ISSN 2545-4366
www.e-mja.finki.ukim.mk

MJA

Macedonian Journal of Anaesthesia

A Journal on Anaesthesiology, Resuscitation, Analgesia and Critical Care

Vol. 6 No 2, June 2022

Journal of the Macedonian Society of Anaesthesiologists
and Macedonian Society of Critical Care Medicine

Publisher:
Department of Anaesthesia and Reanimation Faculty of Medicine,
"Ss. Cyril and Methodius" University, Skopje, R.N.Macedonia

Apotel® 1000mg/6.7ml

I.V. Paracetamol

БЕЗБЕДНА АНАЛГЕЗИЈА

менаџирање на болка кога сте загрижени за безбедноста

I.V. paracetamol за прв пат во Европа е применет во 2001 година, а денес поради неговата докажана безбедност и ефикасност е прв од избор **аналгетик и антипиретик.**

Предоперативна и Интраоперативна Аналгезија:
Предоперативна анелгезија е дефинирана како третман кој што започнува пред оперативниот зафат се со цел да се превенира воспоставувањето на централна сензибилизација на болка.
i.v. paracetamol е безбеден, добро толериран лек со докажана ефикасност како **предоперативна и интраоперативна анелгезија** за умерена до средна болка при оперативни зафати.
Голем број на клинички студии ја докажуваат ефикасноста на **i.v. paracetamol** како **преодоперативна и интраоперативна анелгезија**.

КЛИНИЧКА СТУДИЈА:
Ефект од **предоперативен i.v. paracetamol** за постоперативни аналгетски потреби кај пациенти кои се подлежни на оперативни зафати. A Sreenivasulu , R Prabhavathi, 2015
Цел: Да се утврди ефикасноста на **предоперативната употреба на 1000mg i.v. paracetamol** кај постоперативните болки и анелгетски потреби кај пациенти подлежни на хируршки зафати.
Метод: 60 пациенти беа поделени во две рандомизирани групи од по 30 пациенти.
На I. Група им беше администрирано **ампула од 1000mg i.v. paracetamol разредена 0,9%NaCl** р-ор 30 минути пред индукција **(ГРУПА П)**,
На II. Група им беше администрирано **i.v. 0,9% NaCl р-ор 100мл** 30 минути пред индукција **(ГРУПА НС)**
Сите пациенти беа индуцирани со i.v. thiopentone 5mg/kg, i.v. fentanyl 2μg/kg, i.v. vecuronium 0.1mg/kg
Постоперативниот резултат на болка беше мерен со **Визуелна Аналогна Скала (ВАС) од "0-10"**. Исто така беше забележувана и **постоперативната употреба на tramadol** како спасувачки аналгетик. Инциденцата на **постоперативно гадење и повраќање (ПОГП)** и други компликации исто така беа забележувани во пост оперативниот период.
Резултатот на постоперативната болка беше забележуван во интервали 15 мин, 30 мин, 1 час, 2 часа, и 6 часа.

Резултат:
Табела 1: *Споредба на средниот резултат на болка (ВАС) помеѓу двете групи*

Интервали	I Група П	II Група НС	*P вредност*
15 мин	2.06 ± 0.63	2.61 ± 0.56	0.0006
30 мин	2.35 ± 1.17	3.84 ± 1.55	0.0001
1 час	2.42 ± 1.12	2.87 ± 0.99	0.0989
2 часа	2.13 ± 1.06	2.52 ± 0.89	0.1219
6 часа	2 ± 0.52	2.52 ± 0.89	0.0549

Табела 2: *Споредба за потребите од tramadol помеѓу двете групи*

Интервали	I Група П	II Група НС	*P вредност*
До 1 час	4 (12.90%)	15 (50%)	0.0002
1-2 часа	3 (9.68%)	2 (6.45%)	0.64
2-6 часа	1 (3.23%)	3 (9.68%)	0.301
Вкупно	**8 (25.81%)**	**20 (64.52%)**	**0.002**

Табела3: *Споредба на ПОПГ помеѓу двете групи*

ПОГП	
I Група П	II Група НС
0	4

Заклучок: Предоперативна администрација на **1000mg i.v. paracetamol** кај пациенти подлежни на оперативен зафат обезбедува **статистички задоволителна анелегизија**, и ја **намалува постоперативната употреба на tramadol**. Оттука **1000mg i.v. paracetamol** може безбедно да се администитрира како превенција при оперативни зафати.

i.v. Paracetamol + јак опоид	МНОГУ ЈАКА БОЛКА
i.v. Paracetamol + слаб опоид	ЈАКА БОЛКА
i.v. Paracetamol + NSAID i.v. Paracetamol + rescue medicine	УМЕРЕНА БОЛКА
i.v. Paracetamol + rescue medicine	СЛАБА БОЛКА

Мултимодално менаџирање на постоперативна болка
I.V. Paracetamol е атрактивна компонента за мултиодално менаџирање на болка.

- **Синергистичко делување**
- **Зголемување на аналгетски ефект**
- **Значително намалување на болка**
- **Редукција на дозата на опоидни лекови за - 40% во првите 24 часа**
- **Намалување на несаканите ефекти поврзани со монотерапија на NSAID и опоидни лекови**
- **Ублажување на акутна и хронична болка**

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WHEN EARLY RECOVERY REALLY MATTERS

Дистрибутер за Македонија

FARMA TREJD

Macedonian Journal of Anaesthesia

A Journal on Anaesthesiology, Resuscitation, Analgesia and Critical Care

Publisher
Department of Anaesthesia and Reanimation
Faculty of Medicine
"Ss. Cyril and Methodius" University
Skopje, R.N.Macedonia

Proofreading
Daniela Nacevska Stojcevska

CONTENT

POINT OF CARE AND BEYOND - AI

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Skopje, Macedonia

The last decade was marked with a dramatic turning point in medical sciences. New therapies were introduced for treatment of vast majority of diseases, such as monoclonal antibodies, gene therapies and of course, mRNA vaccines. Furthermore, understanding of the genesis of different clinical entities was supported by advancements in basic medical sciences, such as genetics, immunology, microbiology, physiology. The last two Nobel prizes in medicine and physiology were rewarded for discoveries in basic medical sciences, namely - physiology, and rightly so, since the discoveries helped in better understanding of cell oxygenation and sensory and pain impulses.

Diagnostic procedures are advancing with improvement in technology of imaging methods, but also with advancement in nanotechnology, which will eventually lead to replacing painful endoscopic diagnostic procedures with nanocapsules with video cameras.

But, what about everyday clinical practice? How do these discoveries in basic sciences translate to clinical medicine?

If the previous decade was a decade of evidence-based medicine, this is a decade of personalized medicine. For a clinician, it can be a bit confusing. Merely yesterday our way of approach to treating the patients was „if it works for majority of the patients, it should work for my patient too", an evidence- based approach. Now, we know better, that evidence-based medicine is what works for statistic majority of patients, but what about those patients that are on the margins of statistics? That is why the personalized approach was introduced.

To make it easy, point of care methods of diagnostics and treatment were introduced to clinical practice. This is a concept of bedside diagnostic and treatment, especially helpful in critical patients in ICU.

But what is beyond point of care? Artificial intelligence -Merging medicine with AI, mathematics and engineering is inevitable future of medicine. AI is based on algorithms, and aren't algorithms what we all need for better medical practice? We have algorithms in CPR, but not yet in anesthesiology and critical care, and those are the fields where we rely on recommendations.

Should we fear the day when AI comes in our OR or ICU? Will it take our jobs?

I don't think so. AI will help clinicians in decision making, which will be void of subjective errors in judgement, or just a bad performance of the clinician.

EVALUATION OF BAL PCR FOR DIAGNOSIS OF ASPERGILLOSIS

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ABSTRACT

Introduction: Aspergillosis is a worldwide problem in both patients with compromised immune system and patients with comorbidities treated in intensive care units. Early diagnosis of aspergillosis is still a big challenge for both clinicians and laboratory workers. Standard mycological methods have low sensitivity, and therefore rapid and more sensitive methods for early diagnosis of aspergillosis are necessary.

Aim: The aim of this study was to determine the usefulness of a PCR assay performed in bronchoalveolar lavage fluid in comparison to the standard mycological method (BAL culture) for diagnosis of aspergillosis.

Material and Methods: Specimens of 125 patients divided into four groups and classified according to clinical diagnosis and EORTC/MSG criteria were analyzed at the laboratory for mycology at the Institute of Microbiology and Parasitology, with standard mycological (BAL culture) and molecular methods (BAL PCR), during a 2-years period (2014-2016).

Results: In our study, 71 isolates of *Aspergillus* were confirmed with BAL culture. Out of these, 63.33% were confirmed in patients with chronic aspergillosis, followed by 56.67% of cystic fibrosis patients, 51.43% of primary immune deficiency patients, and 43.33% patients with prolonged stay in ICU. BAL culture demonstrated the following percentages of sensitivity and specificity: 64.29% and 100%, 59.09% and 100%, 54.55% and 12.5%, 100% and 54.17%, in all four groups, respectively. *A. fumigatus* was confirmed in 53 out of 67 positive BAL specimens. Out of these, 17 isolates were detected in the group of chronic aspergillosis, followed by the group of immune deficiency and cystic fibrosis with 14 isolates each, and eight isolates were confirmed in the group of critically ill patients with prolonged stay in ICU. A. flavus were confirmed in 11 positive BAL cultures. Only 3 isolates of A. terreus were recovered from positive BAL cultures. PCR performed in BAL specimens yielded the following sensitivity and specificity percentages in all four groups: 67.86% and 85.71%, 72.73 % and 75%, 40.91% and 50%, 50% and 50% in all groups, respectively.

Conclusion: Results of our study indicate that PCR in BAL specimen is a valuable molecular diagnostic tool for early diagnosis of aspergillosis, especially if it is used along with the standard

mycological methods, like BAL culture, in order to provide valuable information for clinicians to initiate an early antifungal treatment that could enable more favorable clinical outcome.

Key Words: aspergillosis, *Aspergillus*, BAL culture, BAL PCR, diagnosis.

Introduction

Serious fungal infections continue to be significant cause of morbidity and mortality in patients with prolonged steroid treatment, acquired immune deficiency, patients with severe neutropenia, hematopoietic stem cell and solid organ transplantation patients (1). Aspergillosis usually affects the pulmonary system and can be presented as aspergilloma, chronic pulmonary aspergillosis, allergic bronchopulmonary aspergillosis and invasive aspergillosis, which is the leading cause of death, mainly among immunocompromised patients. A delay in initiation of an appropriate antifungal treatment, due to limitation of sensitive diagnostic methods, results in rapid progression of the fungal disease and increased mortality from these life-threatening infections (2). Diagnosis of invasive aspergillosis in the most laboratories still relies on conventional mycological methods, which require a lot of time for incubation of fungi on culture media, and are not sensitive enough (3). Criteria for diagnosis of invasive aspergillosis include clinical, radiological and mycological findings (4). DNA from *Aspergillus* has been previously detected in BAL specimens by means of real-time polymerase chain reaction (PCR). This method has been recently shown to provide valuable data for etiological diagnosis of invasive aspergillosis in both immunocompromised and non-neutropenic patients (5). A recent agreement between scientists enabled this method to be included in the EORTC/MSG criteria (6,7). Chronic pulmonary aspergillosis and allergic broncho-pulmonary aspergillosis (ABPA) are also problematic for diagnosis for both clinicians and laboratory workers (8). From recently, guidelines by the European Society of Clinical Microbiology and Infectious Diseases and the European Respiratory Society (ESCMID/ERS) recommend use of PCR in BAL specimens for the diagnosis of non-invasive aspergillosis with C-II grade (9). PCR-based diagnostic methods have been used in routine clinical practice for many years, and from recently they are used to diagnose or rule out suspected invasive fungal infections. For definitive mycological diagnosis of invasive aspergillosis, an accurate and reliable diagnostic method is specifically needed, due to the serious nature of this infection among immunocompromised patients.

The aim of this study was to evaluate the usefulness of a PCR-based method in BAL specimen, in comparison to the conventional mycological method (BAL culture) for diagnosis of aspergillosis.

Material and Methods

Study Design, Specimens and Methods

A prospective diagnostic study was performed at the Mycology laboratory at the Institute of Microbiology and Parasitology, Faculty of Medicine, Skopje, Republic of Macedonia, in the period of 2 years (2014-2016). BAL specimens from 125 patients divided in four groups,

according to clinical diagnosis and risk factors for development of invasive fungal infection, were analyzed at the mycology laboratory. Invasive aspergillosis was defined according to the EORTC/MSG revised definitions' consensus group (4). Analysis of the samples was performed with standard mycological methods (BAL culture) on Sabouraud and chromogenic CALB medium (Oxoid). BAL specimens were homogenized and divided in two parts. One part of the specimen (1-5ml) was centrifuged, and the suspended pellet (500ml) was directly inoculated on the media for growth of fungi (Sabouraud dextrose agar with chloramphenicol (40μg/ml), and incubated at 37°C during 48 hours, and the other part was frozen at -80°C, and then used for molecular analysis, without sending information to clinicians for the results.

Molecular detection of *Aspergillus* DNA. Extraction of DNA from BAL. BAL specimens were treated with N-acetil cystein-Na hydroxide. BAL specimens were centrifuged at 13.000rpm. The leucocyte pellet was resuspended in 300μl of 1×phosphate buffered saline solution and the mixture was incubated with 100-125 U lyticase, during 30 minutes at 37°C for fungal cells degradation. The residual material was further treated with 500-1000μg proteinase K and 0.5% SDS (Natrium dodecyl sulphate) at 55°C during 1 hour. The residual cell material was then lysed while incubated with additional 100μl 2×Aspergillus buffer for extraction, during 30 minutes at 65°C. Purification of DNA was performed with conventional phenol-chloroform extraction. The precipitation of DNA was performed with 0.7 volume of isopropanol, to obtain a pellet, which was further washed with 70% ethanol and dried on air. Analysis of the DNA concentration was performed with spectrophotometer at wavelength 260 and 280nm. The DNA extracts were frozen at -20°C until the PCR procedure (10).

Controls for Extraction

Negative controls were tubes with purified water without DNA for evaluation of the contamination during extraction. Positive controls were included for every extraction and verification of efficacy, with inoculation of saline solution with approximately 150 CFU of A. fumigatus conidial suspensions, in a volume of 500μl. To determine the total number of injected CFU, 100μl of the suspension containing around 30 CFU, was inoculated on the surface of the Sabouraud dextrose agar, which was incubated for 72 hours at 30°C.

PCR for *Aspergillus*

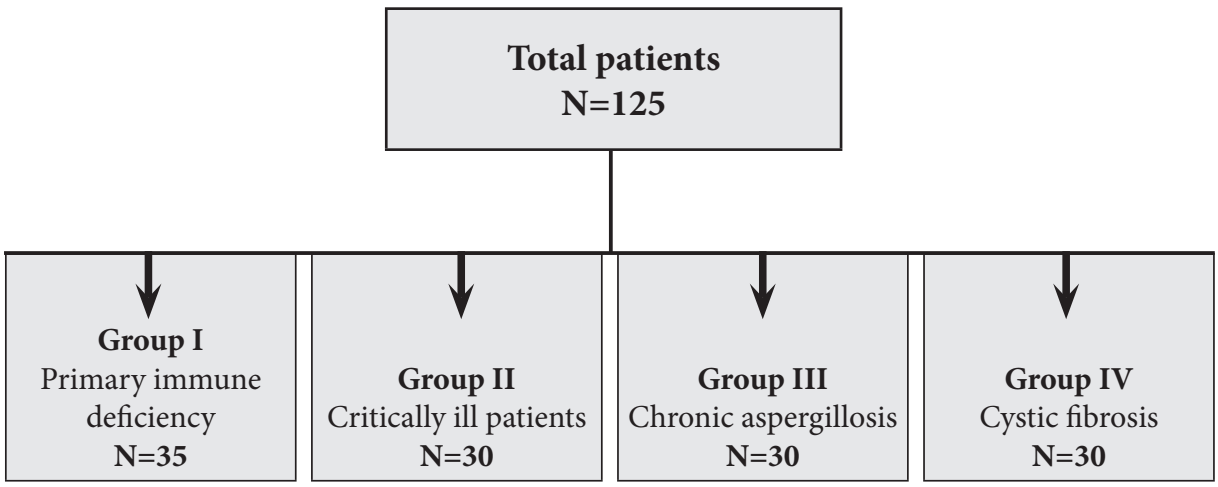
PCR was performed in 25ml mixture containing 50-150 nanograms of DNA like a template. This PCR mixture contained around 0.5 U Taq DNA polymerase, 6.25nmol DNTP, 10pmol primers (for the first PCR step – first set of primers; for the second PCR step – another set of primes). The PCR products were separated with 2.5% agarose gel electrophoresis dyed with ethidium bromide, and visualized with UV light. Control specimens included all components of the reaction mixture, except genomic DNA. As positive and negative controls for PCR, DNA of a human cell line T47D and diluted solution of *A. fumigatus* were used as templates (11).

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows. The results of our study are presented as numbers and percentages. Differences in distribution of proven, probable and possible fungal infections with *Aspergillus* were compared by Pearson Chi square test. P value less than 0.05 was considered statistically significant.

Results

BAL specimens from 125 patients were analyzed in 4 groups of patients, according to clinical diagnosis and EORTC/MSG criteria (Figure 1).

Figure1. *Classification of patients' groups according to clinical diagnosis and EORTC/MSG (European Organization for Research and Treatment of Cancer/Mycoses Study group) criteria*



According to the data of analysis of our participants' gender, men were more frequently distributed in primary immune deficiency group, chronic aspergillosis and cystic fibrosis group (60%, 60%, 53.33% respectively), whereas in the critically ill patients' group, treated in ICU, both genders were equally distributed. Analysis of our participants' age demonstrated that average age was: 40.8±17.7, 59.7±13.3, 64.7±6.3, and 28.9±8.5 years (Table 1).

