Baxter

WHEN EARLY RECOVERY REALLY MATTERS

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CONTENT

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REVOLUTIONIZING RADIATION DOSE MEASUREMENT AND MANAGEMENT SYSTEM - MAKES THE THINGS BETTER

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High levels of exposure to ionizing radiation are known to increase the risk of cancer.

The increasing number of computed tomography exams for diagnostic purposes and interventional radiological procedures became a serious source of radiation dose which continues to be one of the hottest topics in radiology, as government bodies and public health concerns push healthcare teams to find ways how to reduce the dose.

For this purpose, the World Health Organization, the IAEA and many other international organizations have prepared certain recommendations for the use of radiation sources, compliance with legal regulations, measurement of doses and strategies for their reduction, without poverty to patients who are the focus of attention (Figure1).

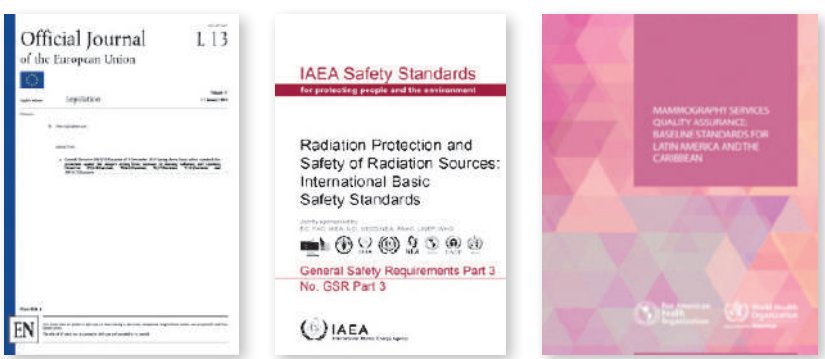


Figure1.

Following the existing European Directive (2013/59/EURATOM) and the increased focus on patients' safety, the international guidelines and regulations, indicate the necessary need for Dose Monitoring and Management Systems (DMMS), which have already been introduced in the radiological departments for medical radiological diagnostics in several countries in Europe and the world.

In doing so, it is necessary to use Systems for measuring radiation doses and automatic reporting.

There are some limitations in dose monitoring and in accordance with the International: Integrating the Healthcare **Enterprise (IHE):** "It is of great importance to know the technical limitations, as well as the limitations that make it difficult to monitor the dose in practice, they can explain the reasons why the monitored values do not give the exact dose delivered to the patient.

Accordingly to this it is important to understand that by calculating the dose using phantoms and calculating with formulas, it gives the calculated estimated and not the real measured dose. The provide values in that case are only calculated estimates, not "measurements".

For computed tomography, "CTDI" is the dose estimated on a standard plastic phantom, not on a human tissue. Therefore, the dose should not be represented as the dose received by the patient. For planar or projection images, the recorded values may be exposure, skin dose, or some other value that may not be the patient's body or organ dose. It is inaccurate to aggregate the estimates of doses which are received from different body parts into a single cumulative value. The concern and attention to monitoring radiation dose estimates is evident in official documents such as: European Directive Euroatom 97/43 and ACR.

In 1981, computed tomography dose index (CTDI) defined as a commonly used index of radiation exposure in X-ray computed tomography (CT). The CTDI unit presented in (Gy), can be used together with the patient's size to estimate the absorbed dose. CTDI and absorbed dose may differ by more than a factor of two for children which is a small patient.

CTDI vol. is based on measurements obtained during a 16cm or 32cm phantom scan. Basically, it represents the output of the scanner. DLP is derived from CTDI vol. but includes a scan length component. Both works as reasonable values for the absorbed dose, but do not represent the patient's actual dose. If the CTDI vol. and/or DLP is twice as high as it could be, then the doses the patient receives will be about twice as high as they could be.

How to calculate the dose?

There are several ways to calculate radiation dose measurements and several different units of measurement. This area is still developing as there is no standardization.

But radiation dose constantly changes during the time.

However, there are some methods used to collect data by using the dose information that is captured automatically by the imaging system and by using multipliers to calculate the estimated exposure to a given bad dose.

With the development of the new imaging technology, dose calculation values change and it becomes hard to explain to the patients or physicians why dose parameters for the same type of exam and the same patient change between scans that are years apart.

An important problem in medical radiological diagnostics is the lack of established national guidelines for standard doses (DRLs), so that dose levels can vary significantly.

There is a wide range of variation in protocols at different centers on CT, and within the same hospital, resulting in the same person having a brain CT scan at five different centers receiving five different dose values.

Why do we need dose measurement and management system?

Radiation dose monitoring in radio diagnostic examinations using X-ray technique is mandatory, to enable reduction of the patient's exposure to radiation, which is of particular importance in Computed Tomography and interventional radiological procedures.

It is necessary to use Systems for measuring radiation doses and automatic reporting remote Quality Control systems that make the data available to all personnel.

For the purposes of quality control (QC) and quality assurance (QA) in modern radiology, systematic monitoring and analysis of dose-related data from radiological examinations is basic.

Radiation dose monitoring software automatically collects, stores and analyzes information about patients' radiation exposure from medical radiology procedures involving ionizing radiation. Dose management solution can automatically monitor, evaluate and optimize the radiation dose that patients receive.

There are also solutions for centralized technical quality monitoring in digital screening programs, such as e.g., breast cancer. Many systems for measuring and managing radiation doses have such MAMMO solutions in their software.

Information about the dose can be collected directly from the imaging device through a picture archiving and communication system (PACS).

The software uses digital imaging and communications in medicine from (DICOM) -standard data sources.

Obtained data on the radiation dose index can help in the optimization of radiation doses, in order to find the lowest reasonable radiation dose with good radiological image quality. (ALARA), Figure 2.

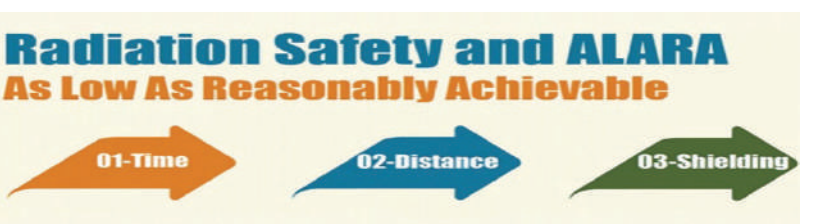


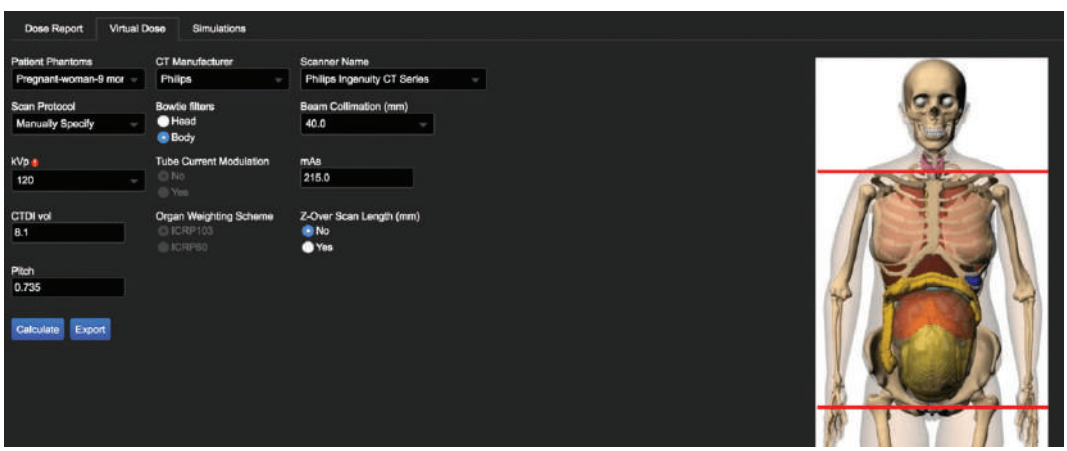
Figure 2.

Dose monitoring systems as a quality management tool enable us the following:

- Real-time performance evaluation and multi-parameter monitoring.
- The procedure can be compared to doses delivered by other procedures with the same study description or for the same anatomical area.
- Quick correction by prompting the change of wrong test parameters.
- Appropriate alerts can be automatically produced, so that improvement strategies can be quickly decided upon.

- Staff training and protocol optimization.
- Calculate dose from dose descriptors based on patients' specific body size, such as specific dose estimation (SSDE) for CT scans, which takes into account difference between the patient's actual size and the standard size of the reference phantom (Figure3).

Dose report simulation.



Daily trend - number of patients and mean dose at daily level.

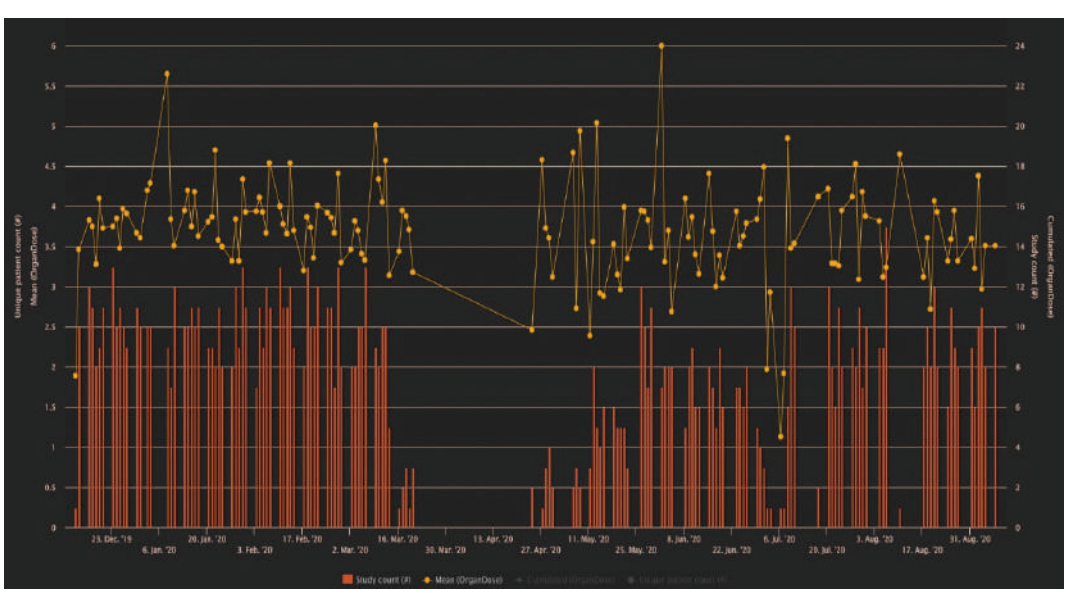


Figure 3.

The management of radiation doses simultaneously provides an opportunity for registration, storage and monitoring of radiation dose, comparison of the information to national DRLs (diagnostic reference levels), issuance of Patient Dose Passports, optimizing patient's dose and improving quality.

Simultaneous storage of data on radiation doses in the iCloud helps certain coordination in the course of work and availability of large amount of data at the same time, saves time, reduces the

workload of data collection staff, facilitates monitoring, creates necessary reports and further improves the quality of health care.

Some of the Dose Monitoring and Management System technologies can help facilitate the management of protocols, personnel dose, usage of contrast media and image quality.

The systematic and continuous monitoring and analysis of radiation dose data can decrease radiation exposure in patients who undergo to the multiple imaging procedures. It can help to meet legal and professional requirements in the hospitals, based on the Medical Exposure Directive 97/43.

In 2019, several hospitals in the Republic of North Macedonia installed software for measuring the radiation doses on CT and mammography devices. They provided information on radiation doses in real time and the possibility of analyzing why certain patients received a higher dose for the same type of examination on the same or on a different device or in a different hospital. The information obtained from this type of monitoring should not scare us but challenge us to be better in the future (Figure 4).

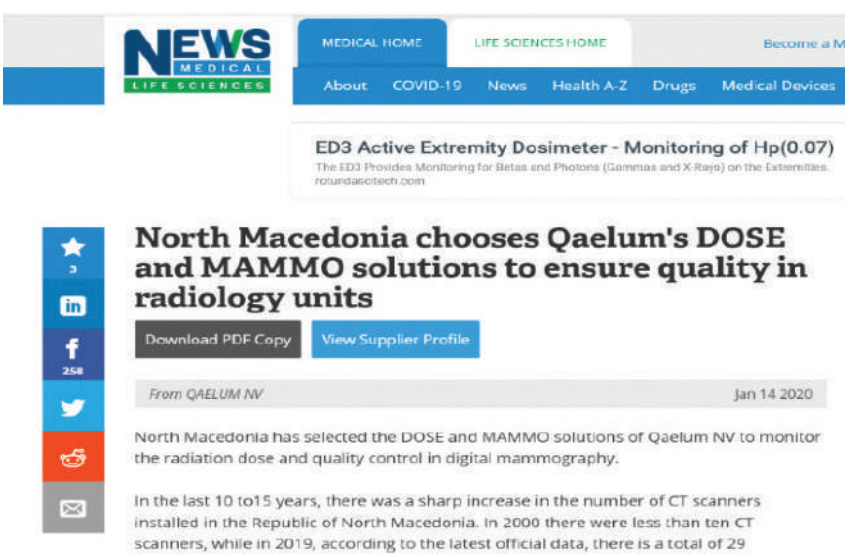


Figure 4.

Conclusion

Software solutions for Dose Measurement and Management are guides for optimized quality, for increased efficiency, compliance with legislation, accreditation and certification, and knowledge management.

Dose monitoring can increase risk awareness among members of the medical staff, which experts considered one of the best ways to improve education of professional workers and raising their awareness for the level of safety procedures for the patient and protection from radiation.

In doing so, the key factors for establishing and maintaining a culture of radiation safety in health care should be defined, in order to improve clinical practice.

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CLINICAL APPLICATION OF THE SONOELASTOGRAPHY IN THE EVALUATION OF THE SOLID BREAST TUMORS: OUR EXPERIANCE IN PRACTICE

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Abstract

Objective: To evaluate the role of breast ultrasound elastography as an emerging sonographic imaging technique that provides additional information in the characterization of solid breast tumors.

