MIDDLE BLACK SEA JOURNAL OF HEALTH SCIENCE

DECEMBER 2017 VOLUME 3 ISSUE 3

Published three times per year by Ordu University

ISSN 2149-7796

MIDDLE BLACK SEA JOURNAL OF HEALTH SCIENCE (MBSJHS)

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MIDDLE BLACK SEA JOURNAL OF HEALTH SCIENCE

The Middle Black Sea Journal of Health Science is published by Ordu University Institute of Health Sciences on behalf of the Middle Black Sea Universities Collaboration Platform

ISSN 2149-7796

Middle Black Sea Journal of Health Science

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Web site: http://dergipark.ulakbim.gov.tr/mbsjohs

Sort of Publication: Periodically

Publication Date and Place: 20 / 12/ 2017, ORDU, TURKEY

Publishing Kind: Online

Indexing: Turkey Citation Index

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The aim of the journal is to publish original articles with highest clinical and scientific quality at the international level. Middle Black Sea Journal of Health Science also publishes reviews covering fundamental innovations in health education, editorial articles, case reports and original images.

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Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) l995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

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English title, author names and institutions.
Abstract (average 200-400 word)
Introduction
Methods
Results
Discussion and conclusion
References (most 30)
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Discussion and conclusion
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MIDDLE BLACK SEA JOURNAL OF HEALTH SCIENCE

DECEMBER 2017 **VOLUME 3** **ISSUE 3**

CONTENTS

EDITORIAL

And the end of the third year...

Sweet tiredness and the end of a year again...

Our magazine, published three times a year, contributed to the literature with 11 articles and 5 case reports, 2 reviews from various health fields.

I would like to offer my endless thanks to all those who have contributed for their hard work.

There are seven publications at the last census including the joint publication of histology, pathology, nursing, orthopedics, physiotherapy, anesthesia and cardiology.

I wish the continuation of your contributions.

Happy New Year....

PhD. Asst. Prof. Ülkü KARAMAN

Editor

Middle Black Sea Journal of Health Science December 2017; 3(3):1-6

RESEARCH ARTICLE

Arthroscopic Fixation of Tibial Intercondylar Eminence Fracture by Fiber Wire Suture and U Screws in Adolescent Athletes

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Received: 4 August 2017, Accepted 26 August 2017, Published online: 20 December 2017

Abstract
Objective: We aimed to present our experience on arthroscopic management of tibial intercondylar eminence fracture in adolescent athletes.
Methods: This was a case series of 9 adolescents (7 males, 2 females) aged 10-16 years diagnosed with tibial intercondylar eminence fracture following a sports activity. According to Meyers and McKeever classification, 4 patients had Type IIIA, 3 had Type IIIB, and 2 patients had Type II fracture. Following percutaneous arthroscopic reduction, the fragments of the fracture were fixed internally and anterior cruciate ligament was reconstructed through two 2.4 mm parallel tunnels at the level of anterior tibia by using fiber wire suture and U screws. Anterior tibial displacement was measured by KT-1000 knee arthrometer, and Lysholm Knee Scoring Scale was used for the patient-reported outcomes.
Results: The duration of operation was 31.6±8.9 min. The patients were followed up for 37.1±19.1 months. Theanterior tibial displacement relative to the femur was 1.4±0.7 mm. TheLysholm score was 95.8±3.1. None of the patients developed infection. The complete fracture healing was obtained in all patients.
Conclusion: Arthroscopic reduction and internal fixation by fiber wire suture and U screws provide perfect anatomic and functional outcome for displaced Type II and Type III tibial intercondylar eminence fracture in adolescent athletes.
Key words: Adolescent, sport injury, knee joint, arthroscopic reduction, tibial intercondylar eminence fracture

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DOI: 10.19127/mbsjohs.332789

Introduction

Sports injuries causing fractures around epiphyseal and apophyseal knee joint is common in pediatric population (Beaty and Kumar, 1994). Among these fractures, the tibial intercondylar eminence fracture is mostly seen in children with an incidence of 3/100,000/year due to incomplete tibial epiphyseal bone and weak nature of anteriour cruciate ligament in skeletally immature population (Leeberg et al. 2014). This fracture has been classified by Meyers and McKeever into three groups according to degree of displacement—Type I, Type II and Type III (Meyers and McKeever, 1959; Meyers and McKeever, 1970).

The tibial intercondylar eminence fracture is relatively rare compared to other common pediatric fractures, thus underdiagnosed; however, when untreated it may result in knee instability and disruption of physis (Leeberg et al. 2014). Although there is no consensus on whether surgery is needed for Type II and III fractures (Molander et al. 1981), arthroscopic surgery is the preferred method of treatment in recent literature (Leeberg et al. 2014; Owens et al. 2003). Compared to open surgery, arthroscopical management of tibial intercondylar eminence fracture is less invasive and provides earlier mobilization (Leeberg et al. 2014; Larsen et al. 2006). However, many different surgical techniques using various sutures and screws have been used during arthroscopic surgery. Therefore, there is a disagrement on the surgical technique for the management of displacedtibial intercondylar eminence fracture. Furthermore, there is a continuous debate on whether to cross physis during fixating the fracture. Therefore, there is still need for more experience on various surgical techniques in order to reach a consensus on the management of this critical fracture.

In the present study, we aimed to present our experience on arthroscopic management of tibial intercondylar eminence fracture in adolescent athletes.

Methods

Study design and population

This was a case series of 9 adolescent athelets (7 males, 2 females) aged 10-16 years who were diagnosed with tibial intercondylar eminence fracture following a sports activity and treated arthroscopically in Hitit University Faculty of Medicine Department of Orthopedics and Traumatology between May 2010 and May 2016. The fractures were classified according to Meyers and McKeever classification (Meyers and McKeever, 1959: Meyers and McKeever, 1970).
The patients and parents were informed about the treatment, and legal represantative of each patient gave written consent before the surgical operation. The study was conducted in accordance to the latest version of Helsinki Declaration.

Arthroscopic procedure and postoperative follow-up

Following percutaneous arthroscopic reduction, the fragments of the fracture was fixed internally and anterior cruciate ligament was reconstructed through two 2.4-mm parallel tunnels at the level of anterior tibia by using fiber wire suture and U screws. On postoperative period, after confirming the stability of the fracture fragments by arthroscopy and C-arm scopy, the knee was immobilized in a brace locked in full extension for 6 weeks. Isometric quadriceps and hamstring exercises were started 2 days after the operation. Partial weight-bearing was allowed after two weeks. The knee brace was removed after 6 weeks, and rehabilitation and strengthening exercises were started. The patients were allowed to make sportive activities after 5 months.

The fracture was evaluated before and after the operation by X-ray, conventional and three-dimensional computed tomography (CT), and magnetic resonance (MR) imaging. On postoperative 12th month, anterior tibial displacement relative to the femur was measured by KT-1000 knee arthrometer (KT-1000, MedMetric Co. San Diego, California, USA) (Arneja and Leith, 2009). For the patient-reported outcomes of the surgery, Lysholm Knee Scoring Scale that measures the effect of knee problem on patient's daily life on a 0 to 100 scale was used (Lysholm and Gillquist, 1982).

The study data were reported using descriptive statistics (e.g., frequency, percentage, mean, standard deviation).

Results

The tibial intercondylar eminence fracture occurred after cycling in 4 patients, wrestling in 3 patients, basketball in 1 patient, and skiing in 1 patient. The fracture was in right knee in 4 patients and left knee in 5 patients. On the basis of Meyers and McKeever classification, 4 patients had Type IIIA, 3 patients had Type IIIB and 2 patients had Type II fracture. The anterior cruciate ligament rupture was present together with eminence fracture in 3 patients. The clinical characteristics of patients were summarized in Table 1.

The mean duration of operation was 31.6±8.9 min (Table 2). The patients were followed up for 37.1±19.1 months on average after the arthroscopic procedure. There was a minimum anterior tibial displacement relative to the femur as measured by

the KT-1000 knee arthrometer, which was 1.4±0.7 m on average. A mean high Lysholm score, which was 95.8±3.1, indicated a favorable patient-reported outcome of the surgical intervention (Table 2). None of the patients developed infection. The complete fracture healing was recorded in control radiographs of all patients. The pre- and postoperative images of a 12-year old male patient were present in Figure 1 and 2, respectively.

Table 1. Demographic and clinical characteristics of study patients (n=9)

Variable	Result
Age (years), mean±standard deviation (range)	12.44±2.0 (10-16)
Gender, n (%)	
Male	7 (77.8%)
Female	2 (22.2%)
Side of eminence fracture, n (%)	
Right knee	4 (44.4%)
Left knee	5 (55.6%)
Sport activity causing fracture, n (%)	
Wrestling	3 (33.3%)
Basketball	1 (11.1%)
Skiing	1 (11.1%)
Cycling	4 (4.4%)
Meyers and McKeever classification of fracture, n (%)	
Type IIIA	4 (44.4%)
Type IIIB	3 (33.3%)
Type II	2 (22.2%)
Concomittant injuries, n (%)	
None	4 (44.4%)
Anterior cruciate ligament rupture	3 (33.3%)
Radius fracture	1 (11.1%)
Elbow fracture	1 (11.1%)

Table 2. Intra- and postoperative findings

Variable	Mean±standard deviation
Duration of operation (min)	31.6±8.9
Postoperative follow-up duration (months)	37.1±19.1
KT-1000 knee arthrometer	1.4±0.7
Lysholm score	95.8±3.1

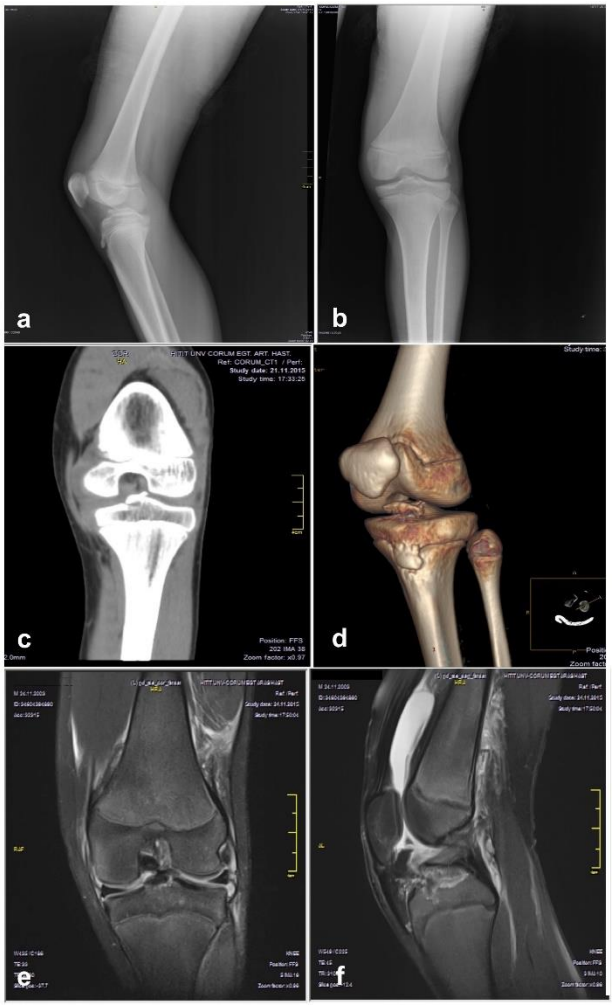

Figure 1. Preoperative radiologic images of 12-year old male patient with Type IIIA tibial intercondylar eminence fracture. a, lateral X-ray image; b, anteroposterior X-ray image; c, coronal CT image; d, three-dimensional CT image; e, coronal MR image; f, sagittal MR image.

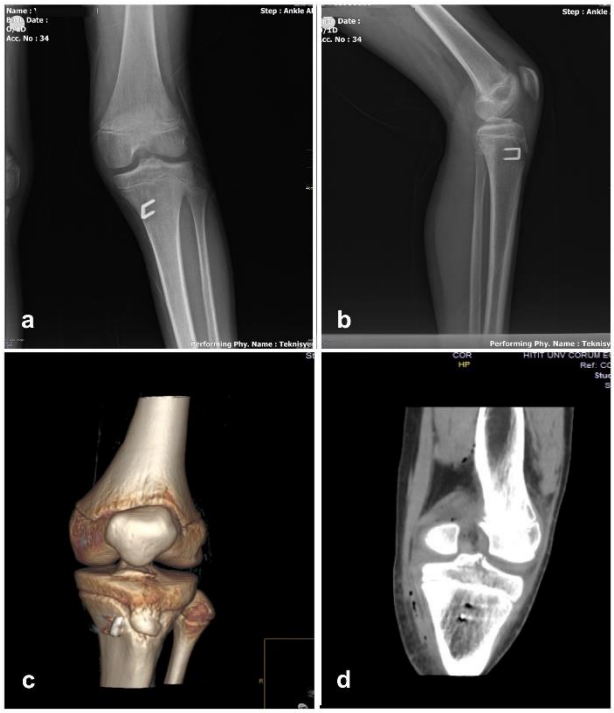

Figure 2. Postoperative images of the patient in Figure 1. a, anteroposterior X-ray image; b, lateral X-ray image; c, three-dimensional CT image; d, coronal CT image.

Discussion

In this case-series, we report our experince with arthroscopic reduction and internal fixation by fiber wire suture and U screws for displaced Type II and Type III tibial intercondylar eminence fracture in 9 adolescent athelets. We obtained good anatomic and functional outcomes without any postoperative complication over 3-year postoperative follow-up duration.

As the compatitive sport activities became popular in adolescents, particularly in males, sport injuries affecting knee are frequently encountered in this age group. The treatment approach against knee injuries at this period has critical importance for the need to preserve both functionality of the knee and the integrity of the physis (Schmittenbecher, 2005). In etiology, the tibial intercondylar eminence fracture is equivalent to the ruptures of the anterior cruciate ligament, thus anatomic reduction is needed to preserve the stability of the joint.

The prognosis is basicly related to the type of fracture, anatomic reduction, articular congruity, and age of patient (Tudisco et al. 2010). Majority of the previous studies suggest that Type I fractures and those in children below 10 years of age can be treated conservatively, which is the closed reduction and immobilization in extension (Tudisco et al. 2010; Atay et al. 2002; Wilfinger et al. 2009). Although some studies suggested that conservative treatment is justified in most cases of Type III tibial intercondylar eminence fracture in children (Molander et al. 1981), for displaced fractures, long-term results were not satisfactory thus surgical treatment should be applied (Atay et al. 2002; Casalonga et al. 2010). Although some recent reports showed very favorable outcome with open reduction and cross wire fixation (Keshet et al. 2015), in comparison to open surgical techniques, arthroscopic reduction and internal fixation showed overall better results (Tudisco et al. 2010; Prince and Moyer, 1995).

For the arthroscopic management of Type III fracture, various techniques were suggested including the usage of the Kirschner wires, Arthrex suture lasso device, folded surgical steels, arthroscopy-guided intra-articular button fixation, Herbert-screw fixation, headless compression screw, and cannulated screw (Su et al. 2011; Oohashi, 2001; Memisoglu et al. 2016; Wiegand et al. 2014; Johnson and Durbin, 2012; Furlan et al. 2010; Senekovid and Veselko, 2003), all of which revealed good functional outcome in short- and long-term. Recent improvements in suture materials provided that sutures with an improved fixation technique are as efficient as cannulated screws (Memisoglu et al. 2016; Wiegand et al. 2014; Johnson and Durbin, 2012). In the present case series, we applied internal fixation by fiber wire suture and U screws and obtained good anatomic and functional outcome assessed by KT-1000 knee arthrometer and Lysholm score.

Most of the previous studies on the arthroscopic management of tibial intercondylar eminence fracture in literature are case-reports or retrospective series. One of the largest reports published recently by Persiani et al. (2016) was a retrospective analysis of 41 adolescent athletes who were treated successfully by conservative approach, open surgery or arthroscopy depending on severity of knee injury. In their study, Persiani et al. (2016) suggested performing a CT exam to exclude an intra-articular physeal fracture in this age group of patients. In our series, pre- and postoperative evaluations were performed by X-ray, conventional and three-dimensional CT, and MR imaging.

Many previous studies used arthroscopy to evaluate the outcomes after surgery (Leeberg et al. 2014). Similarly, we performed arthroscopy and C-arm scopy for postoperative confirmation of

fixation. For long-term follow-up we used control radiographs.

The most common complications of knee arthroplasty in childhood is comminution of the fracture fragments, nonunion, infection, joint instability, stiffness, laxity, extension impingement, growth disturbances, and meniscus lesion (Johnson and Durbin, 2012; Kieser et al. 2011). None of the patient in our series developed any intra- or postoperative complication.

The main limitations of the present study are its small sample size and retrospective design, which preclude us from reaching a definitive conclusion on the surgical technique during arthroscopical treatment of displaced tibial intercondylar eminence fractures in skeletally immature children. On the basis of case-reports and case-series including the present report on various surgical techniques, further larger scale and prospective studies with longer follow-up duration are needed.