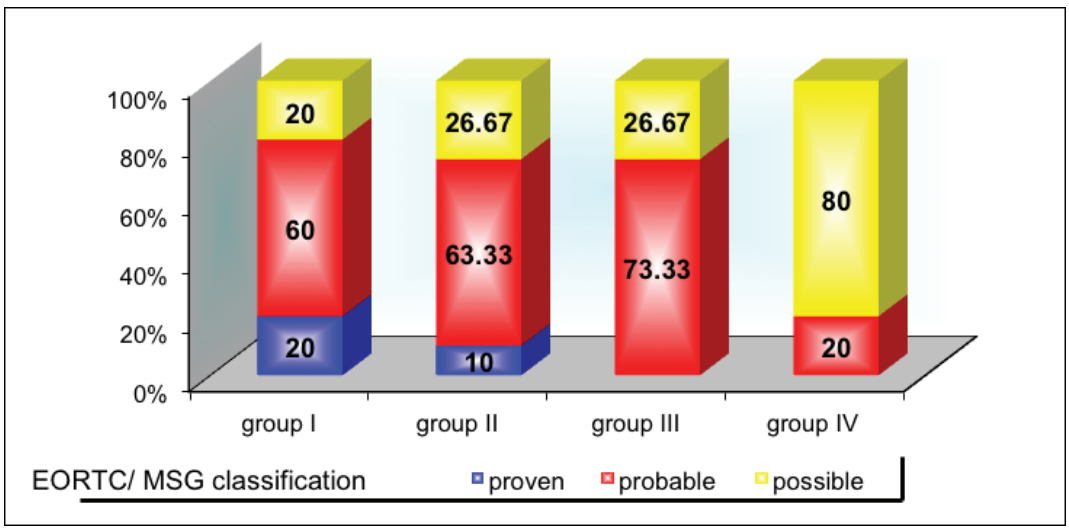
Table 1. *Characteristics of patients according to gender and age*

Aspergillus				
	Group I N=35	**Group II N=30**	**Group III N=30**	**Group IV N=30**
Gender	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Men 70 (56%)	21 (60%)	15 (50%)	18 (60%)	16 (53.33%)
Women 55 (44%)	14 (40%)	15 (50%)	12 (40%)	14 (46.67%)
	[a]p = 0.81			
Age (years) mean±SD, min-max				
	40.8±17.7 5-69	59.7±13.3 4-78	64.7±6.3 52-76	28.9±8.5 18-52

[a]p(Chi-square test)

In Figure 2 the distribution of the participants according to clinical diagnosis is presented for proven, probable and possible fungal infection, following the EORTC/MSG criteria. Only a small percentage of patients had proven infection with *Aspergillus* according to these criteria. Twenty percent of these patients had some form of primary deficiency and 10% had a prolonged stay in an intensive care unit.

Figure2. *Distribution of fungal infections according to EORTC/MSG criteria in all group*



Differences in distribution of proven, probable and possible fungal infection were statistically significant between primary immune deficiency versus chronic aspergillosis and cystic fibrosis group, and between critically ill patients' group versus chronic aspergillosis and cystic fibrosis group (Table 2).

Table 2. *Distribution of proven, probable and possible fungal infections according to EORTC/MSG criteria*

Aspergillus	**group I N=35**	**group II N=30**	**group III N=30**	**group IV N=30**
n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
proven 10 (8%)	7 (20%)	3 (10%)	0	0
probable 68 (54.4%)	21 (60%)	19 (63.33%)	22 (73.33%)	6 (20%)
possible 47 (37.6%)	7 (20%)	8 (26.67%)	8 (26.67%)	24 (80%)
	[b]p < 0.001 I vs II p=0.3 II vs III p = 0.345 III vs IV p < 0.001 I vs III p = 0.03* II vs IV p < 0.001 I vs IV p < 0.001			

[a]p(Chi-square test) [b](Fisher exact test) *p<0.05 **p<0.01

Analysis of BAL culture demonstrated presence of *Aspergillus* in 63.33% in chronic aspergillosis group (19/30), followed by 56.67% in the cystic fibrosis group (17/30), 51.43% primary immune deficiency group (18/35) and 43.33% in critically ill patients' group (13/30). The most frequently encountered species was *A. fumigatus* (79%). Seventeen out of fifty- three isolates of *A. fumigatus* originated from chronic aspergillosis patients' specimens and fourteen isolates were confirmed in both primary deficiency and cystic fibrosis patients' specimens. Other positive findings of *A. fumigatus* isolates were confirmed in ICU patients' specimens (15.1%; 8/53) (Table 3). Three isolates of *A. flavus* were demonstrated in the CF patients' specimens. Two isolates of *A. terreus* were also confirmed in BAL specimens from primary immune deficiency and one isolate in critically ill patients' group.

Table 3. *Bronchoalveolar lavage (BAL) culture and identified fungal species*

	group I N=35	**group II N=30**	**group III N=30**	**group IV N=30**
BAL culture	**n (%)**	**n (%)**	**n (%)**	**n (%)**
negative 58 (46.4%)	17 (48.57%)	17 (56.67%)	11 (36.67%)	13 (43.33%)
positive 67 (53.6%)	18 (51.43%)	13 (43.33%)	19 (63.33%)	17 (56.67%)
	Chi-square: 2.59 p = 0.46			
Identified mold species in BAL				
A. fumigatus n=53	14	8	17	14
A. flavus n=11	2	4	2	3
A. terreus n=3	2	1	0	0

p(Chi-square test)

PCR in BAL confirmed 20 (57.14%) positive specimens with *Aspergillus* in patients with primary immune deficiency, 18 (60%) in patients with prolonged stay in ICU, 13 (43.33%) positive specimens in patients with chronic aspergillosis and 15 (50%) in patients with cystic fibrosis. *A. fumigatus* was confirmed as etiological agent in all positive specimens (Table 4).

Table 4. *PCR in BAL and Aspergillus DNA recovered from BAL in all groups*

group *Aspergillus*				
	group I N=35	**group II N=30**	**group III N=30**	**group IV N=30**
BAL PCR n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
no 59 (47.2%)	15 (42.86%)	12 (40%)	17 (56.67%)	15 (50%)
yes 66 (52.8%)	20 (57.14%)	18 (60%)	13 (43.33%)	15 (50%)
	Chi-square: 2.06 p = 0,6			
BAL PCR – fungus species				
A. fumigatus n=66	20	18	13	15

p(Chi-square test)

Comparative diagnostic performances of conventional (BAL culture) and molecular methods, for diagnosis of infections with *Aspergillus* in the group with immune deficiency are presented in Table 5.

Table 5. *Diagnostic performances of conventional (BAL culture) and molecular methods in the group with immune deficiency*

Test	Se(%)	Sp(%)	PPV(%)	NPV(%)
BAL culture	64.29	100	100	41.18
BAL PCR	67.86	85.71	95	40

Comparative diagnostic performances of conventional (BAL culture) and molecular methods, for diagnosis of invasive infections with *Aspergillus* in the group with prolonged ICU stay, in critically ill patients are presented in Table 6.

Table 6. *Diagnostic performances of conventional (BAL culture) and molecular methods in patients with prolonged ICU stay*

Test	Se(%)	Sp(%)	PPV(%)	NPV(%)
BAL culture	59.09	100	100	47.06
BAL PCR	72.73	75	88.89	50

Comparative diagnostic performances of conventional (BAL culture) and molecular methods, for diagnosis of invasive infections with *Aspergillus* in the group with chronic aspergillosis are presented in Table 7.

Table 7. *Diagnostic performances of conventional (BAL culture) and molecular methods in chronic aspergillosis*

Test	Se(%)	Sp(%)	PPV(%)	NPV(%)
BAL culture	54.55	12.5	63.16	9.09
BAL PCR	40.91	50	69.23	23.53

Comparative diagnostic performances of conventional (BAL culture) and molecular methods, for diagnosis of invasive infections with *Aspergillus* in the cystic fibrosis group, are presented in Table 8.

Table 8. *Diagnostic performances of conventional (BAL culture) and molecular methods in cystic fibrosis*

Test	Se(%)	Sp(%)	PPV(%)	NPV(%)
BAL culture	100	54,17	35,29	100
BAL PCR	50	50	20	80

Discussion

Early diagnosis of invasive aspergillosis still remains a big clinical and laboratory challenge. It should be based on integration of clinical, mycological and radiological data, as well as analysis of risk factors in different patient populations. It should provide early detection and laboratory testing of the antifungal susceptibility pattern of the isolated fungus. Bronchoalveolar lavage (BAL) is a specimen that could enable diagnosis based on microbiologic culture when patients are unable to provide sputum. This possibility also allows application of PCR, which could help in faster identification of particular microbes, especially of a great interest for immunocompromised patient population. This approach enables sooner diagnosis than conventional methods (12).

Positive findings of *Aspergillus* in BAL culture in our study were as follows: chronic aspergillosis (63.33%), cystic fibrosis (56.67%), primary immune deficiency (51.43%) and critically ill patients with prolonged stay in ICU (43.33%), respectively. Sensitivity of BAL culture was 64.29%, 59.09%, 54.55% and 100%, and specificity of BAL culture was 100%, 100%, 12.5% and 54.17%, in all four groups respectively. Data from the study of Tashiro and coworkers show that 165 isolates of *Aspergillus* species were detected in BAL culture of 139 patients. Less than 50% (45%) of these patients were positive for *Aspergillus* without clinical manifestations of aspergillosis. Other patients presented with some clinical form of pulmonary aspergillosis (chronic aspergillosis (48%), aspergilloma (29%), invasive (13%) or ABPA (10%)). In our study, *A. fumigatus* was identified in 79.1% (53/67) of all positive BAL specimens. Seventeen patients out of fifty-three (32.1%) had chronic aspergillosis. In the group with primary immune deficiency and cystic fibrosis, *A. fumigatus* was identified in 14 patients in both groups (26.42%). Eight patients treated in ICUs were also positive for *A. fumigatus* (15.1%). Second the most frequent species identified in our patients was A. flavus, which was confirmed in eleven out of sixty-seven patients (16.42%). A. terreus was detected in three out of sixty-seven patients (4.48%). Four out of eleven isolates of A. flavus were detected in critically ill patients treated in ICU, and 27.3% in the group with cystic fibrosis. Two severely immunocompromised patients (with AIDS) and one patient with metastatic tumor of the brain treated in ICU, were positive for A. terreus. Mennink-Kersten and coworkers showed the following distribution of *Aspergillus* among 165 confirmed isolates in BAL cultures in their study: 41% A. fumigatus, 32% A. niger, A. versicolor (12%), A. terreus (6%), A. flavus (5%), A. nidulans (2%), A. sydowii (1%) and unidentified Aspergillus species (0,6%) (13). A. fumigatus was also confirmed as a predominant species in patients with invasive aspergillosis (82%), aspergilloma (68%) and chronic aspergillosis (54%), while A. niger was on the second place. *A. flavus*, *A. niger* and one case with mixed infection with two species (*A. flavus*/*A. niger*) were detected in the study of Zarrinfar and coworkers (23 %) (14). The most frequent agent in this study was A. flavus, compared to the results of our study, which demonstrated predominance of A. fumigatus.

Laboratory findings of many mycology laboratories show that *A.* fumigatus can sometimes only colonize the respiratory tract, without causing any clinical signs or symptoms of aspergillosis in patients. Demonstration of presence of Aspergillus species in more specimens without appropriate pharmacological response to antibiotic treatment, especially in high-risk patients, should be suspicious to clinicians for a possible development of invasive aspergillosis and a need for prompt

implementation of antifungal treatment (15,16,17). Colonization in the respiratory tract can be transient, but could also indicate development of an invasive infection with Aspergillus (18). Our patients with chronic aspergillosis demonstrated *Aspergillus* in BAL culture in 63.33%, all due to A. fumigatus. Results from the study of Tashiro and coworkers showed similar data to our study. A. fumigatus was also the predominant species in their study (54%) (19). A. fumigatus (69%) was also demonstrated as the most frequent isolate in positive BAL cultures in the study of Perfect and coworkers, followed by *A*. niger (13%), A. flavus (2%) and other species (5%) (20). The allergic form of aspergillosis due to hypersensitivity reactions of the human body to chronic presence of Aspergillus (ABPA), is usually present in patients with cystic fibrosis. In these patients, the predominant cause is A. fumigatus (21). Our patients with cystic fibrosis were the most often colonized with A. fumigatus - 82.4% (14/17), but 10% demonstrated presence of A. flavus (17.6%). These results show that timely identification of *Aspergillus* would allow clinicians to initiate an adequate antifungal treatment depending on the clinical parameters of the patient.

Although considered a gold standard, culture of respiratory samples for diagnosis of aspergillosis is still a major diagnostic challenge. In recent years we have witnessed the development of new diagnostic methodologies and biomarkers that would enable easier detection of patients with aspergillosis. With molecular techniques, scientists tried to find more reliable methods for detection of DNA of Aspergillus in clinical specimens in high-risk patients (7). Aspergillus DNA detection for etiological diagnosis of aspergillosis has been the subject of many studies for more than 20 years (22). Numerous authors have previously demonstrated sensitivities ranging from 72 to 88% and specificities from 75 to 98.7%. Some studies revealed even lower sensitivity (as low as 26%) (23-25).

In our study, we evaluated a PCR method for early detection of DNA in patients with increased risk for invasive fungal infections with *Aspergillus*. Sensitivity and specificity of PCR in our study differ to some previously published studies. Several authors suggest the sensitivity of *Aspergillus* PCR in BAL to range between 80% and 100%, but other authors described much poorer results (26). The values for sensitivity and specificity of PCR in BAL in our study in all four groups were as follow: group I - 67.86% and 85.71%, group II – 72.73% and 75%, group III – 40.91% and 50%, and group IV - 50% and 50%, respectively. In the study of Aydogan and coworkers, in neutropenic mouse, DNA of *Aspergillus* was detected in 7/12 BAL specimens (58.3%), 7/19 blood specimens (36.8%) and 4/22 pulmonary specimens (18%) with Rt-PCR method (27). In an experimental study of Khan and coworkers, 60 immunosuppressed Wistar rats (with cyclophosphamide), were experimentally infected with conidia of *A. fumigatus* (28). After development of invasive aspergillosis, DNA was detected in BAL with nPCR. It was confirmed that sensitivity of nPCR was 70% in BAL. Higher sensitivity of PCR in BAL (90%) compared to serum (60%) was confirmed in the study of Zhang and coworkers, who demonstrated that in non-neutropenic patients, BAL provided higher sensitivity for detection of DNA. These data confirm the hypothesis that DNA of *Aspergillus* can be detected more easily in specimens of the site of infection (like BAL) compared to blood or serum (29). Skladny and coworkers report a sensitivity of 43% for proven and 33% for probable invasive fungal infection, using BAL PCR

(30). But, false negative results in proven invasive fungal infections have been also described in several studies. Buchheidt and coworkers detected negative PCR results in the BAL of two out of three patients with histological proof for invasive aspergillosis and Khot and coworkers reported a negative PCR result from one patient with a positive biopsy (26,31).

The slightly lower sensitivity of the PCR in our study, compared to other studies, might have several explanations. Some studies included only patients with acute myeloid leukemia and hematopoietic stem cell transplant recipients, while others included a large variety of immunocompromised patients. Other studies incorporated only patients suspected to have invasive pulmonary aspergillosis, whereas others included patients under screening surveillance. Several studies selected patients by definite radiographic results of pneumonia, thus improving the pre-test probability of the method, in contrast to our study, where this clinical information was lacking in the most of the patients (31). The impact of active anti-mold treatment or prophylaxis received by some patients at the time of BAL sampling could not be ruled out as well. We also had data that few our patients (insufficient data to be presented in this study), especially in the immune deficiency group, were on chronic anti-fungal therapy at the time of bronchoscopy, which might have decreased the number of organisms present in the BAL fluid, thus impairing identification by BAL PCR. Lastly, despite all our efforts, we couldn't definitively exclude the possibility of a technical failure in the assay procedure, which was still in a process of standardization during the time this study was performed. While our results suggest a lower sensitivity of the *Aspergillus* PCR in the BAL, the specificity of the test, especially for the first and the second group, is in line with previously reported data. Data from previous studies have shown specificities ranging between 84% and 100%, which can be compared to data in our study (26,31,32).

Conclusion

This study demonstrated that PCR in bronchoalveolar lavage highlights the value of the molecular assay as a diagnostic support in the etiological diagnosis of aspergillosis, along with results from conventional mycological investigation (culture), which may have significant implications for its treatment and prophylaxis. Molecular assays also have higher sensitivity and enable detection of fungal DNA during an antifungal treatment, when the possibility to detect viable fungi is much lower with culture.

Results of our study show that PCR assay could help in earlier initiation of an antifungal treatment in order to achieve more favorable clinical outcome, especially in patients with increased risk for development of invasive aspergillosis.

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PERIOPERATIVE ANESTHETIC MANAGEMENT IN REVISION TOTAL HIP ARTHROPLASTIES IN A TERTIARY CARE HOSPITAL

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ABSTRACT:

Background:

The revision total hip arthroplasties are associated to significant perioperative mortality and morbidity which can be due to patient factors, surgical factors and anesthetic factors. The objective of this study is to audit the common anesthesia practices in the revision total hip arthroplasties in the perioperative period.

Materials and Methods:

A total of 39 patients who underwent revision total hip arthroplasty in a period of 2 years participated in the prospective observational study. The preoperative, intraoperative and postoperative data were assessed using a case record form and analyzed using a statistical software.

Results:

There were 26 males (66.7%) and 13 females (33.33%). The mean age was 56.12 years (Range 23-81, SD 15.21). Hypertension was the commonest comorbidity among the study subjects. Regional anesthesia was preferred to general anesthesia (15.38%). The mean blood loss during the surgery was 778.2ml. 20 patients (51%) required blood transfusion. The patients who received tranexamic acid had lesser blood loss compared to those who had not received tranexamic acid. 37 patients (94.87%) recovered uneventfully.

Conclusion:

The role of tranexamic acid in the improvement of perioperative outcome and reduction of the need for allogenic blood transfusion is again confirmed by the study. The usage of neuraxial techniques over general anesthesia is associated to almost similar perioperative outcomes and it requires further research to support these findings. These findings suggest that the decision of anesthetic technique should depend on the patient, surgical and anesthetic risks of morbidity and mortality.

Keywords:

blood loss, blood transfusion, regional anesthesia, total hip arthroplasties, , tranexamic acid.