Introduction: Breast ultrasound elastography is a non-invasive imaging method that enables the differentiation of solid tumors according to the hardness (elasticity) of the tissue they show. Sonoelastography is used to characterize the lesions previously diagnosed using B-mode ultrasound.

Methods: The study was conducted in 56 patients with a previously diagnosed solid breast lesion with mammography, routine US, and sonoelastography using an ultrasound device (ES-AOTE) with a linear multifrequency probe 6-18MHz.

Results: In this study, fifty-six patients were examined by breast ultrasound, sonoelastography and mammography. The findings were confirmed by biopsy. In 45 patients breast lesions were characterized as benign and 11 lesions as suspiciously malignant. The results of our study showed that combined B-mode ultrasound and elastography had 100% sensitivity (CI= 95% 59.04% - 100%) and specificity 91,8 %, (CI = 95% 80.40% - 97.73%) with positive PV 63.64 % (CI = 95% 40.62% - 81.74%) I negative PV 100% (CI = 92.13% - 100%). The accuracy of the reporting method was 92,86% (CI = 95% 82.71% - 98.02%).

Conclusion: Breast sonoelastography is an additional ultrasonographic tool that increases the specificity of conventional B mode US and helps to reduce false-positive results and decrease unnecessary breast biopsies.

Key Words: *Breast sonoelastography; solid breast tumors.*

Introduction

Elastography (virtual palpation) is a non-invasive ultrasound method that characterizes and differentiates solid tumors, according to the hardness (elasticity) of the tissue they exhibit.

Elastography uses the differences in the mechanical properties of the tissue, in response to the applied force, by determining the indices needed to diagnose and characterize the current state

of the change, based on the hardness that the breast tissue shown.

The assessment of tissue hardness has been used for more than a thousand years in diagnostics due to the knowledge that many diseases and conditions lead to changes in the hardness of altered tissues, especially in tumors with an emphasis on malignancy.

Krouskop in 1998 first described the application of sonoelastography in tissue imaging. Sonoelastography of the breast is a method of ultrasound examination of solid changes in the breast, which is used to characterize a lesion already detected in B-mode ultrasound (1).

Sonoelastosonography is generally used for the characterization and differentiation of solid tumors in the breast (Rizzatto et al. 1993) (2).

Elastography is a newer recording technique that assesses the elasticity of tissues after previously obtained information obtained from ultrasound in B-mode (3).

Sonoelastography together with B mode ultrasound, Doppler sonography (color or power doppler) is a part of the multimodal display of tissues and changes in them.

Recent studies show that sonoelastography increases diagnostic accuracy more than conventional B-mode ultrasonography and helps to decrease false-positive results

(increased specificity) and unnecessary breast biopsies (4).

As a result of the type of applied force at the ultrasound elastography technique may be introduced as strain or shear wave elastography.

Strain elastography is a static type of ultrasound elastography which involves tension imaging.

Shear wave elastography is a dynamic type of ultrasound elastography, divided as shear waves and force acoustic radiation pulse recording.

Elastography determines tissue stiffness.

Elastography techniques can be based on strain or wave velocity (strain elastography) or stiffness (Young's modulus) or modulus from share wave elastography (5). Therefore, elastography techniques can be qualitative by determination of elasticity by color which is coded according to tissue strength, semi-quantitative by determining the strain ratio (SR - the ratio of stiffness in the nodule and the surrounding healthy breast tissue) and quantitative by measurement (SE and SWE) (6).

Strain elastography (static or compression elastography) is qualitative type or semi quantitative by determining the strain ratio (SR) of elastography.

Shear wave (transient elastography) is a quantitative type of elastography.

Strain elastography - historically is the earliest elastography technique, where external tissue compression is applied and comparison between ultrasound images and images after compression. The least deformed are the most rigid areas of the image, and the most deformed areas are the softest (7) (Figure1).

Shear-wave elastography uses waves to assess tissue movement in all directions, and compression is induced deep within the tissue by the acoustic radiation force (8).

Elastography appears to have the best application in solid BI-RADS 3 or 4a lesions, increasing confidence in the diagnosis before biopsy.

Cysts, as anechoic structures are not subject to elastography research, because non-viscous fluids are not compressible, and thus simple cysts do not show deformability signals in elastography techniques (9).

Elastography is based on the fact that in malignant tumors the density of cells increases, which changes the elasticity of the tissue itself. Elastography provides an assessment of the deformation of all tissues (fatty, fibroadenomas, or solid lesions) and shows in real-time that benign nodes such as fibroadenomas, papillomas, etc. (Figure1). In malignant lesions, there is a certain inelasticity of the tissue, which is usually the result of neoplastic infiltration of the interstitium, the desmoplastic reaction intra- and extra-nodular. Such is the case with ductal carcinomas, squamous type of carcinoma.Exceptions are some tumors of the mucinous or papillary carcinoma type which are of low malignant consistency.

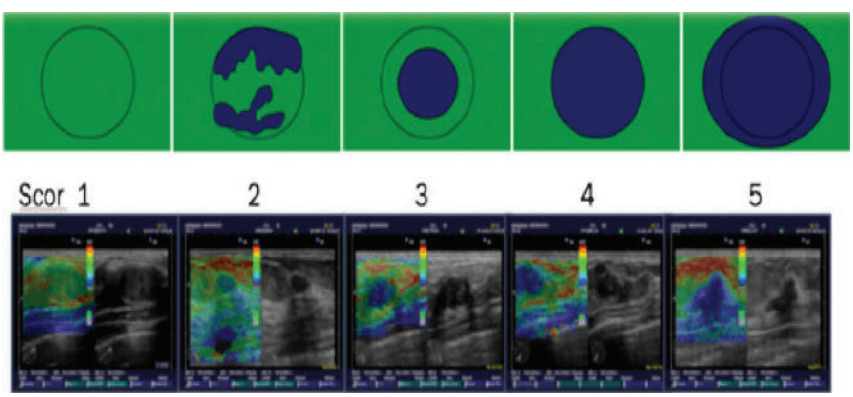

Figure1. Elastography shows in real-time benign nodes such as fibroadenomas and papillomas.

In addition to this is the fact that elastography based on the characteristics of the tissue in terms of its stiffness can increase the sensitivity of ultrasound in the preoperative diagnostic period and can be used as an additional diagnostic tool in the prediction of prognostic factors for cancer, taking into account that the higher stiffness values obtained by elastography correlate with weaker parameters of prognostic factors, worse prognosis (10, 11).

The use of elastography in the clinical practice allows for better characterization and categorization of lesions detected by ultrasound in B mode, better categorization in BI RADS classification groups and increasing the diagnostic confidence of positive or negative findings obtained with ultrasound.

Material and Method

At our clinic in 2022, sonoelastography was applied to 56 patients with breast solid tumors. In 18 patients there was information about a positive family history.

Inclusion criteria were patients with solid breast lesions.

Exclusion criteria - Patients with cystic lesions and non-mass lesions were not considered.

All patients underwent an ultrasonographic examination in B-Mode, Color Doppler sonography and Strain sonoelastography. All patients previously had digital mammography.

We use strain elastography as semi-quantitative method with ESAOT/ elastography ultrasound, multifrequency probe 5-18 Mhz.

Strain Elastography (SE) determines tissue stiffness by determining the SR - ratio of stiffness in the nodule to the surrounding healthy breast tissue and is calculated automatically by a built-in software program in the ultrasound device.

In this study evaluating SR, the cut-off value for the differentiation of benign and malignant lesions was 3.

Sonoelastography achieves maximum specificity and accuracy, in ranges between 2 and 4.

For the characterization and evaluation of breast lesions, the elastography characteristics of changes such as size and elasticity were used. A change in the size of solid nodules as a result of the desmoplastic reaction of the tissue which appears larger on elastography than on B-mode ultrasound is in favor of malignant tumors. If this ratio is greater than 1, the lesion is more suspicious to be malignant (12).

To determine the elasticity of changes, the Tskuba score was used with a rate from 1 to 5 (13, 14) (Figure 2).

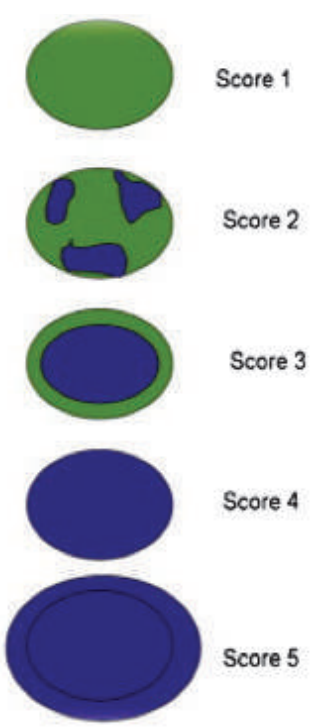

Figure 2. The risk of malignancy increases from 1 to 5.

Tskuba score

Score 1: if the lesion is homogeneously elastic, completely green,

Score 2: if the larger lesion is deformable green, and only small parts of the areas are not deformed and are blue,

Score 3: deformable on the periphery of the lesion, and the center is rigid, blue,

Score 4: non-deformable blue lesion,

Score 5: lesion and adjacent tissues are stiff and blue.

According to Tsukuba score, almost all categories 1-3 are benign, and categories 4 and5 are malignant.

Invasive cancer has the lowest elasticity, followed by non-invasive cancer, fibrous tissue, normal structural tissue, and finally breast fat shows the highest elasticity.

The classification was also done using BI RADS classification groups.

A categorization of the lesions in BI RADS according to their shape, edges, orientation, vascularity and echogenicity was done. According to ultrasonographic elastography criteria, lesions were classified as soft, medium and hard changes.

All patients underwent a core biopsy of the solid nodules.

Results

With sonoelastosonography, 56 patients were examined.

In 44 patients the changes in the breast were characterized as benign, and in 12 patients with elastosonography, the changes were co-characterized as a suspected malignant lesion.

According to BI RADS classification, 44 patients were in BI RADS 3 Classification Group, in BI RADS 4 Classification Group there were 9 patients, and 3 patients were in BI RADS 5 Classification Group.

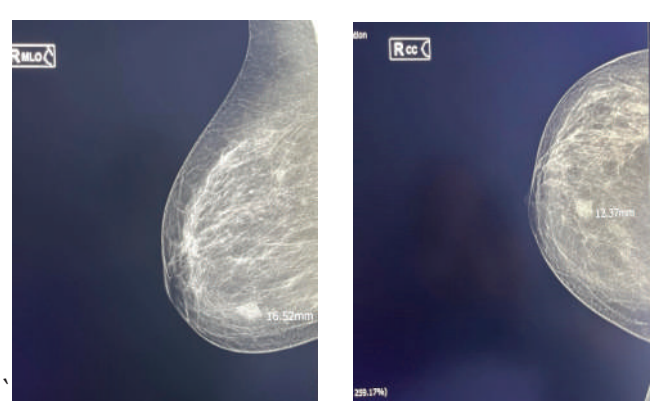

Figure 3. Inv. Intraductal Breast Carcinoma-MG.

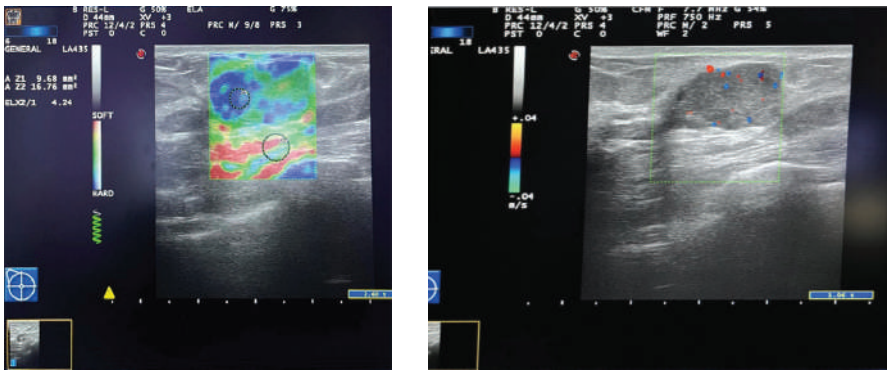

Figure 4. Inv. Intraductal Breast Carcinoma (same patient) - Sonoelastography, US

According to Cito/ptx, 49 changes were found to be benign, and 7 of the changes were more likely to be malignant, Table1.

After the obtained pathohistological results, in 5 patients the classification group was changed from BI RADS 4 to BI RADS 3. In 4 patients in whom the BI RADS classification group was changed from BI RADS 4 to BI RADS 3, the pathohistological findings were in the direction of atypical fibroadenomas with calcifications, in one patient the finding is a radial scar lesion.

Table 1. Results from Elastography (El.Index), Cito/Pathology.

Elastic Index	Ct/Pth		Total number
	(+)	(-)	
(+)	7	4	11
(-)	0	45	45
Total number	7	49	56

Se = 100% - Sensitivity (CI = 95% 59.04% - 100%)

Sp = 91.8% Specificity (CI = 95% 80.40% - 97.73%)

+ PV = 63.64% Positive pred. Value (CI = 95% 40.62% - 81.74%)

- PV = 100% Negative pred. Value (CI = 92.13% - 100%)

Accuracy = 92,86% (CI = 95% 82.71% - 98.02%).

Discussion

According to the literature, invasive cancer has the lowest elasticity, followed by non-invasive cancer, fibrous tissue, normal structural tissue, and finally breast fat shows the highest elasticity (15).

The multicenters study which Barr. et al. performed on 635 lesions (413 benign, 222 malignant, confirmed by cytology) resulted in a sensitivity of elastography of 98.6% and a specificity of

87.4%. There was also a variation of sensitivity between 96.7% and 100% and specificity between 66.7% and 95.4% in the different centers participating in the study.

Regarding the high sensitivity in lesion characterization, there is inter-operator variability between different centers that is related to individual differences in examination technique, suggesting that better standardization of protocols and performances is needed (16).

In the study by Tozaki et al. performed on 100 patients, using Young's modulus in the differentiation of benign from malignant lesions in elastography, yielded sensitivity values of 91.3% and specificity of 80.6% (17, 18).

In the study by Zhi et al. conducted on 296 patients with dense breasts, after comparing the changes in RTE, US and mammography, and the differentiation of breast changes in benign and malignant groups, according to the Itoh scoring system, elastography has the highest specificity of 95.7% and the lowest rate of false positives of 4.3% compared to ultrasound and mammography (19).