Conclusion

In conclusion, arthroscopic reduction and internal fixation by fiber wire suture and U screws provide perfect anatomic and functional outcome for displaced Type II and Type III tibial intercondylar eminence fracture in adolescent athelets. The displaced tibial intercondylar eminence fracture should be treated with arthroscopic reduction and internal fixation. On the basis of our experince, we believe that since fiber wire sutures provide improved fixation in the arthroscopic management of tibial intercondylar eminence fracture in children, they should be preferred to screws.

Ethics Committee Approval: The requirement for the ethics committee approval was waived for the retrospective design and valid legal regulations at the time of the study.
Peer-review: Externally peer-reviewed.
Author Contributions: Idea- M.Ç.; Design M.Ç; Supervision- M.Ç.; Funding- M.Ç; Materials- M.Ç.; Data Collection/Data Process- M.Ç., T.D., Analyze or Comment- M.Ç, T.D., Literature Scanning- M.Ç., T.D.; Writer of Paper- M.Ç., T.D.; Critical Review- M.Ç.
Conflict of Interest: No conflict of interest was declared by the author.
Financial Disclosure: The authors declared that this study has received no financial support.

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Middle Black Sea Journal of Health Science December 2017; 3(3):7-14

RESEARCH ARTICLE

The Protective Effect of Amino-guanidine, an Inducible Nitric Oxide Synthase Inhibitor, on Aluminium Sulphate Neuro-toxicity in the Rat (Wistar albino) Cerebellar Purkinje Cells: Stereological Study

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Received: 16 June 2017, Accepted: 31 August 2017, Published online: 20 December 2017

Abstract

Objective: Aluminium (Al) is quite abundant in nature and humans are frequently exposed to Al in daily life. Aluminium salts can exist in different forms and they may have toxic impacts on several tissues including brain. In this study, potential preventive effects of amino-guanidine (AG) (100 mg/kg, i.p.), an inducible nitric oxide synthase inhibitor, on neuron damage to be created by aluminium sulphate (3 mg/kg, i.c.v.) in cerebellar Purkinje cells were determined.

Methods: 24 female Wistar albino rats were divided into 4 groups with 6 rats in each: Control (C), Sham (S), Aluminium sulphate ($Al_2(SO_4)_3$), Aluminium sulphate + Amino-guanidine ($Al_2(SO_4)_3$+AG). A single aluminium sulphate (3 mg/kg) dose dissolved in 0.9% NaCl was injected intracerebroventricularly to aluminium sulphate and aluminium sulphate + amino-guanidine groups at the beginning of experiments. Following aluminium sulphate injection, amino-guanidine (100 mg/kg) dissolved in distilled water was injected to aluminium sulphate + amino-guanidine group intraperiteonally for 15 days. Nothing was administered to control group, a single dose of 0.9% (3 mg/kg, i.c.v.) sodium chloride (NaCl) was administered to sham group at the beginning of experiments. Cerebellum tissues of the rats were removed 15 days after treatments and they were assessed histopathologically and stereologically.

Results: Stereological optic fractionation method revealed cerebellar total number of Purkinje cells as 417615±16238,8 in control group; 378650±20171,6 in Sham group; 272945±15499,5 in Aluminium sulphate group; 324581±16324,8 in Aluminium sulphate + Amino-guanidine group.

Conclusion: It was concluded based on present findings that amino-guanidine reduced aluminium induced Purkinje cell loss through nitric oxide synthase (NOS) inhibition.

Key words: Aluminium, Amino-guanidine, Cerebellum, Purkinje cell, Stereology

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DOI: 10.19127/mbsjohs.322015

Introduction

Chemical pollutants not only pollute environment, but also they have long-standing impacts on cellular development (Önger et al., 2011). Aluminium (Al) always exists in environment and humans are continuously exposed to aluminium (Yavuz et. al., 2013). It doesn't have a known biological function and it's the third abundant element in nature (Oğuz et al., 2012). Al can be found in broad range of items from drugs to tools, from kitchenware to electric industry, from vehicles

to cosmetics (Yavuz et. al., 2013). Al can get into the human body through oral, penetration, inhalation, skin etc. (Yokel et al., 2008). Just because of abundance in nature, it can accumulate in tissues of organisms to certain extend (Oğuz et al., 2008), may have neurotoxic impacts resulting in Alzheimer and Parkinson-like neurological disorders (Kamal and Kamal, 2013).

Clinical studies with animals revealed that brain was a significant target organ in Al neurotoxicity (Kamal and Kamal, 2013). Al can accumulate in all sections of the brain and may have maximum accumulation in hippocampus. Al accumulation in tissues induces the formation of reactive oxygen species and then these species result in protein, lipid and DNA oxidation. Neural membranes of central nervous system are quite rich in polyunsaturated fatty acids, have low antioxidant enzyme levels and need significant quantities of oxygen for metabolism. Therefore, they are quite more prone to oxidative damage than the other systems. Al has a cytotoxic impact on brain through inhibition of Ca_2+ ATPaz responsible for sustaining quite low Ca_2+ levels in cells by pumping Ca_2+ in brain out of the cells. Increase in neural Ca_2+ activates various protease enzymes of caspase family and may result in irreversible neural damage. Al also increases the quantities of glutamate, an excitatory neurotransmitter existing in about 40% of synapse in brain. When the Al around a neuron reached to a certain level, it annihilates the neuron through apoptosis. An uncontrolled increase in glutamate quantity of synaptic gap activates N-methyl D-aspartic acid (NMDA), increases Na+ and Ca_2+ ion concentrations along the cell membrane and aggravate neurological damage (Çabuş, 2012).

Together with recently increased atmospheric pollution, nitric oxide (NO) is another remarkable compound. NO is known as a basic precursor molecule and called as a free radical molecule because of unpaired electron. While the other free radicals are harmful to cells at any concentrations, NO play a role in quite significant physiological functions at low concentrations. However, excessive and uncontrolled NO synthesis may be harmful for cells (Özgüneş and Atasayar, 2009). In case of excessive production, NO confronts us as a neurotoxin in various nervous system diseases (Satarug et al., 2000). Nitric oxide (NO) is synthesized from L-arginine by nitric oxide synthase (NOS) (Buraimoh et al., 2014). NOS exist in brain tissues of humans and animals at varying concentrations (Türköz and Özerol, 1997). There are three NOS isoforms in brain as of endothelial (eNOS), neural (nNOS) and inducible (iNOS) (Stevanović et al., 2010). iNOS is an enzyme able to produce NO to a level with toxic effects (Gross and Volin, 1995). Cytokines and stimulant substances induced by acute inflammatory changes may also contribute to iNOS enzyme activation just as in immunological or inflammatory stimulations and may produce toxic NO levels which can be expressed as nanomole throughout subsequent couple days of pathological stimulation and ultimately aggravate the damage which may end up with cell death (Önger et al., 2011).

Amino-guanidine (AG), used to reduce toxic impacts of Al on Purkinje cells, structurally resembles to L-Arginine amino acid, inhibits iNOS and thus result in reduced NO formation (Budavari et al., 1989). It was reported in a previous study that AG prevented inflammation in hippocampus as a selective iNOS inhibitor and reduced neuron damage (Anaeigoudari, 2016). It was also reported that AG had scavenging activity in various tissue damage models through scavenging hydrogen peroxide (H_2O_2) derivative hydroxyl radicals (OH-) produced from NO and superoxide (O_2-) (Polat et al., 2006). In this sense, AG prevents lipid peroxidation and formation of reactive oxygen species (ROS) and thus reduces toxicity through the impacts like as an antioxidant agent (Babu et al., 1995).

Cerebellum, over which toxic effects of Al were investigated, is one the most complex sections of central nervous system of mammalian (Tunç et al., 2007). Nearly 50% of all neurons of the brain are located in cerebellum, which takes up only 10% of the total brain volume and receives nearly 200 million afferent fibers (Eweka and Om'Iniabohs, 2007). Cerebellum is responsible for the control of motor movements through comparing information coming to brain from various receptors in periphery with the responds of brain to this information. While performing this function, Purkinje cells are the only output of cerebellum cortex. Therefore, Purkinje cells have a great place in cerebellum functions. These cells are also quite sensitive to alcohol toxicity and ischemia-like pathologic cases (Kozan et al., 2009). High number of NMDA receptors creating neurotoxic effects of NO in cerebellum also aggravates NOS activity (Sefil et al., 2009). It was reported in previous Al studies that with increasing NOS levels in brain tissue (Flora et al., 2003), Al created oxidative stress in cortex and cerebellum (Esparza et al., 2005) and had neurotoxicity on cerebellar Purkinje cells (Buraimoh et al., 2014).

Although brain is the primary target organ in Al toxicity, effects of Al on cerebellum were

investigated in limited number of studies. Therefore, the present study was designed to elucidate the preventive effect of amino-guanidine (AG) as a specific nitric oxide synthase (NOS) inhibitor against potential damage of Al to be created on cerebellum Purkinje cells through stereological optic fractionation method with systematic randomized sampling and unbiased counting.

Methods

Experimental Procedure

Experiments were conducted with Wistar albino rats grown in Laboratory Animals Implementation and Research Center of Ondokuz Mayıs University. About 200±250g 24 same-generation rats were selected and they were randomly divided into four groups with 6 rats in each. These groups were control (C), Sham (S), Aluminium sulphate ($Al_2(SO_4)_3$), Aluminium sulphate + Amino-guanidine ($Al_2(SO_4)_3$ +AG). In this study, 3 mg/kg of aluminum sulphate (Çabuş et al. 2014) and 100 mg/kg of aminoguanidine (Önger et al., 2011) were applied to experimental groups. Rats were placed in plastic cages at 20±22°C temperature, 50% relative humidity and 12 hours' light/dark periods. Feed and water was supplied ad libitum.

Chemicals and Method of Administration

Aluminium sulphate was supplied from Sigma-Aldrich as aluminium sulphate hydrate (in powder, pure form), Amino-guanidine was supplied from again Sigma-Aldrich as amino-guanidine hydrochloride (in powder, pure form).

Rats were weighted before the injections and they were anesthetized through intraperitoneal ketamine (100 mg/kg) and xylazine (10 mg/kg) administration (Sefil et al., 2009). Rats were than fixed to streotaxy device and their scalp was opened 2 cm with an electrical cautery (Ellman Surgitron) from the mid-section along rostro-caudal direction. Tendon and fascia over cranium were removed to see Bregma clearly. As to comply with left lateral ventricle, 1 mm hole was opened at 2 mm lateral and 0.6 mm posterior of Bregma (Kozan et al., 2009). From there, Hamilton micro-injector was introduced and 2 µl aluminium sulphate solution was injected intracerebroventricularly (i.c.v.) to a depth of 4.2 mm at 0.5 µl/min flow rate and 3 mg/kg dose. Nothing was administered to control group. A single dose of 0.9% (3 mg/kg, i.c.v.) sodium chloride (NaCl) was administered to sham group at the beginning of experiments. A single aluminium sulphate (3 mg/kg, i.c.v. $Al_2(SO_4)_3$) dose dissolved in 0.9% NaCl was administered to $Al_2(SO_4)_3$ and $Al_2(SO_4)_3$+AG groups at the beginning of experiments. Amino-guanidine (AG) was injected to $Al_2(SO_4)_3$+AG group for 15 days at a dose of 100 mg/kg, i.p. After 15 days following the last injection, rats were perfused intracardially under ketamine (75 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.) anesthesia. Rat brains were put into 10% neural-tamponed formalin solution for stereological examination.

Sampling via Optical Fractionation

Total number of Purkinje cell in the cerebellum was performed by the optical fractionation method, which is a combination of two stereological applications (fractionation and optical dissector) (Korkmaz et al., 1996; Korkmaz and Tumkaya, 1997; Korkmaz et al., 2000). Systematic random sampling was performed from cerebellum tissue immersed into paraffin in accordance with fractionation principles. The issue to be considered in sampling was to have a proper error coefficient (0.05 or less) and coefficient of variation (0.10). The calculation results below these two values prove the accuracy of the sampling process (Gundersen and Jensen, 1987). Present samplings were performed by considering proper error coefficients and coefficients of variation. In this direction, cerebellum tissues of the all group rats were sectioned from back to front at 30 µm intervals, leaving no tissue unused. Section sampling fraction in systematic random sampling was determined as (f1) 1/7 and the first cross-section based on randomness principle was taken randomly from the 1-4th sections, the other cross-sections were taken from the 7th section through by passing 6th section over the initially selected section. In this way, about 25-28 cerebellum sections were obtained from each rat. The selected sections after sampling were stained with cresyl violet. For section sampling fraction (F2), the approach in West et al., (1991) was tried to be applied. F2 was calculated by dividing small counting area (frame) with step area (X, Y step). Accordingly, F2 was calculated as $40x40\mu m^2/220x220\mu m^2$ = 1/12=0.033. Finally, cerebellum Purkinje cell layer was scanned within the range defined over X-Y axis with systematic random sampling. For cross-section thickness and optic dissector height measurements, 'micro-screw calibration' method developed by Korkmaz and Tümkaya (1997) was used. In this way, thickness sampling fraction (F3) was calculated for each rat separately by dividing average dissector height (hort) with average cross-section thickness (tort)

Cerebellum Purkinje cell counts and calculations

The method developed by Korkmaz et al. (2000) was used for Purkinje cell counts. For this method, Purkinje profile of each preparate was imaged with 10X objective, then acetate template including X, Y steps (large squares) and unbiased counting frames (small squares) were placed over the monitor (Fig 1 and 2). In this magnification, in systematic randomly sampled every seventh area, cross-section thickness (t) was determined with 100X objective (numerical aperture 1.25). In these areas, upper surface of the cross-section was focused and the location of pointer over the scale was determined. Then the lower surface of the cross-section was focused and the unit movement of the pointer with respect to initial position was recorded. The distance covered by a unit of scale connected to micro-screw along Z-axis (1-degree movement of micro-screw) corresponded to 0.27 µm. Cross-sections were scanned in steps and with optic dissector, optically 11 units (2.7 µm, 0.27x11 = 3 µm) were moved downward from the upper surface of the cross-section at Purkinje cell count phase. Cross-section scanning was performed at this level. The parameters obtained in this study were placed in equation of N (Total) = (∑Q-) x (1/ F1) x (1/ F2) x (1/F3) (West et al., 1991). In this way, average number of cerebellum Purkinje cells of each group was calculated.

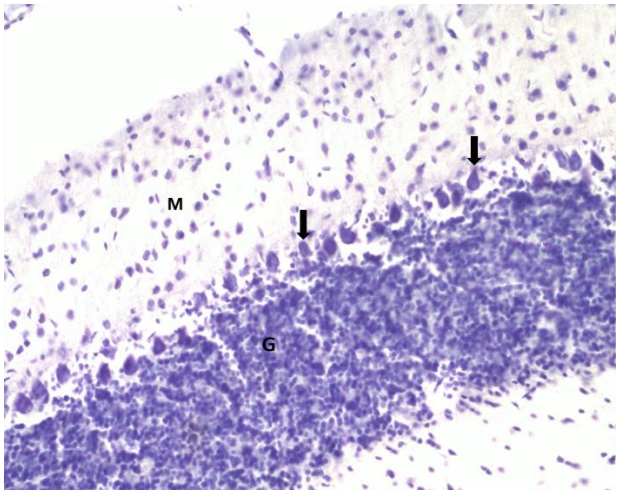

Figure 1. Photomicrograph of cerebellum from control group. G: Granular layer, M: Molecular layer, Purkinje cells (arrows), cresyl violet, 20x

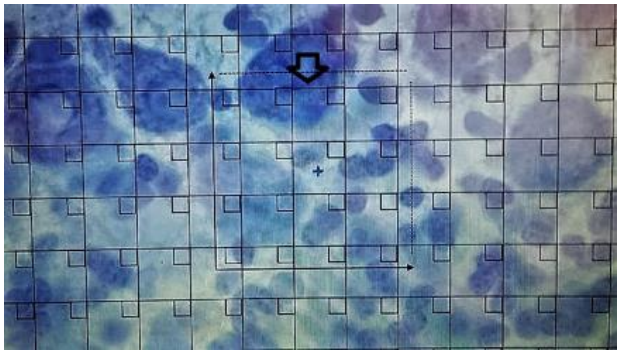

Figure 2. Systematic random sampling area fraction on the sampled section. X, Y steps (large squares) and unbiased counting frames (small squares), Dissector granule (arrow), cresyl violet, 100x.

Data Analysis

Statistical analyses were performed with SPSS (Statistical Package for Social Sciences for Windows) Version 20. One-Way ANOVA was used to compare treatment groups. Differences between the groups means was assessed with post hoc Tukey test.

Results

Average number of Purkinje cells present in cerebellum of rats is provided in Table 1. Coefficient of variation was calculated for each group (a value to be less than 0.10) to prove accuracy of the study. As compared to the control group (C), 34.6% cellular loss was observed in $Al_2(SO_4)_3$ group and 27.9% lose was observed in S group. In $Al_2(SO_4)_3$ +AG group, amino-guanidine reduced cellular loss by 22.3% as compared to C group and by 14.3% as compared to S group (Table 1). The differences in Purkinje cell counts of C and S groups and the differences in Purkinje cell counts of $Al_2(SO_4)_3$ groups were found to be significant ($p<0.01$).