Introduction:

The first recorded hip replacement surgery was attempted as early as in 1891 by Themistocles Gluck (1853–1942) in Germany (1). With the advancements in both the surgical as well as the

anesthetic techniques, the joint arthroplasties have come a long way to improve the quality of life especially in elderly population. With the increasing count of primary hip arthroplasties happening, the number of revision surgeries tend to increase in manifold.

The revision total hip arthroplasties are associated to significant perioperative mortality and morbidity which can be due to patient factors, surgical factors and anesthetic factors. The identification of such factors can help in optimizing the perioperative outcome and might help in reducing the impact on the cost of medical care (2).

The aim of this study was to identify the common anesthesia practices in the revision total hip arthroplasties. The primary objectives were to study the common anesthesia techniques, associated blood loss, blood and blood products used, hemodynamic stability and post-operative recovery of the patient. The secondary objectives were to study the common pain relief practices, demographic and statistical data affecting the outcomes and any anesthesia related complications.

Material and Methods:

Study Design: This was prospective observational study that included all the patients undergoing revision total hip joint replacement surgery during the period of study, older than 18 years of age and willing to participate in the study. The study excluded patients who are not willing to participate in the study.

Study Procedure: This study was conducted in the elective orthopedic operation theatres in a tertiary care hospital over a period of two years after the institutional ethics committee approval. Universal sampling method was used and all patients fulfilling the inclusion and exclusion criteria were included in the study and the informed consent was taken after doing the preoperative assessment.

Data Collection:

The preoperative, intraoperative and postoperative records of all patients undergoing the revision total hip arthroplasties were collected and an appropriate case record form was developed. The following details were collected from each patient's form:

1. Demographic data: Name, age, gender, weight, height, Body Mass Index (BMI), diagnosis, medical history, previous surgery history, medications, addictions, relevant preoperative investigations and ASA (American Society of Anesthesiologists) status of the patient.
2. Anesthesia techniques: General Anaesthesia(GA) , Regional Anaesthesia (RA - Spinal/ Epidural/Block), Combined GA and RA.
3. Intraoperative hemodynamic: Pulse rate, Blood pressure, SpO2, EtCO2, Respiratory rate.
4. Fluid, blood and blood products:
    a) Intraoperative usage of crystalloids, colloids, blood and blood products.
    b) Need for inotropic supports.
        - Inj. Noradrenaline 0.01-0.02µ/kg/min was started as the first choice as a routine practice.
    c) Blood loss.
    d) Use of Inj.Tranexamic acid.

5. Pain management
    - Type of technique used - IV drugs/Epidural boluses/ Continuous epidural infusions/ Blocks/ Local Infiltration/ other method.
    - As per institutional protocol, Inj. Paracetamol 1g 6h was given to all patients. Inj. Tramadol 50-100mg 8h was given on demand basis in the first 24h postoperatively.
    - Epidural boluses of Inj. Bupivacaine 0.125-0.25% 5cc are given with or without Inj. Buprenorphine 30-90µ if epidural catheter in situ.
    - Local infiltration Analgesia given by surgeons' intraoperatively. The routine practice was to give Inj. Bupivacaine 0.5% 2mg/kg + Inj. Clonidine 1µ/kg + Inj. Fentanyl 1-2µ/kg.
6. Postoperative recovery.

Statistical Analysis:

The data was entered in Microsoft Excel sheet and analyzed using SPSS version 25 and EPI Info version 7.3. Chi square test was used to assess the association between categorical variables. Comparison of Categorical variables was done by using counts and percentages. Mean and standard variations were used for continuous variables. P value <0.05 was considered to be statistically significant.

Results:

A total of 39 patients were assessed and included in the study. The data were sorted manually and entered into a Microsoft Excel Sheet and analyzed using statistical software.

Patients' Demographics:

There were 26 (66.67%) males and 13 (33.33%) females. The mean age was 56.12±15.21 years. (Range 23-81, Standard deviation 15.21). The majority of the patients were ASA II followed by ASA I. **(Table I).**

Table I. *Patient demographics and Preoperative data*

Demographic	Variable	Number (%)
Gender, n (%)	Female Male	13 (33.33) 26 (66.67)
Age (years)	Mean Range Standard deviation	56.12 years 23-81 15.21
ASA grading, n (%)	I II III IV	14 (35.90) 23 (58.97) 2 (5.13) 0 (0)

Co-morbidities, n	No co-morbidities Hypertension Stroke Diabetes Mellitus Ischaemic heart disease Old Pulmonary Koch's Ankylosing spondylosis Retroviral disease	15 14 4 3 3 3 2 2
Preoperative Anemia (as per WHO classification)	Males Females	23 (88.46) 12 (92.31)
Number of previous hip surgeries, n (%)	1 2 3 4 5 6	18 (46.15) 13 (33.33) 5 (12.82) 1 (2.56) 1 (2.56) 1 (2.56)

15 patients had no comorbidities. 14 had hypertension, followed by stroke in 4 patients. There were 3 patients of Diabetes mellitus, Ischaemic heart disease and Old Pulmonary koch's each.18 (46.15%) patients had one previous surgery followed by 13(33.33%) patients with 2 previous hip surgeries. 3 previous hip surgeries were done in 5 (12.82%) patients.

Table II. *Type of anesthesia technique employed*

Type of anesthesia	Number	Percentage
CSE	10	25.64
GA	05	12.82
SAB	15	38.46
SAB+EA	08	20.51
GA+EA	01	2.56
Total	**39**	**100**

(Table II) 15 (38.46%) patients were given Subarachnoid Block (SAB) followed by Combined spinal epidural anesthesia (CSE) given to 10 (25.64%) patients. Subarachnoid block and epidural anesthesia (SAB + EA) were given at different levels in 8 (20.51%) patients. General anesthesia (GA) was given in 06 (15.38%) patients.

Table III. *Intraoperative data*

Data	Variable	Number (%)
Duration of surgery (hours)	1-2h 2.1-4h >4h Mean duration	06 (15.38) 20 (51.28) 13 (33.33) 212.5 minutes
Invasive monitoring during surgery (Arterial/Central venous line)	Yes No	02 (5.13) 37 (94.87)
Blood loss during surgery (ml)	≤500ml 501-1000ml 1001-1500ml Mean blood loss	06 (15.38) 25 (64.10) 08 (20.51) 778.2ml
Blood transfusion during surgery(ml)	No Transfusion 1-250ml 251-500ml >500ml Mean blood transfusion	19 (49) 09 (23) 09 (23) 02 (5) 163.4ml
Crystalloids given during surgery (ml)	<1000ml 1000-1500ml >1500ml Mean crystalloids given	09 (23.08) 27 (69.23) 03 (7.69) 1139.2ml
Colloids given during surgery(ml)	Not given 1-250ml 251-500ml Mean colloids given	16 (41.02) 04 (10.26) 19 (48.72) 252.2ml
Inotropes used during surgery	Yes No	06 (15.38) 33 (84.62)

20 (51.28%) patients were operated within 2.1-4 hours followed by 13 (33.33%) patients in more than 4 hours. Only 06 (15.38%) patients were operated between 1 to 2 hours. Among 39 patients - 25 (64.10%) patients lost blood between 501-1000ml during surgery followed by 08 (20.51%) patients who lost 1001-1500ml blood during surgery.19 (49%) patients were not transfused during surgery followed by 9 (23%) patients that were transfused 1-250ml blood and 9 (23%) patients were transfused 251-500ml blood during surgery. Only 02 (5%) patients were given more than 500ml.

When the association of blood loss and tranexamic acid usage during surgery was seen using chi square test, it was found to be statistically significant (p value = 0.04). Out of 6 patients having blood loss of <500ml, 6 (100%) patients were given tranexamic acid. Out of 25 patients having blood loss of 501-1000ml, majority 17 (68%) patients were given tranexamic acid. Out of 8 patients having blood loss of 1001-1500ml, 5 (62.50%) patients were not given tranexamic acid.

Table IV. *Postoperative data*

Data	Variable	Number (%)
Recovery after surgery	Recovery uneventful Intensive care unit (ICU)	37 (94.87) 02 (5.13)
Pain management	Local Infiltration Analgesia Intravenous route Epidural + Intravenous route	28 (71.79) 22 (56.41) 17 (43.59)

(Table IV) For the postoperative analgesia, 22 (56.41%) patients were given intravenous analgesia post-operatively followed by 17 (43.59%) that were given both Epidural analgesia and intravenous analgesia for pain management. Local infiltration analgesia was given by surgeons in 28 patients (71.79%).

Table V. *General Anesthesia versus Neuraxial Anesthesia*

Outcome	General Anaesthesia n(%)	Neuraxial Anaesthesia n(%)
Number of patients	6(15.38)	33(84.61)
Duration of surgery	170 min	220.3 min
Blood loss	650 ml	801.51 ml
Blood Transfusion	151.66 ml	165.63 ml
Inotropic Needs	1(16.66)	5(15.15)
Postop ICU Stay	**0(0)**	**2(6.06)**

[**Table V**] Multivariate analyses of general anesthesia versus neuraxial anesthesia.

When the association was established between age of the patient and fall in blood pressure using chi square test, it was found to be statistically significant. (p value = 0.04).

37 (94.87%) patients recovered uneventfully and only 2 (5.13%) patients were in ICU for recovery. When chi square test was applied to see the association between age and recovery during surgery, it was not found to be statistically significant (P value = 0.8).

When the association was established between age of the patient and the blood loss during surgery using the chi-square test, it was not found to be statistically significant.

Discussion:

Anesthesia management in the revision total hip arthroplasties have always been associated to significant perioperative mortality and morbidity due to elderly population and related co-morbidities, prolonged surgical time, positioning, significant hemodynamic changes, peri-operative blood loss, blood transfusion, postoperative complications, extended hospital stay and anesthetic alterations for the same (3,4). Proper preoperative assessment, risk stratification and necessary preoperative optimization with proper anesthetic planning for stable intraoperative management and postoperative monitoring form the major components in the management of these patients.

In our study, among the 39 patients, majority 10 (25.64%) patients were in the age group of 51-60 years, followed by 9 (23.08%) in the age group of 61-70 years. The mean age was 56.12±15.21 years (Range 23-81). As per Hospital episode statistics (HES) for England, mean age of the patients undergoing revision surgeries was 71.8 years, whereas for primary surgeries was 68.6 years. As per Australian National Registry, the mean age of the first revision is 71.4 years (5,6).

It was found that there were 26 (66.67%) males and 13 (33.33%) females in the study. As per Hospital episode statistics (HES) for England[5], the female rates were higher than males in the age group of 50 years and above. Traven SA et al. found that there were 54.6% females and 45.4% males who underwent revision total hip arthroplasties (4).

The majority of the patients were ASA II (58.97%) followed by ASA I (35.90%). Begun A et al. found that more than 80% of the patients were healthy or had mild systemic disease (ASA 1-2) at the date of surgery (7). Traven SA et al. found that 1.8% belonged to ASA 1, 39.7% to ASA 2, 53% to ASA 3 and 5.5% to ASA 4 among 13,948 patients who underwent revision total hip arthroplasties (4).

In our study, Central Neuraxial Blockade (CNB) was preferred to general anesthesia (15.38%). Awake fiber-optic intubation was done in 2 patients with ankylosing spondylosis. Memtsoudis SG et al. found that in a large study of total arthroplasties from 2006-2010, 74.8% surgeries were performed under general anesthesia (8). O'Hara DA et al. found in a study of 9,425 elderly patients for hip surgeries that general anesthesia was used in 6,206 (65%) patients and regional anesthesia in 3,219 patients (9). Though GA was preferred in many Western literature, CNB was preferred in our institute in view of multiple factors like the most of the study's population undergoing arthroplasties were elderly patients and their age related comorbidities, to avoid multi-drug therapy, to reduce the opioids usage, to reduce postoperative nausea and vomiting, to encourage

early feeding, early mobilization and early recovery, to avoid post-anesthesia care unit stay, better postoperative pain management and better compliability of the Indian patients (8, 10-14).

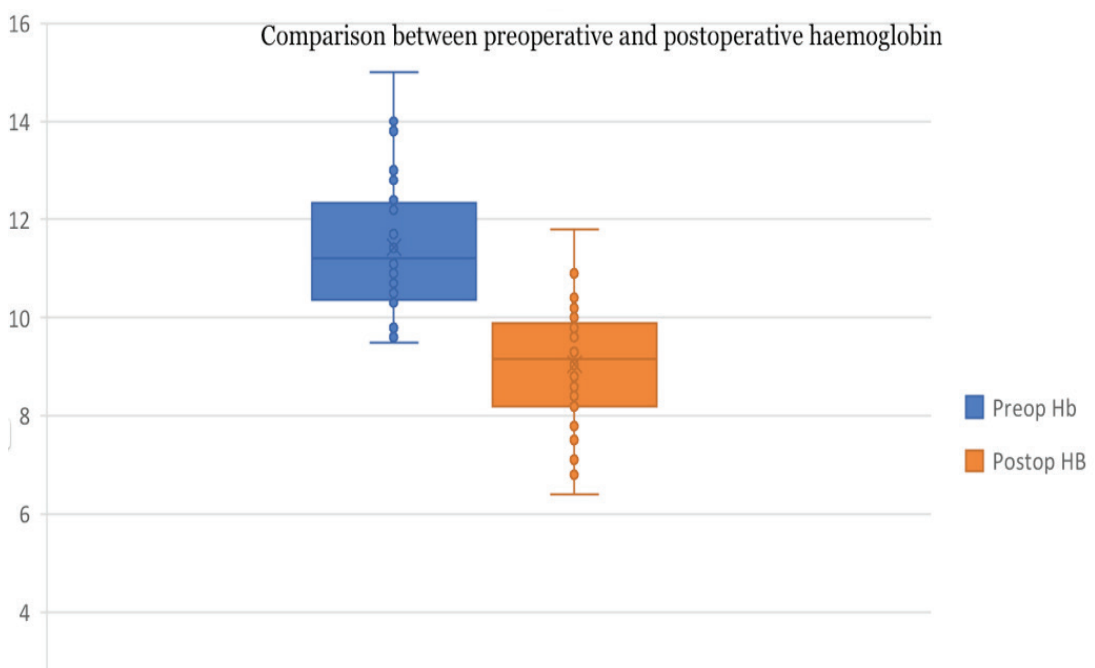
GA was preferred in patients with active cardiac conditions, difficult spine, anticipated higher blood loss, expected surgical difficulties and longer duration of surgery. The informed decision was taken after discussion with the patient and the surgeon.

Hypertension was the commonest comorbidity in 14 patients followed by stroke in 4 patients. There were 3 patients with Diabetes mellitus, Ischaemic heart diseases and Old Pulmonary Koch's each. Memtsoudis SG et al. found that in a large study of total arthroplasties from 2006-2010 in US, 16.9% patients had uncomplicated diabetes, 14.1% had Chronic obstructive pulmonary disease (COPD), 3.7% had previous myocardial infarction and 3.6% had rheumatic disease (8). Wei C et al. found in a retrospective study of 5,759 patients, that common comorbidities were hypertension (59.84%), diabetes mellitus (13.63%) and COPD (5.70%) (10).

The mean duration of the surgery in the study was 212.5 minutes. Habicher M et al. found that in a study of 130 patients, the duration of surgery was 135 minutes (107-171 minutes) in the goal directed fluid therapy group and 125 minutes (99-159 minutes) in the control group (15).

The mean preoperative hemoglobin was 11.43g/dL and the mean postoperative hemoglobin was 9.05g/dL. There was a difference of 2.3 g/dL. The mean blood loss in the study was 778.2ml. Singh J et al. found that the mean intraoperative blood loss was 489ml (without tranexamic acid) and 339ml (with tranexamic acid) (16). Peck J et al. found that the estimated intraoperative blood loss was 845ml (with tranexamic acid) and 1,095ml (without tranexamic acid) (17).

Figure I. *Comparison between preoperative and postoperative hemoglobin*



Singh J et al., Peck J et al. and Park KJ et al. found that the blood loss was lesser with tranexamic acid (16-18). It was found to be similar in our study as seen in Table 4.

Out of 26 males, 23 (88.46%) were anemic pre-operatively and out of 13 females, 12 (92.31%) were anemic pre-operatively as per World Health Organization (WHO) classification for anemia. E Saleh et al. found that the prevalence of anemia in elective major orthopedic surgeries is 20% and perioperative transfusions could be avoided(19).

The mean blood transfusion during the procedure was 163.4ml. 20 patients (51%) required blood transfusion during surgery. Only one patient (2.56%) was given Fresh Frozen Plasma (FFP) in the study. E Saleh et al. found that 12 out of the 16 patients who underwent revision hip surgeries required blood transfusion (19). Mahadevan D et al. found that 73 patients (50%) out of 146 patients who underwent revision hip arthroplasties, required blood transfusion.[3]

The mean crystalloids given during the procedure was 1139.2ml. Habicher M et al. found that in a study of 130 patients, average of 725ml crystalloids (500-100ml) were given in the goal directed fluid therapy group and average 1,500ml was given in the control group (15).

The mean colloids given during the procedure was 252.5ml. 23 patients (58.97%) were given colloids in the study. Habicher M et al. found that in a study of 130 patients, average of 1,250ml (1000-1750ml) colloids were given in the goal directed fluid therapy group and average of 500ml (500-1000ml) was given in the control group (15). 6 (15.38%) patients needed the requirement of inotropes during the surgery. The inotropes were started in view of major blood loss and non-maintenance of hemodynamics. Out of 6 patients, 4 were weaned off of inotropic supports in the immediate postoperative management. Habicher M et al. found that in a study of 130 patients, 28 patients in the goal directed fluid therapy group and 1 patient in the control group required inotropes during the surgery (15).

2 patients (5.12%) were shifted to PACU for postoperative monitoring in view of major blood loss, non-maintenance of hemodynamics and need for inotropic supports. Both of them were induced under CNB and had a drop of postoperative hemoglobin by around 3g/dl.

Limitations:

- The limitations of this study include the single center study, lack of randomization and the lack of information about the type of implants and their influence on the perioperative outcome (3,7).[3], [7]

Conclusion:

The role of tranexamic acid in the improvement of perioperative outcome and reduction of the need for allogenic blood transfusion was again confirmed by the study. The usage of neuraxial techniques over general anesthesia is associated to almost similar perioperative outcomes and it requires further research to support these findings. These findings suggest that the decision of anesthetic technique should depend on the patient, surgical and anesthetic risks of morbidity and mortality.