According to our experience elastography shows high sensitivity 100% with CI= 95% (59.04% -100%) and specificity 91,8% with CI=95 (89,40% - 97,73%) regarding the characterization of lesions. Accuracy = 92, 86%, CI=95% (82,72%- 98,02).

Despite the high sensitivity and specificity, elastography shows certain advantages and disadvantages.

The disadvantages mainly refer to the fact that all malignant tumors are not rigid, taking into account the different histopathological forms of cancer to avoid false negative or false positive results.

The greatest advantage of elastography is the high sensitivity regarding characterization and assessment of solid breast lesions which increases the sensitivity of ultrasound in detecting the malignant tumors and positive lymph nodes in breast cancer, which is especially important in the preoperative diagnostic period (20,21).

The medical device industry is launching a series of advanced ultrasound devices and software intended for elastography. Realizing the benefits of elastography as an added value to ultrasound, EFSUMB (European Federation of Societies for Ultrasound in Medicine and Biology) and WFUMB (World Federation for Ultrasound in Medicine and Biology) have issued a guide to these innovations in ultrasound diagnostics and clinical application of elastography (22.23).

Conclusion

Sonoelastography is a new diagnostic modality for examining and characterizing solid tumors in the breast that cannot completely replace other imaging methods but is an excellent complementary method in the detection and differentiation of solid breast lesions. Sonoelastography is a tool to help characterize changes in the breast, it is not a detection tool. Sonoelastography is an example of the added value of ultrasound and in accordance with the so-called multimodal US approach improves the specificity of ultrasound, increases the confidence of the diagnostician, and can reduce the number of unnecessary biopsies and patient's anxiety.

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PHARMACODYNAMICS OF PROPOFOL INFLUENCE OF GABRE AND ABCB1 GENES

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Abstract

We live in a world where the pharmaceutical industry is experiencing its rise and attention, and every day we face different reactions, different response to different drugs in different people. On the other hand, we are witnessing a wave of encouraging new drugs, especially in the field of oncology, which are based on the concept of individualized therapy. The aim of our study was to investigate the influence of the cytochrome, γ -aminobutyric acid type A (GABAA) receptor γ1 subunit *GABRA1* (rs2279020) and ATP-binding cassette sub-family B member 1 *ABCB1* (rs1045642) gene polymorphisms on propofol therapeutic outcomes in the patients undergoing abdominal hysterectomy. Ninety patients aged 29-74 years, with different ethnicities were included in this study. The presence of polymorphisms was analyzed using TaqMan SNP genotype analysis on Stratagene MxPro 3005P real-time polymerase chain reaction (qPCR). Our study did not detect a statistically significant influence of the *GABRA1* (c.1059+15G>A) and *ABCB1* (c.3435T>C) variants on the variability of clinical parameters (doses for induction in anesthesia, additional doses, induction time and wake time after anesthesia and side effects of propofol). The observed trend on the possible influence of the *GABRA1* (c.1059+15G>A) and A*BCB1* (c.3435T>C) variants warrant an extension of these studies in a larger number of patients.

Key Words: *ABCB1 gene; GABRA1 gene; Pharmacogenetic; Propofol.*

Introduction

We live in a world where the pharmaceutical industry is experiencing its rise and attention, and every day we face different reactions, different response to different drugs in different people. On the other hand, we are witnessing a wave of encouraging new drugs, especially in the field of oncology, which are based on the concept of individualized therapy. The response to the same drug varies among different individuals, and this is often due primarily to variations in genes that determine drug disposition.

Pharmacogenomics is defined as the search for genetic variations that can be observed in how a drug works, and the possibility of improving the efficacy and safety of the drug through a personalized approach. On the other hand, pharmacogenetics is concerned with linking genetic variation and inter-individual variation.

Propofol (2,6-diisopropylphenol) is the most popular intravenous anesthetic used in modern medicine. The main cardiovascular effect is the reduction of arterial blood pressure. It acts on

the respiratory system as a respiratory depressive agent, possibly causing apnea after the induction dose. The majority of propofol (about 70%) is metabolized to propofol glucuronide, for which UDP-glucuronosyltransferase enzyme encoded by the UGT1A9 genome (UDP-glucuronosyltransferase family 1, polypeptide A9, MIM 606434) is responsible. Alternative pathways for biotransformation of propofol (approximately 29%) are under the action of enzymes encoded by genes CYP2B6 (MIM 123930) and CYP2C9 (MIM 601130), as well as SULT1A (MIM 171150) and NQO1 (MIM 125860) (12,53).

The GABRE gene is responsible for the synthesis of proteins that modulate inhibitory neurotransmission through the GABAA receptor in various regions of the central nervous system, while the ABCB1 gene encodes transmembrane proteins that play an important role in maintaining the barrier and protecting the brain from accumulation of toxic components.

A study was conducted to determine the variability in response to propofol as a result of the genetic information of each organism separately.

The aim of this research is to determine whether the single nucleotide polymorphisms (SNP) of the genes GABRE and ABCB1, that is, whether their established variations (homozygous and heterozygous) affect induction time, propofol dose and awakening time, as well as the side effects of the anesthesia in patients undergoing abdominal hysterectomy during general anesthesia.

Through this set of tested genes, we tried to answer the question whether patients with different genotypes show a difference in the response to the dose of propofol, which will be manifested in the difference in certain parameters such as: induction time, entropy time, time under anesthesia, time of awakening and the presence of certain side effects of propofol (nausea, vomiting and prolonged sedation).

Material and Methods

This is a cohort, prospective, longitudinal study performed at the University Clinic for Gynecology and Obstetrics and at the Center for Biomolecular Analysis at the Faculty of Pharmacy, in Skopje, R. N. Macedonia.

The study was approved by the Ethic Committee for Human Research of the Medical Faculty, "Ss. Cyril and Methodius" University in Skopje, Republic of Macedonia, no. 03-242/1, Ethics Committee of the Faculty of Medicine in Niš, Republic of Serbia, no. 12-3182-2/7 and from the Professional Collegium of the University "Ss Cyril and Methodius" - Faculty of Pharmacy, Skopje no. 03-51/1.

Ninety (90) female patients scheduled for abdominal hysterectomy were included in this study. All patients signed an informed consent before entering the study. Inclusion criteria were age between 25 and 75 years, body weight within 20% above and below ideal, ASA classification 1-2-3.

Propofol was administered according to a standard protocol based on the status and individual characteristics of the study group, as well as empirical medical data obtained from the instructions for use (0.1–0.15 mg/kg/min. IV for 3–5 minutes). This was a non-interventional study

that involved the use of propofol according to a standard dosing protocol and monitoring the clinical response of the patients under general anesthesia. The patients were not divided into groups and there was no deviation from the usual plan of administration of anesthesia. All data were recorded in the anesthesia card as an integral part of medical documentation, and they were subsequently analyzed.

After adequate preoperative preparation, a peripheral 16G or 18G intravenous line was placed. Non-invasive monitoring - blood pressure (BP), electrocardiogram (ECG), heart rate (HR), saturation with O2 (SatO2) and capnography was used to monitor vital functions, and entropy was used to monitor depth of anesthesia. All patients received general endotracheal anesthesia. For induction: midazolam 0.1mg/kg, fentanyl 2mcg/kg, propofol 1% given at a rate of 400ml/hour until values of SE entropy of 40 to 60 were achieved with loss of eyelash reflex (dose of 1.5 to 2.5 mg/kg) and rocuronium bromide (0.4–0.6 mg/kg). For maintenance: propofol 50–150 mcg/kg/min, boluses of rocuronium bromide of 0.3mg/kg, fentanyl 2mcg/kg, lung ventilation with oxygen and nitrous oxide in a ratio of 50:50%. At the end of the intervention, neuromuscular block reversal was achieved with 2.5mg of neostigmine and 1mg of atropine, after which the patient was extubated and transferred to a recovery room.

During maintenance of anesthesia, propofol was dosed based on hemodynamic parameters: heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure, which were measured every 5 minutes, as well as continuous entropy readings with the goal of maintaining values between 40 and 60.

Entropy parameters are the following: Response Entropy (RE) are values in the range from 0 to 100, and State Entropy (SE) are values in the range from 0 to 91. RE reacts faster, starting with facial muscle activation, while SE is a stable parameter which monitors the hypnotic effect of the anesthetic used. SE values are always identical or slightly lower than RE.

In the study we also analyzed opioid side effects: nausea, vomiting and level of sedation. Adverse effects were observed 24 hours after the operation. We assessed the presence of nausea with a nausea score: (0 – no nausea, 1 – mild nausea, 2 – moderate degree of nausea, 3 – severe nausea). Sedation was assessed according to the Ramsey sedation score (0 – awake, 1 – anxious, 2 – cooperative, oriented, 3 – reacts to command, 4 – reacts to tactile stimuli, 5 – weakly and slowly reacts to verbal and tactile stimuli, 6 – no reacts to strong and painful stimuli).

Genetic Analysis

Before the start of anesthesia, 4ml of blood sample was taken from a total of 90 patients who underwent abdominal hysterectomy under total intravenous propofol anesthesia at the Gynecology and Obstetrics Clinics in Skopje. Genomic DNA (deoxyribonucleic acid) was extracted from the sample. As a source of DNA, the patient's whole blood was used, which was previously sampled with EDTA as an anticoagulant and kept at -20°C until the moment of DNA isolation. An automatic extractor Mag CoreHF16 Plus (RBC Bioscience, Taiwan) was used for DNA isolation. Amplification of DNA was performed using chain reaction DNA amplification and analysis of restriction fragment length polymorphism - Real-time PCR system. Real time PCR method of chain amplification DNA, tested by analysis of polymorphism length of restriction fragments, consisting of a Taq Man probe molecule, which consists of a nucleotide, the sequence of which is complementary to specific alleles in the desired amplification region. A fluorophore

is attached to the 5' end of the sequence, and a so-called "quencher" is found at the 3' end. The presence or absence of characteristic alleles is defined by baseline Ct values characteristic of an allele-specific sample.

Statistical Analysis

Statistical data processing was performed in the software statistical program SPSS 21 for Windows. Kolmogorov-Smirnov and Shapiro-Wilk's tests were used to test the normality of data distribution. Descriptive data processing included absolute and percentage frequency values. Continuous variables are represented by mean value and standard deviation. Chi square test, Fisher's exact probability test, Student's T test, ANOVA (post-hoc Bonferroni test) were used to rank three genotypes in relation to the analyzed variable. Correlation between the consumption of propofol in relation to the age of the patients and the duration of the operation was analyzed based on the Pearson correlation coefficient. A value of $p<0.05$ was taken for statistical significance.

Results

The study included 90 female patients from the Clinic of Gynecology and Obstetrics in Skopje, who underwent abdominal hysterectomy. The patients were aged between 29 and 74 years, with an average age of 51.5 ± 8.8 years. The patients' body weight ranged from 48 to 131 kg, with an average of 77.7 ± 16.6 kg. The largest ethnic group of participants consisted of Macedonian women, accounting for 73.3% (66).

Table 1. Patient characteristics.

Demographic characteristics	
Age (mean χ±SD) / years	51.5 ± 8.8
Weight (mean±SD) / kg	77,6 ± 16,6
Ethnicity (n/%)	
Macedonian	66 (73.3)
Albanian	23 (25.6)
Turkish	1 (1.1)

In three genotype groups of GABRA1, women of Macedonian ethnicity were predominantly homozygous with the genotype GG - 79.4% (27), while women of Albanian nationality were predominantly heterozygous with the genotype AG - 28.95% (11). The patient of Turkish nationality was homozygous with the genotype AA. There was a statistically insignificant difference in the expression of the three genotypes of the GABRA1 gene concerning the ethnic structure of the patients (Table 2).

Table 2. Demographic characteristics of patients with GABRA1 genotypes – ethnicity.

Ethnicity n (%)	GABRA1			p value
	genotype AA (n = 18)	genotype AG (n = 38)	genotype GG (n = 34)	
Macedonian	12 (66.67)	27 (71.05)	27 (79.41)	p = 0.41 ns
Albanian	5 (27.78)	11 (28.95)	7 (20.59)	
Turkish	1 (5.56)	0		

p (Fisher exact)

AA – homozygotes with two normal alleles

AG – heterozygotes with one normal allele and one mutated allele

GG – homozygotes with two mutated alleles

The genetic polymorphism of GABRA1 did not exhibit a significant influence on various parameters, including the duration of induction (p=0.53), the time required to reach entropy values of 40–60 (p=0.52), the duration of anesthesia (p=0.78), the time to awakening (p=0.78), and the overall duration of anesthesia from commencement to completion (p=0.7). Similar median induction and entropy times were observed across all three genotype groups (median = 60 seconds and 30 seconds, respectively). Among patients, those homozygous for the normal AA genotype showed marginally shorter mean anesthesia durations compared to individuals with other genotypes (median = 88.5 minutes vs 100 minutes vs 101 minutes). Similarly, the mean time to awakening was slightly shorter in the AA genotype group compared to AG and GG genotypes (median = 13 minutes vs 15 minutes vs 15 minutes). Additionally, patients homozygous for the normal AA genotype also exhibited slightly shorter total anesthesia durations compared to those with pathological genotypes, AG heterozygotes, and GG homozygotes (median = 102 minutes vs 114 minutes to 117 minutes).