Table 1. Average number of Purkinje cells in cerebellum, standard error of the mean (SEM) and coefficients of variance (CV).

Groups	Average number of Purkinje cells ± SEM	Coefficient variation (CV)
C	417615±16238,8	0,06
S	378650±20171,6	0,06
$Al_2(SO_4)_3$	272945±15499,5	0,06
$Al_2(SO_4)_3$+AG	324581±16324,8	0,08

Post hoc Tukey test revealed that differences in Purkinje cell counts of the experimental groups were significant ($p<0.01$). One-Way ANOVA test revealed that $Al_2(SO_4)_3$ group was significantly different from C and S groups ($p<0.01$). There were significant differences also between $Al_2(SO_4)_3$ group and $Al_2(SO_4)_3$ +AG group ($p<0.01$) (Fig 3).

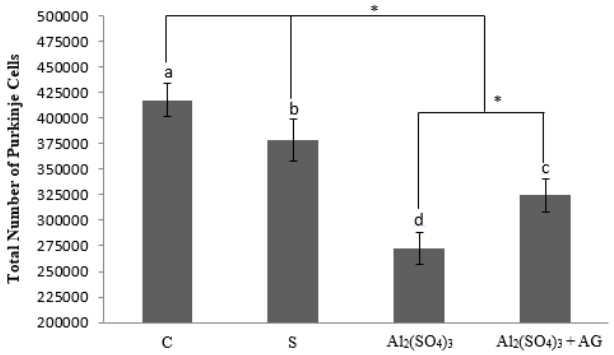

Figure 3. Cerebellum Purkinje cell counts for C, S, Al2(SO4)3 and Al2(SO4)3 + AG groups. a, b, c, d express different groups of post hoc Tukey test. * $p<0.01$ significance level used to compare the groups with one-way ANOVA.

Discussion

Accumulation and damages of different Al forms on target organ and in body tissues were reported in previous studies (Kutlubay et al., 2007a; Oğuz et al., 2008, 2012). Exposure to high Al levels results in neural degeneration characterized by programmed and selective neuron loss (Stevanović et al., 2010). Al has neurotoxic impacts through inhibiting DNA repair enzymes (Bharathi et al., 2008), destroying cell membrane integrity (Zatta et al., 2002; Stevanović et al., 2010), increasing production of reactive oxygen species (ROS) (Ogasawara et al., 2003) and reducing neurotransmitter biosynthesis (Cheng et al., 2014).

Al is a source of oxidative stress and results in lipid peroxidation through the abundance of polyunsaturated fatty acids in cerebellum (Chaudhary et al., 2014). Al actualizes such impacts through increasing cerebral NOS levels (Bondy et al., 1998). In such cases, reduced forms of excessively produced NO increases. Excessive reduced NO reacts with superoxide (O2-) and thus increases proxy nitrite (ONOO-) and free radical formation. Increased free radicals eject electrons from cell membrane lipids and results in lipid peroxidation. Lipid peroxidation then accelerates cell deaths (Marangoz, 1996). Sharma et al. (2007) treated rats orally with 172.5 mg/kg-day aluminium chloride for 10 weeks and reported significant decreases in SOD, GSPx and CAT antioxidant enzyme levels and significant increases in lipid peroxidation levels. Similar results were also reported in another study carried out with aluminium lactate-treated rats (Ogasawara et al., 2003). There are evidences that Al induced apoptosis-mediated neural deaths. Çabuş et al. (2014) carried out a study on rats treated with aluminium sulphate (3 mg/kg i.p.) and assessed the neurons in stratum pyramidale layer of left-hemisphere with TUNEL method and reported significant decreases in number of neurons of aluminium-treated rats, then indicated aluminium as a neurotoxic agent and also indicated that neural death mechanisms might have been resulted from apoptosis. It was also showed that Al might result in cell damages in different tissues like thyroid follicles. It was reported in a previous study that 5% aluminium chloride supplementation of drinking water created significant damages on thyroid follicles of rats ($p<0.05$) (Aktaç and Bakar, 2002). Malekshah et al. (2005) reported that aluminium chloride treatments (150 mg/kg, i.p.) for 10, 11 and 12 days created anomalies in fetus and reduced body weight of pregnant rats. Al may also reduce DNA and RNA synthesis and thus inhibit protein synthesis (Darbre, 2006). Buraimoh et al. (2014) in a study investigating the effects of Al on Purkinje cells, treated rats with aluminium chloride (40 mg/kg) for 4 weeks and reported significant decreases in Purkinje cell counts of treated rats through neuro-degeneration as compared to untreated control rats.

In present stereological study with systematic random sampling, there was 34.6% decrease in number of Purkinje cells in cerebellum of Al (3 mg/kg, i.c.v.) treated group as compared to control group. Such a case revealed that Al had neuro-toxic impacts on Purkinje cells and the case may be attributed to increased NOS production (Esparza et al., 2005; Kozan et al, 2009; Buraimoh et al., 2014). It was reported in previous studies that toxic impacts

of aluminium may reduce antioxidants like vitamin E (Kutlubay et al., 2007b), AG (Stevanović et al., 2010), taurine (Kozan et al., 2009). The AG used in this study to reduce the toxic impacts of Al was proved to reduce neurotoxic impacts resulted from increased aluminium sulphate-induced NOS levels (Önger et al., 2011). Sefil et al. (2009) reported that AG reduced iron-induced Purkinje cell loss from 25% to 12%. It was reported in another study carried out on Wistar albino rats that AlCl3 treatments increased NO production in CA1 region of hippocampus 3 hours after the treatments, subsequently initiated neuro degeneration process, but combined AlCl3 + AG treatments rapidly reduced NO production 3 hours after treatments (Stevanović et al., 2010). In another study carried out with AG, neuron damage resulted from excessive iNOS induced NO production was eliminated with AG (100 mg/kg, i.p., day) treatments (Lu et al., 2002).

It was observed in present study, investigating the preventive effects of AG against cerebellar Purkinje cell loss, that Al2(SO4)3 + AG treatments reduced Purkinje cell loss by 22.3% and such a reduction revealed the preventive effects of AG against neuron damage. These findings support the earlier findings of researchers indicating AG as a specific iNOS inhibitor and may have preventive effects against neurotoxicity (Eroğlu et al., 2008; Gökçe et al., 2011). Neuron preventive effects of AG are realized through inhibiting the formation reactive oxygen radicals (ROR), inhibiting lipid peroxidation (LPO) in cell and tissues, scavenging hydrogen peroxide derivative hydroxyl radicals and prevention from oxidant-induced apoptosis (Özgüneş and Atasayar, 2009).

Conclusion

It was concluded based on present findings that AG, also known as an iNOS inhibitor, had preventive effects against neuron damage in cerebellum Purkinje cells resulted from Al-induced increased NOS levels. Nowadays, the use of Al in many areas especially on a sectoral basis causes people to be directly or indirectly exposed to toxic effects of Al. Therefore, the present study shows that amino-guanidine can be used to reduce the toxic effects of Al, and it contributes to the literature in this issue.

Ethics Committee Approval: All experiments were conducted in accordance with the guidelines for care and use of laboratory animals and protocols were approved by the local ethical committee on experimental animals (2014/14), Ondokuz Mayıs University, Samsun, Turkey.
Peer-review: Externally peer-reviewed.
Author Contributions: Concept HG; Design BB; Supervision HG, BDY; Materials HG, BB; Data collection and/or Processing BB; Analysis and/or Interpretation BB, BDY; Literature Review BE, BDY, BB; Writing BDY; Critical Review BE, BDY.
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: Funding was provided by Ondokuz Mayıs University Research Grant PYO.FEN.1904.14.012.

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Middle Black Sea Journal of Health Science December 2017; 3(3):15-19

RESEARCH ARTICLE

Evaluation of the Relationship between Cervical Intraepithelial Neoplasia Grades and Connexin 43

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Received: 3 August 2017 Accepted: 15 November 2017, Published online: 20 December 2017

Abstract

Objective: Cervical intraepithelial neoplasia (CIN) is a premalign cervical disease. The microscopic features of CIN indicates an alteration leading to dedifferentiation and loss of maturation in the squamous epithelium. Disruption of connexins are frequently reported in malignant cell lines. Here, it is aimed to show the relationship between the dysplasia grades and connexin.

Methods: 79 cases were included in the study who were referred to the pathology department between 2014 and 2015 and who had CIN (grade 1, 2, 3). Sections of 3 micrometer thickness were taken from the paraffin blocks of the uterus on the polylysine slide. Cx43 antibody with ABC tecnique were performed to these sections. Staining cells were defined as positive. The cases were graded according to the intensity of the staining.

Results: The distribution of 79 dysplastic cases was as follows. 41 of these cases had CIN 1. The average age of these women was 44.93. 16 women were diagnosed with CIN2. The average age of these women was 42.06. 22 women were diagnosed with CIN 3. The average age of the women was 48.87.

Conclusion: In this study, complete loss of Cx43 expression was observed in all dysplastic cervical cases.

Key words: Cervical intraepithelial neoplasia, degree of dysplasia, Cx43

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DOI: 10.19127/mbsjohs.332613

Introduction

Cervical cancer is seen all over the world, after breast and colorectal cancers in women. It is still the second most frequent cancer in developing countries, in the developed countries frequency ranks has decreased to the 10th from sixth with help of the main screening programs (Parkin et al., 2005; Ferlay et al., 2010).

Cervical intraepithelial neoplasia (CIN) is a premalign cervical disease, also called cervical squamous intraepithelial lesion (LSIL). The microscopic features of CIN indicate an alteration leading to dedifferentiation and loss of maturation in the squamous epithelium; which is characterized by proliferation abnormalities in the basal and parabasal layers (Atasü and Aydınlı, 1996).

Gap junctions (GJ) play an important role in the proliferation, differentiation, migration and other cellular functions of cells, and homeostasis and tumor suppression. GJs play a role in intercellular communication in many tissues and organs with

epithelium, muscle and nerve tissues (Hong and Lim, 2008).

The connexins (Cx's) are structural precursors of GJs. Cx's are widely distributed in all mammalian cells. Recent studies have shown that Cx's can affect cellular homeostatic balance independently of intercellular communication (Ferlay et al., 2010).

There are alternative mechanisms that can sustain tissue function if one of the molecules of the Cx family in many cell types is mutated or not synthesized. However, in numerous studies conducted in recent years, mutations in genes encoding Cx proteins have been found to result in severe and chronic illnesses. In many cases, single-point mutations cause dramatic consequences due to the insufficient amount of Cx and the lack of internalization (Atasü and Aydınlı, 1996). The Cx classification is based on two systems. The first refers to the molecular weight predicted from the cDNA sequence. For example, Cx 26, Cx 32, Cx 43 refer to molecular weights of 32 kDa and 43 kDa, respectively (Beyer et al., 1987).

Although the presence of Cx is unknown, it has recently been shown that these proteins are superimposed on cell and tissue proliferation. Together with these studies, the values of Cx in cell and tissue types were tried to be revealed (Atasü and Aydınlı, 1996).

There are different results in the literature showing the relation of cx 43 with the dysplasia grades. We aimed to investigate this relationship in this study.

Methods

79 cases were included in the study who were referred to the pathology department between 2014 and 2015. In this cases had CIN grade 1, 2 and 3.

Sections of 3 micrometer thickness were taken from the paraffin blocks of the uterus on the polylysine slide. Cx 43 antibody with ABC tecnique were performed to these sections.

Immunohistochemistry

The sections were held in the 60 ° C for 1 hour then were passed through xylol and alcohol steps. Tissue sections were incubated in 3% hydrogen peroxide (H2O2) for 10 minutes to remove the endogenous peroxidase and then were washed in distilled water for 5 minutes. Antigen was retrieved through retrieval step. Immunohistochemical staining was performed with Avidin-Biotin Peroxidase Complex (ABC) technique. The antigen was washed in PBS after the retrieval protocol. Primer antibody Cx43 (dilution ratio 1: 200) was applied. The sections were then plunged into AEC (3-amino-9-ethylcarbazole) chromogen substrate (10 minutes), washed with water, stained with hematoxylin (3 minutes) and covered with mounting medium. The stained sections were examined with a Nikon eclipse Niu microscope and photos were taken. Immunohistochemically stained preparations were examined. Cells showing staining were evaluated as positive. It was noticed that it was stained in endocervical glands and that there was no staining in the squamous epithelium (Fig. 1-3).

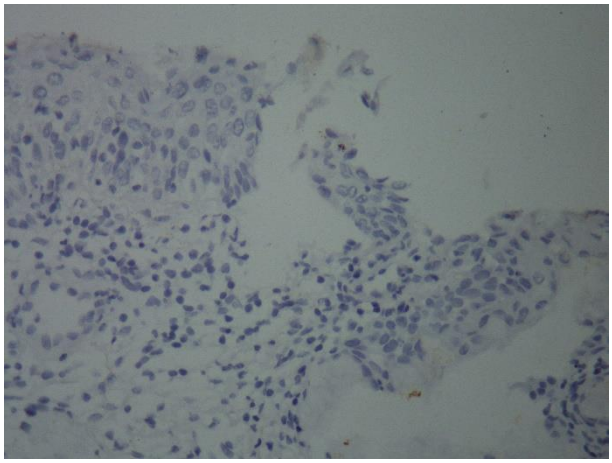

Figure 1. No staining in the presence of CIN-3 (Cx43x400)

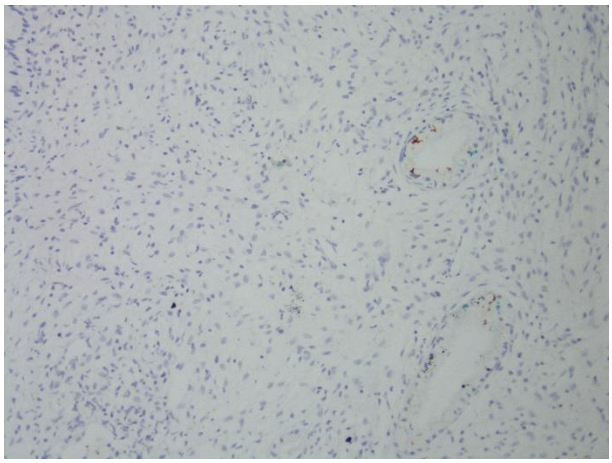

Figure 2. Staining was observed in endocervical glands (Cx43x200)

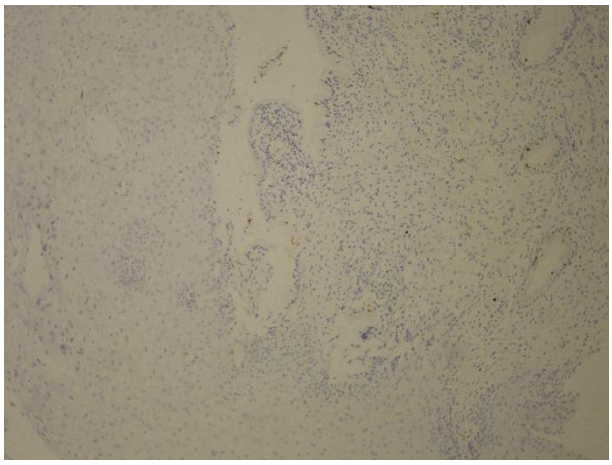

Figure 3. No staining in CIN-1 epithelium, there is a weak staining in the endocervical epithelium (Cx43x100).

Statistical Analysis

Descriptive values that measured in the study are shown as mean, minimum, and maximum.

Results

41 of these cases were diagnosed with CIN 1. The average age of these women was 44.93. The ages were ranged between 31 to 66 years. 16 women were diagnosed with CIN 2. The average age of these women was 42.06 and the ages were ranged between 28 to 65. 22 women were diagnosed with CIN 3. The average age of the women was 48.87 and the ages were ranged between 32 to 63 years.

CIN1, CIN2, and CIN3 were found to have grade 0 (negative) in staining with Cx43. Positive staining was observed in endocervical glands in all cases. There was no meaningful relationship between displasia levels and staining. Since dysplastic areas were stained negative with Cx 43, they could not be evaluated statistically according to grades (table-1).

Table-1. Cx 43 staining results in dysplastic epitheliium according to grades

CIN grades	Number	Cx 43 stain		Total
		Negative	Positive	
I	41	41	0	41
II	16	16	0	16
III	22	22	0	22
Total				79

Discussion

Some Cx's are very specific and are expressed in many tissues. One of them, Cx 43 has been reported to be expressed in 35% of the excess tissue (Beyer et al., 1995; el Aoumari et al., 1990).

The loss of cell junctional communication (GJIC) is due to abnormal proliferation and increased neoplastic phenotype. Several human tumors, including HeLa and cervical carcinoma line, have been reported to be inadequate for expression of the gap junction protein Cx43 and GJIC. To determine whether this is an early event in the carcinogenesis, King et al. screen a series of cervical biopsies using immunohistochemical techniques. They showed that there was a large reduction in Cx43 expression in the dysplasia regions as a result of the study (King et al., 2000).