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MULTIMODAL LOW-OPIOID ANALGESIA IN OPEN RADICAL CYSTECTOMY

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ABSTRACT

The concept of multimodal analgesia has been introduced as a technique to improve analgesia and reduce the occurrence of opioid-related side effects. In the intra-operative period, it was achieved to obtaining hemodynamically stable anesthesia with less usage of opioids and less need for opioids in the postoperative period, and thus the side effects of opioid use were reduced. It can be used in patients who are undergone for cancer surgery; thus opioids will be withdrawn and they are responsible for progression of cancer cells.

Key Words: multimodal low-opioid analgesia, open radical cystectomy, postoperative pain.

Introduction:

Open radical cystectomy with construction of Bricker bladder is the standard treatment in patients with muscle-invasive bladder cancer. This procedure is followed with significant intra- and postoperative pain, infection, bleeding, prolonged hospital stay (5-10 days), as well as opioid related adverse drug events (ORADEs) such as nausea, vomiting, constipation, sedation, delirium, pruritus and agitation (1). Opioids alone or combined with non-opioid analgesics are important for pain management in cancer patients (2). It has been shown that opioids can affect cancer development through their modulation of cell proliferation and cell death. The concept of multimodal balanced analgesia is consisted of giving different analgesic drugs in purpose to change the pathophysiological process which is included in nociception, in a way to receive more effective intraoperative analgesia with less adverse effects. Multimodal analgesia is especially important in patients where we have withdrawn epidural analgesia from the patient.

Case Report:

Female patient 49 years old (height 170, weigh 67 kg) ASA 3 classification, was scheduled for open urological operation, where urinary bladder was planned to be removed. Previously she had 2 surgeries, tonsillectomy in child age and urinary bladder operation (TUR-T) one month before. She had previous history of hypertension, anemia and psychosis. One and a half month ago she was treated in another hospital, where left kidney wasn't functioning well and percutaneous nephrostomy on right side was done. Because she had high values of urea, creatinin and potassium during her hospital stay, she underwent on several dialysis. During her stay in hospital, she got SARS COVID-19 infection and recovered well.

Before she underwent surgery, she refused to have epidural anesthesia or erector spine plane block for pain treatment during and after operation. After placement of standard monitoring, introduction into anesthesia was started.

The anesthesia introduction was with midazolam 0.04mg/kg (3mg), lidocaine 1mg/kg (70mg), 100 micrograms fentanyl, propofol 2mg/kg (140mg), ketamine 0.5mg/kg (35mg) and rocuronium bromide 0.6mg/kg. Prior to surgery we gave the patient dexamethasone 0.1mg/kg (7mg) and inserted intraarterial line for continuous measurement of blood pressure. Anesthesia was maintained with sevoflurane MAC 0.7-1 and continuous infusion with lidocaine 2 mg/kg/h, ketamine 0.2 mg/kg/h and magnesium sulphate 8.5 mg/kg/h (total 3 gr during operation). This type of surgery involves removal of the bladder, uterus, fallopian tubes, ovaries and anterior vaginal wall and creating a new way to store urine.

Surgery lasted for 5 hours and the patient remained stable all the time during surgery. Fentanyl was not given additionally. At the end of surgery 1gr paracetamol was given as an infusion and continuous infusion with multimodal analgesics was switched off. The patient was extubated in the operative room and had no pain. She was transferred in post-anesthesia care unit and stayed there for 2 hours. Analgesia regime consisted of giving metamizol 1gr if visual analogue scale (VAS) score was 4-6, and tramadol 1mg/kg for VAS score 7-10. As a rescue analgesic was used 1gr paracetamol. Moderate pain was recorded 12, 36, 48 and 72 hours after surgery and 1gr metamizole was given. The worst pain had appeared 7 hours and 24 hours after surgery with VAS score 9 and 8 accordingly, and 100mg tramadol was administered. There was no need of giving rescue analgesia. All time during her hospital stay the patient remained stable, without any complications and on the 7th postoperative day she was discharged home.

Discussion

Urological operations with open approach are followed by high pain scores, during and after operation, as well as other complications such as ileus, infection and longer hospital stay. These procedures require midline incisions on the pubic symphysis. If pain is not well managed, then chronic pain can appear, which is very difficult for treatment. Patients with such surgery can develop persistent post-surgical pain (PPSP) and that's why intraoperative and postoperative analgesia are of utmost importance.

In many studies, the direct effect of opioids to the carcinoma cell and faster metastasis spread has been described. Opioids can promote the progress of carcinoma (malignant disease), because they have various direct effects on cancer cell and can speed up the spread of malignant cells (3). They increase the concentration of mu-opioid receptors, increase angiogenesis and increase the carcinoma itself. It must be emphasized that severe pain itself has a significant immunosuppressive effect. The concept of multimodal analgesia has been introduced as a technique to improve analgesia and reduce the occurrence of opioid-related side effects. Multimodal analgesia is achieved by combining different analgesics that act through different mechanisms, in different places in the central nervous system. The aim is to achieve adequate analgesia through the additive or synergistic effect between different analgesics and at the same time to reduce the dose of each individual drug, and thus the possibility of side effects from the same drugs. Multimodal pain treatment is the best way to reduce the needs for opioids. Multimodal analgesia is based on the administration of small doses of opioids in combination with regional anesthesia (epidural analgesia and peripheral nerve blocks) and non-opioid analgesics: alpha-2 agonists, non-steroidal anti-inflammatory drugs (NSAIDs), lidocaine, dexamethasone, magnesium sulphate, ketamine, paracetamol, gabapentinoids and metamizole.

In our case report, it has been shown that multimodal approach had sufficient benefit not only in the intraoperative period, but in the postoperative period as well. The patient didn't complain of having high pain scores in the postoperative period and no other complications were recorded and she recovered soon. The total amount of tramadol during postoperative period was 200mg.

Lidocaine acts on protein G receptors, NMDA receptors, and A-delta and C nerve fibers. Indirectly it blocks NMDA receptors by inhibiting protein kinase C, thereby affecting postoperative hyperalgesia and opioid tolerance. The analgesic effect of ketamine is due to binding of ketamine to sigma and delta opioid receptors. Ketamine blocks the release of potassium out of the cell and thus prevents the transmission of painful impulses. Magnesium is not primarily an analgesic. It has this effect because it is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist and blocks calcium channels. By giving magnesium the conduction of the painful impulse can be stopped. It blocks the entry of sodium and calcium into the cell and thus prevents the transmission of pain. Dexamethasone given prior to surgery has been shown to have antiemetic effect and due to his anti-inflammatory effect leads to lower pain scores and thus has effect on postoperative analgesia.

Niraj et al. in their observational study found out that combined erector spinae plane block and intrathecal opioid analgesia, lead to reduced incidence of postoperative ileus and reduced length of hospital stay after open radical cystectomy (4). Other group of authors implemented reduced opioid utilization (ROU) protocol and stated that opioid use was decreased by 77% without compromising the pain control or increasing the rate of complications (1). This protocol was consisted of multimodal opioid-sparing pain regimen. The study of Xu et al. showed that patients who underwent enhanced recovery after surgery (ERAS) protocol used significantly less opioids per day, reported more pain, experienced significantly lower incidence of postoperative ileus and have shorter length of hospital stay, comparing to those who were treated with the traditional protocol.[5]

Conclusion

Multimodal low-opioid analgesia in open radical cystectomy was successful in reducing needs for opioids during surgery, the request for opioids was less in the postoperative period too, and no complications afterwards were recorded. It can be used as a good alternative when patient refuses epidural analgesia or truncal block.

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THE ROLE OF OPTICAL COHERENT TOMOGRAPHY IN DIAGNOSIS AND EVALUATION OF EYE DISEASES IN PEDIATRIC POPULATION

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ABSTRACT

Introduction: Optical coherence tomography (OCT) is a non-invasive technique that provides high-resolution images by making cross-sections of the retina in the macular region, the optic nerve head, and the retinal nerve fiber layer. Although it offers many advantages over clinical examination, such as greater sensitivity and better localization of the pathology at the level of individual retinal layers, its value in the pediatric population may be insufficiently recognized.

Aim of the Paper: To emphasize the clinical importance and application of optical coherence tomography in the pediatric population.

Materials and Methods: This paper is a review of literature for which PubMed and Medline medical databases were searched by keywords. 163 papers were found, 25 of which were used for our paper.

Discussion: The need for optical coherence tomography in the pediatric population for better diagnosis and monitoring of diseases of the retina (namely optic nerve and macula), vitreous and choroid, which is confirmed by numerous studies.

Conclusion: Optical coherence tomography has become an integral part of diagnosing and monitoring retinal diseases in the pediatric population. Potentially, by contributing to the timely treatment of diseases that occur in the plastic period of vision development in children, OCT may be the key to improving visual function by normalizing the development of the retina and optic nerve.

Key Words: macula, optical coherence tomography (OKT), optic nerve, pediatric population.

Introduction

Optical coherence tomography (OCT) has revolutionized clinical practice in ophthalmology. It is a non-invasive technique that provides high resolution images. The images are generated by cross-sections of the retina (macula), the retinal nerve layer, and the optic nerve head (1). Ophthalmology is a dominant field in the medical branches, where the opportunities offered by OCT technology are the best adapted to the needs for diagnosis and monitoring of a number of ophthalmic diseases. The main factors for this are considered to be the transparency and high permeability of the ocular media which participate in the refraction of the eye, combined with the high sensitivity and accuracy of this method (2).

The application of OCT in clinical practice has increased exponentially in the past 10 years due to technological advances and its wide availability. In adults, OCT is used to diagnose and monitor macular degeneration, such as age-related macular degeneration (ARMD), diabetic macular edema (DME) as part of diabetic retinopathy, cystoid macular edema (CME), secondary to central vein occlusion (OVCR) or branch venous occlusion (BRVO). It is also used as a routine method for diagnosing optic nerve disease, monitoring of retinal nerve fiber thickness (RNFL) and ganglion complex (GCC) in patients with glaucoma (3).

Regarding the clinical examination, which is an integral part of the ophthalmological examination, OCT offers many advantages, such as high sensitivity and localization of the pathology of individual retinal layers (3).

The method is non-contact, non-invasive and without contraindications for its application. It is fast and it does not require prior significant preparation for the patient. The only prerequisite is the transparency of the optical media, which makes it quite suitable for application in everyday ophthalmic practice in children (4).

According to the World Health Organization, there are approximately 1.4 million blind children under the age of 15 worldwide (4). More than 80% of the total, live in the poorest areas, such as Asia, Africa and South America. In the United States alone, more than 50,000 are registered as legally blind (5). The main causes of vision loss in children in Europe, the United States and Japan are retinal diseases, optic nerve atrophy and diseases that affect the visual pathways (6).

Due to the age and difficult cooperation for examination in the pediatric population, the application of OCT is important for the diagnosis, monitoring of changes and effects of treatment of certain ophthalmic diseases. With this simplified approach, OCT provides timely treatment of certain ophthalmic diseases, and thus prevention of blindness and disability for life.

This paper aims to focus on the clinical relevance and application of optical coherence tomography in the pediatric population (6).

Materials and Methods

This paper is a review of literature for which PubMed and Medline medical databases were searched by these key words: optical coherence tomography, macula, optic nerve, pediatric population. 163 papers were found, 25 of which were used for our paper.

Macular and Retinal Diseases

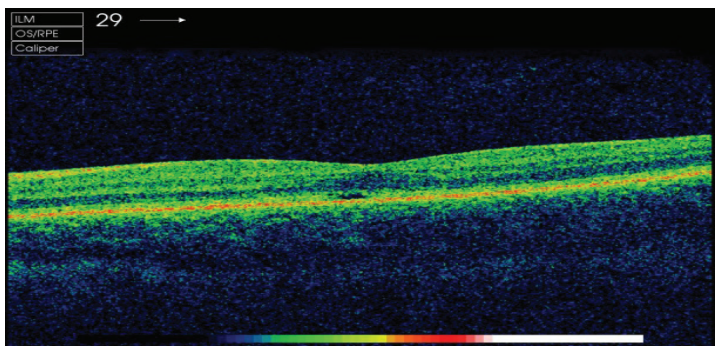
Hereditary retinal dystrophies are a major cause of severely progressive vision loss in children. They include a large group of clinically and genetically heterogeneous disorders affecting approximately 1 in 3,000 children with more than 271 causative genes identified to date (7).

Examination of the fundus may be normal or nonspecific in the early stages. Therefore, early recognition and diagnosis of dystrophies is essential for the timely preservation of vision,

especially in the period of visual development, as well as for timely genetic diagnosis and possible gene therapy (7).

Electrophysiological methods such as electroretinogram (ERG), electrooculogram (EOG) and visible evoked potentials (VEP) are the gold standard in the diagnosis of macular dystrophies. However, the importance of OCT in the pediatric population must be emphasized, especially because of its speed, non-invasiveness, practical evaluation and applicability even in 3-years-old patients. (8)

Figure 1. *OCT tomogram in occult macular dystrophy*

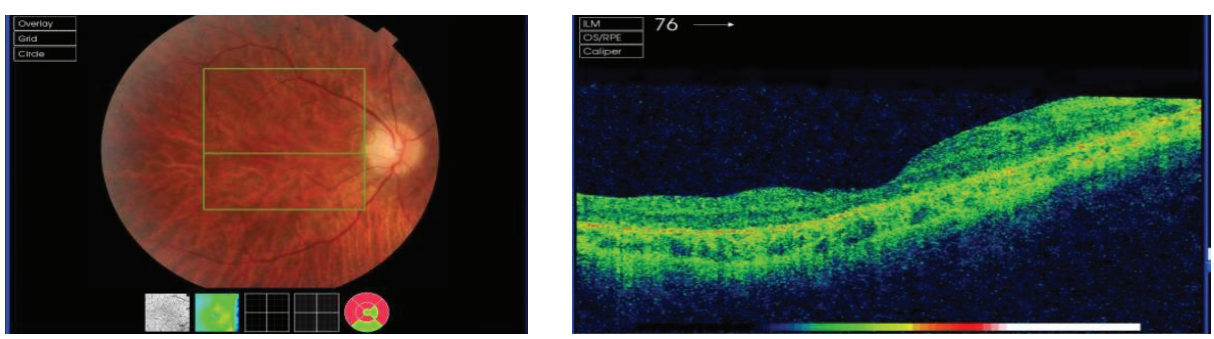


There are numerous types of retinal dystrophy in which OCT is routinely used for diagnosis and monitoring (8).

Retinitis pigmentosa (RP) is one of the most common retinal dystrophies, which includes a group of heterogeneous disorders that lead to progressive degeneration of retinal photoreceptors and are usually manifested by loss of peripheral vision and difficulty seeing at night (8).

Several studies have been published suggesting the use of OCT in Retinitis pigmentosa, the most of which demonstrate the method's ability to detect and monitor retinal changes at the photoreceptor layer level and their integrity (9).

Figure. 2 a, b. *Photo fundus imaging and OKT tomogram in Retinitis pigmentosa*

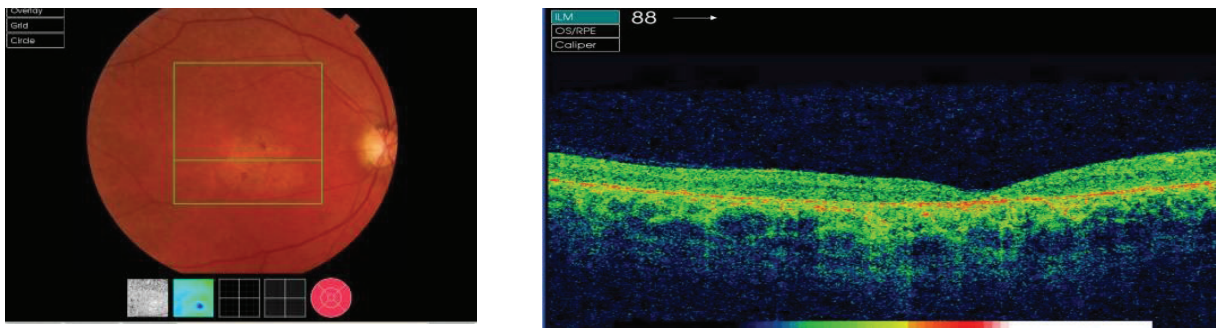


Another macular dystrophy is Stargardt's disease, which is inherited autosomal recessively and leads to progressive central vision loss. The main cause is the accumulation of lipofuscin in the retinal pigment epithelium (RPE), which is toxic to photoreceptors (9).

The clinical picture is manifested by bilateral central vision loss, including dyschromatopsia and central scotomas, with characteristic macular atrophy and yellowish-white spots at the level of the RPE fundus (fundus flavimaculatus) (9).

The onset is the most often in childhood, with the next peak being early adulthood and the rarest in later adulthood. A better prognosis is generally associated to the later onset. (9) In the final stage of the disease there is a large retinal central atrophy extending into the deeper layers of the posterior pole, so it is difficult to differentiate only by examination of the fundus, but it is clearly detected on OCT (10,11).

Figure 3a, b. *Fundus photo and tomogram in Stargardt macular dystrophy*

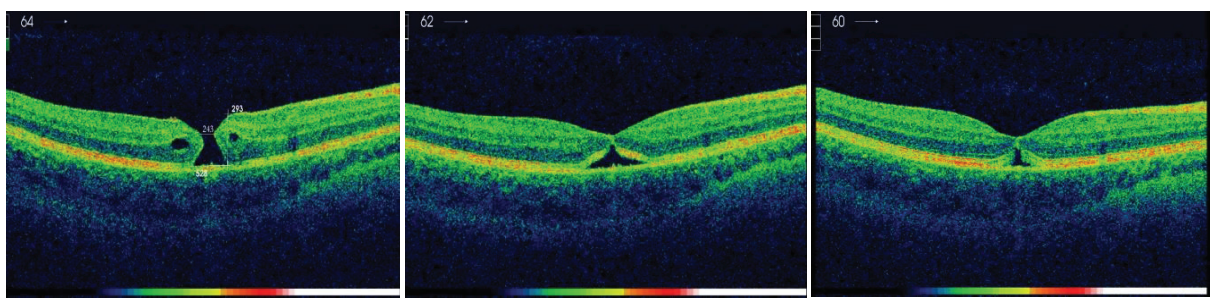


Best vitelliform macular dystrophy is caused by an autosomal dominant mutation in the BEST1 gene (12).

