosed with BG associated with aspergillosis. However, we were unable to obtain a radiological response, although the symptomatic response was achieved after treatment. There was no recurrence, progression, or additional pathology observed during follow-up.

CONCLUSION

Bronchocentric granulomatosis has no specific clinical, immunological, and radiological findings, and the definite diagnosis can be made only by performing a histopathological examination. Open lung biopsy should not be avoided in this disease because achieving the differential diagnosis is challenging, and it can be difficult to distinguish BG from many diseases radiologically. It is also crucial to diagnose the tissue and reveal the underlying cause to tailor the treatment effectively, particularly in symptomatic patients.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.K., Y.A., F.A., D.A.; Design - M.K., Y.A., F.A., D.A.; Supervision - M.K., Y.A., F.A., D.A.; Resources - M.K., Y.A., F.A., D.A.; Materials - M.K., F.A.; Data Collection and/or Processing - M.K., Y.A. Analysis and/or Interpretation - M.K., Y.A., F.A., D.A.; Literature Search - M.K., Y.A., F.A.; Writing Manuscript - M.K., Y.A., F.A.; Critical Review - M.K., Y.A., F.A.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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Letter to the Editor

Ranitidine, A Potential Option for *Helicobacter pylori* Eradication

Rinaldo Pellicano

Unit of Gastroenterology, Molinette–SGAS Hospital, Turin, Italy

Dear Editor,

I have read with great interest the study reported by Şahin and Yılmaz (1), which described the case of a 15-year-old male patient diagnosed with *Helicobacter pylori* (*H. pylori)* infection and allergy to both all proton pump inhibitors (PPIs) and famotidine. The bacterial infection was eradicated using a quadruple treatment comprising ranitidine, bismuth, metronidazole and tetracycline. This case provides us with an important message for clinical practice.Because a profound acid suppression is required to eradicate *H. pylori* infection, the Maastricht V/Florence Consensus Report recommends using a combination of a PPI and two or three antibiotics to eradicate *H. pylori* infection (2). Several studies demonstrated a remarkable reduction in the activity of the main antibiotics used against *H. pylori* after reducing the pH from 8 to 5. This is because concentration of these drugs in the mucosa, a key factor for *H. pylori* eradication, decreases concomitantly with pH reduction (3). As PPIs are membrane-permeable weak bases that accumulate in acid spaces of the active parietal cell, they share the same pharmacodynamics. Conventional PPIs are prodrugs that are activated by acids and covalently bind to their target, the H^+/K^+-ATPase (or proton pump) (4).

Histamine represents the most important stimulus of the gastric parietal cells. Because this stimulatory action is mediated by the H_2 subtype receptors, selective H_2 receptor antagonists (such as ranitidine) are inhibitors of acid secretion. Despite the preference for PPIs, the use of ranitidine at high dosage (300 mg twice daily) permitted similar eradication rates (3). Furthermore, several studies reported that ranitidine can be safely co-administered with other drugs (4). To confirm the efficacy of ranitidine, in a previous study we showed that a ranitidine-based eradication treatment was not inferior to a similar PPI-based regimen (p=0.9) (5).

In conclusion, in a setting where PPIs are not available or cannot be prescribed, ranitidine is an appropriate drug in a combined regimen for *H. pylori* eradication. It is probable that the availability of vonoprazan, a potassium-competitive acid blocker, as a new type of effective acid suppressant will offer new options in this field (4).

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Author's Reply

Re: How Should *Helicobacter Pylori* Eradication Be Performed in Cases of Extensive Allergies to Proton Pump Inhibitors?

Dear Editor,

We appreciate the interest shown by Pellicano in our article (1) and for the valuable comments.

We agree with Pellicano's all comments. The vonoprazan is not available in Turkey, because of that we could not experience this new drug.

In conclusion, we wanted to emphasize that cross-reactivity between proton pump inhibitors (PPIs) should be considered before HP treatment in patients with allergies to PPIs in our case report. The choice of treatment should be planned based on the results of allergic evaluations. In addition to that if there is an extensive

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ORCID ID of the author: R.P. 0000–0003–3438–0649

Corresponding Author: Rinaldo Pellicano **E–mail:** rinaldo_pellican@hotmail.com

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allergies to PPIs or PPIs are not available, we also wanted to emphasize that ranitidine can be safely used in a combined regimen of HP eradication therapy as suggested by Pellicano (1-4).

Yasin Şahin[1], Özlem Yılmaz[2]
[1]Division of Pediatric Gastroenterology, Mersin City Training and Research Hospital, Mersin, Turkey
[2]Division of Pediatric Allergy, Mersin City Training and Research Hospital, Mersin, Turkey

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ORCID IDs of the authors: Y.Ş. 0000-0002-7394-4884; Ö.Y. 0000-0003-2971-283X.

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Corresponding author: Yasin Şahin
E-mail: ysahin977@gmail.com

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