There is extensive literature knowledge that suggests that these junctions are associated with cellular growth control and tissue differentiation, and tumor suppressor. It has been suggested that impairment of intracellular communication of GJ protein expression, abnormal cytoplasmic localization. Gap junctions are important events in carcinogenesis, invasion and metastasis (Nicolson et al.,1988; Carystinos et al., 2001). However, the role of Cx's in carcinogenesis and metastasis is controversial, since it is still unclear whether Cx expression is required for invasion and metastasis (Carystinos et al., 2001).

In a study by Bišanin et al., Cx43 expression was reported to be high in high grade dysplastic adenomas ($p = 0.047$), large adenomas ($p = 0.015$) and villous adenomas ($p = 0.02$) (Bišćanin et al., 2016). In adenomas, Cx 43 expression was reported to be no differences between the degree of dysplasia ($p = 0.87$) (Bišćanin et al., 2016).

In this study, Cx 43 expression was not observed in the dysplastic epithelium so there was no change in expression according to the degree of dysplasia.

In a study carried out by Hieber et al., carotenoids have been shown to increase Cx 43 expression in message and protein levels in suprabasal layers of human keratinocytes in human and mouse fibroblasts and in organotypic cultures (Hieber et al., 2000).

In a study has been reported to be a significant observation in terms of apparent suspension formation in the growth of human tumor cells (Sutherland and Bennett, 1984). Thus, Cx43 expression strongly inhibits the in vitro marker of malignancy (Sutherland and Bennett, 1984).

Expression of Cx43 in human carcinoma cells has been shown to decrease both in vivo and in vitro (Sutherland and Bennett, 1984; Nicolson et al., 1988; King et al., 2000; Hieber et al., 2000; Carystinos et al., 2001; King et al., 2002; Bišćanin et al., 2016).

Again, in a study on connexins and cancer, dysplastic epithelium staining was observed, as well as dysplasia-free glandular epithelium staining. There was no difference between staining grade and dysplasia grade (Bertram, 2004).

There have been recent publications showing that Cx 43 was negative or weakly positive in poorly differentiated carcinoma (Puzzo et al., 2016).

In the study performed by Wilgenbus et al., benign tumors and some malign tumors were studied. They reported that renal and breast cancer and sarcomas showed a significant decrease in gap-junction proteins as opposed to normal tissue (Wilgenbus et al., 1992).

Tada et al. observed that Cx expression was weak in BCC and SCC, and expression was absent in ecrine and apocrine glands (Tada and Hashimoto, 1997).

In a study by Schneider et al., Cx 43 reported cases of basal, parabasal, and middle-layer connexin (Schneider et al., 2002).

In a study on cervical dysplasia was reported that Cx 43 expression is very low in normal cervix (100%) but, Cx 43 expression in low-grade squamous intraepithelial lesions (64%) increased in the parabasal cells. As well as loss in staining (47%), weak-full-thickness Cx 43 staining (53%) were observed in high-grade squamous intraepithelial lesions. In the same study, it was noted that Cx expression disappeared as dysplasia increased (Hagemann et al., 2012).

In this study, it was seen that there was no staining in all the layers of the dysplastic epithelium. When evaluated according to dysplasia grades, it was also seen that there was a loss of full staining. Weak staining of endocervical glands was evaluated as an internal control. Normal cervix epithelium could not be evaluated because it was not included in this study. therefore, normal epithelium and dysplasia epithelium could not be compared.

Conclusion

In this study, no staining with Cx43 was observed in dysplastic surface epithelium, compared with normal endocervical gland epithelium. This condition is thought to be related to the reduce of gap junction protein in dysplastic epithelium. However, no difference was found between dysplasia grade and loss of expression

Ethics Committee Approval: Ethics committee approval was received for this study from in Clinical Research Ethics Committee of ORDU University.
Peer-review: Externally peer-reviewed.
Author Contributions: Concept – H. E., M. A. Ç.; Design H. E., M. A. Ç.; Supervision- H. E., M. A. Ç.; Materials - H. E., M. A. Ç.; Data Collection and/or Processing - H. E., M. A. Ç.; Analysis and/or Interpretation – H.E.; Literature Review - H. E., M. A. Ç.; Writing H.E.; Critical Review – H.E.
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study hasn't received no financial support.

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Middle Black Sea Journal of Health Science December 2017; 3(3):20-25

CASE REPORT

Paraspinal and Extradural Hydatid Cyst of the Spine: A Report of Three Cases and A Review of the Literature

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Received: 14 August 2017 Accepted: 25 November 2017, Published online: 20 December 2017

Abstract
Hydatid cyst of the spine is a rare form of parasitic infection, but it is a serious clinical condition that may cause paraplegia, tetraplegia, or radiculopathy. In this report, we have presented three patients with paraspinal and extradural hydatic cysts aged 36 years, 49 years, and 66 years. Diagnoses were made using computed tomography and magnetic resonance (MR) imaging. The cysts were surgically resected and patients were given albendozole treatment postoperatively. We lost one patient during follow-up due to myocardial infarction. The other two patients had no recurrence of their hydatid cysts at six months and one year after the operation. Hydatid cyst of the spine should be considered in the differential diagnosis of patients with common symptoms of spinal cord compression. MR imaging should be performed to reach a definitive diagnosis. Hydatid cyst can only be treated by complete resection of the cysts while preventing the lesion from penetrating neighboring tissues. Antihelmintic therapy started before or after the operation and maintained further reduces the risk of recurrence.
Key words: Hydatid cyst, spine, magnetic resonance imaging, albendozole

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DOI: 10.19127/mbsjohs.334582

This study was presented orally in 8th National and 1st International Congress of Hydatidology at 13-15 April 2017 in Corum, Turkey.

Introduction

A hydatid cyst is a parasitic infection caused by the larval stage of Echinococcus granulosus and Echinococcus multilocularis, predominantly involving the liver, lungs, and brain. It is endemic to areas of the world where many people raise sheep, including the Mediterranean region (Ito and Budke, 2017). Hydatid cyst disease is a public health problem in Turkey (Turgut, 1997; Karaman et al., 2015). Bone involvement affects only 1–3% of patients with hydatid cysts, half of which have the disease in their spines (Turgut, 1997; Islekel et al., 1998). Although it is a rare form of hydatid cyst, spinal disease is a serious clinical condition that may cause paraplegia, tetraplegia, or radiculopathy (Joshi et al., 2007). Spinal instability and recurrence are common complications of hydatid cysts with vertebral involvement (Somay et al., 2014). The most common site of spinal involvement is the thoracic

region (50%), followed by the lumbar (20%), sacral (20%), and cervical regions (10%) (Bhake and Agrawal, 2010). Hydatid disease of the spine can be classified into five types according to the location of the cyst: primary intramedullary, intradural extramedullary, extradural intraspinal, vertebral, and paravertebral (Braith and Lees, 1981). In this report, we have presented three cases of paraspinal and extradural hydatic cysts and discussed our findings in light of the current literature.

Case Report

The first case was a 36-year-old male patient who presented to our clinic with pain in the lumbar region. The patient had an L4–5-disc hernia that been operated on six years previously. He reported a history of falling from a two-meter height one year before presenting at the clinic, and he had experienced pain in his back and left sciatic nerve track since then. On physical examination, there was no pain at 30 degrees during the Laseque test and no sensory loss. His reflexes were normal. On

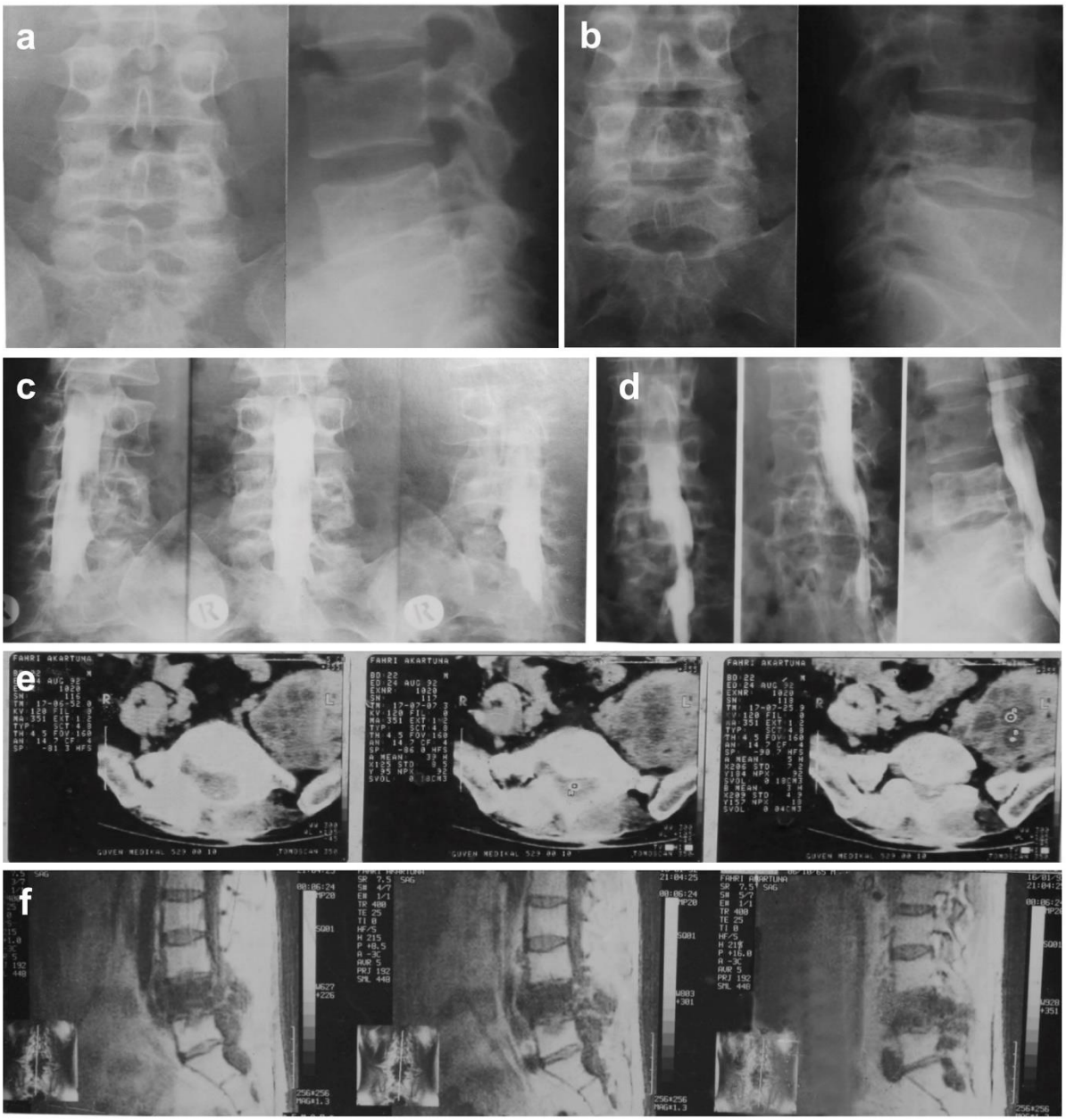

Figure 1. Preoperative X-ray (**a, b**), myelography (**c, d**), CT (**e**), and MR images (**f**) of a 36-year-old male patient with a spinal hydatid cyst.

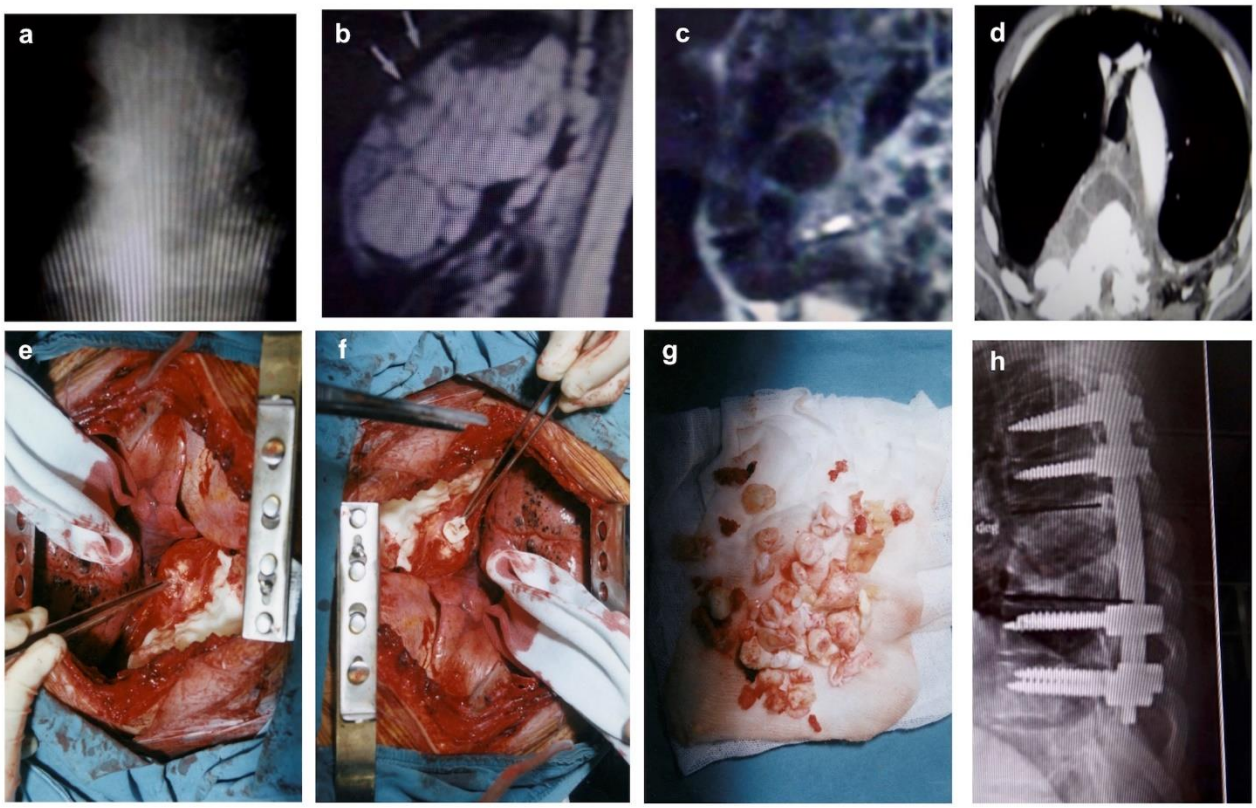

Figure 2. Preoperative X-ray (**a**), MR (**b, c**), and CT (**d**) images (**e**) of a 49-year-old male patient with a spinal hydatid cyst, who had an operation (**e, f**) in which the cysts were excised (**g**). Posterior intrumentation and fusion was performed at the T3–T8 level during the second session of surgery (**h**).

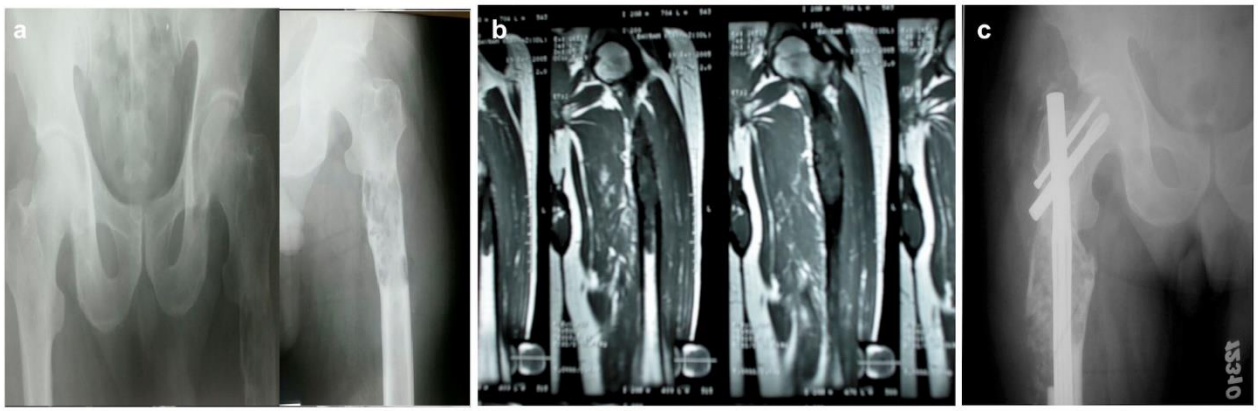

Figure 3. Preoperative X-ray (**a**) and MR images (**b**) of a 66-year-old male patient with a spinal hydatid cyst showing lytic lesions on the proximal femur in the hip joint. Postoperative X-ray image (**c**) showing the excised lesion and femoral nails used for fixation.

plain radiographs, irregular osteolytic lesions were detected at the L4 level. Myelography showed disc prolapsus of the operated discs. Computed tomography (CT) images showed intramedullary-extradural soft tissue lesions. On magnetic resonance (MR) images, there were multiple cystic lesions (Fig. 1). The patient was operated on while in the lateral Sims' position. Posterior laminectomy, clearance of cystic lesions, corpectomy, anterior fusion, and instrumentation were performed in this one-session operation. The patient's symptoms improved after the operation, and muscular strength returned to normal. He was given two doses of albendozole 800 mg/day for 12 months. There was no recurrence during one-year postoperative follow-up

The second patient was a 49-year-old male who attended to our clinic with symptoms of progressive loss of sensation and muscular strength in the lower extremities The patient was walking with a pair of armrests. Before admission to our clinic, paravertebral and extradural cystic lesions at the thoracic T5 level had been detected at another center, and the patient had refused an operation. He had been given albendozole 800 mg/day for two months. Preoperative studies included X-ray, myelography, CT, and MR imaging (Fig. 2). These showed cystic lesions. The patient had two operations one week apart. The first session was performed using the anterior-transthoracic approach. Hypertonic saline solution (20%) was injected into the cysts, and after six minutes, the cysts were excised. These were confirmed as hydatid cysts (Fig. 2). A tricortical bone graft from the iliac wing was used to reconstruct spinal defects after corpectomy. In the second session, posterior intrumentation and fusion was performed at the T3–T8 level. The patient was scheduled to continue albendozole treatment for one year. He began to walk with a single armrest at three months postoperatively. The patient died of myocardial infarction at six months after the operation.