Clinically, the disease is presented with the classic appearance of 'egg yolk' in the macular region, with RPE involvement initially and often progressing to retinal atrophy and RPE atrophy. Although the visual prognosis is typically good, the condition can lead to significant vision loss due to atrophy or choroidal neovascularization (CNV) (13). In this disease, OCT is used as standard in the diagnosis, with typical tomogram findings showing disruption of the outer layer of the retina and the presence of vitelliform material beneath the retina. Central RPE atrophy and choroidal neovascularization (CNV), which occur in the later clinical stages of the disease, can also be seen on OCT (13).

Some studies have shown benefits from using anti-VEGF drugs as a treatment for CNV, and OCT have proven to be a good method of monitoring results (14).

Figure 4 (a-c). *OCT tomograms in traumatic macular hole, evaluation of spontaneous closure of TMH at 8 years. child in pencil injury. a) 3rd day after injury, b)14th day after injury, c) 2 months after injury.*



Diseases of the Optic Nerve

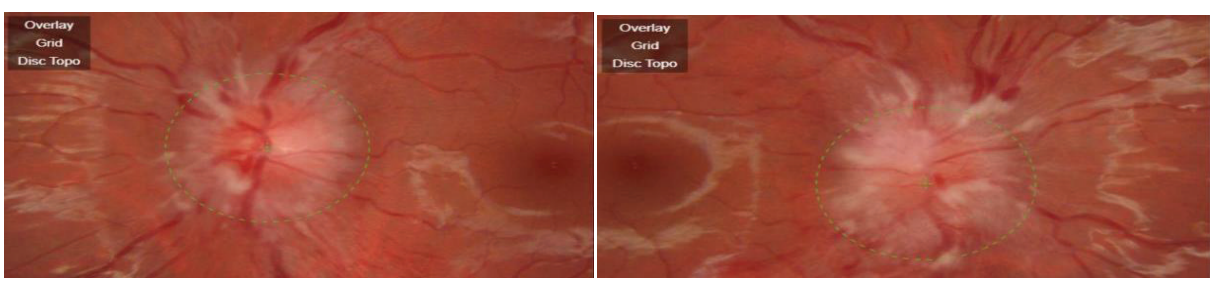
OCT can help diagnose and monitor treatment outcomes in children suspected of having optic nerve pathological conditions, such as glaucoma and optic neuropathy. In cases of pediatric glaucoma, OCT has proven to be a sophisticated method for measuring retinal nerve fiber thickness (RNFL) and macular thickness (15).

The process of diagnosing and monitoring glaucoma is more difficult in children than in adults, due to the challenge of accurately measuring intraocular pressure and testing the visual field (perimetry). In infants and newborns with congenital glaucoma, the tests are usually performed under general anesthesia, due to the technical difficulty of performing OCT in this group of patients. Therefore, there is a lack of literature on the use of OCT in congenital and infantile glaucoma, whereas many OCT studies overestimate children with juvenile glaucoma. (15)

Children with juvenile glaucoma are found to have a thinner RNFL and macula than their peers. Furthermore, the thickness of the RNFL and the macula decreases as glaucomatous damage progresses. These findings further support the importance of the application of OCT in the early diagnosis and monitoring of pediatric glaucoma (15).

OCT is also used in the diagnosis of non-glaucomatous optic neuropathy. OCT has been proven to measure RNFL thickness with excellent sensitivity, and its role in the diagnosis and monitoring of various optic nerve abnormalities is increasingly used in the pediatric population. In comparison to healthy children, thicker RNFL was observed in children with pseudotumor of the brain, while thinner RNFL was measured in children with multiple sclerosis involving the optic nerve, acute disseminated encephalomyelitis and optic neuritis (15).

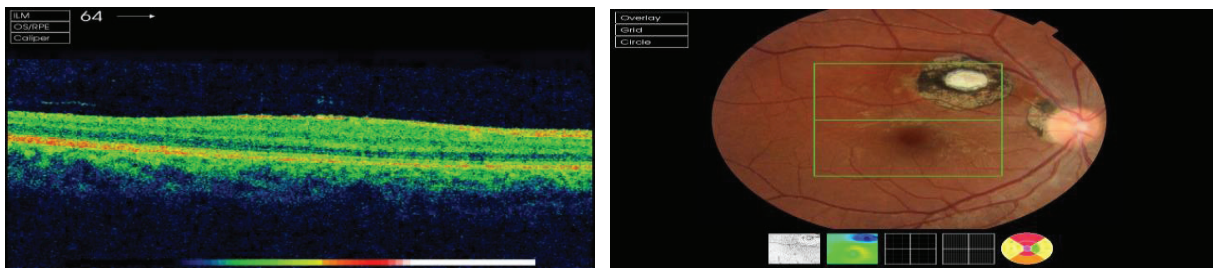
Figure 5. *Bilateral papilloedema, Stasis papillae, in an 11-years-old girl*



Congenital Infections

Toxoplasmosis is a parasitic infection known to cause congenital retinal defects with characteristic chorioretinal scars. OCT may show activity by detecting subretinal fluid and preserved RPE layer. These findings are useful in the diagnosis and monitoring of subtle recurrence of ocular toxoplasmosis and especially in assessing the severity of ocular infection (16).

Figure 6 a, b. *Fundus photo and tomogram in a child with toxoplasmosis*



Rubella is another congenital infection with known findings of OCT. A prospective study analyzed images of OCT in 13 children (24 eyes) diagnosed with rubella congenital syndrome, and found that these patients were significantly more likely to have U-shaped foveal dip (61.1%) and absent RPE. (85%) (17).

Amblyopia

Amblyopia is one of the most common causes of preventable permanent visual impairment in children. The most common causes of amblyopia are strabismus and refractive errors. Bitirgen et al. found that children with both strabismus and hyperopic amblyopia had significantly greater peripapillary choroidal thickness of OCT compared to the control group even after stabilization of the refractive anomaly (18, 19).

Several papers describe the increased central macular thickness in amblyopic patients, which correlates with the severity of amblyopia (18,19).

In the study of Yen et al. it has also been shown that children with amblyopia may have an increased thickness of the retinal nerve fiber layer (RNFL), which is thought to be due to a reduction in normal postnatal ganglion cell apoptosis due to a lack of the sharp focus required for normal development (20).

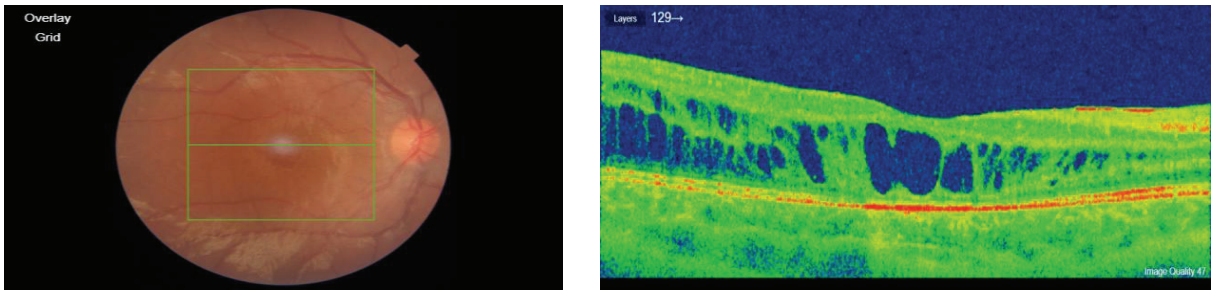
Although the findings of OCT in amblyopia are subtle and relatively new, they can be used to understand the mechanism of visual impairment in patients with amblyopia, and its use in clinical practice is likely to increase with further research. (20).

Uveitis

The most cases of uveitis in the pediatric population are idiopathic. However, etiological factors can be confirmed with certainty in some cases. The most common etiological cause is juvenile idiopathic arthritis, which accounts for about 75% of all anterior uveitis in childhood (15)

Macular involvement may be missed during clinical examination if subtle. In a study of 24 eyes in children with uveitis in juvenile idiopathic arthritis, OCT detected macular edema in 25%, which was mild and clinically inconspicuous. Therefore, OCT may be an additional diagnostic tool with very high sensitivity for detecting maculopathy, as a significant complication of uveitis in children with juvenile idiopathic arthritis (15).

Figure 7 a, b. *Fundus photo and tomogram in a child with intermediate uveitis*



Discussion

In a short period of time, OCT has become a widely used method for diagnosing and monitoring a wide range of ophthalmic diseases, mainly due to its ability to visualize ocular structures in high resolution. OCT is dominant in the field of ocular diagnostics because of its advantages: completely non-invasive, non-contact, fast and informative. It is an in vivo technology for obtaining structural images of the eye in people of any age and status.

In addition, it is constantly upgraded in terms of technical performance, such as penetration depth, scanning speed, axial resolution, etc. Thus, depending on the stages of their development, there are different generations of devices (21).

The use of OCT in the pediatric population is needed for better diagnosis and monitoring of diseases of the retina (optic nerve, macula), vitreous and choroid.

A number of studies using OCT as a diagnostic method have highlighted the importance of OCT in quantitative monitoring of cystoid macular edema, for example in Coats's disease after intravitreal administration of an antiangiogenic agent. Its application is further emphasized in the examination of toxoplasma foci in the macula and in the diagnosis of ocular nerve diseases, such as glaucoma, optic atrophy and hypoplasia, optic glioma, and pseudotumor cerebri (22,23).

An important parameter often used in quantitative studies for OCT is the thickness of the retinal nerve fiber layer (RNFL). Because OCT devices do not have a normative database for children, and OCT parameters differ significantly from those in healthy human population, measured RNFL thickness in children is considered pathological only if progressive thinning of the RNFL is observed on several consecutive examinations. It is also important to use the same OCT model in the quantitative analysis of the results of subsequent examinations (22).

Study conducted by El-Dairi et al. in patients with pseudotumor cerebri, in which peripapillary RNFL thickness and macular thickness are evaluated with the help of OCT, showed increased thickness of both the RNFL and the macula (24). While a study by Javaneh et al. showed a reduction in macular thickness, i.e., thinning in both the inner and outer layers of the retina in children with unilateral hypoplasia of the optic nerve (25).

Conclusion

OCT has become an integral part of diagnosing and managing pediatric retinal diseases. The ability to perform OCT to examine retinal and optic nerve diseases in children provides important insights into the nature of these conditions. These diseases in children are much more dynamic than in adults, which suggests that retinal diseases in early childhood result in abnormal retinal development, as opposed to diseases in adults. Potentially, timely treatment of diseases occurring during the period of plasticity of vision development may be key to preserving visual function by normalizing retinal and optic nerve development.

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PREGNANCY WITH POLYCYTHEMIA VERA - AN OBSTETRIC CHALLENGE

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ABSTRACT

Polycythemia vera (PV) is a rare chronic myeloproliferative disorder of the haematopoietic stem cell type characterized by increased erythrocyte production. The disease is associated to a high risk of clinical complications - arterial and venous thrombosis, especially in pregnancy, bleeding, possible evolution to myelofibrosis and acute myeloid leukemia.

We present the case of a 28-years-old patient, whose diagnosis was made 2 years before pregnancy (positive for mutation JAK2 V617F, bcr-abl negative, MPL, CALR negative). She was regularly monitored at the Hematology Clinic, had therapeutic venipunctures performed and anticoagulant therapy was prescribed. Pregnancy was regularly followed, with proper fetal growth and development, regular screening for fetal abnormalities, under anticoagulant therapy and under the supervision of a hematologist.

At 34 weeks gestation, due to bleeding and pain, she was hospitalized in the Peripartal Intensive Care Department suspected of placental abruption. A caesarean section was performed immediately, a premature fetus was delivered in relatively good condition, and during the operation abruption of 1/3 of the placenta was found. The operative and postoperative periods were stable, the patient received replacement therapy and was discharged from the hospital on the 5th postoperative day in good general condition. The newborn was stabilized and discharged in good general condition after 3 weeks of stay at the Neonatal Intensive Care Department.

Conclusion: Pregnancy in patients with this disease carries serious risks to the life and health of both mother and fetus, which requires special attention during pregnancy in order to reduce antenatal and postnatal morbidity.

Key Words: aspirin, bleeding, polycythemia vera, pregnancy.

Introduction

Polycythaemia vera (PV) is a clonal myeloproliferative disorder of haematopoietic stem cells characterized by increased erythrocyte production (1). The incidence increases during reproductive age (0.04-0.25 per 100,000 patients) (2). Clinical complications include arterial and venous thrombosis, bleeding, and the possibility of transformation into myelofibrosis or acute myeloid leukemia. Normal blood flow to the uterus and placenta is essential for a normal

pregnancy. In the first trimester of pregnancy, the trophoblast invades the blood vessels of the endometrium and the spiral arteries as the placenta develops. Then comes the conversion from low volume, high circulation resistance to large volume with low resistance. This condition can be detected by a Doppler scan and may be a marker for early placental dysfunction. This disorder can lead to miscarriage, fetal growth retardation (IUGR), preeclampsia and placental abruption, which are serious complications in these pregnancies.

Polycythaemia vera is caused by a mutation in the JAK2 gene (JAK2V617F), which is present in approximately 90% of patients with PV. The gene responsible for the synthesis of specific proteins, called kinases, is responsible for cells proliferation (3).

The focus of treatment in pregnant women with PV is to maintain a hematocrit level less than 45% or within the normal range of pregnancy (30-39%). For the treatment of pregnant women interferon is recommended (cytoreductive agent, having lower teratogenic potential than hydroxyurea, acylating agents, ruxolitinib). In addition, low doses of aspirin are strongly recommended in the management of patients with PV.

Case Report

A 28-years-old patient with her first controlled pregnancy was referred by her family gynecologist to the University Clinic for Gynecology and Obstetrics as a high-risk pregnancy in the 9th week of gestation. The patient was diagnosed with polyglobulia two years ago, due to which she was evaluated by a hematologist at the University Clinic of Hematology. In the period when the disease was diagnosed, the values of blood sample were: Hgb-174g/l, Hct-0.55, Tr-403, Le-6.7, with normal peripheral smear. Antiaggregating therapy was prescribed - acetylsalicylic acid 100mg daily and 6 therapeutic venipunctures were performed for hematocrit higher than 0.45 in a period of 18 months until pregnancy.

Molecular analysis was performed for the presence of mutations, the patient is positive for mutation JAK2V617F, BCR-ABL negative, MPL and CALR negative. Diagnosis is PRV.MPS (JAK2 V617F +). An examination by an internist was performed, an ultrasound examination of the abdomen was performed by a gastroenterohepatologist and a finding was within normal limits. During the pregnancy, two venipunctures were performed up to 11 weeks of gestation.

As far as pregnancy is concerned - biochemical screening in the first trimester was with low risk for aneuploidy and ultrasound screening in the first trimester showed eutrophic growth and development. The patient received acetylsalicylic acid 100mg once a day for up to 32nd week of gestation (gw) and then she was switched to low molecular weight heparin therapy for prophylaxis. At the last antenatal examination at 34th gw, the fetal growth was at the 35th percentile with a normal amount of amniotic fluid, with the first/ second-degree placental maturity, the patient was normotensive and biochemical analyzes and hemostasis were in reference values, only D-dimer values were up to 1100mg/ml (still normal for 34th gw). At the last control, three days before delivery, the patient was normotensive, without subjective complaints, with normal biochemical analyzes and fetal ultrasound with eutrophic fetal growth with regular fetoplacental flows.

At 34th week of gestation, due to bleeding and pain, she was hospitalized in the Peripartal Intensive Care Department (PIN), where there was a suspicion of placental abruption. A caesarean section was performed immediately, a premature fetus was delivered in relatively good condition and abruption of 1/3 of the placenta was found intraoperatively.

The operative and postoperative courses were stable, the patient received symptomatic therapy and was discharged in good general condition on the 5th postoperative day. The newborn was stabilized and discharged in good general condition after 3 weeks in the Neonatal Intensive Care Unit. The patient came for a follow-up examination 2 weeks after delivery. She had regular ultrasound findings, regular hemogram and hemostasis results, only moderate hypertension was reported and treatment with antihypertensive therapy was prescribed.

Discussion

The specificity of the case of PV in pregnancy that is presented here explains the difficulties in diagnosing this pathology in a woman of reproductive age. The need for an interdisciplinary approach is necessary to achieve a safe outcome for both mother and fetus (4).

Pregnancy is a prothrombotic condition and is characterized by an increased risk of venous thromboembolism, especially in patients with thrombophilia.

A study by Robinson et al., which worked on 18 patients with PV, compared maternal and obstetric outcomes before and after the introduction of a defined pregnancy management protocol. There was a total of 11 live births, 4 miscarriages in the first trimester, 3 stillbirths, 1 neonatal death, 3 cases of intrauterine growth restriction (IUGR) and 3 preterm births. Maternal morbidity in this study is low, with one patient having pulmonary embolism and 3 cases of preeclampsia (5). There are limited studies in the literature debating the management of PV in pregnancy.

The ECLAP (European Collaboration on Low-Dose Aspirin in Polycythemia Vera) study suggests that it is necessary to maintain balanced blood count and that 100mg of aspirin daily reduces the risk of serious life-threatening complications (6). The mechanism of action of low-dose aspirin is the irreversible inhibition of the enzyme COX-1 in the vascular endothelium, necessary for the production of thromboxane A2 (the factor responsible for platelet aggregation and vasoconstriction).

Regarding the administration of LMWH, prophylactic use is not recommended in patients without active thrombosis or a history of major thrombotic events (7). In this study, aspirin was used at a dose of 150mg daily to prevent preeclampsia, IUGR, placental abruption and stillbirth. Low molecular weight heparin is administered to patients with peripheral venous insufficiency, thrombocytosis and advanced maternal age. It has been confirmed that better results are achieved using cytoreductive treatment along with low-dose aspirin, while the use of anticoagulants is recommended according to individual case assessments.

Conclusion

Pregnant women with PV have an increased risk of miscarriage in all trimesters, IUGR, and prematurity. This study, as the largest to date, supports the use of therapy adjusted to each patient, depending on the condition of the disease (8). Because PV is a rare clinical condition, a multidisciplinary approach is needed, as well as further research into this disease.