Table 3. The correlation between GABRA1 genotypes and the following parameters was examined: induction time, time to achieve entropy values of 40–60, duration of anesthesia, time to awakening, and overall duration of anesthesia from commencement to completion.

variable	GABRA1			p value
	genotype AA (n = 18)	genotype AG (n = 38)	genotype GG (n = 34)	
Induction time (seconds)				
mean ± SD	64.2 ± 30.2	91.7 ± 150.5	93.5 ± 86.6	P = 0.53 ns
median (IQR)	60 (35–75)	60 (60–60)	60 (60–120)	
Time to achieve entropy of 40-60 (seconds)				
mean ± SD	32.8 ± 13	28.4 ± 10.1	32.7 ± 22.9	p = 0.52 ns
median (IQR)	30 (20–45)	30 (20-35)	30 (20-35)	

variable	GABRA1			p value
	genotype AA (n = 18)	genotype AG (n = 38)	genotype GG (n = 34)	
Duration of anesthesia (minutes)				
mean ± SD	92.6 ± 31.6	104 ± 55.25	104.1 ± 42.1	p = 0.78 ns
median (IQR)	88.5 (75–125)	100 (80–110)	101 (75–125)	
Awakening time (minutes)				
mean ± SD	13.1 ± 5.1	14.3 ± 6.8	14 ± 8.2	p = 0.78 ns
median (IQR)	13 (10–15)	15 (10–20)	15 (10–15)	
Total duration from the beginning to the end of anesthesia (minutes)				
mean ± SD	105.7 ± 33.1	118.3 ± 55.2	118.1 ± 41.4	p = 0.7 ns
median (IQR)	102 (88–130)	114 (90–130)	117 (86–135)	

p (Kruskal-Wallis)

AA – homozygotes with two normal alleles

AG – heterozygotes with one normal allele and one mutated allele

GG – homozygotes with two mutated alleles

Analysis of the impact of GABRA1 gene polymorphism on the occurrence of adverse effects showed that the three genotype groups had insignificantly different frequencies of nausea (p=0.54), vomiting (p=0.33), and sedation (p=0.96).

Table 4. Adverse effects in patients across three genotype groups of the GABRA1 gene.

variable	GABRA1			p value
	genotype AA (n = 18)	genotype AG (n = 38)	genotype GG (n = 34)	
Nausea – number n (%)				
0	18 (100)	36 (94.74)	32 (94.12)	p = 0.54 ns
1	0	1 (2.63)	0	
2	0	0	2 (5.88)	
3	0	1 (2.63)	0	
Vomiting – n (%)				
0	18 (100)	37 (97.37)	32 (94.12)	p = 0.33 ns
1	0	0	2 (5.88)	
2	0	1 (2.63)	0	
Sedation – n (%)				
0	18 (100)	34 (89.47)	31 (91.18)	p = 0.96 ns
1	0	1 (2.63)	0	
2	0	1 (2.63)	2 (5.88)	
3	0	1 (2.63)	1 (2.94)	
4	0	1 (2.63)	0	

AA – homozygotes with two normal alleles

AG – heterozygotes with one normal allele and one mutated allele

GG – homozygotes with two mutated alleles

Propofol consumption, both initial, additional, and total, did not significantly depend on the genotype of the GABRA1 gene (p=0.78, p=0.33, p=0.22). The mean initial propofol consumption across all three genotype groups was 150mg; the mean supplementation was slightly higher in the homozygous GG group compared to homozygous AA and heterozygous AG groups (150 vs 115 vs 100mg); the overall mean intraoperative propofol consumption was slightly lower in the group with the pathological AG genotype, i.e. in patients with one normal and one mutated allele, compared to groups with two normal and two mutated alleles (median = 250 vs 300 vs 300) (Table 5).

Table 5. The correlation between propofol consumption and GABRA1 genotypes.

variable	GABRA1			p value
	genotype AA (n = 18)	genotype AG (n = 38)	genotype GG (n = 34)	
propofol for induction of anesthesia / mg				
mean ± SD	156.1 ± 39.7	146.8 ± 43.3	152.1 ± 41.5	p = 0.78 ns
median (IQR)	150 (120–200)	150 (100–200)	150 (120–200)	
additional dose of propofol for maintenance of anesthesia / mg				
mean±SD	136.12 ± 51.2	122.92 ± 46.7	140.9 ± 4.6	p = 0.33 ns
median (IQR)	115 (100–200)	100 (100–150)	150 (100–200)	
total intraoperative propofol consumption / mg				
mean±SD	292.2 ± 70.3	269.7 ± 77	292.9 ± 66.1	p = 0.22 ns
median (IQR)	300 (250–350)	250 (200–300)	300 (250–350)	

p (Kruskal-Wallis)

AA – homozygotes with two normal alleles

AG – heterozygotes with one normal allele and one mutated allele

GG – homozygotes with two mutated alleles

From women of Macedonian ethnicity, 81.8% (18) had the CC genotype for the ABCB1 gene, 71.1% (32) had the CT genotype, and 73.9% (17) had the TT genotype. Albanian women accounted for 18.2% (4), with 28.9% (13) having the CC genotype, 21.7% (5) having the CT genotype, and 21.7% (5) having the TT genotype. The patient of Turkish nationality was a carrier of the TT genotype for this gene. No significant difference in the expression of the three ABCB1 genotypes was found concerning the ethnic structure of the patients (p = 0.43) (Table 6).

Table 6. Demographic characteristics of patients with ABCB1 genotypes – ethnicity.

ethnicity n (%)	ABCB1			p value
	genotype CC (n = 22)	genotype CT (n = 45)	genotype TT (n = 23)	
Macedonian	18 (81.82)	32 (71.11)	17 (73.91)	p = 0.43 ns
Albanian	4 (18.18)	13 (28.89)	5 (21.74)	
Turkish	0	0	1 (4.35)	

p (Fisher exact)

C – homozygotes with two normal alleles

CT – heterozygotes with one normal allele and one mutated allele

TT – homozygotes with two mutated alleles

No significant difference was found among patients with CC, CT and TT genotypes for the ABCB1 gene regarding the duration of induction (p=0.15), time to achieve adequate entropy values (p=0.93), duration of anesthesia (p=0.51), awakening time (p=0.94), and total anesthesia time (p=0.53). The same median induction time and entropy time were observed in all three genotype groups (median = 60 seconds and 30 seconds, respectively). Patients with the TT genotype had slightly shorter mean anesthesia durations than the other two genotype groups (median = 85 vs 101 vs 100 minutes); the mean awakening time was slightly shorter in the TT genotype group compared to CC and CT (median = 13 vs 15 vs 15 minutes). The total mean duration from start to finish of anesthesia was also slightly shorter in the TT genotype group for the ABCB1 gene (median = 100 vs 116 vs 115 minutes).

Table 7. The correlation between ABCB1 genotypes and the following parameters was examined: induction time, time to achieve adequate entropy values, duration of anesthesia, awakening time, and total duration from the beginning to the end of anesthesia.

variable	ABCB1			p value
	genotype CC (n = 22)	genotype CT (n = 45)	genotype TT (n = 23)	
Induction time				
mean ± SD	90.9 ± 94,1	98.7 ± 141.5	60.1 ± 31.2	p = 0.15 ns
median (IQR)	60 (60–120)	60 (60–120)	60 (30–60)	
Time to achieve entropy values of 40-60				
mean ± SD	30.2 ± 10.2	29.1 ± 9.4	35.2 ± 28.3	p = 0.93 ns
median (IQR)	30 (25–40)	30 (20–35)	30 (20–48)	
Duration of anesthesia				
mean ± SD	104.6 ± 38,6	106 ± 54	90.8 ± 8.2	p = 0,51 ns
median (IQR)	101 (90–120)	100 (75–130)	85 (75–110)	

variable	ABCB1			p value
	genotype CC (n = 22)	genotype CT (n = 45)	genotype TT (n = 23)	
Awakening time				
mean ± SD	13.8 ± 6.6	14.1 ± 8.1	13.7 ± 5.1	p = 0.94 ns
median (IQR)	15 (10-20)	15. (10-15)	13. (10-15)	
Total duration from the beginning to the end of anesthesia				
mean ± SD	118.5 ± 38,9	120.1 ± 53.8	104.5 ± 34.9	p = 0.53 ns
median (IQR)	116 (95–130)	115 (88–150)	100 (86–130)	

p (Kruskal-Wallis)

C – homozygotes with two normal alleles

CT – heterozygotes with one normal allele and one mutated allele

TT – homozygotes with two mutated alleles

Analysis of the impact of ABCB1 gene genotypes on the occurrence of adverse effects showed that the three groups had insignificantly different frequencies of nausea (p = 0.68), vomiting (p = 0.43), and sedation (p = 1.0).

Table 8. Adverse effects in patients across three genotype groups of the ABCB1 gene.

variable	ABCB1			p value
	genotype CC (n = 22)	genotype CT (n = 45)	genotype TT (n = 23)	
Nausea – number n (%)				
0	21 (95.45)	42 (93.33)	23 (100)	p = 0.52 ns
1	1 (4.55)	0	0	
2	0	2 (4.44)	0	
3			0	
Vomiting – n (%)				
0	22 (100)	42 (93.33)	23 (100)	p = 0.75 ns
1	0	2 (4.44)	0	
2		1 (2.22)		
Sedation – n (%)				
0	21 (95.45)	41 (91.11)	21 (91.30)	p = 0.88 ns
1	0	1 (2.22)	0	
2	0	2 (4.44)	1 (4.35)	
3	1 (4.55)	0	1 (4.35)	
4	0	1 (2.22)	0	

p (Fisher's Exact Test)

CC – homozygotes with two normal alleles

CT – heterozygotes with one normal allele and one mutated allele

TT – homozygotes with two mutated alleles

The initial dose of propofol was insignificantly correlated with the age of patients with the CC genotype (p=0.18), but significantly correlated with the age of patients with CT and TT genotypes of the ABCB1 gene (p=0.001, p=0.047). These two correlations were negative, suggesting that with increasing age of patients carrying two combined alleles and two mutated alleles for the ABCB1 gene, the administered propofol dose was lower (ro = -0.462, ro = -0.417, respectively). The additional dose of propofol was insignificantly correlated with the age of patients with CC and CT genotypes (p=0.56, p=0.26, respectively), but significantly correlated with the age of patients with the TT genotype for the ABCB1 gene (ro= -0.552, p=0.006). The additional dose of propofol was lower in older patients with the pathological TT genotype, and vice versa.

Table 9. Consumption of ABCB1 genotypes.

variable	ABCB1			p value
	genotype CC (n = 22)	genotype CT (n = 45)	genotype TT (n = 23)	
Propofol for induction of anesthesia / mg				
mean ± SD	161.4 ± 36	149.3 ± 42	143 ± 45.6	p = 0.4 ns
median (IQR)	150 (120–200)	150 (120–200)	150 (120–200)	
Additional dose of propofol for maintenance of anesthesia / mg				
mean ± SD	1382 ± 51	132.2 ± 50.3	126.9 ± 45.5	p = 0.78 ns
median (IQR)	100 (100–200)	100 (100–200)	100 (100–150)	
Total intraoperative propofol consumption / mg				
mean ± SD	299.5 ± 62.4	281.6 ± 73.8	270 ± 76,3	p = 0.35 ns
median (IQR)	300 (250-350)	270 (230-330)	250 (230-300)	

p (Kruskal-Wallis)

CC – homozygotes with two normal alleles

CT – heterozygotes with one normal allele and one mutated allele

TT – homozygotes with two mutated alleles

Discussion

Preceding scientific investigations have suggested a correlation between diverse patients' responses to propofol in general anesthesia and polymorphisms of genes involved in its metabolism (1).

The aim of this research was to determine whether individual single nucleotide polymorphisms (SNPs) of the GABRE and ABCB1 genes, and their identified variations (homozygous and heterozygous), influence the induction time, propofol doses, awakening time, as well as the adverse effects of anesthesia.

The study was conducted to ascertain the response variability to propofol as a consequence of the genetic information of each individual organism separately. The GABRE gene is responsible for synthesizing proteins that modulate inhibitory neurotransmission via GABAA receptors in various regions of the central nervous system, while the ABCB1 gene encodes transmembrane proteins that play a crucial role in maintaining the blood-brain barrier and protecting the brain from the accumulation of toxic components. Through this set of tested genes, we attempted to answer whether patients with different genotypes would demonstrate differences in response to the administered dose of propofol, which would manifest in variations in certain parameters such as induction time, entropy time, duration of anesthesia, awakening time, and the presence of certain undesirable propofol effects (nausea, vomiting, and prolonged sedation). However, in the obtained results, we did not find a correlation for any of the tested genotypes of the mentioned genes with the clinical parameters we investigated. This could be due to the small sample size, study design, but also the fact that propofol metabolism, and thus its clinical effects and adverse effects, are much more complex and depend on many other factors that are not genetic based(patient condition, age, comorbidities, gender, etc.).

The only significant difference observed in our study was the correlation between the age of the patients and the requirement for propofol. Older patients required a lower dose of the medication to achieve adequate anesthesia (2,3). This observation has been noted by other authors as well. Schüttler and Ihmsen demonstrated that blood concentrations of propofol were significantly higher in older individuals compared to younger ones due to reduced minute volume and hepatic blood flow in the older population (4). However, minute volume and hepatic blood flow are not reduced in all older patients and vary individually. Furthermore, no other factor influencing propofol pharmacokinetics can be attributed solely to the fact that patients are older (5).

It was concluded that anesthesia doses required to achieve the same anesthetic state in older patients can be up to half lower than those needed for younger patients (2) The authors believe that the lower anesthesia requirements of older individuals are a consequence of changes in cardiovascular, respiratory, hepatic and renal functions that occur with aging. However, according to these authors, the primary cause of different anesthetic effects lies in the central nervous system. This is supported by the fact that the incidence of delirium and postoperative cognitive dysfunction after general anesthesia and sedation increases in older patients who exhibit typical aging, defined by anatomical and physiological changes that occur in the brain over the years. Therefore, more attention should be paid to the brain and how typical brain aging affects anesthesia requirements and increased susceptibility to cognitive impairment. These findings have important implications for clinical monitoring and management of general anesthesia in older patients.

The induction dose of propofol in healthy adult patients: Participants ranged from 2–2.5mg/kg, but varied due to various factors in each patient, such as age, gender, body mass index, but primarily from preoperative levels of albumin in the blood, as well as concurrently administered medications (6). Ethnicity also influenced the concentrations of doses required for propofol induction.

Gender differences in metabolite elimination could also contribute to the overall observed differences. Gender differences were discovered in the formation of propofol metabolites, which manifested as significantly higher levels of these metabolites in the plasma of female patients. Therefore, the results indicate a significant contribution of gender to the degree of glucuronidation and hydroxylation of this drug during anesthesia. Further research is necessary to clarify the clinical impact of these findings (7).

The GABRE gene has four polymorphic variations. Literature data relating to the influence of the GABRE gene on induction time in anesthesia, time to BIS <70, and time to response to stimulation are available, but they did not show a statistically significant correlation between the four polymorphic variations of the GABRE gene and these parameters. However, the influence of this gene on propofol anesthesia cannot be ruled out (1,8). The data obtained in this study also indicate that there is no significant correlation between GABRE genotypes and the parameters examined.