The third case was a 66-year-old male patient who presented at our clinic with hip pain. Based on the MR images showing lytic lesions on the proximal femur in the left hip joint, the prediagnosis was aneurysmal bone cyst or hydatid cyst (Fig. 3). The patient had an operation to excise the lesions on the proximal femur, and a femoral nail was used for fixation (Fig. 3). Pathological examination of surgical specimens supported the diagnosis of a hydatid cyst. The patient was treated with albendazole 8000 mg/day for six months. In the postoperative follow-ups, union was seen, and no recurrence was detected.

Discussion

Hydatid cyst disease is a parasitic infection that affects various systems and organs of the body. Its diagnosis and treatment is difficult. Hydatid cyst disease involves the spine through vertebral-portal anastomosis (Schnepper and Johnson, 2004). Hydatid cyst of the spine is a life-threatening condition associated with high mortality and morbidity (Celik et al., 2010). Furthermore, it can persist without significant clinical symptoms, which makes diagnosis difficult. In this report, we presented three rare cases of paraspinal and extradural hydatid cyst. The primary intramedullary, intradural extramedullary, and extradural intraspinal presentations of hydatid cysts are rarer than vertebral and paravertebral disease (Onbas et al., 2004; Kahilogullari et al., 2005; Lakhdar et al., 2009). Primary intradural extramedullary hydatid cysts are an extremely rare form of parasitic infection (Kahilogullari et al., 2005; Arif and Zaheer, 2009; Lotfinia et al., 2013). In the present cases, considerably more common forms of spinal hydatid cyst (those with paraspinal, extradural, vertebral, and paravertebral involvement) coexisted.

Patients with spinal hydatid cysts are usually asymptomatic or present with compressive myelopathy or radiculopathy, with signs and symptoms varying from simple low backache to paraplegia (Joshi et al., 2007; Lakhdar et al., 2009). However, spinal hydatid cysts are often misdiagnosed, as the lesion imitates various other pathologies, such as aneurysmal bone cysts, giant cell tumors, solitary bone cysts, arachnoid cysts, neurofibromatosis, fibrocystic diseases, chondrosarcoma, and tuberculosis (Lotfinia et al., 2013; Singh et al., 2016). Since patients usually present with common signs and symptoms of spinal cord compression, diagnosis is commonly made during surgery (Pamir et al., 2002). The present cases were admitted to our clinic with back pain, loss of sensation and muscular strength in the lower extremities and hip pain, which are common symptoms of spinal cord compression.

Misdiagnosis of hydatid cysts can cause severe complications, such as rupture of the cyst and arachnoiditis (Singh et al., 2016). Therefore, clinicians should be aware of characteristic radiological signs on MR imaging with diffusion-weighted images, which are cysts with thin, regular walls that look like flattened sausages without septations or debris in the lumen, and CT should be sought for correct differential diagnosis (Berk and Erdogan, 1998). On MR images, extradural cysts are usually multiple and involve the bone (Fahl et al., 1994). Lesions appear hypointense on T1-weighted images and hyperintense on T2-weighted images (Arif and Zaheer, 2009; Eksi et al., 2014). CT and MR imaging are more valuable in the diagnosis of this condition than conventional radiography (Sami et al., 1996). Sensitivity of serologic methods have been reported between 80–100% for abdominal

disease, but 25–56% in extrahepatic involvement, which limits their use in diagnosis and follow-up of hydatid cyst of the spine (Pamir et al., 2002). The differential diagnosis includes aneurysmal bone cysts, giant cell tumors, solitary bone cysts, arachnoid cysts, neurofibromatosis, fibrocystic diseases, chondrosarcoma, and tuberculosis. In the present cases, diagnostic studies were performed using X-ray, myelography, CT, and MR imaging. Of these facilities, MR imaging provided findings most characteristic of hydatid cysts, which were multiple cystic and lytic lesions. The prediagnoses in our patients were aneurysmal bone cyst, malignancy, and disc hernia in addition to hydatid cysts.

Although hydatid cysts are symptoms of infectious disease, clinically, they behave like local malignant tumors localized in the spine. There is no generally accepted algorithm for the treatment of spinal hydatid cysts due to the limited number of cases reported in the literature. Complete resection of the spinal hydatid cyst is currently accepted as the standard treatment (Sami et al., 1996; Baykaner et al., 2000). However, surgical excision of spinal hydatic cysts is difficult due to surrounding anatomical structures and the neural foramen. In order to prevent recurrence, it is recommended that surgeons irrigate the cyst and contaminated tissues with formalin, 5% silver nitrate, or hypertonic saline during surgery. It has been reported that the lowest concentration of hypertonic saline to be used is 20% for a duration of at least six minutes (Ozdemir et al., 2011). In the present cases, we removed the hydatid cyst surgically and applied albendozole for six months to one year postoperatively. We lost one patient during follow-up due to myocardial infarction. The other two patients had no recurrence of hydatid cysts up to one year after the operation.

Conclusion

In conclusion, hydatid cyst disease of the spine should be considered in the differential diagnosis of patients with common symptoms of spinal cord compression. A definitive diagnosis should be performed using MR imaging. Hydatid cyst disease can only be treated by complete resection of the cyst while preventing the lesion from penetrating neighboring tissues. Antihelmintic therapy started before or after surgery and maintained further reduces the risk of recurrence.

Informed Consent: Necessary information using the patient information form and consent form was taken from the patients
Peer-review: Externally peer-reviewed.
Author Contributions: Concept- M.C., Design- M.C., Supervision M.C., Funding- M.C., A.U.S., Materials- M.C., Data Collection and/or Processing- M.C, Analysis and/or Interpretation- M.C, Literature Review- M.C, A.U.S., Writing- M.C., Critical Review- M.C, A.U.S.,
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not for profit sectors.

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Middle Black Sea Journal of Health Science December 2017; 3(3):26-31

CASE REPORT

Physiotherapy Outcomes in a Male Patient with Post-Traumatic Bilateral Facial Nerve Paralysis: A Case Report

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Received: 7 November 2017 Accepted: 17 December 2017, Published online: 20 December 2017

Abstract

Bilateral Facial Nerve Paralysis (FNP) due to the temporal bone fracture is rare condition. Management of the bilateral FNP is challenging. There is no study on the results of the physiotherapy in bilateral FNP. This report represented the outcomes of physiotherapy in a twenty-one years old, male patient with bilateral FNP. The functional status of the patient progressed from grade V to grade II in House-Brackmann classification. His facial symmetry also improved. The physiotherapy methods, such as massage, electrical stimulation, exercises, are useful to restore the normal facial function in this case. In conclusion, physiotherapy approaches also are effective in the treatment of bilateral FNP. It can be used as an alternative in the conservative treatment of FNP.

Key words: Physiotherapy, facial muscle, facial nerve paralysis, temporal bone fractures

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DOI: 10.19127/mbsjohs.349732

Introduction

Bilateral facial nerve paralysis (FNP) is one of the rare conditions for a physiotherapist. Its incidence is 1/5.000.000 in the world (Keane, 1994). Temporal bone fracture is a well-known cause of facial paralysis, and is responsible for approximately 3 percent of bilateral FNP (Li et al., 2004). The treatment of bilateral FNP often requires a multidisciplinary approach. In general, the earliest surgery is the first choice for treatment in severe FNP (Bascom et al., 2000). Therefore, though physiotherapy is included in the multidisciplinary approach, physiotherapists are rarely encountered with these patients in the clinic. They mostly treat Bell's palsy and report positive results (Pereira et al., 2011). Here in this report showed the physiotherapy outcomes of bilateral FNP in a male patient.

Case Report

A twenty –one years old male patient referred to us with bilateral paralysis in the facial muscle due to falling down from 8th floor, nearly one month ago. He reported that his consciousness was closed, the score of Glasgow Coma Scale score was 7/15 in the first week after the accident. The audiometric examination, showed any conductive/ sensorineural hearing loss. A high-resolution Computed Tomography (CT) of the head showed bilateral temporal bone fractures. Furthermore, the transverse fracture of right petrous bone was extended from squamous portion. The longitudinal fracture of left petrous bone fracture was distinctly (Fig. 1). The other cranial nerves were intact and there was no neurologic deficit. Only the facial nerve was disturbed with periferal involvement. The grade of House-Brackmann (HB) classification of bilateral facial paralysis was VI during hospitalization period. He started 25 mg prednisolone twice a day after the onset of paralysis and he used it during a month. In additionally, he did not receive any medical treatment. The patient was recommended to consult the physiotherapy clinic.

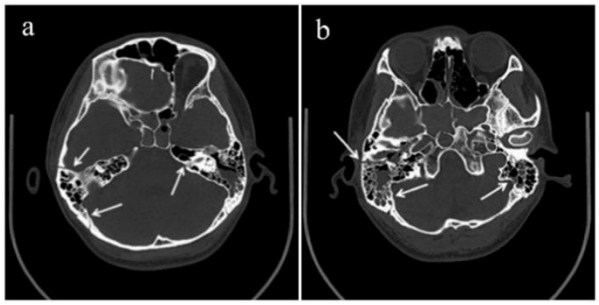

Figure 1(a,b): High-resolution CT scan showing bilateral temporal bone fractures

When the patient consulted to us, nearly six weeks after the onset of FNP, he was seen that in the grade V of HB. There was more pronounced paralyzed in the right side of the face when compared with the left side. The function of 5 facial muscles was evaluated: the frontalis, orbicularis oculi, major zygomatic, orbicularis oris, and corrugator supercilii. He had difficulty to initiate pursed lip. He could not close the right eye, whereas he could close the left eye. However, the closure was not complete. He complained of dry eyes, so he closed manually his eyes and used eye pads and drops. Any motion on the forehead was not observed. However, the contraction was taken between the eyebrows. He was compansating the movements of the eyebrows with cervical motion. Both nasolabial fold was weak. After initial neurological examination, his first electrodiagnostic testing was done by the therapist through the diagnostic charachteristics of Chattanooga Intelect Advanced Combo. The Strength-Duration Curve (SDC) was taken to the type of nerve injury (Friedli and Meyer, 1984). The results showed sign of axonal degeneration. The reobase and chronaxie values were1.7 mA and 40ms (Fig. 2). The photography of voluntary facial expressions was taken. The patient was informed that these photographs could be used clearly in this report. The patient was evaluated three times (before treatment, after treatment and at follow up period of 3 months later). Because the patient lived in a different city, the 3rd evaluation was based on photographs, so results of SDC are missing. A different physiotherapist evaluates the patient to prevent bias.

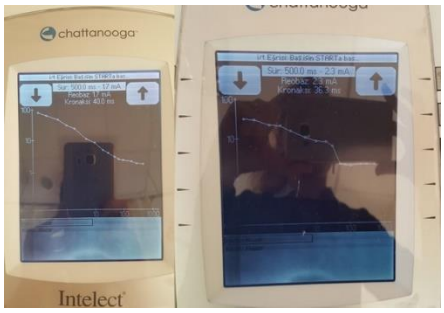

Figure 2: The illustration of the Strength-Duration Curve

He received total thirty sessions of treatment (during 6 weeks, per week 5 sessions, 60 minutes for every session). His treatment program consisted of massage, Neuromuscular Electrical Stimulation (NMES) to facial muscles, and facial exercises based on Proprioceptive Neuromuscular Facilitation (PNF) techniques. All patients were given home exercise program, that described below.

The infrared therapy was applied to prepare the muscles for massage, for 20 minutes, before the face massage. Face massage was used to regulate normal muscle tone following infrared therapy, through stroking and kneading (Diels, 2000).

Galvanic current (rectangular monophasic waveform) was used to stimulate the facial musclesThe on period of the current was 100 msec. and the off period was 500 msec. to avoid the fatigue in muscle fibers (Şimşek et al., 2015). The stimulation was applied through Chattanooga

Intelect Advanced Combo. The pencil electrode was used as active electrode, which was placed over the motor point of each muscle, whereas the carbon electrode was placed over the ipsilateral biceps brachii. The intensity was increased until the externally observed contraction. Thirty contractions of three set was taken from each muscles (Tuncay et al., 2015). The resting interval was given each thirty contractions.

Exercises were done by using a mirror to take visual feedback and check the correctness of the movement. Each exercise was repeated 10 times. The facial exercises were conducted according to (PNF) technique: rhythmic initiation, repeated contractions, tapping of the muscle belly and tendon. The propagation feature of PNF techniques between the muscles facilitiate the contraction in weaker muscles. Rhythmic initiation was used when the patient could not have started the movement. This technique improves the coordination and initiate the movement. If the function was achieved by the patient, the physiotherapist progressed the exercise from passive range of motion to manually resistive. Repeated contractions was utilizied through the range toincrease contribution of the muscle fibers, when the therapist feels that the contraction is decreasing. The reapeted contractions may be requested at any point during the movement. Tapping on the muscle belly and tendon could also facilitiate the weak contraction (Sardaru et al.,2013). The exercises based on PNF techniques were that closing his eyes, raising his eyebrows, frowning, wrinkling his nose, smiling with closed mouth, smiling with showing the teeth, pursing the lip, moving upward and downward direction the angle of lips, closing his mouth, inflating the cheek, that were applied by the author' assistance.

The home program consisted of the same exercises which were executed in the session. In additionally, the blowing balon, and the reading loudly the vowels in front of the mirror were given the patient who repeated each exercises 5 times a day, 10 repetitions.

At the end of the study his HB grading was improved grade III. The result of the last electrodiagnostic testing improved in the direction of regeneration, the curve shifted to the left. The reobase and chronaxie values changed 2.3 mA and 36.3 ms. The right hemifacial muscles did not get resistance for 6 weeks, whereas after 3 weeks, he could initiate facial expression. However, the movements in the right hemifacial could not be completed at the end of the therapy. The some of the left hemifacial muscles, corrigator supercilii and frontalis, got the resistance. His right orbicularis oris was more effective to purse lip. Both nasolabial fold was distinct. He could close the eyes and the closure of the left eye was stronger than the right one. The left frontalis could contract efficient, whereas the right frontalis was inefficient, only the contraction was taken. The frowning of the eyebrows was visible (Fig. 3-7).

Figure 3: The improvements in the closing eyes

Figure 4: The improvements in the pursing lip

Figure 5: The improvements in the smiling with showing the teeth

Figure 6: The improvements in the frowning the eyebrows

Figure 7: The improvements in the raising the eyebrows

The last evaluation which is at the follow–up period, 3 months after the treatment, was done on the photography (Fig. 3-8). His HB grading progressed to grade II. He could close his eyes without the need of maximum effort. He could frown and raise the eyebrows symmetrically. He could smile while he shows teeths. He could purse lip in the middle line. His resting facial symmetry and coordination between face muscles was exellent (Fig. 8).

Figure 8: The coordination and symmetry in the facial muscles

Discussion

Facial expression is essential for an effective human communication. Loss of facial expression after facial nerve injury have a great impact on the psychosocial conditions of the patients (Kiese-Himmel et al., 1993). Therefore, FNP should be treated immediately to restore facial function and the decrease the psychosocial impact on the patients. Treatment of FNP included pharmacologic therapy, physical therapy, chemodenervation, and surgical interventions. Massage, termotherapy, NMES, facial exercises, and biofeedback are approaches of physical therapy that have been used for unilateral FNP (Teixeria et al., 2011). In my knowledg, there is no study about physiotherapy outcomes of bilateral FNP in the literature. The present report showed that the physiotherapy is effective to improve the facial function after the post-traumatic bilateral FNP in a male patient.

Bilateral traumatic FNP occurs after longitudinal petrous fractures across the skull base. Longitudinal fractures of the petrous bone account for 90% of all fractures and causes bilateral FNP in 10-25% of patients (Li et al., 2004). The recovery of the longitudinal fractures is better than the transverse fractures, so the physiotherapy and rehabilitation program may also have resulted successful for this case.

Rehabilitation of nerve injury is difficult for complete recovery. The success of rehabilitation is related to the type of injury, acute or late-onset, severity of paralysis, localization of the injury, the time for initiation of physiotherapy, and the patient's compliance. Almost complete recovery was seen in this case, 5 and a half months after injury. He reported that he was pleased with his development. The patient's positive thoughts about the treatment shows that physiotherapy can be used as an alternative method after the bilateral FNP.