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TEMPORARY PACING FOR SYMPTOMATIC BRADYCARDIA IN TRAUMATOLOGY INTENSIVE CARE UNIT

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ABSTRACT

Introduction: Cardiac complications are not uncommon during surgical procedures. Not infrequently surgical medical problems are combined with cardiac conduction diseases with electrical disorder in the conduction system of the heart. The aim of this paper is to present a case report with such a combined condition and the need for setting of temporary pacemaker. We present a patient with a history of atrial fibrillation, arterial hypertension, chronic kidney disease and diabetes mellitus that was admitted at orthopedic department for femoral neck fracture. Patient had atrial fibrillation (AF) with complete AV block conduction, and heart rate around 40bpm, and with cardiologist consultations it was decided that the patient needed cardiac pacing at the time. At that time in patient a temporary endocardial pacing in intensive care unit was done. This report shows the importance of multidisciplinary approach and overall emphasizes the global knowledge for the need and the ways and different sites of cardinal pacing in complex cardiac diseases.

Key Words: complete AV block, femoral neck fracture, temporary pacing.

Case Report

A 75-years-old woman with known history of AF, HTA, diabetes and chronic kidney disease was admitted in traumatology intensive care unit for recompensating the metabolic/electrolyte, hemodynamic, respiratory disorders, because of delayed treatment of femoral neck fracture. She had a low energy hip fracture 7 days before. The anamnesis revealed a syncope that was postural hypotension by mechanism. Her medication history was specific in the beta blocking agents (bisoprolol) and cardiotonic (digitalis) for rate control and coumarin for anticoagulation with INR in therapeutic range. Although she had only arterial hypertension, she had an advanced diabetes mellitus with kidney, neural, microvascular complications.

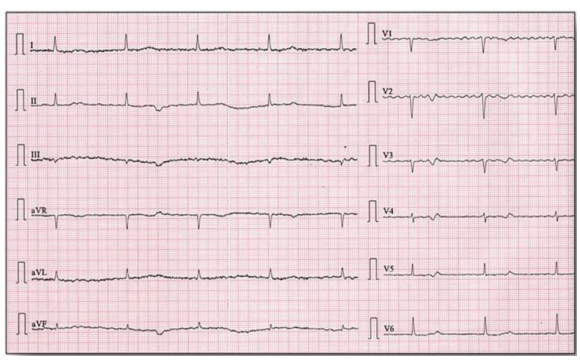
On presentation, she had a blood pressure of 90/50mmHg, heart rate round 40/min, pale skin, cold extremities with tachypneic involving the abdominal muscles for breathing; Her BMI was 36kg/m2. On auscultation a systolic murmur was 3/6 whole precordium with punctum maximum apical. The lungs were inaudible in the basal parts. Her lab analyses showed moderate anemia Hgb 82, K was 5.2, Creatinine 252, C reactive protein 170, WBC 17,8 with NLR range stressing out a moderate degree of stress inflammation, and the troponin I was 105.9ng/L (less than 15.6 women's normal range). Her resting electrocardiogram showed regular but slow heart rate round 40bpm, P wave was not seen. She was referred by anesthesiologist to cardiac pacing physicians for management of the slow heart rate.

The same day a temporary transvenous pacing was performed using the blind anatomy oriented axillary vein approach. The lead position was reassured by using portable CXR in the operating room. The following day the patient was operated and perioperatively period went uneventful.

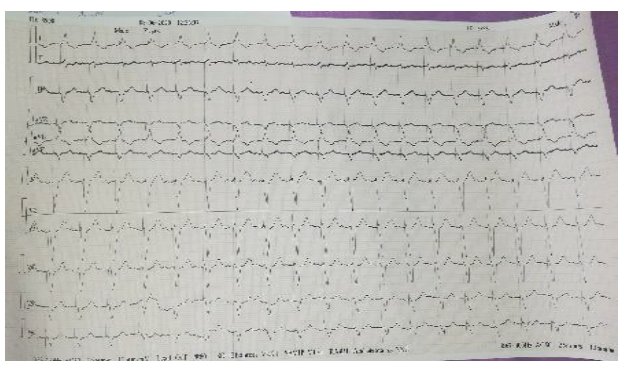
The temporary pacemaker was removed and patient was verticalized. After the surgery on the 10th day she was discharged from the hospital with normal heart rate (Picture 1, 2, 3, 4).

On the fifteenth day a holter monitoring was placed at the Clinic for Cardiology, and the Holter monitoring showed the lowest heart rate of 35bpm during sleep and the highest was 100bpm, without other abnormalities registered. This confirmed that there was no indication for permanent pacing.

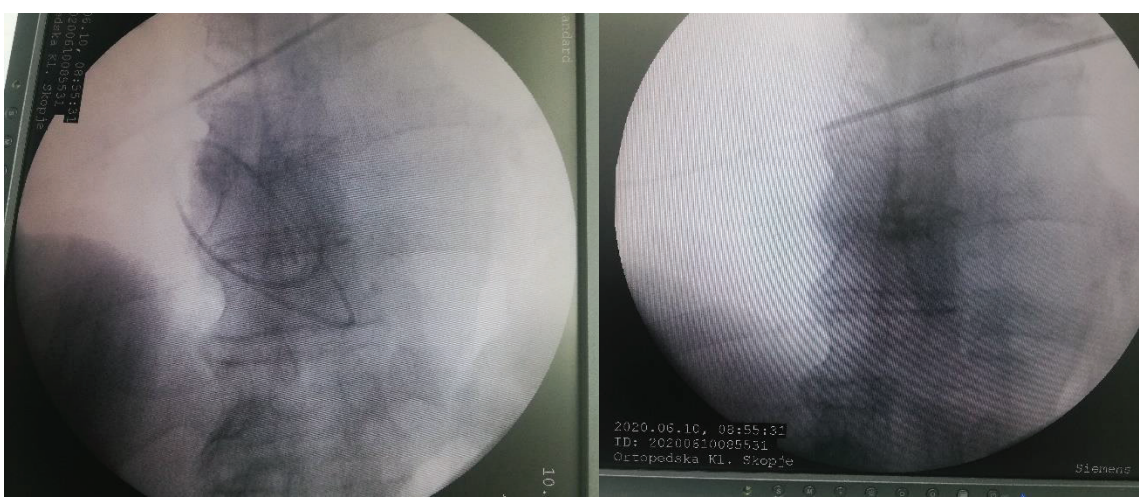
Picture 1. *ECG before temporary pacing*



Picture 2. *ECG after temporary pacing*



Picture 3, 4. *Lead position after implantation of temporary pacemaker*



Discussion

Hip fractures are injuries, especially seen in the elderly population. Urgent diagnosis and treatment are required to prevent erroneous joint complications. Femoral neck fractures are type of intracapsular hip fracture. The femoral neck is prone to fractures since it is the connection part of joint complex. In elderly, femoral neck fractures are associated to low energy falls. Commonly associated risk factors for these fractures are gender (female), decreased mobility, and low bone density (1,2,3,4).

Temporary cardiac pacing is needed for bradyarrhythmia treatment, until it resolves, or furthermore a permanent pacing as a solution can be applied (5,6,7). Indications for temporary pacing is symptomatic bradycardia, which leads from acute to permanent and reversible cause of cardiac instability (5,6,7,8,11). With this state, not rarely it can be bridged to permanent pacing, or it can be used as a way to treat the condition while the reversible conditions are addressed. Mainly reversible conditions found in the literature are drugs (digoxin, beta blocker, antiarrhythmics, calcium channel blockers), acidosis, electrolyte disturbance, cardiac surgery, central nerve system injury, autonomically mediated syndromes, infectious diseases etc. (11,13,14).

There are two types of temporary pacing options, transcutaneous firstly described and performed seven decades ago by Zoll. For successful application of transcutaneous pacing, pacemaker pads, cables, pulse generator unit, ECG patches and monitoring equipment are needed. In these situations, analgesia and sedation are preferred since it is painful procedure and deep cautiones should be considered referring severe hemodynamic instability of usage of sedatives or pain medications (9-13). Temporary endocardial pacing is the most stable in the mean for temporary pacing. It is not painful and is well tolerated, ones it is applied. Furthermore, depending on the type of electrode catheter used, patient can remain ambulatory.

The tools for transvenous pacing continuously evolve and are the same as the transcutaneous except for the pacing catheter that is balloon tipped, mostly with different grade of stiffens that is inserted through large vein (femoral, internal jugular, subclavian, axillary vein) using modified Seldinger technique. Typically, these catheters are inserted using fluoroscopy and it is recommended in all settings whenever possible. Also surface ECG is for sure a good tool in mean for electrode position using the typical QRS morphology and main axis in frontal plane. There are several issues regarding to loss of capture due to temporary pacing such as catheter dislodgment, peroration, local myocardial necrosis, oversensing that all can be managed (14-18).

Conclusion

Temporary vs pharmacologic treatment of symptomatic bradycardia can lead to hemodynamic disarrangement and instabilities. So far literature has not shown clear survival benefit and as such, current guidelines suggest that pacing is considered only in those patients that do not respond to pharmacologic approaches. In patients with asystole or pulseless electrical activity is not recommended. Always have in mind that reversible causes a treatable and that permanent pacing can solve only the conduction disturbance and coming hemodynamic compromise.

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COMPLICATIONS OF STRABISMUS SURGERY

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ABSTRACT

Introduction: Strabismus is corrected surgically usually when other modalities of treatment, such as refraction correction, occlusion, and orthoptic exercises, do not work, and in conditions of congenital and paralytic strabismus where no improvement is expected after a period of time. Like all other surgeries, strabismus has a small percentage of complications, which can be intraoperative or postoperative.

Aim: The aim of this paper is to identify intraoperative and postoperative complications, in order to timely identify and treat.

Materials and Methods: This paper is a review of the literature, where the larger databases of medical publications Medline and Pubmed are used, with the following key word inputs: strabismus, complications. We have found more than 200 articles related to our search for the last 30 years, out of which 35 have been used for this review. In this review paper we have presented the most important observations from the literature, as well as our observations from the research in this direction.

Conclusion: All surgeries carry some risk of complications and there is no way to completely avoid them. When a complication occurs, it is important to recognize it first and then manage it appropriately to ensure the best possible outcome.

Key Words: *complications, intraoperative, postoperative, strabismus,*

Introduction

Strabismus surgery is usually recommended when the patient's eye misalignment can no longer be treated with conservative methods, such as glasses, occlusion, prisms and orthoptic exercises. Like many other ophthalmic procedures, strabismus surgery is very safe and effective, but complications can occur and need to be diagnosed and treated as early as possible to optimize the postoperative outcome. Many of the complications diminish or disappear over time. The most of them withdraw with conservative treatment, while some require additional surgery (1).

Conjunctival injection and mild scarring are almost universal complications after strabismus surgery, but only rarely have long-term clinical significance. There are several important complications that are less common, but have significant long-term consequences, including

muscle slippage, lost muscle, incarcerated scars, periocular infections, orbital cellulitis, scleral perforation, retinal detachment, endophthalmitis, anterior segment ischemia (1, 2).

Complications of strabismus surgery are divided into: intraoperative and postoperative. Postoperative ones are divided into complications arising from surgery and complications from strabismus. Intraoperative surgical complications are: scleral perforation, lost muscle, slippery muscle and oculocardiac reflex. Postoperative complications arising from the surgical act are: postoperative infection, allergic reaction, pyogenic granuloma, inclusive cyst of the conjunctiva, conjunctival scars, fat deposition, Dellen, ischemia of the anterior segment, retraction or ptosis of the eyelid and change in refraction. Postoperative complications of strabismus are: unsatisfactory eye alignment, diplopia, iatrogenic Brown syndrome and blocked-elevation syndrome (1, 3).

On the other hand, postoperative complications are divided into: early postoperative (which occur up to 7 days after surgery) and late postoperative (after 7 days of surgery).

Early postoperative complications include: the lost muscle after surgery, orbital cellulitis, endophthalmitis, ischemia of the anterior eye segment, diplopia, allergic reaction. Late postoperative complications include: hypocorrection or hypercorrection, subconjunctival cyst, Tenon capsule prolapse, Dellen, conjunctival irregularities (1-3).

Intraoperative complications

Bleeding

Bleeding during surgery may be from the conjunctival blood vessels or a muscle injury. Intra conjunctival and intramuscular hematoma may occur. In operations on the upper and lower oblique muscle (m. obliquus superior et inferior) care should be taken not to cut the vorticose veins. And when transposing muscles, care should be taken not to injure the anterior ciliary arteries. If bleeding does occur, compression or cauterization should be performed if the bleeding vessel is clearly visible (1, 4).

Scleral perforation

Scleral perforation usually resolves without sequelae, but less frequently can cause intraocular bleeding, retinal detachment, cataracts, hyphema, glaucoma, endophthalmitis and phthisis bulbi. Not all pigment lesions of the fundus after muscle re-insertion are always caused by perforation, but they also occur due to a local tissue reaction due to sutures. Scleral perforation occurs if the suture needle goes too deep into the sclera. The tip of the needle should always be seen through the transparent scleral lamella. With the introduction of spatula needles, the percentage of perforations is greatly reduced (4, 6). The incidence of this complication is estimated at 2-10%.

Scleral perforation is much more common in patients with thin sclera, such as high myopia with staphylococcus or if there are significant scars or hemorrhages (more common in reoperations) that may interfere with scleral visualization (5, 6). If the perforation is behind the ora serrata, it means that the needle has passed through the choroid and retina and there is a high risk of retinal detachment. Recent studies have shown that scleral perforations are

much more common in retroposition of straight muscles and in the use of S-24 needles. In anteroposition of the m.obliquus inferior the macula may be injured (3, 5, 6).

Lost muscle

Muscle loss can occur during surgery or be noticed after surgery. If this happens during the operation the muscle can be found, which is easier with retroposition of the muscle than with resection.

Postoperatively, muscle loss may be noted as an inability to move the eye in the direction of action of the affected muscle and urgent intervention is required (7, 8). Careful exploration is then performed and the muscle can be found and sutured.

A retroposition of the ipsilateral antagonist or a transposition of the two adjacent rectus muscles may be performed. The risk of developing "lost muscle" increases with the presence of large scarring changes from previous muscle interventions or in inelastic muscles, such as dysthyroid orbitopathy (9, 10).

Complications due to anesthesia are: oculocardiac reflex, cardiac arrest, malignant hyperthermia, suxamethonium hypersensitivity and hepatic porphyria. These complications are rare but can be very dangerous.

The oculocardiac reflex (OCR) occurs as a result of stimulation of the trigeminal nerve during extraocular muscle tendon tension or as a vagal bradycardic response to ocular compression. The incidence of oculocardiac reflex ranges from 14% to 90% and decreases with age (11, 12).

Postoperative complications associated with surgery

Postoperative infections

Postoperative infection may occur if the sterile technique is impaired or if the patient has a pre-existing condition such as blepharitis or nasolacrimal stenosis that increases the number of bacteria at the surgical site. The most of infections occur around the primary surgical incision in the conjunctiva and manifest in the first week postoperatively. Rarely, the infection may penetrate deeper into the orbit manifesting as orbital cellulitis with clinical signs such as proptosis, eyelid edema, chemosis and erythema. Rarely, endophthalmitis occurs as a complication, which can occur due to perforation of the sclera, but also without it. The most commonly isolated microorganisms are Staphylococcus aureus (MRSA and MSSA), group A Streptococcus and coagulase-negative Staphylococcus (13, 14).

Orbital cellulitis occurs 2-3 days after surgery and is manifested by proptosis, chemosis, erythema, edema of the palpebrals, limited motility and pain (15).

Another infectious complication is suture abscess, which can occur as an acute allergic reaction that occurs between 24 hours and 7 days after surgery, with conjunctival hyperemia and swelling of the lids, or as a late foreign body reaction between days 4 and 8 after surgery. Topical antibiotics are used to treat conjunctivitis, and systemic antibiotics are used to treat preseptal and orbital cellulitis.

Endophthalmitis after strabismus surgery is a very rare complication, with an incidence of 1: 3500-1: 185000, but the most serious and severe complication, which can lead to vision loss,

phthisis bulbi and enucleation (13, 14). It is the most commonly characterized by persistent postoperative pain, conjunctival hyperemia, decreased visual acuity, anterior chamber flare, with hypopyon and vitreous haze. It usually occurs 3-4 days after surgery. The most common causes are: Streptococcus pneumoniae, Haemophillus influenzae and Staphylococcus aureus. Early diagnosis and treatment are important to maintain visual acuity. It is treated with topical, intravitreal and systemic antibiotics according to an antibiogram from a vitreous sample (13-15).

Pyogenic granuloma

A foreign body granuloma or pyogenic granuloma may develop in hypersensitive patients, usually several weeks after surgery. Pyogenic granuloma, also known as lobular capillary hemangioma, occurs due to capillary proliferation with edema at the site of the conjunctival incision. The risk of developing a pyogenic granuloma appears to be related to the suture material. Corticosteroids in the form of drops are used for several weeks, and if no improvement is noticed, a surgical excision is made (16).

Conjunctival inclusion cyst

Conjunctival inclusion cyst occurs when conjunctival epithelial cells are trapped below the surface of the conjunctiva during surgery. These cells proliferate over time and form a subconjunctival cyst, which manifests clinically within a few days to several years after surgery. The incidence of inclusive conjunctival cysts ranges from 0.25% to 0.4%, occurs when part of the conjunctival epithelium is trapped in the suture of the conjunctival suture (17 - 19).

Conjunctival scarring

Conjunctival scarring occurs when the conjunctiva, instead of returning to its typical translucent white appearance, remains chronically hyperemic, especially after second or third surgery. The risk of conjunctival scarring is higher with reoperations and surgical resection of muscles (20).

Dellen

Dellen is a shallow, clearly defined excavation at the edge of the cornea or sclera. Occurs due to improper lubrication of the eye surface during blinking, due to thickened bulbar conjunctiva, due to scarring, hemorrhage or swelling. Any disruption in the layers of tear film covering the sclera or cornea, which in turn causes local tissue dehydration, can lead to Dellen (21, 22).