Our results indicate that the frequency of these polymorphisms in our patients is similar to that in other population studies. In our study, we found differences in the doses of propofol administered to patients with different genotypes studied. Our results show that the ABCB1 (c.3435C>T) variant does not influence the clinical parameters in our patients undergoing propofol anesthesia. Although there is limited information on the impact of this variant on propofol anesthesia, our findings are consistent with those reported by Zakerska-Banaszak and colleagues, who did not find a significant statistical difference in the effect of propofol among ABCB1 genetic variants (9,10).

Conclusion

The potential impact of GABRA1 and ABCB1 gene variants on the pharmacodynamics of propofol in abdominal hysterectomies suggests that pharmacogenetic studies on larger number of genes are necessary in the form of prospective clinical trials involving large number of patients to determine the benefit and cost-effectiveness of genotyping in therapy individualization in anesthesiology.

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COMPARISON OF THE EFFECTS OF DESFLURANE AND SEVOFLURANE IN AWAKENING AND COGNITIVE FUNCTION AFTER A GENERAL ANESTHESIA

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Abstract

Introduction: The pharmacokinetics of desflurane and sevoflurane favor improved intraoperative control of anesthesia and led to faster postoperative recovery. These anesthetics have a lower blood/ gas coefficient than isoflurane and halothane. The low fat/ gas coefficient and low brain/ blood coefficient of desflurane lead to faster elimination and faster awakening from anesthesia. This leads to a quicker return of cognitive functions and speedier discharge from the Post Anesthesia Care Unit (PACU).

Objectives: The purpose of this study is to compare the emergence time and time of return of cognitive functions in patients with general inhalation anesthesia (general anesthesia) maintained to inhalant anesthetics desflurane and sevoflurane, respectively, under standardized conditions.

Material and methods: This study included ASA I and II patients undergoing colorectal abdominal surgery who were randomly assigned into two groups: the first group received the inhalation anesthetic desflurane in combination with the analgesic remifentanil for anesthesia maintenance, while the second group was kept under using sevoflurane in combination with fentanyl. We used standard hemodynamic monitoring, the Train of Four (TOF) and the Bispectral Index System (BIS) to determine the depth of an anesthesia. We recorded the time required for extubating, the opening of the eyes, verbal response, the modified Aldrete score of 9, the Mini Mental State Examination (MMSE) of 25 and the Short Orientation-Memory-Concentration Test (OMCT).

Results: The results, expressed in minutes and obtained in both patient groups, demonstrate a significantly shorter time for regaining cognitive functions in the patients who received a desflurane inhalation anesthetic with remifentanil compared to the patients who received a sevoflurane inhalation anesthetic with fentanyl. This is thought to be due to the faster pharmacokinetic profile of desflurane, leading to an accelerated elimination in the patients. Desflurane, in combination with remifentanil, a short-acting opioid, further shortens the recovery time of cognitive functions.

Conclusion: This study underscores that the time required for early recovery from anesthesia is markedly shorter in patients receiving desflurane compared to patients given sevoflurane when administering general anesthesia. This finding emphasizes the potential benefits of desflurane in optimizing perioperative outcomes, including faster emergence from anesthesia and cognitive recovery.

Key Words: *cognitive function, desflurane, inhalational anesthetics, opioid, sevoflurane***.**

Introduction

As developed countries push to save hospital resources, doctors are under increasing pressure to develop targeted strategies for a faster postoperative recovery of patients and, thus, a shorter hospital stay. Desflurane and sevoflurane are inhalant anesthetics with clinical and pharmacological profiles that make them ideal for the rapid recovery of patients (1,2). The development of minimally invasive surgical techniques has led to an increased need for rapid awakening of patients from general anesthesia after surgical procedures. An anesthesiologist can make a difference through physiological mechanisms that relieve pain and shorten the time it takes to recover protective reflexes, especially those related to the airways, and regain cognitive functions. As a result, there is an increasing need for anesthetics that induce sufficiently deep anesthesia while making the emergence from it quick, i.e. quickly restoring vital functions without any side effects (3).

Inhalation anesthetic agents are used to induce and maintain general anesthesia, and they are delivered in the patient through a mixture of carrying gases, most commonly air/ oxygen. They exert their effect on the CNS to cause loss of consciousness, the establishment of anesthetic sleep and the loss of the response to harmful stimuli, while the depth of anesthesia is proportional to the partial pressure of an anesthetic in the lungs and brain. Since the concentration of the inhalation aesthetic in these two organs cannot be measured (except in a computer simulation), the alveolar end-tidal partial pressure of the inhalation anesthetic is used as a replacement for the concentration of the inhalation anesthetic at the site of action (4).

Desflurane is a volatile anesthetic that is the latest to enter anesthetic practice and it is used to maintain general anesthesia. It is desirable for surgical techniques that require rapid induction and rapid awakening from anesthesia, such as major and long head and neck surgeries. Its low solubility (blood/gas coefficient of 0.42) and low distribution volume are useful for patients undergoing long surgery and bariatric surgery, in which the distribution volume of drugs soluble in lipids is higher. Desflurane's pharmacological profile makes it even more suitable for general anesthesia (5). Compared to other inhalation anesthetics, its low solubility makes it easier to reach an equilibrium between alveolar and inspired concentration. Therefore, we have a rapid induction of general anesthesia and rapid awakening from anesthesia. Only a small percentage of desflurane, 0.02%, is metabolized in the body, while 99.98% of it is exhaled unchanged through the lungs.

Cognitive status disorders in the postoperative period are common after major surgeries, and general anesthesia is considered the main cause. Postoperative cognitive disorders can be classified into postoperative delirium, postoperative cognitive dysfunction and dementia (6,7). Postoperative cognitive dysfunction is a mild neurological disorder characterized by impairments in memory, concentration, linguistic understanding and social relationships. The diagnosis is formulated days after surgery and can result in a lifelong decrease to the patient's quality of life. The pathophysiological mechanism responsible for postoperative cognitive disorders in patients remains unclear (8). Predisposing factors include age and degree of education, presence of a preoperative cognitive disorder, chronic use of opioids and benzodiazepines, the existence of comorbidities, cerebrovascular disorders and the appearance of postoperative delirium (9,10).

Other factors that increase the risk of cognitive disorders are duration of anesthesia, re-operation, infection and postoperative pulmonary complications.

Goal

The purpose of this scientific study is to examine the effects of volatile anesthetics on patients' cognitive functions. Therefore, we compare the impact of two inhalation anesthetics, desflurane and sevoflurane act, on the cognitive functions of patients who, due to the type of surgical intervention, had to be placed under general anesthesia. Our second goal is to prove that the short-acting inhalation anesthetic, desflurane, along with the short-acting opioid anesthetic, remifentanil (not fentanyl), is among the best combinations for patients who need a long surgical intervention and general anesthesia with no postoperative impact on cognitive functions. To achieve these two goals, we will evaluate and compare the time of the return of reflexes to the airways and regaining of cognitive functions after general anesthesia with desflurane and sevoflurane, with the former being combined with remifentanil and the latter in a typical combination with fentanyl. All other factors affecting waking time from general anesthesia will be the same for both groups of examinees.

Material and methods

In this observational study conducted at the Clinic for Anesthesia, Resuscitation and Intensive Treatment (KARIL), the University Clinic for Traumatology, Orthopedic Diseases, Anesthesia, Reanimation, Intensive Care and Emergency Centre (UC TOARILUK) over a period of 24 months, included 60 respondents, 26 of whom received halogenated inhalational desflurane (MAC=0.7-1), while 34 respondents received halogenated inhalational sevoflurane (MAC=0.7-1) to administer general anesthesia. In the desflurane group, thirteen subjects received fentanyl intraoperatively, while 13 subjects were maintained under anesthesia by remifentanil, and in the sevoflurane group, 17 received fentanyl, while 17 were maintained under anesthesia by remifentanil. Inclusion criteria for the study encompassed ASA 1.2 and 3 with BMI below 35 and an age limit of 18–65 years for both genders. The subjects received elective general anesthesia with an inhaled anesthetic desflurane or sevoflurane for colorectal pathology during an elective surgery lasting between 2 and 3 hours. The depth of anesthesia was monitored by the Bispectral Monitoring Index, which ranged from 45 to 55 in both groups, corresponding to stage 3 surgical anesthesia. The awakening time from anesthesia was measured from the cessation of the inhalation of an anesthetic to the return of reflexes to the airways (laryngeal reflex). Then, the extubating time was measured, followed by the time of the first opening of the eyes in response to a verbal command, the moment of holding the head raised for 5 seconds, and the orientation to person, place and time, using a modified Aldrete score that needed to be above 9. Cognitive functions were evaluated according to the time required to complete the Mini Mental State Examination (MMSE) test and the Orientation-Memory-Concentration Test (OMCT), which were filled in for each patient 4 times: preoperatively, in the recovery room (PACU) and on the first and second postoperative days. The study's exclusion criteria were ASA over 3, age under 18 and over 65 years, morbid obesity, BMI over 35, existence of neuromuscular diseases, history of possible malignant hyperthermia, obstructive lung disease with regular use of bronchodilators and the presence of preoperative cognitive disorder, which originates from chronic opioid or benzodiazepine use, as well as cerebrovascular disorders.

Work protocol

At the operating room, patients were connected to a monitor to observe the ECG, non-invasive blood pressure, pulse oximetry and Bispectral Index. A peripheral neurostimulator was installed to monitor The Train of Four (TOF). The patients were reoxygenated with 100% oxygen within 3 minutes with a flow of fresh gases of 6L/min and anesthesia was induced with a standardized induction approach using sedative midazolam 0.03mg/kg i.v., fentanyl 1-2mcg/kg, propofol 2mg/kg and muscle relaxant rocuronium 0.6mg/kg. The respiratory pathway was secured with an adequately-sized endotracheal tube and connected to an anesthesiology ventilation machine with an inhaled anesthetic desflurane (3–6%), (1–2%) to mas=0.7–1, with a flow of fresh gases of 2L/min, 50% air with 50% oxygen. Tidal capnography etSO2, the inspiratory faction (Fi) of anesthetic gases and the expiratory faction (FE) of volatile anesthetics were monitored. Minute ventilation was set with a respiratory volume of 6–8ml/kg, a 12/min respiratory frequency and an inhale exhale ratio of 1:2 to maintain a 30–40mmHg CO2 tidal. The dosage for maintenance of intravenous and inhaled anesthetic agentswas titrated to maintain BIS from 45–55. Additional bolus doses of fentanyl at a dose of 0.5mcg/kg were given as needed. Remifentanil was given at a dose of 0.125–0.25mcg/kg/min. Muscle relaxation was maintained with intermittent doses of rocuronium at a dose of 0.15mg/kg. The volatile anesthetic was reduced 15 minutes before the surgery ended to MAS=0.5 and was interrupted after the last surgical stitch was placed. The flow of fresh gases was then increased to 6L/min with 100% oxygen. After achieving TOF≥3, a reversion of the neuromuscular block with Neostigmine 0.03mg/kg and Atropine 0.01mg/kg was administered. i.v..

Statistical analysis

The data analysis was performed in statistics programs Statistics 7.1 for Windows and SPSS 23, in series of numerical variables (ASA, age, BMI, length of intervention), Description Statistics (Mean; Std. Deviation; ±95,00%CI; Median; Minimum; Maximum). The difference between the values of the parameters analyzed in relation to the gender of the respondents was done by applying t-test, independent, by groups (t/p) depending on the distribution of the data. The correlation between two variables was derived with Pearson's correlation coefficient (r) and Spearman Rank Order R (R), depending on the distribution of the data. Significance was determined for $p<0.05$.

Results

The results (expressed in minutes) obtained in the both patient study groups are significantly shorter in the group of patients who received a desflurane inhalation anesthetic with the opioid remifentanil, compared to the group of patients who received a sevoflurane inhalation anesthetic with fentanyl or remifentanil, when administering elective general anesthesia.

Table1. Demography and duration of surgical intervention.

	Group D-f. (n=13)	Group D-r. (n=13)	Group S-f. (n=17)	Group S-r. (n=17)	p-value
Sex (m/f)	8/5	7/6	9/8	10/7	p<0.05*
ASA I/II/III	2/6/5	1/6/6	2/9/6	1/8/7	p<0.05*
Age	61±8.7	63±7	64±9.3	62±8.1	p<0.05*
BMI	22.23±.1	21±7 PM	23.5±4.0	22.2±3.1	p<0.05*
Length of intervention	149.4±11.2	151.1±9.3	157±8.5	156±7.7	p<0.05*

BMI=Body Mass Index, ASA=Physical Status Classification System, Group D-f=Fentanyl Desflurane, Group D-r=Remifentanil Desflurane, Group S-f=Fentanyl Sevoflurane, Group S-r=-Sevoflurane with Remifentanil

- The group maintained under anesthesia by desflurane with remifentanil, marks a shorter time of extubating, from the last surgical stitch of the operational operation, i.e., from discontinuation of the inhalation anesthetic to extubating.
- The patients with desflurane-remifentanil anesthesia mark shorter time of the opening of the eyes, the time from the last surgical stitch, from the cessation of the inhalation of anesthetic to the opening of the eyes in response to a verbal command given by the examiner.
- Patients with desflurane-remifentanil mark shorter time of a verbal response after the last surgical stitch.
- The desflurane-remifentanil group marks shorter time from discontinuation of the inhalation anesthetic to achieving Aldrete's score of 9.
- Cognitive function returns more quickly to the desflurane group after the patient's awakening, i.e. the time from interruption of desflurane to time required to complete the Mini Mental State Examination (MMSE) in the recovery room with a score of more than 25 is shorter in the desflurane-remifentanil group.
- The Mini Mental State Examination (MMSE) test on the first postoperative day showed a higher score of cognitive function by patients who received desflurane-remifentanil.
- Patients who received desflurane-remifentanil achieved a better score on the Orientation-Memory-Concentration Test (OMST) when they were examined for the second time, i.e. in the recovery room.

Table 2. Time of emergence from anesthesia.