The numerous modalities in physiotherapy are used for treatment of Bell’s palsy (Brach and Van Swearingen, 1999), however there is lack of high quality evidence to support the use of these strategies. Electrical stimulation, exercises, biofeedback, manual therapy, shortwave and laser were evaluated in some studies, but only trials involving electrostimulation and exercise had the minimum methodological quality (Teixeria et al., 2011). The use of NMES for nerve palsy is still controversy. Cederwall et al. reported that NMES was harmful for reinnervation (Cederwall et al., 2006). In contrast, Foecking et al. showed that NMES enhanced the regeneration in rats (Foecking et al., 2012). Tuncay et al. highlighted that the positive improvements occur when NMES combined with the conventional therapy (Tuncay et al. 2015). Similar to this study, in present report, NMES was used together infrared therapy,

massage, exercises based on PNF techniques, showed successful functional outcomes of physiotherapy.

In the treatment of FNP includes also other medical treatment methods and surgery. Bodonez et al showed that good results (grades I to II on the HB scale) were obtained in 63% of cases (n=38) after medical management and in 39% of cases (n=26) after surgical treatment in patients with facial paralysis following temporal bone fracture. However, they also showed poor improvement in 13% of medically-treated patients and 42% of surgically-treated patients (Bodonez et al. 2006). The choice of the treatment method may vary depending on the extent of the injury, patient compliance and patient characteristics.

Besides physiotherapy approaches, the evaluation method is also important. Which treatment is applied in the treatment of facial paralysis, it is also necessary to evaluate the treatment outcomes through an objectively and visibly method. The assessment by photograph was practical to determine the improvement of facial function. In this case, the assessment by photograph has made visible the improvement of the facial function in time. This method provides a concrete proof of the treatment outcomes to the patient, thus contributing to the emotional state of the patient.

The lack of last SDC results is limitation for the present case report. Further studies are needed controlled, larger sample of size to determine the efficiency of physiotherapy in bilateral FNP with different severity.

Informed Consent: The written consent form was taken from the patient.
Peer-review: Externally peer-reviewed.
Author Contributions: Concept- S.A.C., Design- S.A.C., Supervision- S.A.C., Funding- S.A.C., Materials- S.A.C.,Data Collection and/or Processing- S.A.C., Analysis and/or Interpretation- S.A.C., Literature Review- S.A.C., Writing- S.A.C.,Crictical Review- S.A.C.
Conflict of Interest: No conflict of interest was declared by the author.
Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not for profit sectors.

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Middle Black Sea Journal of Health Science December 2017; 3(3):32-40

REVIEW

Do Not Resuscitate Order and Elderly

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Received: 19 Semtember 2017 Accepted: 18 November 2017, Published online: 20 December 2017

Abstract
Cardiopulmonary resuscitation is a choice that must be made between the return of life and the end of life. It is still a matter of controversy when and where cardiopulmonary resuscitation will be implemented, and this discussion has brought the "Do Not Resuscitate" order to the agenda. For this reason, "Resuscitation" and "Do Not Resuscitate" order lead to many ethical and legal dilemmas. The "Do Not Resuscitate" order, which is a difficult decision to make, becomes more difficult in the old age when ethical problems are frequent. Because of chronic diseases and deterioration in cognitive functions, the ability to make decisions about health practices of elderly individuals who are becoming increasingly dependent in terms of physical and psychosocial dimensions are also diminishing. In addition, lack of awareness, sensory/emotional barriers and communication deficits prevent elderly people from participating in health care decisions; it makes difficult to determine care target among the elderly and health professionals. Especially to be adequate to the needs of nursing care for the elderly, the problems related to "Do Not Resuscitate" instruction which is an important part of end-of-life maintenance need to be solved. For this purpose, the "Do Not Resuscitate" order should be handled by health professionals and lawyers in a versatile manner and necessary legal arrangements should be made.
Key words: Elderly, Nursing, Do Not Resuscitate, DNR Order

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DOI: 10.19127/mbsjohs.338904

Introduction

Every moment of human life is very important. In modern societies, the common goal of all medical interventions is to protect life, to restore individual health, to relieve pain and to limit loss of function according to priority order (Yokusoglu et al., 2008; Cicekci and Atici, 2013). However, as a consequence of the directing of social values, the moment of birth and death has become more important for all people. In parallel with the rapid development of medical technology, the beginning and the end of life can be intervened, the moment and the shape of death, as well as birth, has also become a condition that can be intervened medically. Some medical interventions are separated from others. Because they make us feel that human life and moments in life are the most precious things. In numerous medical interventions, "cardiopulmonary resuscitation" (CPR), which has a separate importance in the thin line between life and death, is an error-free intervention that must be done correctly with

correct technique (Gonenc, 2015). CPR applied at a critical point between life and death; is defined as sustaining the airway opening and supporting the respiratory and circulatory system of the patient whose respiratory and circulatory system stop functioning for any reason (Karatas and Selcuk, 2012; Kozaci, 2013).

Today, the debate over whether CPR practices are implemented in patients who are at end-stage and with a life expectancy that is very short after the resuscitation is very common and frequent (Sert et al., 2007). The goal in CPR, which is as old as human history, is to return the clinical death when it is still in recovery (Yokusoglu et al., 2008). As a general approach, the decision to administer CPR should be based not only on the development of the arrest but on the individual evaluation of the underlying disease and the patient. This brings the implementation of "Do Not Resuscitate" (DNR) orders to the agenda (Kellum and Dacey, 2009; Tel, 2012). The changing age structure in the world and Turkey suggests that these discussions will focus on the elderly with the least life expectancy and with most frequent chronic illnesses in the coming years (Seder et al., 2014). In addition, the decision for CPR or DNR in the elderly is much more important because being elder reduces the chance of survival after CPR and the quality of life after survival (Glind et al., 2013).

Young people are more likely to give DNR orders than older people (Cherniack, 2002). It has been reported that older age is the strongest factor in making DNR decision, as well as facilitating various factors such as comorbid conditions, psychiatric disorders, oncologic diseases, low quality of life and poor prognosis (Glind et al., 2013). In recent studies, elder ages have laid the groundwork for DNR decision making by strengthening other factors (Chevaux et al., 2015); it was found that with increasing age, the rate of giving DNR order increased (Messinger-Rapport and Kamel, 2005). Cherniack states that, regardless of prognosis, older patients are given DNR order more often than younger patients (Cherniack, 2002). In addition, end-of-life care is an important part of overall patient care, and the DNR decision is an important part of end-of-life care. Together with DNR instruction, the elderly person himself, family or surrogates can actively participate in the treatment process, become involved in the care, and reduce useless medical interventions (Phillips et al., 2011; Yang et al., 2012).

There are more ethical problems in treatment and care due to the elderly person has chronic diseases, impairment of cognitive functions and decision making, economic, social, physical dependencies and inadequacies. As the elderly person can experience problems in monitoring and evaluating progress in treatment, care, technological development, ethical dilemmas can arise as a common problem in decisions about self (Karadakovan, 2014). For this reason, the dilemma of applying resuscitation in the elderly can be discussed with a long discussion about the rules in which the "DNR" order can be decided on the legal framework. In this review, the aim is to raise awareness of DNR instruction, attitudes towards the DNR order in the elderly, guidelines for the DNR instruction, recommendations and the ethical / legal dimension in relation to DNR, which is a controversial subject in the world and in Turkey.

“Do Not Resuscitate” Order, Physician Attitudes and Nursing

"Do Not Resuscitate" is defined as "Do not apply preventive supportive care for the life of patient whose cardiac and respiratory functions come to an end or do not apply all the measures in practice in this process " (Sert et al., 2007). However, DNR order is a treatment option written in treatment of the sick individual with poor prognosis and who wants to die clinical conditions (Glind et al., 2013; Sumrall et al., 2016).

Physicians' attitudes about DNR orders varies in many countries. Most physicians in the UK and Japan are ready to write and implement DNR orders even if the patient is against it. Doctors in Israel believe that more communication needs to be made about the treatments that keep patients alive. The attitudes of physicians regarding DNR orders vary according to the area of specialization of the physician. Geriatricologists in the UK are more likely to choose resuscitation than do other physicians. Many doctors in Saudi Arabia state that their own decisions and legal situations are also important, while not considering DNR orders for previously healthy patients (Cherniack, 2002).

American practitioners' attitudes towards DNR orders are contradictory. Half of all physicians and nurses reported that they acted against their consciences in the resuscitation of patients with end-stage illnesses. It is stated that most physicians

in USA want the patient's participation in the decision-making process, but many physicians are uncomfortable discussing DNR instructions and rarely discuss the possibility of CPR with patients other than special issues (eg fatal sickness). It is stated in the literature that 34% of physicians abandon CPR despite the request of the patient and only 40% of physicians in USA say that they will never regard the DNR order as valid even though it is requested by the patient or evaluate the CPR application useless. Also, physicians reported that hospitals had low levels of support and knowledge for DNR policies (Cherniack, 2002).

Nurses, who have an important place in the prevention of end-of-life interventions and the symptoms that may develop for the patient and the family, provide services directly to the patients and their families for their needs. Nurses who are leaders and advocates of decent care for human dignity should actively participate in the process of performing appropriate interventions for mediacal care and evaluating the outcomes in order to reduce the treatments that patients may not want or may suffer from (AHA, 2015). In addition, adequate informing of getting the constent of patients before care-related practices is one of the ethical obligations of nurses. As stated by the International Council of Nurses (ICN), ethical codes of nursing are based on ethical principles of "fundamental human rights, individual respect and justice". As stated in the Universal Declaration of Human Rights, which is the cornerstone of nursing ethical codes, the fundamental rights of a person, in particular 'the right to life', must be respected (ICN, 2012).

In addition, the American Nursing Association (ANA), which supports the right of patients to make free decisions, offers nursing care that protects patient autonomy, honor and rights that will contribute to the resolution of ethical problems. American Nurses Association; encourages nurses to support their patients and their families to make end-of-life decisions, including DNR instructions, and to make choices. ANA adopted the DNR procedure and nursing care report in 2003, on the basis of a report published in 1991 entitled "Providing comfort and relieving pain for the dying patient," which indirectly addressed the DNR order (ANA, 2012).

Nurse should play an active role in initiating discussions on DNR order with families and members of the health care team and be supportive in decision-making. However, despite all the facilities offered for making choices to patients, families and legal surrogates, the dilemmas and challenges of DNR instruction still exist. In this context, nurses find it difficult to discuss the DNR order with patients. The most important reason for this is the fear that patients may suffer from such disputes and refer patients to severe anxiety or hopelessness. Again elderly individuals; can not participate in decisions regarding their own health even if they want because of lack of awareness, fear and emotional hurdles, ineffective communication, lack of trust, inability to deputy assignment and cultural factors. This creates obstacles between the nurse and the patient in terms of understanding the care goals supported by the nurses and to give a decision for written DNR orders (ANA, 2012; Fadıloglu, 2014).

It is an opinion accepted by both the health care team and other individuals (family, close friends, etc.) that elderly people should participate in this decision about using or not using resuscitation (Fadıloglu, 2014). However, when the discussion of this order emerges as a need, the elderly person may no longer have the ability to participate in the decision-making process (Akpinar and Ersoy, 2012). In addition, because it is the choice which must be made between returning to life and ending the life, applying or not appliying CPR can lay the groundwork for complex ethical and legal problems. For this reason, it is important and necessary that DNR orders are prepared earlier. In this respect, if the report published by the American Health Association (AHA) for all sick individuals regardless of age about the preparation of the DNR order is examined, it appears that there are three main items in the preparation of this order. These are; "Taking the patient's choice as a basis for refusing to practice CPR", "Taking the choises of patients' relatives or surrogetes as a basis for refusing to practice CPR", and "Based on the judgment of the physician about the patient and not applying resuscitation to the patient" (AHA, 2015).

Preparation of "Do Not Resuscitate" Order

1. Taking the elderly patient preference as the basis for refusing to apply CPR:

Adequately informed individuals have the right to permit or deny the medical interventions, including CPR both ethically and legally (AHA, 2015). Although most elderly patients want to express

their desire for CPR, it is discussed by the physician whether resuscitation is requested (Cherniack, 2002). The data of Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment Project states that only one quarter of the approximately 1000 elderly patients seriously discuss CPR with physicians. In a study with approximately 400 elderly patients living in a nursing home, similarly one quarter of elderly people were asked by physicians whether they had a desire for CPR (Cherniack, 2002). The right to refuse medical treatment does not depend on whether the patient is in the end-stage, whether the family members agree or do not agree and the aproval of the physicians (AHA, 2015). The individual may have already reported in detail the desire of he or she does not want to undergo CPR in the event of a cardiac arrest, and this may form the basis for the preparation of this DNR order. DNR orders; facilitate autonomous movements, and allow treatments to extend their life span to be implemented in line with their own preferences with the condition that individuals have the ability to make decisions (AHA, 2015). When the cognitive abilities necessary for elderly individuals to decide on CPR practice deteriorate and CPR request stated before by the elderly patient and the current CPR request conflict with each other, physician and family members' requests are reported to be very important (Cherniack, 2002).

2. Taking as a basis for the decision of refusing resuscitation from relatives of patients or other surrogates:

Decision to stop resuscitation of elderly patient in a hospital with a severe condition is usually provided by family members rather than by the patient itself and the physician (Cherniack, 2002). If the individual does not have the capacity to make a DNR decision, the decision is made by the person designated as the surrogate (AHA, 2015). The choice of surrogates is determined by the preferences of the individual in advance. If the patient's preference is not known, the patient's beliefs and life expectancies are taken into consideration. In this case, the patient's physician may take into account the detailed preferences of the patient or decision resuscitation may be taken by a suitable surrogate. Detailed preferences include; speeches, written directives and witnesses. The most common form is the patients' speech with patients' relatives, friends or physicians before they lose their abilities. In some cases, the individual chooses the person who will be surrogate in the presence of a lawyer before losing his or her competence. If a surrogate is not selected by the patient in this way, the law will assign relatives as surrogates (AHA, 2015). However, family members may misinterpret the elders' wishes. It is stated in the literature that family members interpret patients' CPR preferences lower than they are, and even when they prefer DNR, they often do not realize this, but they understand CPR more than elderly patient and predict the probability of success of CPR (Cherniack, 2002).

3. Taking as a basis for the decision of not to apply resuscitation for the patients based on physician's judgment about the patient:

The decision of physician, which is making the CPR application useless, is the basis for the preparation of the DNR order. All health professionals are asking patients to be actively involved in making this decision when a DNR decision is made. However, this is not practiced literally in practice. The absence of individual at the decision stage, the failure of application of medical procedures during resuscitation, the probable prognosis of CPR, and the failure to take into account the individual's own values and preferences during the application of decisions may lead to false impressions (AHA, 2015). The inability of physicians to provide the participation of patients and even family members in the decision to DNR order for elderly patients may suggest that physicians are biased towards elderly and make ageism (Cherniack, 2002). Therefore, a guide has been prepared by the AMA to help the health team in order to make a decision about whether CPR is appropriate, or not for the patient and be able to prepare DNR intructions in this direction. This guide, first published in 1973 by the Council on Ethical and Judicial Affairs-CEJA and American Medical Association-AMA, was updated in 2005 as the last.

Guidelines Prepared by the American Medical Association for the Proper Use of the DNR Order:

1. CPR is administered in patients with cardiac or respiratory arrest, or is not administered when CPR administration is considered to be ineffective or inconsistent with the patient's wishes and values.

2. Health professionals should discuss the possibility of cardiopulmonary arrest with appropriate patients (AMA, 2016). In the United States, elderly outpatients want to discuss CPR with their physicians and expect that their physicians bring the issue to the agenda when their health is better. However, most older people do not talk to their physicians about their CPR, and those who speak about CPR stated that they are able to understand very little about what CPR is exactly (Cherniack, 2002). Elderly individuals at risk for cardiac or respiratory insufficiency should be encouraged to report their CPR preferences in detail. These discussions and all other procedures within the CPR should be described and should be made at the earliest stage, if possible, at the outpatient clinic or hospital admission, and most importantly when the elderly has mental decision-making capability (AMA, 2016). The majority of elderly patients who are treated as outpatients, who are in severe condition and who live in nursing homes in the United States want CPR and want to be part of the CPR decision-making process (Cherniack, 2002). Early discussions on CPR can help patients actively participate in decision-making. In addition, periodic interviews can change the patient's preferences, along with the treatment alternatives that can change over time (AMA, 2016). In a study of approximately 1000 elderly patients with a critical condition, it was determined that one of five elderly patients changed their mind after two months (Cherniack, 2002).

3. If the elderly is unable to make a decision about the use of CPR, and if the preference of the elderly is not known before, a surrogate is assigned taking into account the most valuable aspects of the patient.