The risk of Dellen formation is higher in a limbal (6.5%) than in a non-limbal (2.2%) incision, as irregularity of the perilimbal conjunctiva can cause tear film disruption of the anterior sclera and cornea. Dellen is more common after muscle resection than recession. It usually presents in the first 2 weeks after surgery (21, 22).

Ischemia of the anterior eye segment

It occurs the most often during surgery of 3 extraocular muscles of the same eye and is more common in older patients. There is a reduced blood supply to the anterior ocular segment through the ciliary blood vessels (24, 25). After 24 hours, corneal edema, anterior chamber flare (iritis anterior), segmental atrophy of the iris, irregular pupil and clouding of the anterior lens capsule occur. The most cases of this complication end without significant sequelae. Very rarely, necrosis of the anterior segment of the eye and phthisis bulbi of the operated eye may occur.

The risk of anterior segment ischaemia can be minimized by limiting the number of muscles operated on each eye, by using botulinum toxin, and by using special surgical techniques to spare the ciliary vessels during muscle surgery (23 - 26).

Postoperative complications

Postoperative diplopia

The most of the surgeons are afraid of this postoperative complication. Postoperative diplopia in young children up to 8 years of age recedes and never becomes a problem because children in the new eye position respond with suppression. This complication is a problem in older children and adults. Diplopia can be persistent, even lasting a lifetime. The psychological factor is a very important element, because psychologically stable patients do not complain of diplopia, unlike labile ones.

The appearance of diplopia is especially common in high-angle strabismus, especially in ARC and hypercorrection, because the image then comes out of the suppression zone, this is the so-called - paradoxical diplopia.

A prismatic adaptation test (PAT) should be performed preoperatively to indicate possible postoperative diplopia, so such patients should not be operated on, hypocorrected, or adjusted suture should be used (27, 28). The treatment is with prisms to relieve diplopia. Monocular occlusion with patch or occlusion foil can be used when prisms are not effective. In some cases, additional strabismus surgery may be necessary to correct the diplopia (27, 28).

Inadequate correction of strabismus

Postoperative hypocorrection. Whether it is hypocorrection can be concluded at least after a week postoperatively and not immediately after surgery, because the most often the effect of strengthening the muscle after surgery is stronger, later decreases, and may even lead to hypocorrection. This is especially true of the upper oblique muscle (m.obliquus sup.).

If there is postoperative hypocorrection, reoperation is required. In case the patient does not have binocular vision, the second operation should be postponed and done later. And if the binocular vision is normal, the operation can be done 10-12 days after the first operation (29).

Postoperative hypercorrection. Hypercorrection often occurs in monocular amblyopia, with retroposition of the m.rectus medialis, especially if both muscles are working simultaneously.

Therefore, in these cases the angle should never be corrected to orthophoria in children up to 6 years, but a convergent angle of 5 degrees should be left. In elderly patients, the correction should be performed completely. And it is always necessary to treat amblyopia first, and only then to perform surgical correction of strabismus.

Postoperative hypo and hypercorrection can be avoided if careful and complete preoperative evaluation is performed, with accurate intraoperative measurement. Preoperative evaluation includes multiple deviation measurements and a prism adaptation test (PAT).

Treatment can be with prisms or re-surgery. Fresnel prisms can be temporarily or permanently implanted in the glasses and further surgery may be delayed (20, 29).

Discussion

Like all other ophthalmic interventions, strabismus surgery carries a risk of complications, which fortunately more often have a positive outcome.

According to one study, the most commonly reported complication is scleral perforation (19 [0.08%), followed by muscle slippage (16 [0.067%), severe infection (14 [0.06%), and scleritis (6 [0.02%) and lost muscle (5 [0.02%). (30) In addition to the complications mentioned above, cases of retraction and dislocation of the caruncula lacrimalis have been described, as a complication of strabismus, more precisely in operations on m.rectus medialis, which resulted in permanent epiphora (31).

Tenon capsule prolapse can occur when the conjunctiva is not well sutured. This complication can be prevented by carefully closing the wound (1).

Another complication is a change in refraction postoperatively, which results from a change in the force that the extraocular muscle gives to the cornea by attaching it to the sclera. Usually over time this new refractive anomaly resolves. This complication can be minimized by proper preoperative measurement and avoidance of hypercorrection. The treatment of refractive anomaly is usually with glasses, although for the most part it resolves spontaneously (32).

Retraction of the eyelids or ptosis may occur after strabismus surgery. This can happen because the retractors of the eyelids, especially in the lower eyelid, attach to the intermuscular septum and the fascial tissue around the vertical rectus muscles. This connection creates a displacement in the eyelid position during standard recession surgery or resection of the vertical rectus muscles.

One study examining this complication found that 91% of patients who had a recession of superior rectus muscle developed upper eyelid retraction, while as many as 94% of patients with a recession of inferior rectus muscle developed lower eyelid retraction (33).

Other complications mentioned in the studies include iatrogenic Brown syndrome and anti-elevation syndrome. Brown syndrome can occur after superior oblique tightening procedures. It is characterized by limited elevation of the eye in adduction.

Anti-elevation syndrome is characterized by limited elevation of the eye in abduction, which occurs after anterior displacement of the inferior oblique muscle. Anti-elevation syndrome has been reported to occur more frequently in patients where the lower oblique muscle is sutured to more than 1mm prior to lower rectal insertion. The risk of anti-elevation syndrome can be reduced by avoiding lower oblique muscle insertion before lower rectal insertion (34, 35).

All of the above complications in strabismus surgery, with the exception of endophthalmitis, have an excellent prognosis with adequate and timely treatment. Many complications resolve on their own over time or with conservative treatment, while others are resolved with additional surgical treatment. Anterior segmental ischaemia can very rarely lead to necrosis and phthisis bulbi (1, 2).

Conclusion

All surgeries carry some risk of complications and there is no way to completely avoid them. Strabismus surgery is no different. There are methods to reduce the risk of complications during or after surgery, and these steps should always be taken. When a complication occurs, it is important to recognize it first and then manage it appropriately to ensure the best possible outcome.

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CASE REPORT OF SPORADIC TYPE OF MEDULLARY THYROID CARCINOMA

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ABSTRACT

Background: Medullary thyroid carcinoma (MTC) constitutes around 5% of all thyroid cancers and it usually arises from parafollicular C-cells. Both sporadic and familial forms are seen. The prognosis of MTC is worse in comparison to other differentiated thyroid cancers. Hereby, we present the case report of one patient with sporadic MTC.

Case Report: We present a 67-years-old male with presence of one dominant hypoechoic nodule in the right lobe (4x3x5cm) on thyroid ultrasonography. Fine-needle aspiration biopsy (FNAB) of the right lobe was done twice in a 10 months period, with no malign cells discovered. Three months after the second FNAB, scan with Technicium 99 was done, which showed 'cold zone' in the middle of the right thyroid lobe. Computer Tomography (CT) of the neck revealed cystic lesion in the same thyroid lobe. The patient underwent right lobectomy. The final histopathological finding was MTC: pTNM = pT1 pNx pMx G2 Cx. After getting the results, additional surgery was done and this time the total right lobe thyroidectomy was performed.

Conclusion: MTC can occur as sporadic, as well as genetic disease. We showed that this case of MTC was a sporadic type on account of absence of family history, normal plasma and urinary catecholamine levels, negative genetic testing for mutations in RET, normal CT scan of abdomen and normal Cromogranin A.

Key Words: Medullary thyroid carcinoma, multiple endocrine neoplasia, thyroid nodus.

Introduction:

Medullary thyroid carcinoma (MTC) is seen in about 5% of all thyroid cancers (1). It accounts for as much as 13% of all thyroid cancer-related deaths (2,3). MTC usually arises from parafollicular C-cells. They secrete numerous peptide hormones such as serotonin, calcitonin

and vasoactive intestinal peptide. There are sporadic and familial forms of MTC. The sporadic form accounts for 70% of the cases and familial form for 10–20% of the cases. The prognosis of MTC is worse in comparison to other differentiated thyroid cancers, with a 10-years survival rate of 95.6% of the patients, if present solely to the thyroid gland, and 40% for those presenting with metastasis (4). Hereby, we present the case report of one patient with sporadic MTC.

Case Report:

A 67-years-old male presented with progressively increasing midline swelling for 9 months. Neck examination revealed 4cm×3cm×5cm swelling on the right side of the neck, extending from midline to the anterior border of sternocleidomastoid. On palpation, it was firm and mobile. He had raised levels of thyroid-stimulating hormone being 1.11uiU/ml with free T4 0.915ng/dl. Ultrasonography of the neck showed the presence of one dominant hypoechoic nodule in the right lobe of thyroid without calcifications (Figure 1). Fine-needle aspiration cytology (FNAC) of the right lobe of thyroid was done and the result revealed acellular smear consisting of erythrocytes. No malign cells were discovered. After 10 months, another FNAB was done, with almost identical result, acellular smear consisting of erythrocytes, neutrophiles and colloid. No cells with characteristics of malignity were discovered. Three months after the second FNAB, scan with Technicium 99 was done (Figure 2), which showed 'cold zone' in the middle of the right thyroid lobe (Figure 3). Computed tomography scan of the neck (Figure 4) was done and cystic lesion in the right lobe of thyroid was discovered, measured 41x38x55mm, with hypervascular capsule, clearly demarked (Figure 5), with notably displacement of the neck structures by the cyst. No lymphadenopathy was seen. Thyroid hormones were in reference range.

Figure 1. *Ultrasound of thyroid right lobe*

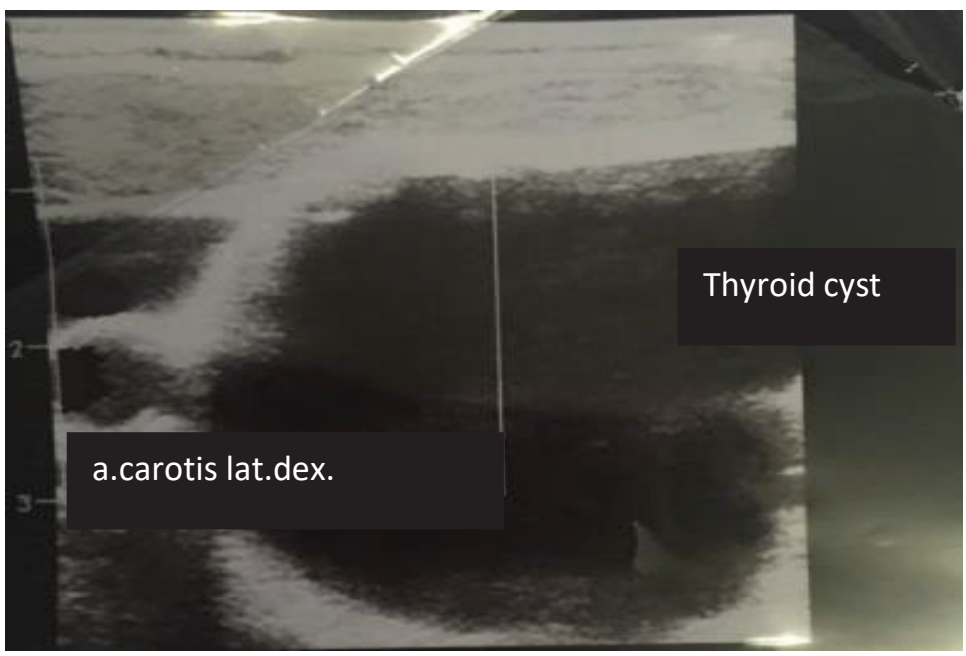


Figure 2. *Scan with Tc (cold zone)*

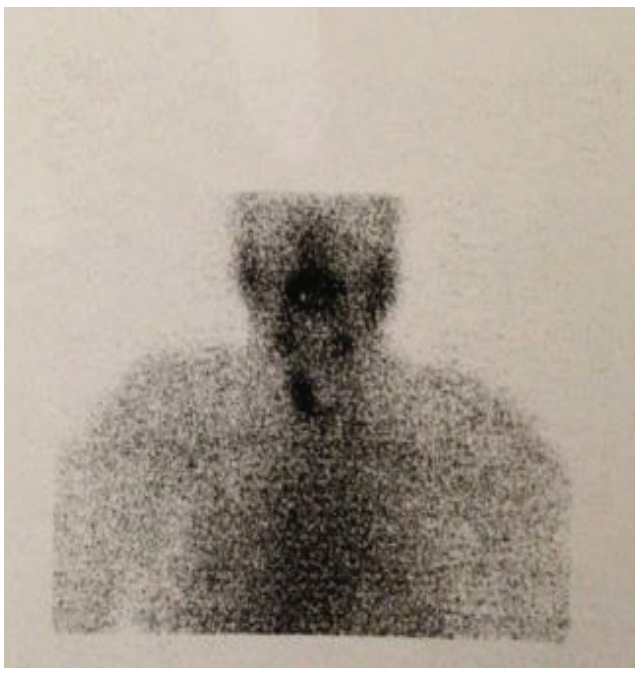


Figure 3. *Scan with Tc (cold zone)*

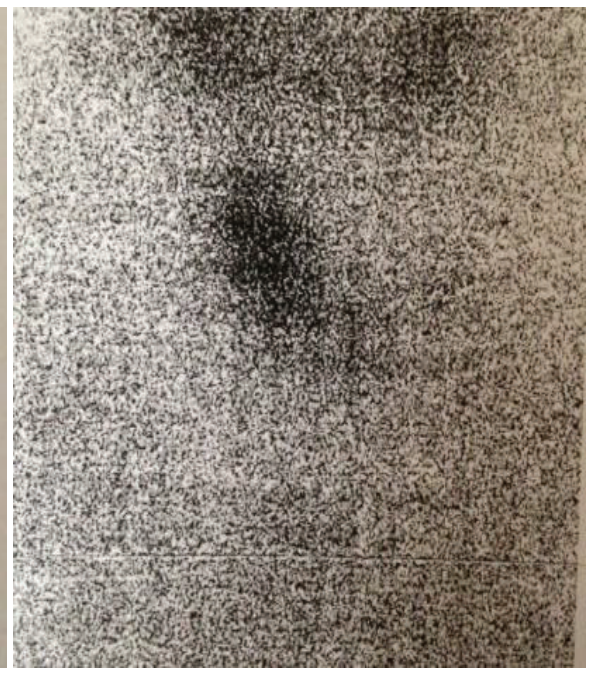


Figure 4. *CT of the neck*

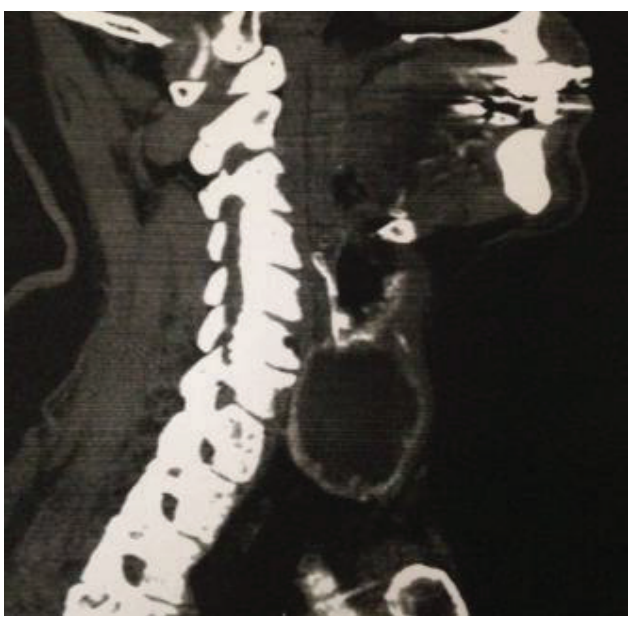
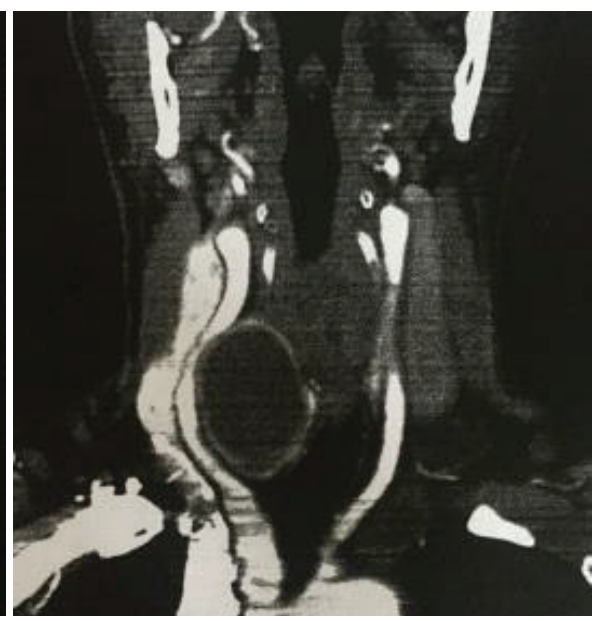


Figure 5. *CT of the neck*



The patient underwent right lobe thyroidectomy. The final histopathology showed nests and sheets of cells with moderate-to-abundant cytoplasm, eccentrically placed nucleus surrounded by dense hyperchromatic nucleus, and the tumor infiltrated thyroid capsule. Additional immunohistochemical investigations showed that malign cells are diffusely positive for calcitonin, cytokeratin 19, S 100 protein, synaptophysin, chromogranin and thyroid-transcript factor, and negative for thyroglobulin, Melan A and HBM-45 antibody. The final histopathological finding was pTNM = pT1 pNx pMx G2 Cx (Figure 6, 7&8).

Figure 6.

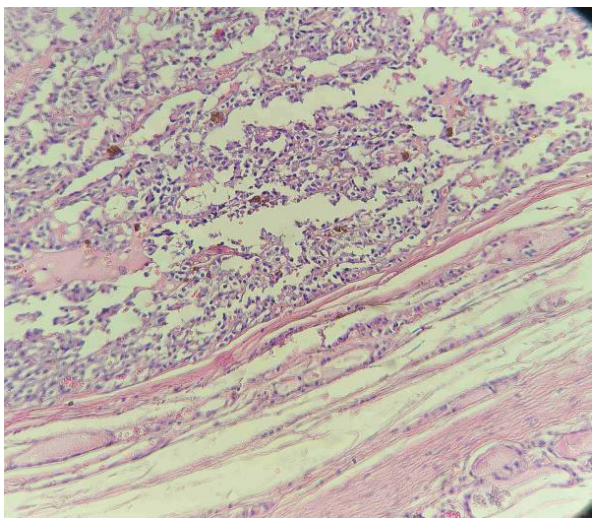


Figure7.