	Group D-f	Group D-r	Group C-f	Group S-r	r value
Extubating	7.2 ±1.6	7±8.3	8.9 ±2.0	8.4±1.1	p<0.05*
Eye opening	6.8 ±3.1	6.5±5.4	7.5 ±4.2	7.1± 3.4	p<0.05*
Verbal response	7.6 ±1.8	7.2±2.0	9.3 ±4.1	8.2±2.6	p<0.05*
Modified Aldrete score>9	13.3 ±5.0	13.1±1.2	16.7 ±3.9	15.5±4.4	p<0.05*
MMSE>25	60 ±7.2	57.8±1.8	64.3 ±3.3	61.3±3.4	p<0.05*
OMST<10	74±2	72±3.7	77.71±2.3	74.3±6.3	p<0.05*

MMSE=Mini Mental State Examination Test, Orientation-Memory-Concentration Test (OMCT) Group D-f=Fentanyl Desflurane, Group D-r=Remifentanil Desflurane, Group S-f=Fentanyl Sevoflurane, Group S-r=Remifentanil Sevoflurane

Discussion

The purpose of this study was to compare the waking time and time of return of cognitive functions in patients after elective general anesthesia maintained with inhalant desflurane in one group of patients, and inhalant sevoflurane in another group of patients. The inhaled anesthetics were combined with opioid anesthetics, fentanyl or remifentanil.

The results showed that the waking time in all patients maintained under anesthesia by a desflurane was shorter than that of patients maintained under anesthesia by sevoflurane. The extubating time with desflurane anesthesia was 7.2 ±1.6 minutes, which was significantly shorter than the time of extubation with sevoflurane, 8.9 ±2.0 minutes, while the verbal response time for desflurane anesthesia was significantly smaller, 7.6 ±1.8 minutes, versus the time of verbal response to sevoflurane anesthesia, which was 9.3 ±4.1 minutes. This is thought to be due to the faster kinetic profile of desflurane, which leads to a faster elimination from the patient. We used the Bispectrality Monitoring Index, BIS, to ensure an adequate depth of anesthesia, i.e. to achieve values between 40 - 60, correlated with loss of consciousness and surgical anesthesia, and independence between the two inhalation agents. The BIS value was compared at the introduction to anesthesia and during waking up.

After the cessation of the inhalation anesthetic and after the last stitch was made, in the early postoperative period, higher BIS values were observed in the desflurane group with opioid remifentanil, unlike the sevoflurane fentanyl group, where BIS values increased later.

Conclusion

The resulting values obtained from the cognitive function tests in the recovery room showed that in patients maintained under anesthesia by desflurane and remifentanil, cognitive functions returned faster than in patients maintained under anesthesia by desflurane-fentanyl. The same results were obtained in the sevoflurane-remifentanil group compared to the sevoflurane-fentanyl group.

This study contributed to an awareness of the differences in impact between the two inhalation anesthetics on cognition and remembering after waking up from general anesthesia. However, like any research, it can be extended through further studies with their own findings, eighter they are positive or negative, from which we distance ourselves. This study did not measure the level of inhalation anesthetics in the operating room, as gases are eliminated through an evacuation system in the external environment, nor has the concentration of the inhalation anesthetic been measured in the external environment. Desflurane is known to damage the ozone hole, but it cannot affect as much as global warming affects the country's weather disasters. We leave this field of research to the specialists that deal with it.

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HEPATITIS B IMMUNIZATION IN THE MATERNITY WARD OF THE UNIVERSITY CLINIC FOR GYNECOLOGY AND OBSTETRICS IN R. N. MACEDONIA

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Abstract

Introduction: The beginning of the fight against infectious diseases is marked by receiving the first dose of Hepatitis B (HepB) vaccine in the maternity ward. It is a recombinant viral vaccine that stimulates active immunity. Unfortunately, on a global level, there is a decline in vaccination coverage of children for all vaccines. Our study aims to assess the coverage of the first dose of vaccine against the HepB among newborns in our hospital during 2023.

Material and Methods: This is a retrospective study and it included data for HepB vaccination from all newborns born at the University Clinic for Gynecology and Obstetrics from 01.01.2023 to 31.12.2023.

Results: There were 3,917 live births in total in our maternity hospital in the year 2023. 3,235 (82.6%) of the newborns were vaccinated against the HepB virus, while 682 (17.4%) of the newborns remained unvaccinated. In the first 24 hours after the birth and the first 7 days, 2,912 and 323 newborns were vaccinated respectively. Out of the 682 unvaccinated, 30 have been transferred to another health facility, 8 were unvaccinated due to the written consent from the parents for postponing vaccination, and 644 newborns remained to be vaccinated in the vaccination dispensary, where individual calendars for immunization would be created.

Conclusion: In order not to lose the battle with infectious diseases at a time of intensive technical-technological development, it is necessary to be more active and to continuously participate in the process of immunization at all levels of the health care. Immunization of newborns with HepB vaccine is an effective measure to control HepB infection and prevent liver cirrhosis and hepatocellular carcinoma.

Key Words: *HepB infection, immunization, newborns, vaccine.*

Introduction

HepB virus is a DNA virus of the Hepadnaviridae family that causes infection of the liver. It is 50-100 times more infectious than Human immunodeficiency virus (HIV) and among the most resistant viruses in the external environment and disinfectants, with a very small infectious dose (0.00004ml), without a teratogenic effect.

Infection with the virus occurs by vertical transmission (from mother to newborn) and by horizontal transmission (by contact with blood and other body fluids) of an infected person. Whether the infection will be acute or chronic depends largely on the age at which it occurs. About 90% of infants, 20-50% of children aged 1-5 years and 5% of adult patients infected with the virus develop chronic infection. Around 25% of them will develop cirrhosis of the liver and 5% hepatocellular carcinoma (1,2). World Hepatitis Day is celebrated on July 28th, at which occasion the WHO published data about 1.1 million deaths as a result of HepB virus infection in 2023, 3 million newly infected each year, and over 300 million with chronic hepatitis infection B and C in the world (3). The most infected are in the African and the Western Pacific region, while in Europe, 14 million have chronic Hepatitis B infection or 1% of the population (Greece 3.4%, Romania 5.6%) (4). According to the data of the Institute for Public Health of the Republic of North Macedonia, the number of new infected cases, as well as cases with chronic HepB in our country is increasing (Table 1).

Table 1. Data from the Institute for Public Health of the Republic of North Macedonia.

	2020	2021	2022	2023
Infected with HepB	37	29	43	56
HBsAg+	18	12	11	17
Infected with chronic HepB	5	5	17	26
Deceased as a result of infection with HepB	0	1	5	2

The virus causes a silent epidemic, as 90% of infected people living with HepB are unaware that they have it. Timely information, prevention and treatment of the disease can reduce mortality from HepB infection.

Vaccination against the HepB virus in Macedonia began in October 2004, and soon reached the optimal level of 95% coverage of the population. According to the official data by the Ministry of Health of the Republic of North Macedonia (5) - HepB vaccine coverage with all three doses is given in Table 2.

Table 2. HepB vaccine coverage, data by Ministry of Health of the Republic of North Macedonia.

	2020	2021	2022	2023
Fully vaccinated with HepB vaccine	83,6%	78,7%	84,1%	No data

Our study presents the data for receiving the first dose of vaccine against the HepB among newborns in the University Clinic for Gynecology and Obstetrics during 2023.

Material and Methods

This is a retrospective study performed at the University Clinic of Gynecology and Obstetrics that included newborns in a period from 01.01.2023 to 31.12.2023.

The study included newborns in term (370/7 – 416/7), late premature (34 0/7 – 366/7) and premature newborns smaller than 34 0/7 week of gestation.

All newborns with transfer to another health facility - hemodynamically unstable with complex congenital heart anomalies or respiratory unstable with the need for long-term mechanical ventilation - were excluded from the analysis.

Immunization with the first dose of the vaccine was carried out in the first 24 hours after birth, while for newborns with a birth weight below 2,000g, or smaller than the 34th week of gestation or with unstable vital parameters, the vaccine was given in the first 7 days at the latest. Immunization was carried out by intramuscular application of the Engerix vaccine, in a dose of 0.5ml, with a sterile needle 25G (length 16mm), in the area of the left m. vastus lateralis. The newborns were monitored for adverse effects of the vaccine during their stay in the Department of Basic Care. Newborns from HBsAg positive mothers received specific immunoglobulins 125 IU, in the first 12 hours after birth, on the contralateral side of the vaccine application, in the area of the right m. vastus lateralis. The same is recorded in the history of the newborn and in the birth certificate, as a document. For newborns whose mothers refuse immunization in the maternity ward, the parents were counseled and gave written consent for their decision.

Results

In the period from 01.01 to 31.12.2023 there were 3,917 live births in total at our maternity hospital. 3,235 (82.6%) of the newborns were vaccinated against the HepB virus, while 682 (17.4%) of the newborns were unvaccinated.

In the first 24 hours after birth, 2,912 newborns were vaccinated, including 6 from HBsAg+ mothers who received specific immunoglobulin in addition to the vaccine and 3 newborns from HIV positive mothers.

In the first 7 days of birth, 323 newborns were vaccinated, out of which 285 with asphyxia and/ or infection and/ or respiratory distress, and 38 newborns in the 34th week of gestation and/ or with a birth weight of less than 2,000 grams and are staying in the Department for basic newborn care.

There were 682 unvaccinated newborns in our maternity hospital, 30 of them have been transferred to another health facility (Children's Surgery, Cardio Surgery, Clinic for Children's Diseases), 8 were with written consent from the parents to postpone vaccination, and the rest 644 were discharged from the Intensive Care Unit (ICU). The parents of discharged newborns from the ICU, were advised to go to vaccination dispensary, where individual calendar for immunization would be created.

Discussion

Our study presents the actual situation with HepB vaccination in the 2023 year, and it is similar to the coverage described from several surrounding countries such as Albania and Bulgaria. All countries are committed to achieving the WHO strategic goal of the elimination of the vaccine-preventable disease.

The importance of the introduction of the HepB vaccination can be seen from the results and analysis of several studies. For example, a study by Petro et al. from 2014 (6), which included 2,670 newborns born in 1986, before the introduction of the HepB vaccine in maternity hospitals in Gambia, and 4,613 newborns born in 1990, after the introduction of the vaccine, showed massive reduction in the prevalence of chronic HepB infection as a result of the introduction of regular immunization with HepB vaccine. The effectiveness of vaccine is described to be 94% successful.

Additionally, the importance of the vaccination could be seen from other studies, such as the study by Shefa Al-Amleh (7) that determined the prevalence of HepB in children born from HbsAg positive mothers. The study included 125 HBsAg positive mothers of different ages who gave birth of in a total of 386 children. They found 42 (10.9%) HBsAg-positive children. Transmission was described to be higher among the lower socioeconomic class in rural areas of Palestine.

Although there was a global decline in the overall vaccination and the COVID-19 pandemic additionally affected this process, Dugovich et al. (8) in an analysis of a total of 8,000 newborns, at Children's Hospital, Charleston, South Carolina, concluded that the COVID-19 pandemic had no significant impact on the administration of the first dose of the HepB vaccine. Before the pandemic, immunization was 92.3% of 3,583 included newborns versus 90.9% of 3,928 newborns, so, there was a drop of 1.4%. Factors such as white race, married mothers, and TT below 2000g, had a greater impact on receiving the first dose vaccine than the COVID-19 outbreak itself.

According to WHO data on immunization against HepB globally, from the 2022 year to June 2023 (updated every July), 45% of the newborns were vaccinated with the first dose of HepB vaccine (in the maternity ward) and 84% of children with all three doses (9).

According to UNICEF data (10), for the same period, 97% of newborns were covered by the first dose in all maternity hospitals in R. N. Macedonia, and 84% of children with three doses. Compared to countries from our region, for example Serbia, 99% of newborns received the first dose of HepB vaccine and 92% of children received all three doses. In Albania 99% of the newborns and 97% of children are vaccinated, and in Bulgaria 97% of the newborns received the first dose and 91% of children have received 3 doses of HepB. There are no official data for Montenegro and Greece, but the available data indicate a lower percentage of immunization with the other two doses of vaccine, which is probably due to a lower response to the vaccine, in the conditions of the Covid-19 pandemic (March 2020-May 2023).

The obtained data indicate an increased percentage of those vaccinated with the first dose of vaccine compared to data from previous years. According to our records, the first dose of the vaccine against the HepB virus in year 2022, at our maternity ward was received by 75.5% (3,146 newborns from 4,169 live births), compared to our survey for 2023 when 82.6% of live births were immunized.

Considering that the most complicated pregnancies and deliveries of extremely premature newborns are completed at our facility, there are still a lot of newborns that cannot be vaccinated at our hospital. Their immunization is carried out according to an individually created calendar depending on the correct age, in vaccination dispensaries. So, for these newborns we do not have much opportunity to increase the percentage of vaccination with HepB vaccine.

Unfortunately, globally, there is a declination in vaccination coverage for all children, for all vaccines, including immunization with the HepB virus vaccine. Not a single case of adverse reactions was observed after vaccination. Of course, there is room for improving the screening of pregnant women, the registration of HBsAg+ pregnant women, of newborns who received specific immunoglobulins in addition to the vaccine. With that, we are actively participating in the realization of the goals of the WHO, adopted at the 75th World Assembly in 2022 (11). The goals are to reduce the number of newly infected people with HepB by 90%, reduce the mortality caused by infection with the HepB virus for 65%, achieve coverage of newborns with the vaccine by 90%, and increase of the first dose of vaccine by 90% by 2030.

Primary vaccination in the maternity hospital is one of the steps on the way to the set goals. For a complete picture of vaccination coverage with HepB vaccine, data from revaccinations after one and after 6 months of primary vaccine in outpatient clinics are taken into account (12).

Conclusion

Despite the turmoil on the vaccination and immunization scene, the HepB vaccine is a safe and proven weapon in the fight against hepatitis infection and its sequelae. The enhanced and continuous engagement of all health institutions and individuals involved in the immunization process leads to the achievement of high collective immunity and good control, as well as elimination and eradication of this infectious disease.

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LOCATION OF THE PLACENTA IN DETERMINING THE CLINICAL PICTURE OF PREECLAMPSIA

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Abstract

Introduction: Preeclampsia is a syndrome that affects 4-9% of pregnancies. It is a systemic disease characterized by a combination of hypertension and proteinuria after 20 weeks of gestation in previously normotensive pregnant women.