4. The health team must adhere to the ethical preferences set by the elderly or surrogate. The own value judgments about the quality of life of health professionals should not interfere with the preferences of the patient or his / her surrogate regarding the use of CPR (AMA, 2016). However, older people with lower quality of life may also have a lower CPR preference due to illness. In the US, CPR preferences of the elderly have been found to be associated with some demographic variables such as "being younger, being more functional, being less educated, believing in technology and male gender" (Cherniack, 2002). In addition, if CPR treatment is deemed ineffective according to the physician, the DNR instruction must be written in the patient's file. In addition, if CPR treatment is deemed ineffective according to the medicine, the DNR instruction must be written in the patient's file. If sufficient time is available, the elderly person should be informed and if the elderly can not decide, the content and application of the DNR order should be explained to the surrogate with its basic reasons (AMA, 2016). Elderly individuals have low CPR desires in terminal illness, permanent cognitive or functional impairment (Cherniack, 2002).

5. Resuscitation is deemed ineffective if it can not restore cardiac or respiratory functions or if the intended purposes of the informed elderly can not be achieved.

6. DNR order should be written by the patient's physician in the patient's file as it is in practice.

7. DNR guidelines foreseeing limiting the applications bringing back to life only in cardiopulmonary arrest situations and should not affect other medical interventions appropriate for the patient.

8. The hospital medical personnel should periodically repeat their experience with the DNR procedure, and the hospital's DNR policy should be appropriately renewed. In addition, physicians should be trained in accordance with the role in the DNR decision-making process (AMA, 2016). It is reported that physicians may sometimes ignore DNR instructions, may be reluctant to practice CPR, and may develop uncertainty or opposition to hospital DNR policies (Cherniack, 2002).

Similar to the guidelines prepared by the American Medical Association, the American Nurses Association also make suggestions to nurse practitioners to overcome the difficulties in the implementation of DNR orders;

Recommendations of the American Nurses Association:

1. Clinical nurses should discuss the changing care goals with patients, families and other important persons on a timely and frequent basis and actively initiate the discussion of DNR treatment (AORN, 2016). Nurses in the United States indicated that they would like to participate more in the DNR decision process (Cherniack, 2002).

2. Nurses should register the patient's DNR orders clearly and update this order at regular intervals to determine the care goals that vary according to the circumstances of the patient.

3.Admin nurses should support practitioner nurses to start the discussion of DNR order.

4.Nursing home managers and hospital nursing managers should develop a standard form that can be used between institutions in DNR order.

5.Admin nurses should provide palliative care support for all patients.

6.The nurses providing education should teach practitioner nurses that DNR order does not mean stopping or reducing the treatment and other practices. DNR does not mean “do not cure”. Attention to this point is the most important thing and different naming such as “do everything”, “do nothing”, or “reduce treatment and care” should not be used to indicate the presence or absence of the DNR order.

7.The trainer nurses should develop and implement special education programs for physicians and other members of the interdisciplinary health care team for DNR order including conversations and discussions about DNR order, achieving natural death.

8.Researcher nurses must investigate the DNR process in all directions to create a proof-based practice.

9.All nurses should be sure that the DNR decision is a clear discussion between the health care team, the patient and the family (or a designated surrogate), and that decisions are made in line with the request of the patient (AORN, 2016). British and American nurses indicate that patient requests should never be invalidated and that the patient preference should be strongly considered in the DNR or CPR practice (Cherniack, 2002).

10.All nurses; should be able to participate in interdisciplinary mechanisms for the resolution of disputes between patients, their families and clinicians and should facilitate the DNR order (AORN, 2016). German nurses are more inclined to resuscitation than British and Swedish nurses; Australian nurses believe that their effects for resuscitation decisions are high; almost half of the Japanese nurses participate in the DNR decision, and one-third of them believe that the DNR order should not be written without the patient's consent (Cherniack, 2002).

11. All nurses should actively participate in the work for the development of DNR policies at the institutions they work. In particular, policies should be addressed or explained as follows:

•Patients who have evidence that they do not want CPR but who do not give written DNR order should be directed to apply to health professionals.

•Medical documents should be established stating how this decision was made for the DNR order.

•The duties and responsibilities of the various health professionals who will communicate with the patient and the family in relation to the DNR order should be determined.

•It should be ensured that the DNR order is explained effectively to the other institution during patients' transfer between institutions.

•Effective communication between health personnel should be made in order to prevent stigmatization and confidentiality violations for the patient who give DNR order.

•The practitioner should be guided for special cases (such as patients who are to be operated or undergone invasive procedure etc.) for which the DNR order needs to be revisited.

•The needs of the patients with special status such as pediatrics or geriatrics for the DNR order should be determined.

Legal Dimension of the "DNR" Order

The limitation of CPR practice in the world was considered a professional mistake before 1990, but after 1990, the US Senate issued a law requiring patients to make their own decisions about treatments to be applied to their own names. It has been stated in this law that came into force since December 1991 that individuals have the right to "refuse medical treatment and formulate their detailed preferences". In addition, it has been stated that health institutions should pass written documents containing advanced directives to the records (Sert et al., 2007).

Although there is no special provision or section regarding the restriction of DNR or resuscitation in the Turkish Penal Code (TPC), there is a section under the name of "euthanasia" dealing with the question of whether the right to refuse treatment is available or not, or if it is, to what extent and who can use these rights. The article 25 of the Turkish Penal Code includes this state that “The patient has the right to refuse or stop treatment." (Yuksek Saglik Surası, 1970). The first principle for this is autonomy. Autonomy means that an individual has

the right to determine interventions to his or her body or health according to their own values and priorities. According to this principle prerequisite for medical intervention is the patient's informed consent; the patient has the right to refuse his or her life-sustaining treatment (Fadıloglu, 2012). However, there are provisions for euthanasia and passive euthanasia and Article 13 of the TPC states that euthanasia is prohibited (Yuksek Saglik Surası, 1970).

In the Patient Rights Regulations, consisting of nine sections and 51 items and prepared based on Basic Law on Health Services No. 3359 dated 5/15/1987, Updated in May 2014, and the eighth and 40th articles of Decree-Law No. 663 dated 10/11/2011 on the Organization and Duties of the Ministry of Health and its Affiliates;

"Article 13- Euthanasia is forbidden. Regardless of medical requirements or whatever the circumstances, life can not be waived. No one's life can be discontinued even if he or someone else's request is made."

"Article 14- The healthcare professional demonstrates the medical care required by the condition of the patient. Even if it is not possible to save the patient's life or protect his or her health, it is imperative to try to reduce or relieve suffering."

However, even if the exact equivalent of the DNR order is not included in the TPC, in the same regulation;

"Article 24- The consent of the patient is required for the medical interventions."

"Article 25- Apart from the cases that are legally obligatory and when the responsibility of the negative consequences that may arise belong to the patient; the patient has the right to refuse or to stop the treatment that is planned or being applied to him / her" (Mevzuati Gelistirme ve Yayin Genel Mudurlugu, 1998).

Conclusion

It is anticipated that CPR, which is known to be widely applied all over the world, will need to be implemented more and more with the changing population structure. This will raise questions more frequently about the conditions under which CPR should be applied. In this regard, health care team, patients, patients' relatives and patients' surrogates have important responsibilities. This decision brings as much difficult and heavy responsibilities as it is important. Because it can create dilemmas for health professionals in terms of ethical and moral values as well as legal responsibilities. Again, high-probability situations such as impairment of cognitive functioning and lack of mental competence to give these instructions in the elderly stand out against the health care team as a background to other problems. There are guidelines and recommendations that have been prepared by health associations such as AMA, AHA and ANA for DNR decision to minimize all these difficulties and to overcome the controversy. Health professionals should use frequently these guidelines and recommendations when preparing DNR instructions the instruction system should be structured to determine the advanced directives that elder people can give the DNR instructions first. In order to make this decision, patient autonomy, values and individual priorities should be taken into account and patients should be actively involved in this decision. "Hospital Ethics Committees" should be established to consult especially for elderly patients for surrogates if the patient does not have the ability to make decisions, for health care team in order to consult other colleagues if the patient does not have surrogate. At the same time, these initiatives mentioned should be addressed by health professionals and lawyers in a multi-faceted way by taking into account their own values of the society and ethical principles should be set forth. These principles should be supported by legal regulations and should lead to practices in health institutions.

Peer-review: Externally peer-reviewed.
Author Contributions: Concept- B. C., Design- B. C., Supervision- S. H., Literature Review- B. C., S. H., Writing- B. C., S. H., Critical Review- B. C., S. H.
Conflict of Interest: No conflict of interest was declared by the author.
Financial Disclosure: The authors declared that this study has /hasn't received no financial support.

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Yuksek Saglık Surası 25.2.1970/ 6324, Yargıtay 4. Ceza Dairesi 28.2.1970, 28.2.1945/1394.6. 1970.

Middle Black Sea Journal of Health Science December 2017; 3(3):41-48

REVIEW

Perioperative Arrhythmias

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Received: 15 November 2017 Accepted: 06 December 2017, Published online: 20 December 2017

Abstract
Arrhythmias are the most commonly encountered cardiovascular complications during anesthesia administration. Perioperative arrhythmias disrupt the hemodynamic state of the patients and are known to cause increases in mortality and morbidity. Anesthetic agents and methods affect cardiac conduction and cause arrhythmia. At the same time, patients with additional cardiac diseases and other systemic diseases affecting the cardiovascular system have increased risk of perioperative arrhythmia. For the patient, regardless of whether due to the surgical procedure or anesthesia type, the most important effect of intraoperative arrhythmias is undoubtedly the resulting hemodynamic instability. It is possible to encounter a broad range of serious rhythm and hemodynamic disorders from rare ventricular extrasystole to malignant character arrhythmia and sudden cardiac arrest. Temperature changes occurring in the intraoperative period, hypoxia, acid-base disorders and variations in electrolyte balance are significant factors affecting the occurrence of arrhythmia. As there are many factors and mechanisms in the etiology, identifying arrhythmia under anesthesia and performing the necessary intervention in the shortest time possible has vital importance. This review deals with the importance of arrhythmia occurring in the perioperative period and methods of approach for arrhythmia.
Key words: Arrhythmias, perioperative period, anesthesia

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DOI: 10.19127/mbsjohs.353187

Introduction

Arrhythmias are cardiovascular complications commonly encountered in the perioperative period that may be very serious. The rate of arrhythmia encountered with general anesthesia administration is known to reach up to 70% (Erdemli and Çekmen, 2010; Yapıcı and Azizoğlu, 2015; Kwon and Kim, 2017). During the patient's hospital stay beginning in the period before surgery, anesthesia and reanimation clinicians encounter arrhythmias and have to intervene. Perioperative arrhythmias are known to lengthen hospital stays and increase mortality and morbidity (Polanczyk et al., 1998; Thompson and Balser, 2004). The patients' clinical properties, surgical procedure and anesthesia method play an important role in the occurrence of perioperative arrhythmias. During physical examination, patients without any rhythm disorder identified may have diseases or syndromes that

cause arrhythmias (Timuralp, 2010). Arrhythmias that are usually identified during preoperative assessment and can be controlled by appropriate methods may be encountered many times unexpectedly during the intraoperative and postoperative period. Generally, these arrhythmias, occurring linked to an underlying disease, occur independently of the predisposing factors of surgical cases (Tyler, 2015). The localization and dimension of the surgical procedure may facilitate the occurrence of arrhythmias. For example, strabismus surgery is a risk factor for bradycardia, while cardiac surgeries may precipitate different arrhythmias (Kwon and Kim, 2017). Anesthetic agents may affect the cardiovascular system with different mechanisms and cause severe arrhythmias. It will be beneficial to discuss the normal cardiac cycle to better understand arrhythmias. As is known, normal cardiac conduction begins with cardiac impulses coming from the sinoatrial (SA) node. From here the impulse first passes the atrioventricular (AV) node, then reaches the His bundle and Purkinje fibers transforming into conduction causing ventricular contraction (Beton and Tandoğan, 2011; Kwon and Kim, 2017). The normal heart rate of adults is 60-100 beats/min. Arrhythmias occur depending on disorders in the formation of this impulse and/or during conduction (Zoghi and Duygu, 2006).

Perioperative arrhythmias

To identify the arrhythmias, anesthesiologists need to know how to interpret basic ECG procedure (Fig 1).

- Analysis P wave
- Analysis QRS complex
- Determine PR interval
- Determine ventricular rhtyhm or regularity
- Determine atrial rate or regularity
- Analysis T wave
- Determine heart rate
- Interpret the rhythm

Figure 1. Basic procedure of rhythm analysis

Sinus bradycardia: This is defined as a regular rhythm with heart rate below 60 beats/min (Fig 2). It may be observed as normal in healthy elderly patients and sportive young people. Additionally, it is observed in situations with the use of anti-

Figure 2. Sinus bradycardia

arrhythmics (beta blockers, etc.), the effect of anesthetic medications (opioids, inhalation agents, succinylcholine), increased reflex vagal stimuli and increased intracranial pressure. Symptomatic bradycardia should be treated with atropine; if no response occurs, giving adrenalin or inserting a pacemaker should be considered. As the American Society of Anesthesiologists (ASA) classification risk increases, it is known the probability of bradycardia increases (Erdemli and Çekmen, 2010; Timuralp, 2010; Yapıcı and Azizoğlu, 2015).

Sinus tachycardia: This is defined as a regular rhythm with heart rate generally above 100 beats/min (Fig 3). It is most commonly observed in situations with hypovolemia, increased body temperature, pain sensation, hypercarbia, anemia and hyperthyroidism. Tachycardia accompanying anesthesia may be related to dangerous situations like malignant hyperthermia and myocardial ischemia. This arrhythmia generally resolves with intervention to the underlying cause, and symptomatic tachycardia disrupting hemodynamics should be rapidly treated (Yapıcı and Azizoğlu, 2015; Kwon and Kim, 2017). Treatment choices include non-dihydropyridine calcium channel blockers (diltiazem, verapamil), beta blockers and digitalis.

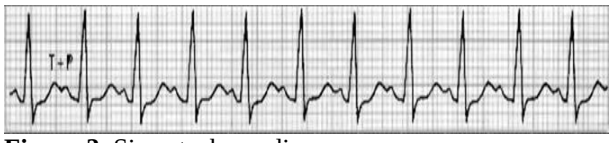

Figure 3. Sinus tachycardia

Sinus arrhythmia: This is an arrhythmia related generally to respiration with no significant clinical and hemodynamic importance. There is a pattern of increasing with inspirium and reducing with expirium. It occurs due to the SA node being affected by vagal stimuli (Timuralp, 2010; Yapıcı and Azizoglu, 2015). It is generally observed in children and young people. It does not require treatment.

Sick sinus syndrome: This is defined as the combination of bradycardia and SA block. It should be recalled when elderly patients under anesthesia develop sudden bradycardia. Pacemaker treatment has the most importance for treatment (Erdemli and Cekmen, 2010).

AV Blocks: AV node diseases occur with increased vagal tonus, coronary artery disease, infections, endocrine causes, neuromuscular diseases and some medications (Fig 4).

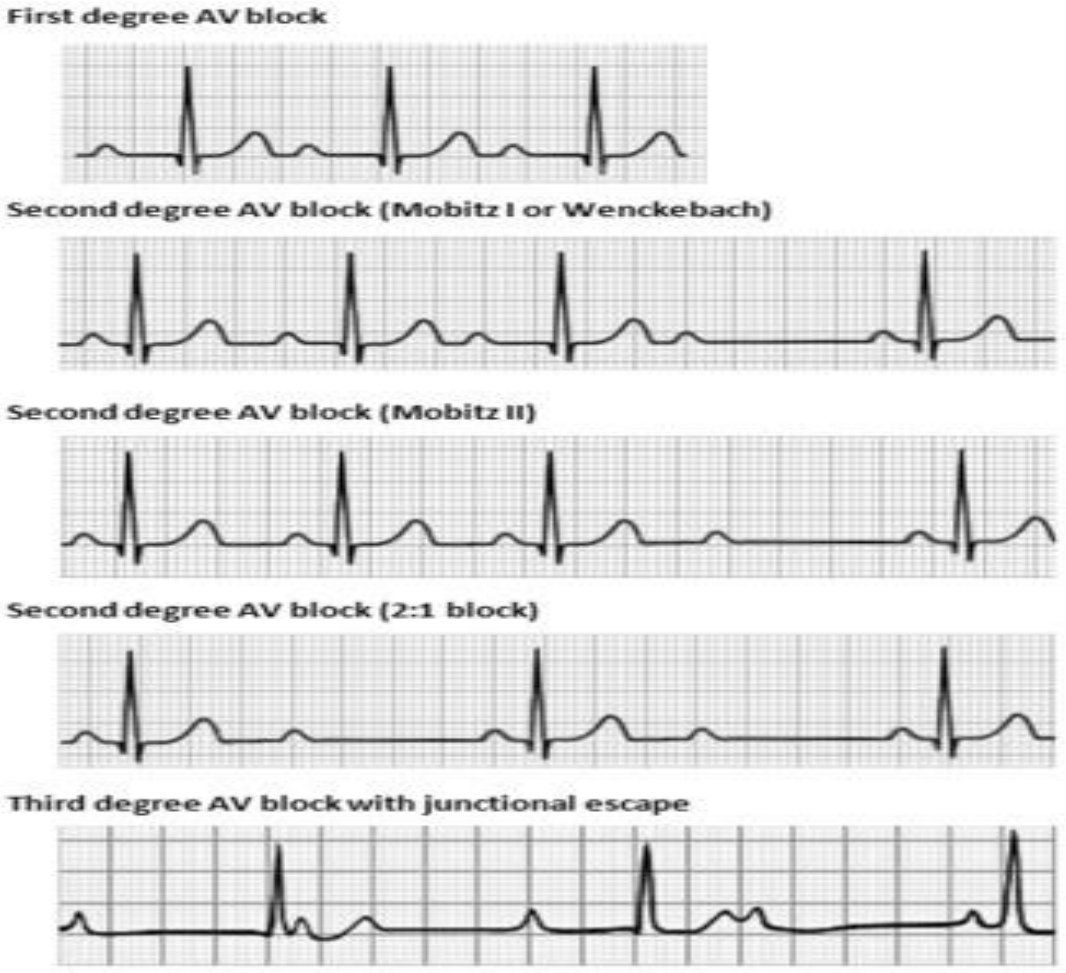

Figure 4. AV Blocks

In first degree AV block, a lengthened PR interval is present. It may be observed in normal individuals and generally does not require treatment.
Second degree AV block may be separated in two as Mobitz type I (Wenckebach) and Mobitz Type II. In Mobitz type I the PR interval continuously increases. In some Mobitz type II cases no P wave passes the ventricle and 2:1 or 3:1 block forms occur. If it is symptomatic, iv atropine or a pacemaker may be required.
In third degree AV block no atrial impulse passes the Purkinje system. The atrium and the ventricles spasm independently and the heart fails to produce sufficient cardiac output. There are indications for a pacemaker in these cases (Erdemli and Cekmen, 2010; Timuralp, 2010).