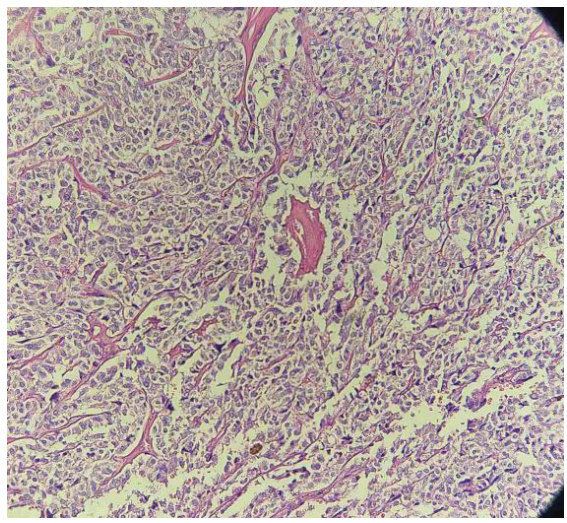
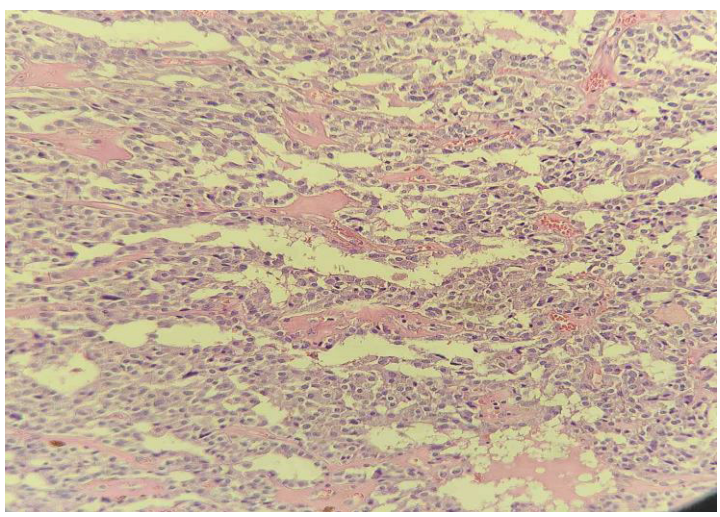


Figure 8.



After getting the results, the patient underwent another surgery, this time total right lobe thyroidectomy. The second histopathological finding from the right thyroid lobe was normal.

After the surgery and getting all the results from histopathology, all the necessary investigations for obtaining the form of medullary carcinoma were performed. A blood test for the mutation in the RET proto-oncogene mutations was done and it was negative. We concluded that this was sporadic form of medullary carcinoma.

Discussion:

Medullary thyroid carcinoma (MTC) is a malignancy with neuroendocrine characteristics, originated from the parafollicular C cells of the thyroid gland. It represents 3–12% of all thyroid cancers. Usually, it is sporadic, but in approximately 25–30% of cases MTC is inherited,

associated to one of three familial syndromes: multiple endocrine neoplasia (MEN) syndrome type 2A, MEN type 2B, and familial MTC (5).

For all types of MTC, the average 5-years survival rate is 78–92% and the 10-years survival rate is 61–75%. The main prognostic factor for MTC is the stage of the disease at presentation. The main treatment for MTC is surgery. Therefore, there has to be accurate FNAB diagnosis in order to avoid multiple unnecessary surgeries. In our case, two FNAB's were done, and both revealed absence of any type of malignant cells. The ultrasound characteristics, i.e hypoechogenicity and absence of calcificates, together with FNAB results, did not give us a suspicion of malignancy. The decision for surgery in our patient was done solely based on the size of the node.

MTC usually metastasizes early, the most frequently to regional lymph nodes in the neck and to the upper part of the mediastinum. Therefore, when the surgery is performed, some of the lymph nodes are dissected together with the thyroid, even if they are not palpable or seen with the visual techniques. Postoperatively, CEA and calcitonin serum levels are obligatory to monitor, for identification of recurrence or metastatic disease (6). In our case, there were no regional lymph nodes enlarged, and those few that were extracted revealed normal features. Postoperatively, serum calcitonin and CEA levels were routinely monitored and were in reference range.

There was no family history of MTC in this patient. We performed abdominal CT scan which turned out to be normal, plasma catecholamine levels were also normal, and excretion of vanilmandelic acid and metanephrine in a urine sample collected after 24 hours showed normal reference range. In order to rule out inherited form of MTC, we looked for RET germline mutations (7). After the surgery, the patient underwent genetic testing for detecting mutations in RET germline and it came out to be negative. Chromogranin A was also examined and it was in normal range.

Tumor markers for diagnosis, monitoring and prognosis of MTC are serum calcitonin and carcinoembryonic antigen (CEA) (8). If levels of CEA and calcitonin are elevated, the survival rate is decreased (9-11). In 40 to 60% of patients with MTC there is lymphadenopathy at the time of diagnosis, while in 10–30% there are distant metastasis present (12,13). The prognosis for MTC is generally good, with survival rate greater than 90% at 20 years. If there is presence of metastatic disease, the survival goes down to 40% at 20 years. MTC usually gives metastases in bones, liver and lungs (10,14). Other factors involved in decreased survival include male gender, age, tumor size (>4 cm), extrathyroidal metastases, lymph node involvement, family history and vascular invasion (10,15).

There are a lot of studies looking for correlation between serum calcitonin and severity of the disease. There was correlation between calcitonin levels and the tumor size, metastatic lymph nodes and rates of distant metastasis (16). It has been shown that decreasing of calcitonin levels after surgical procedure has positive impact of the prognosis (13). Increased calcitonin levels during monitoring indicate worsening of the disease and need of reoperation (13,17). If there are metastases present, calcitonin levels will increase (14,18). However, even a 50% reduction in calcitonin levels is enough to slow the disease progression (19). In our case, preoperative calcitonin and CEA analysis were not performed. We had no suspicion that the malignant process is going on, after benign characteristic on ultrasound, two negative results

on FNAB and all standard laboratory assessment being in reference range. After the surgery, calcitonin and CEA levels were in reference range. The patient is having his regular check-ups at Endocrinology Clinic in three months interval. So far, all analyses are in reference range. He is and will be on life time Levothyroxine therapy.

Conclusion

MTC is a rare form of thyroid cancer. The management of MTC is different than that for dxczifferentiated thyroid cancers. Early diagnosis, extensive preoperative work up, total thyroidectomy with/without lymphadenectomy are the cornerstones of cure and long-term survival. Genetic testing of familial syndromes should always be considered in MTC patients. All patients should be on regular life-long monitoring to avoid recurrence.

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VENTRICULAR ENLARGEMENT OR BENIGN FORM OF ECG IN ATHLETES

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ABSTRACT

Abnormalities of electrocardiogram (ECG) in athletes are challenging and often misdiagnosed. Despite consensus documents recommendations and guidelines for electrocardiogram interpretation in athletes, this method has a lack in specificity and sensitivity and the most of the time further evaluation is needed for proper diagnostic and treatment. This report, through case report, has a goal to rise the knowledge of novel ways of ECG interpretation in athletes. Although it is not as specific or sensitive as a diagnostic method, knowing the basics and some of ECG irregularities can help clinicians to proper evaluate some cardiovascular disorders in athletes that can lead to erroneous consequences, such as malignant electrical disorders and sudden cardiac death (SCD).

Key Words: Athlete's heart, cardiomyopathy, electrocardiogram, sudden cardiac death.

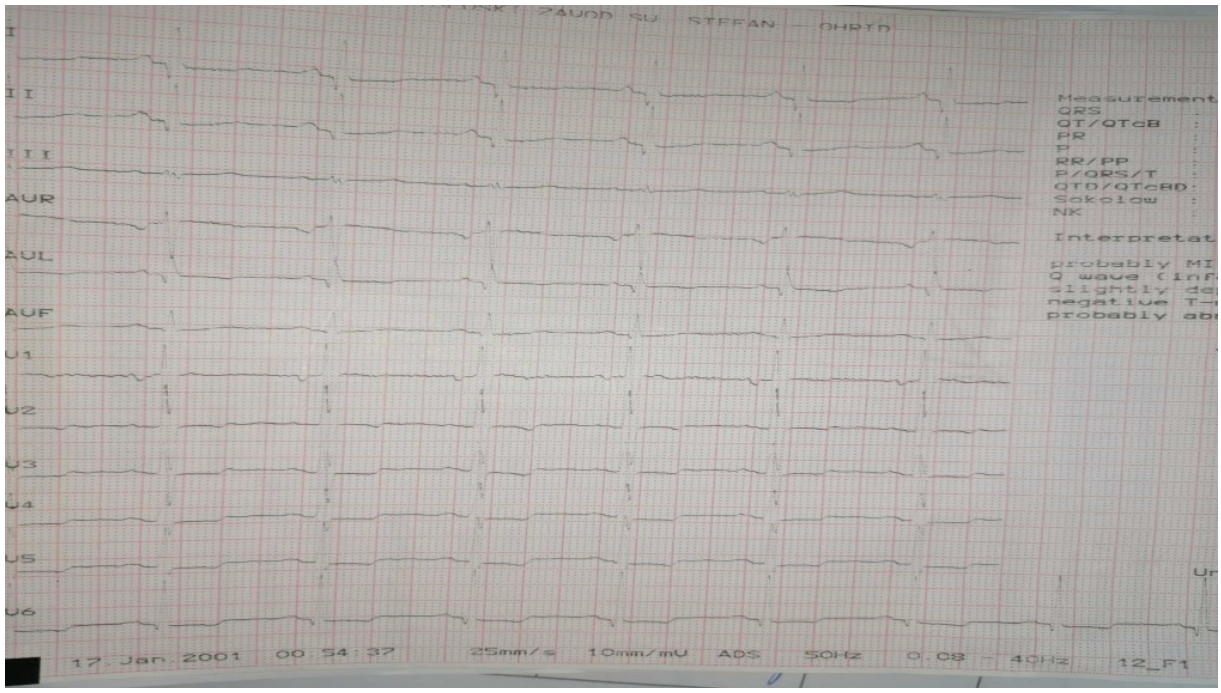
Case Report

We report a case of a 17-years-old professional male handball player that referred to a routine medical examination on our clinic. Patient's medical history reveals no personal, either familial history of cardiovascular disease. Furthermore, patient had no other relevant medical conditions or discomfort or problems when training.

However, on the routine ECG revealed asymmetric biventricular hypertrophy with right atrial enlargement. The sport physician assumed that this is not common condition, so he was referred to the University Clinic for Cardiology.

We conducted further and repeated ECG (Figure 1) and Holter diagnostic, and we confirmed that there were not any abnormalities in this patient, but his state was in coexistence with the "athlete heart".

Figure 1. *ECG in athlete*



Discussion

The standard 12 lead ECG has more or less 9 features that need to be systematically examined: Rate and regularity, P wave morphology, QRS complex morphology, T wave morphology; next to the intervals and segments: PR interval, QTc interval, ST segment and the last cardiac rhythm. Observation of these features should be initially considered to determine whether the recording is normal or abnormal. The right decision is challenged by the wide ranges of normal limits of each of these features.

We will not explain in details all the ECG features, but the common variations from normal seen in the athlete's heart. ECG changes are common in the athletes due to the physiological adaptations that occur in impulse formation, conduction and repolarization as a response to athletic conditioning and alteration in the autonomic tone. In the majority percentage the athlete's heart is a benign increase in cardiac mass with ventricular and vascular alteration in response to endurance or strength training. Sometimes this changes mimic findings are associated to cardiovascular disease (CVD), either morphological such as cardiomyopathies or electrical disorders seen in sudden cardiac death. In sports medicine as in cardiology is equally important to distinguish benign ECG changes from the one seen in an underlaying CVD (1,2, 3,4,5).

Cardiovascular remodeling in the conditioned athlete is frequently associated to physiological ECG changes. Abnormalities, however, may be detected which represent expression of an underlying heart disease that puts the athlete at risk of arrhythmic cardiac arrest during sports. It is mandatory that ECG changes resulting from intensive physical training are distinguished from abnormalities which reflect a potential cardiac pathology. When the ECG of an athlete is

examined, the main objective is to distinguish between physiological patterns that should cause no alarm and those that require action and/or additional testing to exclude (or confirm) the suspicion of an underlying cardiovascular condition carrying the risk of sudden death during sports.

Electrocardiogram changes in athletes are common and usually reflect structural and electrical remodeling of the heart as an adaptation to regular physical training (athlete's heart) (3-10). However, abnormalities of athlete's ECG may be an expression of an underlying heart disease which carries a risk of SCD during sport (11,12,13). It is important that ECG abnormalities resulting from intensive physical training and those potentially associated with an increased cardiovascular risk are correctly distinguished.

From the historical point of view the interest in proper ECG work up and follow up in athletes started in late nineties of the preceding century with evaluating of ECG changes in HCM-1998, two years later ECG abnormalities were classified in three categories and these were associated to a different prevalence of underlying echo abnormalities. Later, in 2005, the first consensus document presented criteria for ECG interpretation in preparticipation athletes, in 2010 the ESC criteria and the division of ECGs in two groups were presented. The past ten years brought out the modern concept of interpretating ECG using Seattle, C.R.Y criteria and new international criteria from 2018.

The athlete's ECG changes are divided into two groups: common and training-related in up to 80% of population (Group 1) or uncommon and training-unrelated in less than 5% of population (Group 2). This classification is based on prevalence, relation to exercise training, association to an increased cardiovascular risk, and the need for further clinical investigation to confirm (or exclude) an underlying cardiovascular (Table 1).

Table 1. *Classification of ECG abnormalities in athletes*

Table 1
Classification of abnormalities of the athlete's electrocardiogram

Group 1: common and training-related ECG changes	Group 2: uncommon and training-unrelated ECG changes
Sinus bradycardia	T-wave inversion
First-degree AV block	ST-segment depression
Incomplete RBBB	Pathological Q-waves
Early repolarization	Left atrial enlargement
Isolated QRS voltage criteria for left ventricular hypertrophy	Left-axis deviation/left anterior hemiblock
	Right-axis deviation/left posterior hemiblock
	Right ventricular hypertrophy
	Ventricular pre-excitation
	Complete LBBB or RBBB
	Long- or short-QT interval
	Brugada-like early repolarization

RBBB, right bundle branch block; LBBB, left bundle branch block.

Right or left atria enlargement, that historically was presumed as atrial hypertrophy in nearly 25% of patients examined in several studies and registries, is shown as a normal variant and mostly in runners it is seen nothing in the P wave. Having that in mind, right atrial enlargement seen on ECG in not due to exercise induced cardiac remodeling, and the presence of congenital or acquired heart disease associated to increase right atrial size, should be excluded.

The heart axis-sum QRS vector in vertical plane is rightward at birth and shifts leftward in infancy and childhood. Generally asymptomatic athletes with QRS axis -30 to 120 degrees don't need further investigation. The QRS voltage as representation of both right and left ventricular mass using the Sokolow-Lyon voltage criteria is a parameter that need to be properly interpretated because the endurance and strength conditioning leads to enlargement of ventricular mass, increasing of wall thickness and changes in diastolic pressures of right and left ventricle. When determination left ventricular hypertrophy Coronel and Sokolow-Lyon criteria are used interchangeably (14,15,16).

Repolarization changes such as ST segment elevation, depression, and T wave inversions seem to be the most challenging features in the ECG interpretation as having in mind that the heart repolarization process is the most vulnerable electrical point of the impulse generation and propagation. The most of the features such as early repolarization in anterolateral precordial leads is common in near half of white athletes and inferior leads ST elevation is seen in quarter of participants. ST segment elevation in V1, V2 should be carefully evaluated because this pattern is seen in Bragada syndrome, also ST elevation with increase QRS voltage may be seen in hypertrophic cardiomyopathies. ST segment depression and T wave inversions aren't common variant in trained athletes. As a general rule ST segment depression more the 0.5mm from the PR interval seen in anterolateral Leedsand assorted with T wave inversions should be further evaluated to exclude underlying heart disease (15,16,17).

Conclusion

ECG interpretation in athletes can be confusing for many medical practitioners. To prevent sudden cardiac death in athletes caused by ventricular arrhythmia or any other pathological manifestation of athletic heart, it is necessary to regularly perform cardiac examinations performed by an experienced cardiologist - arrhythmologist with experience in sports medicine.

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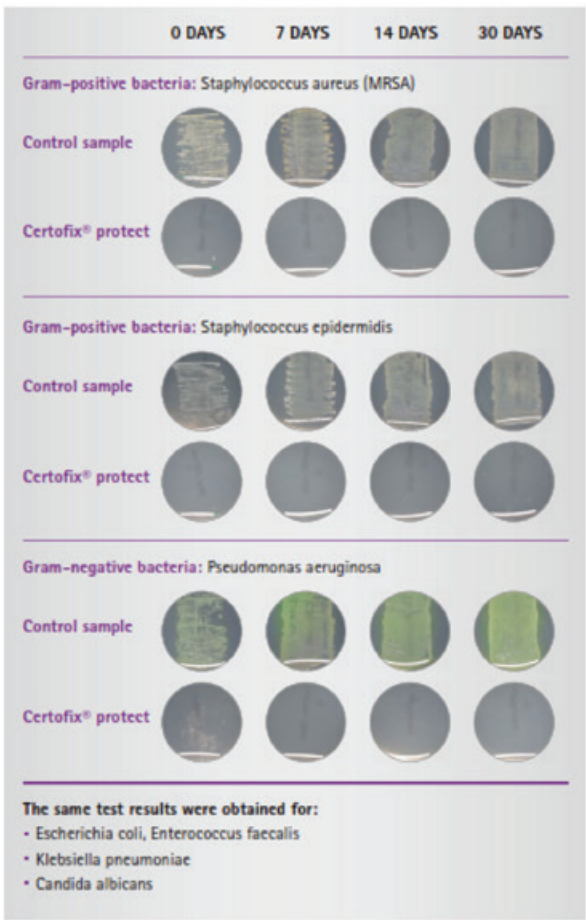

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