Purpose: To determine the correlation between the location of the placenta and the occurrence of preeclampsia.

Material and Method: 50 patients were examined during the second screening in pregnancy and were controlled during the period of 30-34 gestational weeks in order to determine whether they were hospitalized with symptoms of preeclampsia.

Results: Out of the examined patients, 27(54%) had a central location of the placenta, 17(34%) had a lateral location, 4(8%) had a posterior location and 2(4%) had a fundal location of the placenta. Out of the 50 patients in the study, 6 (12%) developed symptoms of preeclampsia. Out of the 50 patients in the study, 27(54%) had a central location of the placenta, 4 of them (14.81%) developed symptoms of preeclampsia and 23(85.19%) of the patients were normotensive. In patients with preeclampsia, 4 of them (14.81%) had a central location on the placenta.

Discussion: The incidence of preeclampsia in the studied group is 12%. After screening in the third semester, 27(54%) patients had a central location and 4(14,81%) had a tendency to develop preeclampsia, severe preeclampsia, postpartum hemorrhage. The resulting neonates had a lower birth weight and a lower Apgar score than in normotensive patients.

Conclusion: Preeclampsia is a serious condition, and its prevention is of great importance. Any test that can predict possible complications must not be dismissed, but carefully considered.

Key Words: *Bed, preeclampsia, second semester screening.*

Introduction

Preeclampsia is a syndrome that affects 4-9% of pregnancies and is an important cause of maternal and perinatal mortality and morbidity. It is a systemic disease characterized by an inflammatory response and endothelial disruption and is clinically identified as a combination of hypertension and proteinuria after 20 weeks of gestation in previously normotensive pregnant women (1).

One in three cases of maternal morbidity is associated with preeclampsia. Preeclampsia is the cause of 50,000 maternal deaths annually worldwide.

Preeclampsia can be moderate or severe, according to clinical and laboratory parameters and the presence of maternal and fetal complications.

Also, preeclampsia can be classified as early, which occurs before 34 weeks of gestation, and late, which occurs after 34 weeks of gestation. Early preeclampsia occurs due to abnormal uteroplacental perfusion, and this leads to low-birth-weight neonates. They are associated with poor maternal and neonatal outcomes. Late preeclampsia occurs in patients associated with a chronic inflammatory condition. It has a lower degree of fetal distress (1,2).

The placentas of patients with preeclampsia are associated with placental hypoperfusion, such as infarcts and fibrin deposits. Ischemia and hypoxia from inadequate trophoblast invasion increase the production of proinflammatory cytokines in the placenta. Tumor necrosis factor alpha and interleukin 1 levels are increased and secreted from the placenta of patients with preeclampsia.

Decreased production of the anti-inflammatory cytokine interleukin 10 increases the production of pro-inflammatory cytokines (1).

The placenta is a source of angiogenic molecules that play an important role in the formation of blood vessels in the maternal-fetal space. Imbalance of placental production and release of pro- and antiangiogenic factors contributes to systemic endothelial cell dysfunction in patients with preeclampsia. Therefore, reduction of angiogenic placental growth factor (PLGF) and vascular endothelial growth factor (VEGF), and increased production of antiangiogenic factors soluble endoglin (sEng) and soluble fms-like tyrosine kinase-1 (sFlt-1), are associated with the pathogenesis of preeclampsia (1,2).

This study is devoted to the correlation of the location of the placenta and the severity of the clinical picture of preeclampsia.

No test for the diagnosis of preeclampsia is perfect, and therefore the search for a test that will improve the diagnosis of preeclampsia continues. There are studies that link the location of the placenta to the occurrence of preeclampsia. During the screening in the second semester, the position of the placenta is determined. If the placenta is found to be anterior wall or lateral, the patient can be monitored at the tertiary level for developing preeclampsia.

Material and Method

This is a prospective study. 50 health patients were examined during the second screening in pregnancy, in the outpatient polyclinic section at the tertiary level (University Clinic of Gynecology and Obstetrics, Skopje) and were controlled during the period of 30-34 gestational weeks in order to determine whether they were hospitalized with symptoms of preeclampsia. All patients were delivered at University Clinic of Gynecology and Obstetrics.

The patients were divided into two groups:

1. A group of healthy patients who did not develop symptoms of preeclampsia, and

2. A group of patients who developed symptoms of preeclampsia.

The patients were examined on an ultrasound device Voluson E10, from the company General Electrics.

The review is performed on a Voluson E 10 device in the outpatient department, and on a Voluson S6 in the hospital department of the tertiary institution in the period from November 2022 to September 2023.

Inclusion criteria include:

A singleton pregnancy with normal tension, during the second screening in our institution; and

Female patients agreeing to contact the tertiary level in the event of an increase in blood pressure.

Exclusion criteria are**:**

- Patients with thyrotoxicosis,
- Severe anemia,
- Multiple pregnancies,
- Vascular diseases,
- Gestational diabetes mellitus,
- Vascular disorders,
- Renal disease,
- Epilepsy,
- Cardiovascular disorders.

Laboratory analysis for preeclampsia and blood pressure were taken in the patients hospitalized in the department with a diagnosis of preeclampsia.

The placenta is noted as the central, lateral, fundal and posterior position, determined during the second trimester screening. Hypertensive disorders are considered if the diastolic pressure is over 90mmHg in a period of 6 hours or over 110mmHg.

Results and Discussion

Out of the examined patients, 27 (54%) had a central location of the placenta, 17 (34%) had a lateral location, and 4 (8%) had a posterior location and 2 (4%) had a fundal location of the placenta.

Out of the 50 patients in the study, 6 (12%) developed symptoms of preeclampsia.

Out of the 50 patients in the study, 27(54%) had a central location of the placenta, and 4 of them (14.81%) developed symptoms of preeclampsia, and 23(85.19%) of the patients were normotensive. In patients with preeclampsia, 4(14,81%) of the patients with preeclampsia had a central location on the placenta.

Table1. Location of the placenta

Placental location	Normotensive	Preeclampsia	Total
Central	23(85,19%)	4(14,81%)	27(54%)
Lateral	15(88,23%)	2(11,76%)	17(34%)

Fisher's exact test is considered to be not statistically significant.

Patients with a lateral position of the placenta were 17 (34%), 2 (11.76%) patients with lateral position of the placenta developed preeclampsia. The remaining 15 (88.23%) were normotensive.

Severe preeclampsia was diagnosed in 2 (33.33%) of the patients diagnosed with preeclampsia, and in 4 (66.67%) patients, moderate preeclampsia was diagnosed. Both patients with severe preeclampsia had a central placental location.

Table 2. Preeclampsia severity

Severity of preeclampsia	Central placenta	Lateral placenta	Total
Moderate	2	2	4
Severe	2	0	2
Total	4	2	6

Fisher's exact test is considered to be not statistically significant.

13 of all examined patients had postpartum hemorrhage, out of which 10(20%), normotensive patients and 3(6%) patients with preeclampsia with a central placenta location.

The incidence of admission of neonates to the Intensive Care Unit in patients with preeclampsia has increased.

The incidence of preeclampsia in the studied patients is 12%. After screening in the third semester, 27 (54%) patients had a central location and 4 of them (14.81%) had a tendency to develop preeclampsia, severe preeclampsia, postpartum hemorrhage. The resulting neonates had a lower birth weight and a lower Apgar score than in normotensive patients.

Although the etiology of preeclampsia is not reliably defined, there is evidence that indicates that disorders in the placenta are the most important factors responsible for the development of the disease and its severity (3).

Conclusion

This study confirmed correlation of the location of the placenta and the severity of the clinical picture of preeclampsia. Attention should be paid to placental location during second-trimester screening (4,5). Placental location can be used as predictor of the development of preeclampsia, and to reduce maternal and neonatal complications. In the central location of the placenta, more

frequent and more careful monitoring of pregnant women and fetuses is needed, in order to detect the occurrence of preeclampsia in time and to respond promptly to avoid possible severe consequences.

The statistical insignificance is considered to be due to the small number of patients examined so far in the study. The study continues, and with the larger number of patients, statistical significance will be reached. Until then, vigilance remains for patients where the placenta is centrally located for the development of symptoms of preeclampsia.

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OPTIMIZATION IN COMPUTED TOMOGRAPHY

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Abstract

New medical CT technologies and devices have undoubtedly made great improvements in the diagnosis and treatment of human diseases. Simultaneously, inappropriate, or unqualified use of these technologies and medical equipment can cause unnecessary or unintended exposures and potential health hazards for the patients and medical personnel. These risks can be largely controlled, and benefits can be maximized by choosing appropriate procedures and methods to reduce patients' exposure without reducing clinical efficacy. In the last few years, there has been an increased number of CT examinations in medical clinical practice which represents a large part of the collective dose of radiation from diagnostic examinations. At the same time average annual per capita radiation dose for diagnostic purposes is also increasing which contributed to growing the concern about radiation hazards among the population. Due to the increasing concern about the potential dangers of CT radiation, many strategies have been developed to reduce and optimize CT dose in order to maximize the benefit-risk ratio of CT examinations. Lifetime risks of CT examinations, the cumulative dose of CT radiation per capita, is very important especially in the young population who have higher radio-sensitivity and expectancy of longer life than the old ones. In this presentation, the currently available strategies for optimized CT protocols and reducing the CT dose are presented, which can lead the appropriate utilization of CT in diagnostic manner through good medical practices which can contribute to adequate radiation protection on patients.

Key Words: *Computed tomography, optimization, radiation dose.*

Introduction

Modern medical CT technologies and devices have undoubtedly made great improvements in the diagnosis and treatment of human diseases. Simultaneously, inappropriate, or unqualified use of these technologies and medical equipment can cause unnecessary or unintended radiation exposures and potential health hazards for the patients and medical personnel. These risks can be largely controlled, and the benefits can be maximized, by choosing appropriate procedures and methods to reduce patients' radiation exposure without reducing clinical efficacy (1). With the increased utilization of CT, the average annual per capita radiation dose for diagnostic purposes is also increasing. It raises concerns about radiation hazards among the population. In addition to that is the fact that the effective dose per capita has doubled in the last 10 years. Although the utility of modern diagnostic procedures is considerable, and the individual risk associated with radiation exposure from medical examinations is still generally low, the increasing number of examination with ionizing radiation and the number of exposed persons who have

multiple examinations annually, is general public health issue, taking into account the fact that more than two-thirds of the radiation for diagnostic purposes are attributed to the computed tomography (head, chest, abdomen, pelvis) Figure 1.

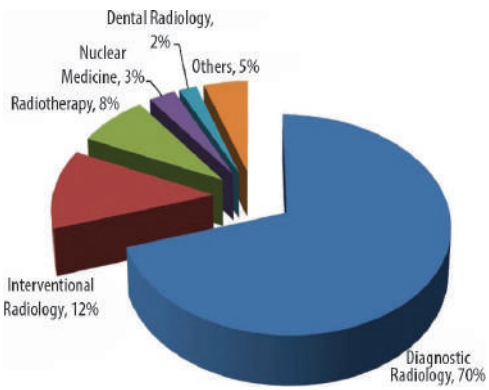

Figure1.

For those reasons, CT is the primary focus of attention. Modalities such as fluoroscopy, angiography, interventional radiological procedures are also in the center because of the radiation doses. With the rise of the number of CT examinations, there is also growing concern about the danger of increased radiation from performing a greater number of examinations, at the same patients several times per year (2). For this reason, in recent decades much attention has been given to the optimization of the dose on CT examinations by radiologists, technologists and medical physicists. With the purpose to ensure the quality and safety in radiology, it is mandatory to systematically monitor and analyze the data concerning the dose from the radiological examinations, as well as monitoring of the images' quality. New strategies for reducing the radiation dose during radiological diagnostic procedures are continuously being developed and radiologists have a key role in these dose management activities.

Most of the strategies to reduce CT dose are focused on the choice of the CT scan as an appropriate diagnostic test, limiting the examination to the anatomic area which is required, and optimizing the parameters of scanning (especially in pediatric patients). Only by applying optimized technical parameters radiation exposure could be reduced by up to 65%.

In the process of the dose optimization, multiphase examinations that include series without i.v. contrast and post contrast series (arterial, venous late series) should be considered especially in cases where one or fewer phases in the examination are sufficient. Multiphase CT studies (repeated scans before and after contrast injection) are potentially very important source of medically unnecessary radiation due to the dose multiplier effect of dose in the additional phases. Despite the facts that high levels of exposure to ionizing radiation increase the risk of cancer, the data for lower doses of radiation obtained in sequences or from multiple examinations are less clear and still controversial (3). Because of insufficient clarity surrounding this issue, the American College of Radiology, Health Physics Society, IAEA and other concerned organizations, have embraced the ALARA principle. This principle dictates that physicians should strive to reduce radiation exposure to the lowest achievable levels, focusing on what is medically necessary.

Regarding multiphase examinations, the American College of Radiology recognizing the need for guidelines, in 1993 developed the ACR Evidence-Based Appropriateness Criteria, that de-

scribe scanning protocols with specific phase selections for various clinical conditions (4). In 2014, ESR nominated experienced radiologists to develop European guidelines for imaging referrals according to eligibility criteria of the American College of Radiology. These guidelines are integrated into the ESR iGuide platform. Current international requirements linked to the medical use of ionizing radiation also take a part in International Basic Safety Standards (IAEA Safety Standards Series No. GSP Part 3) (5).

Regarding the improvement in medical clinical practice, establishing and maintaining a culture of radiation safety in health care, the three fundamental principles of radiation protection are important: Justification, Optimization, and Dose limit (6).

While quantifying the lifetime risks related to CT examinations involves uncertainties, it's crucial to minimize the cumulative dose of CT radiation per person. This is particularly critical for younger individuals, given their heightened radiosensitivity and longer life expectancy compared to the older population (7).

CT Dose Parameters and Radiation Dose

Patient's radiation exposure associated with CT is assessed using 3 main metrics:

1. Volume CT dose index (CTDI) vol.- represents the output dose of radiation from the scanner,
2. The dose length product (DLP) - represents the dose from the total scan and is derived from the CTDI volume including a scan length component,
3. The effective dose (ED) which measures the equivalent dose to the whole body with the same risk of biological effect. ED expressed as millisieverts (mSv), is formulated as a sum of absorbed doses of individual organs, weighted for their sensitivity to radiation.