Sinoatrial blocks: These occur when stimuli from the sinus node do not stimulate the atrium. For treatment atropine may be administered. Hemodynamically unstable cases should be assessed for a pacemaker.

Intraventricular blocks: These occur due to blockage or delayed conduction in the right or left branch of the His bundle. Widened QRS is present.

a) Right bundle branch block: A second R wave (R') observed on precordial derivations (V1-3) and deep S wave observed on DI, aVL, V5 and V6 derivations. Just as it may be observed in healthy individuals, it may be observed with ischemic heart disease, rheumatic heart diseases and hypertension (Akyel and Tavil, 2010).

b) Left bundle branch block: QRS duration is longer than 0.12 s, notching of the QRS complex on V5, V6, DI and aVL, monophasic broad R waves on DI, DII, V5 and V6 derivations and deep S wave pattern on V1-3. Left bundle branch block accompanies cardiac diseases like ischemic heart diseases, aorta stenosis, hypertension, cardiomyopathies and rheumatic heart diseases. Treatment of the cause is priority (Akyel and Tavil, 2010).

Atrial extrasystole: This is observed as early and abnormal depolarization of the atrium and following this a normal QRS wave. It is sourced in an ectopic focus in the atrium apart from the SA node. Generally, it does not require treatment; however, it may be a harbinger of other atrial arrhythmias like atrial fibrillation (Yapıcı and Azizoglu, 2015; O'Neal et al., 2017).

Junctional rhythm (Nodal Rhythm): This occurs when the pacemaker activity of the AV node exceeds the sinus node with the stimuli returning within the atrium. It may be divided into 3 groups as slow, moderate and rapid. The rate is generally between 50-180 beats/min. It may cause a fall in blood pressure and cardiac output. If it is symptomatic atropine and ephedrine may be administered (Erdemli and Cekmen, 2010; Timuralp, 2010).

Supraventricular tachycardia: This may be observed with heart diseases, systemic diseases, thryotoxicosis, digital toxicity, pulmonary emboli and pregnancy. It may cause serious hemodynamic changes.

Paroxysmal supraventricular tachycardia (PSV): This is a regular and fast arrhythmia with QRS waves close to normal shape. It begins suddenly with rate generally from 150-250 beats/min. The duration of the attacks is variable, and may cause no problems in healthy individuals. However, in situations with cardiac ischemia it may cause severe hemodynamic disruption and respiratory distress. Carotid massage and vagal stimulation are effective for stopping attacks; however, in situations without resolution medications like adenosine, verapamil, edrophonium and digitalis or cardioversion may be administered.

Atrial tachycardia: This is an arrhythmia type sourced in the atrium and frequently indicates some primary disease (Fig 5). The most important cause of this arrhythmia is automaticity increasing. The heart rate is variable. For treatment, beta blockers and adenosine may be used (Erdemli and Çekmen, 2010; Yapıcı and Azizoğlu, 2015).

Figure 5. Atrial tachycardia

Atrial flutter: This may be defined as rapid atrial tachycardia. In the majority of cases, "re-entry" forms the basic mechanism. Heart rate is 250-350 beats/min and f waves with saw-tooth appearance are typical. The ventricular rate is regular and the ratio is commonly 2:1, 3:1 and 4:1. It may be observed together with hyperthyroidism, ischemic heart diseases or rheumatic heart diseases (Yapıcı and Azizoglu, 2015). Medication treatment with verapamil, digitalis and beta blockers is rarely effective. If cardioversion is administered, treatment is effective for 90% of cases and generally it is used as the first treatment choice (Erdemli and Cekmen, 2010).

Atrial fibrillation (AF): This is an arrhythmia type sourced in more than one focus in the atrium. Insufficient contraction causes a reduction in ventricular filling. The ventricular rate is lower than the atria and irregular. On EKG there is no P wave and pulse deficit is present. QRS waves are generally narrow and irregular (Fig 6). While atrial rate is 350-500 beats/min, ventricular rate is in the interval 60-170 beats/min. AF is observed in nearly 10% of geriatric patients in the general population and is the most common arrhythmia type in the elderly. It accompanies situations like mitral valve disease, myocardial infarctus, heart failure, HT, diabetes, obesity, hyperthyroidism and COPD. It

Figure 6. AF

causes cerebrovascular and systemic embolism due to atrial thrombus. The main aim of treatment is to bring the ventricular response under control and specially to begin anticoagulant prophylaxis due to the risk of thromboembolic stroke. For medical treatment, verapamil, beta blockers, amiodarone and digoxin are appropriate. For newly begun AF, the most appropriate treatment choice is medical or electrical cardioversion accompanied by anticoagulants (Erdemli and Cekmen, 2010; Melek, 2010; Yapıcı and Azizoglu, 2015).

Ventricular extrasystole (VES): This may be due to any focus in the ventricle. It is commonly linked to myocardial ischemia and indicates poor prognosis for ischemic heart diseases. In ECG trnascription there are broad abnormal QRS waves and following this T waves in the inverse direction are observed. There is no P wave in ECG before QRS waves (Fig 7). The first choice for medical treatment is lidocaine. Quinidine, bretylium, propranolol and verapamil are other appropriate choices in treatment (Erdemli and Cekmen, 2010; Hasdemir, 2010, Yapıcı and Azizoglu, 2015).

Figure 7: VES

Ventricular tachycardia: This appears as rapid and regular QRS complexes on ECG; however, the P/QRS ratio is not fixed. There is a tachycardia source in the ventricles with rate in the interval 120-220 beats/min. Carotid massage commonly provides no response. Ventricular tachycardia is a very serious arrhythmia. The majority of the time it may occur as a complication of hypoxia, hemorrhage, some medications (like adrenalin and atropine) and serious heart diseases. However, the most common cause is ischemic heart disease. Attacks may sometimes last hours. In situations with hemodynamic instability and collapse, the patient should immediately have the inspired oxygen concentration increased, iv lidocaine should be administered and emergency synchronized cardioversion applied. Other medical choices may be amiodarone and propafenone. Additionally, it is necessary to terminate the surgical operation and anesthesia (Erdemli and Cekmen, 2010; Hasdemir, 2010; Yapıcı and Azizoglu, 2015).

Ventricular Fibrillation (VF): Rapid and irregular electrical activity causes a situation where the ventricles do not contract synchronously causing sudden loss of cardiac output (Fig 8). It is a malignant arrhythmia occurring with myocardial ischemia, hypoxia, hypothermia, electrolyte imbalance and medication effects. The patient will only survive with cardiopulmonary resuscitation and defibrillation. These should be applied together with supportive care (Erdemli and Çekmen, 2010; Hasdemir, 2010; Yapıcı and Azizoglu, 2015).

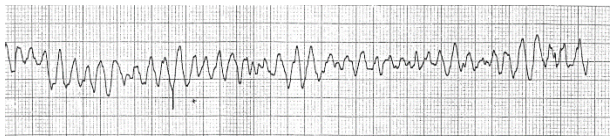

Figure 8: VF

Wolf Parkinson White Syndrome; This may be coincidentally identified on ECG during preoperative examination. The P waves have normal shape and the PR interval is short. There is a wave called a “delta wave” at the beginning of the R wave lengthening the QRS complex. Commonly it is observed together with ST depression or T wave inversion. When accompanied by atrial fibrillation there is a risk of sudden death. For treatment, radiofrequency catheter ablation should be used. In this patient group, antiarrhythmic medications like beta blockers suppressing the AV node and non-dihydropyridine group Ca channel blockers are contraindicated (Erdemli and Cekmen, 2010; Yapıcı and Azizoglu, 2015).

Cardiac arrest/asystole: This is an arrhythmia type with no ventricular activity. The ECG is in the form of a fully straight line. It requires immediate intervention. The only treatment is cardiopulmonary resuscitation (Erdemli and Cekmen, 2010).

Causes of perioperative arrhythmias: Common causes of perioperative arrhythmias are shown in Table 1 and primary treatment methods are shown in Table 2. The perioperative arrhythmia incidence for patients with predisposing pathologies is higher compared to other patients (Flegal et al.,

2009; Erdemli and Cekmen, 2010).

Table 1. Common causes of perioperative arrhythmias

- Anesthetic agents (volatile or intravenous agents, neuromuscular blockers, opioids)
- Local anesthetics
- Hypotermia
- Acid - base or electrolyte imbalance
- Hypoxia - hypercarbia
- Anesthesia depth
- Surgery types (ocular - cranial interventions, peritoneal traction…)
- Comorbidities (cardiac, endocrin, others)
- Laryngoscopy, intubation, other irritating factors
- Alternative drugs (adrenaline…)
- Artifacts

Table 2. Primary treatment approach of common perioperative arrhythmias

Sinus bradycardia	Atropine, adrenalin or pacemaker
Sinus tachycardia	Calcium channel blockers (diltiazem, verapamil), beta blockers and digitalis
Sick sinus syndrome	Pacemaker
Paroxysmal supraventricular tachycardia	Carotid massage, adenosine, verapamil, edrophonium, digitalis, cardioversion
Atrial tachycardia	Beta blockers and adenosine
Atrial fibrillation	Anticoagulant prophylaxis, verapamil, beta blockers, amiodarone, cardioversion
Ventricular extrasystole	Lidocaine, quinidine, bretylium, propranolol and verapamil
Ventricular fibrillation	Cardiopulmonary resuscitation and defibrillation

Disruption of acid-base or electrolyte balance affects the conduction system, especially causing arrhythmias with the re-entry mechanism. The most common causes of anesthesia-related arrhythmias are disruption of oxygenization and carbon dioxide excretion. In the early period, arrhythmia occurs with stimulating effects from the aorta and carotid receptors, while in the later period inhibitory mechanisms are effective. In disrupted oxygenation, slightly lower oxygen saturation levels compared to normal have a stimulating effect, while lower oxygen values cause depressant effects. Increased carbon dioxide level increases the oxygen requirements of the myocardium and causes acidosis, bradycardia and a fall in cardiac output (Trappe et al., 2003; Erdemli and Cekmen, 2010). Another important factor causing arrhythmia is whether anesthesia is slightly or deeply. While blocks and asystole may be caused by deeply anesthesia, slightly anesthesia is the most common cause of tachycardia (Balser, 2002). General anesthesia, laryngoscopy and intubation procedures linked to it cause sympathetic activation and trigger tachycardia and disrhythmia especially. Ocular interventions, cranial surgeries and the other surgeries where the peritoneum is pulled cause arrhythmias and bradycardia due to different mechanisms (Balser, 2002; Trappe et al., 2003; Erdemli and Cekmen, 2010). As is known, one of the most important effects of anesthetic agents on the cardivascular system is arrhythmia. Inhalation agents change the autonomous nervous system or conduction speed in cardiac cycle causing arrhythmia. Agents with halogene hydrocarbon structure cause arrhythmia formation with the re-entry mechanism. Halotan affects the myocardium sensitivity to catecholamines showing arrhythmogenic effect. Nitrous oxide is an agent with cardiac depressant effects. Intravenous anesthetics blocks the uptake of noradrenalin from adrenergic nerve endings like ketamine causing sympathetic stimulation and facilitate the occurrence of arrhythmia (Balser, 2002; Erdemli and Cekmen, 2010). Thiopental causes significant tachycardia and arrhythmia during induction. Increases occur in heart rate and oxygen consumption of the myocardium. During apnea in thiopental induction, administering high concentrations of oxygen to the patient is reported to be beneficial to prevent arrhythmia (Erdemli and Cekmen, 2010). Propofol clearly reduces blood pressure, causing variable effects on heart rate. With severe aorta stenosis and hypertension, it should not be forgotten that propofol reduces coronary perfusion causing myocardial ischemia. Etomidate is the agent with fewest cardiac side effects among iv induction agents and is the most appropriate induction agent for patients with additional cardiac pathologies. Among benzodiazepines, diazepam causes reflex tachycardia while midazolam shows a negative inotropic effect. Opioids depress the SA node with direct effect, while they indirectly increase acetylcholine release and cause bradycardia. Fentanyl causes bradycardia linked to vagal stimulation, while morphine has a positive chronotropic effect with dose-linked endogenous

catecholamine increase. Meperidine causes significant histamine release leading to tachycardia. The neuromuscular blocker of succinylcholine is well known to have arrhythmogenic and bradycardiac effects. Especially with the potassium increase it causes, the incidence of arrhythmias increases. Repeated succinylcholine doses trigger arrhythmia. Vecuronium has bradycardiac effect, while atracurium causes tachycardia via histamine release. Mivacurium and rocuronium have fewer cardiac side effects encountered (Hunter 2002). The arrhythmic effect of local anesthetics forms due to binding in voltage-gated sodium channels in the nerve cell membrane. Local anesthetic toxicity is a serious event progressing to cardiovascular collapse. All anesthetic workers should be informed about this topic and close monitoring of the patient is important. It is reported that administering lipid solution before cardiovascular collapse occurs increases survival (Suzer et al., 2011).

Perioperative approach: First it should be stated that it is necessary to complete the preoperative evaluation of patients effectively and linked to this, to determine the most appropriate anesthesia management. It is possible to encounter predisposing factors or cardiac pathologies in every age group; however, all these situations do not always cause ECG changes in the preoperative period and unfortunately the majority of the time arrhythmias occur unexpectedly (Mandim et al., 2004). Preoperative assessment should determine firstly the patient's history, medications used, biochemical values and predisposing factors for arrhythmia (Duncan and Wijeysundera, 2016). Patients in the risk group should have detailed assessment and then consultation with cardiology and it is important to prepare the patient in the best conditions for surgery and share risks based on this recommendation. Situations like acid-base balance disorder, electrolyte imbalances, cardiac pathologies, hypoxia and variations in body temperature that prepare the way for arrhythmias should be resolved at optimum levels to ensure the patient is stable (Rafiq et al., 2017). With regional anesthesia, patients should be more closely monitored for hypotension, bradycardia and sudden cardiac arrest, with patients monitored for rhythm, respiration and hemodynamics during every type of anesthesia administration. Carefully rhythm monitoring in perioperative period is undoubtedly the most important method for diagnosis. One topic that should be mentioned related to rhythm analysis is artifacts. These images observed on ECG that cannot be interpreted should be identified by the anesthesiologist and confirmed as artifacts. If confirmation is not possible, monitoring should be performed with a different device and confirmation of any incompatibility between simultaneous arrhythmia imaging and the clinical and hemodynamic findings of the patient made.

Conclusion

It is known that that possibility of encountering arrhythmia at every stage of routine anesthesia practice is high. The patient should be carefully assessed for the possibility of every type of arrhythmia and ECG analysis should be accurately completed. For this topic, anesthesiology specialization students should be given sufficient rhythm analysis training. It is clear that simulation training involving arrhythmia scenarios including cardiopulmonary resuscitation will be beneficial. All operating rooms should have monitors, defibrillators and all material necessary to deal with arrhythmias present and ready for use and these should be checked daily. Operating rooms and delivery rooms should definitely have 20% lipid solution for use in local anesthetic toxicity ready. Additionally, an action plan should be created for emergency situations with personnel informed about their responsibilities for procedures in the plan. Early diagnosis and early intervention are life saving for arrhythmias.

Peer-review: Externally peer-reviewed.
Author Contributions: Concept- A.A., N.T., O.B., Design- A.A., Supervision- A.A., N.T., Literature Review- A.A., N.T., Writing- A.A., N.T., O.B., Critical Review- A.A., N.T., O.B.,
Conflict of Interest: No conflict of interest was declared by the author.
Financial Disclosure: The authors declared that this study has /hasn't received no financial support.

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