Scan length (L) (Depends on patient height). Figure 2.

$$DLP = CTDI \times L$$

$$DLP_{total} = DLP_{series} \times N^{o}\ (series)$$

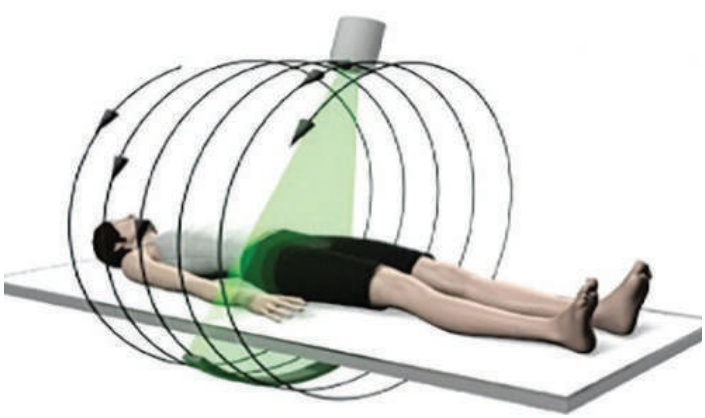

Figure 2.

Parameters that Affects Radiation Dose and Images' Quality in CT

Factors which directly affect the dose and image quality in CT include quality reference tube current, quality reference image noise, tube voltage, quality reference contrast to noise ratio, beam dimensions (width, height, z length), rescanning, reconstruction kernel, and iterative reconstruction algorithms (8).

Why the dose is so important?

The importance of radiation doses derives from the basic concepts of radiation and the evidence linking radiation exposure for medical purposes to the risk of developing cancer. Deterministic effects of radiation or so-called tissue reactions, such as skin erythema and hair loss, which result from cell death or radiation-induced damage, are in contrast with stochastic harmful effects on the population, such as cancer, which result from mutations. At the same time, the concepts of risk and dose were opposed. Certain radiobiological studies also indicate an increased risk for stochastic effects in pediatric and young adult population, compared to older adults for the same radiation exposure. Given that expression of stochastic damage takes many decades to become apparent, we may be just at the threshold of an increasing MDCT-induced cancer rate (9).

With the increased use of CT in recent years, there has been growing concern about the stochastic risks of radiation and safety in patient care.

Although CT accounts for only 17% of imaging studies obtained, statistics show that it is responsible for nearly half of the collective effective dose from medical procedures in the United States (Mettler et al. 2009). Risk projection models for radiation-induced carcinogenesis predict that in a few decades, 1.5–2% of all cancers in the United States may be attributable to CT use (Brenner and Hall 2007). Although diagnostic CT examinations are generally performed for assumed clinical indication in which the net benefit to the individual patient outweighs the theoretically increased risk of radiation, induced malignancy growth in the use of CT exams, generally increases the likelihood of stochastic harmful effects on the population (expression of a cancerous disease). Because of this potential radiation risk from the increased use of CT, it is especially important that CT doses are kept as low as reasonably possible (10).

How to reduce the dose?

In order to reduce the radiation dose, the first step is to consider the clinical indication and justification of a particular CT examination. The process of dose optimization often involves multiple stakeholders: referring physician, radiologists, CT technologists, medical physicists and patients.

To comply with the "as far as reasonably practicable" principle, appropriate strategies to optimize CT examinations should also be developed (11).

CT equipment manufacturers are also striving to develop new techniques to reduce radiation dose while maintaining or improving image quality. Part of them are new types of detectors, automatic exposure control (AEC) systems and iterative reconstruction (IR) algorithms, as part

of the most modern techniques for radiation dose optimization in CT.

An optimization approach to minimize the absorbed dose in patients undergoing a CT examination, at the same time, means maintaining a certain image quality of the diagnostic image, suitable for establishing a diagnosis, taking into account correlation with the image quality.

Regarding that, our practical goal is to find an optimization approach to minimize the absorbed dose in patients undergoing CT examination, while maintaining a certain quality of the diagnostic image.

CT scanners differ in their features both depending on the generation of the scanner and between different manufacturers type.

At the same time, the different indications require appropriate protocols that are in accordance with the clinical question. However, an essential primary step before any CT scan is to justify the medical need for the CT scanning. Radiologists influence the patient's radiation dose by selecting imaging protocols and targeting body-specific and disease-specific protocols that can minimize dose. The goal when choosing protocols is not to create an image of the highest technical quality, but to generate a diagnostic image that enables the diagnosis of pathological changes, using the lowest possible dose.

That's why strategies to reduce exposure to medical radiation largely have two primary goals:

1. Achieving greater awareness of the significance of medical radiation exposure.
2. Using new technology to obtain high-quality images from inherently noisier data.

According to that, CT dose reduction is a combination of different approaches or strategies.

These include Justification of CT diagnostic procedure; Optimization of scanning protocols and appropriate adjustments according to age or weight; Reduction of unnecessary examinations; Development of appropriate exposure protocols by manufacturers; Sufficient training and education for radiologists and radiologic technologists.

Dose Optimization

Optimization is the process of maintaining diagnostic image quality while minimizing the dose of ionizing radiation required to capture an image.

Optimization of CT radiation dose is an important issue that should be pursued first, starting with the choice of CT equipment and the proper training of the radiologists, radiologic technologists, and medical physicists.

To optimize CT examination protocols, an understanding of CT scan parameters and their effect on image quality is fundamental. There is also a need for standardization of CT diagnostic reference levels **(DRLs)** in accordance with the recommendations of the International Commission on Radiation Protection to reduce dose variations and facilitate comparison of doses (12). The same can be done by adopting international DRLs or making a DRL on the national level.

How to achieve an optimized dose?

The optimization of the radiation dose can be achieved by: Setting appropriate technical parameters; Optimizing the protocol according to the clinical question; Focusing on the training of professionals who are directly involved in the process of CT imaging and diagnosing changes, such as radiologists, technologists and medical physicists.

The best way to achieve dose optimization is to understand all the factors and parameters that can affect radiation dose and image quality and how they can be changed in the direction of dose reduction by designing or modifying scanning protocols.

CT parameters that affect the patient's radiation dose are detector configuration, tube current, tube potential, pitch, patient positioning, scan range, reconstructed slice thickness, shielding (13).

CT Dose Optimization Strategies

In order CT examinations to comply with the "as far as reasonably practicable" principle, appropriate dose optimization strategies need to be developed.

CT machine manufacturers are striving to develop techniques to reduce radiation dose while providing diagnostic-quality images. New improved detectors, Automatic Exposure Control (AEC) systems and Iterative Reconstruction (IR) algorithms are the newest techniques for radiation dose optimization in CT diagnostics (14,15).

However, in a large proportion of CT studies submitted to the literature, CT examinations have been performed with multiphase scanning protocols that are not always appropriate according to the clinical indication. Additional phases effectively multiply the radiation dose, so multiphase trials are an important source of unnecessary additional radiation, especially if extrapolated to larger populations. The majority of patients were noted to have multiphase CT scans, with at least 1 phase which is not indicated (late phase or native non contrast series). Routine multiphase CT scans of the abdomen and pelvis can be considered a source of additional unnecessary radiation exposure because a large proportion of clinical indications concerning the abdominal viscera can be effectively addressed with a single portal-venous phase series, even in a clinical context of acute abdominal pain. This source of excess radiation can be corrected by a personalized approach to the patient's needs and the correct choice of CT protocol according to the clinical question and the patient's clinical condition and guided by the ACR Appropriateness Criteria or other evidence-based criteria. In doing so, the general guiding principles for optimization and dose reduction include Minimizing scan length; Use of tube current modulation; Minimizing tube current; Minimizing the potential; Tailoring a scan to a patient with appropriate scan phases; Scan series reduction; Iterative reconstruction; Periodic review of CT studies (18-20).

Conclusion

Optimization and CT dose reduction is a process of combining different approaches or strategies. These include adequate equipment selection and development of better exposure protocols by manufacturers, justifying the use of CT examination according to clinical indication and re-

ducing unnecessary examinations, correct selection of the CT examination protocols and optimization of scanning protocols and adjustments according to age or weight, continuous training and education for the technologists, radiologists and medical physicists.

Achieving low-dose scanning is a team effort that requires tailoring the patient's scan according to the medical question, continuously improving image quality while reducing the dose to the lowest possible level. Achieving this goal in practice requires a substantial knowledge base in the fields of radiation physics, biology and epidemiology, radiology and other various clinical applications.

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CHALLENGES IN POSITIVE ANESTHETIC ALLERGIC TESTING

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Abstract

Allergy is becoming very often medical problem all over the world, especially during

anesthesia. There are increased numbers of allergy tests, due to positive anamnestic facts obtained from patients that are planning operations. Every patient with positive allergic reactions to 2 groups of medications or allergic reactions in previous anesthesia, are usually tested for allergic reaction for all the medications we use in anesthesia. We noticed that there is increased number of patients that are positive on some anesthetic drugs. There are patients allergic to muscle relaxants depolarizing like Suxamethonium - (Succinylcholine) or non-depolarizing drugs especially on rocuronium, also on opioids and other drugs such as Propofol, Ketamine. We would like to discuss a few cases and the way we solve the difficulties. Finding out the cause of an allergic reaction is complicated. A person can experience an allergic reaction to other factors or medications (such as antibiotics, muscle relaxants or latex) than anesthesia. If a medical professional administers anesthetic medications to a person who is allergic to them, they will develop anaphylaxis. We take these reactions very seriously and whenever we have these patients, we prepare anesthesia protocols in advance. There is not a general rule for all the patients. What approach we will choose, depends on operation, medicaments that are available in that moment, and consensus of the patient for anesthesia acknowledging all the difficulties, as well as accepting the operation and anesthesia protocols that he will have to challenge.

Key Words: *allergy, allergy tests, anesthesia..*

Introduction

In the early 2000s, the European Academy of Allergology and Clinical Immunology proposed to define acute nosological entity called allergy as "a severe, life-threatening, generalized or systemic hypersensitivity reaction" primarily mediated by type E immunoglobulins (IgEs) (1). This clinical entity was defined by the second National Institute of Allergy and Infectious Disease/ Food Allergy and Anaphylaxis Network symposium. They gave a definition of anaphylaxis as "Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death (2). The European Academy of Allergology and Clinical Immunology committee recommended that the term anaphylactoid, that is used for non–IE-mediated anaphylactic reactions, should no longer be used (1). We are also aware that this suggestion was not always accepted. The pathophysiological mechanism is known. On re-exposure on some allergens, the multimeric allergen cross-links two specific IgE receptors are creating a bridge between two IgE. These two IgE receptors aggregate and start a transduction cascade. Due to this cascade, there are lot of mediators that

are systemically released. These mediators are histamine, neutral proteases (tryptase, chymase) and proteoglycans (heparin). They are releasing from intracellular granules in the cells, and then enter the blood stream within tissues and blood. Some of these mediators, for example histamine, can initiate increasing of production of nitric oxide. Then there are new proinflammatory phospholipid-derived mediators. They are to be released very soon. After that, mast cells release chemokines and cytokines. These substances start to recruit and to activate inflammatory cells. The target organs are cardiovascular, respiratory, CNS - Central Nervous System, skin and mucosa and gastrointestinal system. The cardiovascular system can initiate symptoms like diaphoresis, dizziness. The signs are cardiac arrest, hypotension, collapse decrease in Et CO2, tachycardia, bradycardia, dysrhythmias.

The respiratory system has symptoms like acute shortness of breath, chest discomfort, wheezing. The clinical signs are acute respiratory failure, bronchospasm, decreased compliance, edema of larynx stridor. Manifestations of skin and mucosa tissues are burning, itching, tingling. There are signs such as erythema, flushing, edema urticaria. The patients with allergic reactions have neurological symptoms like increasing sense of doom, malaise with signs (if they are awake and not in general anesthesia) like loss of consciousness and confusion. Gastrointestinal tract has symptoms like cramps, nausea with signs of diarrhea, vomiting. Clinical manifestations can be graduatted in four severety grades. The most danagoures is the grade four – when cardiac arrest appear.

The most frequently reported drugs that are causing allergic reactions are antibiotics, neuomuscular blocking agents. Less frequently reported are latex, gelatins, hypnotics, opioids, contrasts that are used in radiological investigations. Allergies on local anesthetics are rarely reported.

Allergy is becoming very often medical problem all over the world, especially during anesthesia. There are increased numbers of allergy tests that are taken, due to positive anamnestic facts obtained from patients that are planning operations. Every patient with positive allergic reactions to two groups of medications or allergic reactions in previous anesthesia, are usually tested for allergic reaction for all the medications used in anesthesia. We noticed in recent years that there is increased number of patients that are positive on some anesthetic drugs. Very often they are positive on two or three groups of anesthetics drugs. There is increased number of patients allergic to opioids like fentanyl and remifentanil. Also, there are patients allergic to muscle relaxants depolarizing like Suxamethonium - (Succinylcholine) or non-depolarizing drugs especially on rocuronium. Also, there are patients that are allergic on sedatives like Propofol, Ketamine. There is no need to have doubts on the dermatological testing. During Prick's tests, anesthetic drug is diluted three to four times. If on the diluted drugs that are tested, patient has positive reaction, that means that the patient will be allergic on that drug without any doubt.

We would like to discuss a few cases that we encountered in our daily practice and the way we solve the difficulties.

The first case: Obese patient with body mass index -BMI 28 had previous operation for umbilical hernia. During that operation she had allergic reactions to opioids. She was admitted at our hospital for ventral hernia. We have done tests for allergy, and she was found to be allergic on opioids - Fentanyl, Remifentanil. Also, she was allergic on Ketamine, non-depolarizing muscle relaxants and nonsteroid anti-inflammatory drugs. She was not allergic on Paracetamol, Bupivacaine and Propofol. We decided to give her a high spinal anesthesia L1-L2 with 4ml of 0.5% Bupivacaine. Operation finished smoothly.

The second case: We had a patient with diverticulosis, who was planned to be operated. Hemicolectomy was suggested as an operation by the surgical team. She had anamnesis on allergies, and allergic reactions to Non steroid anti-inflammatory drugs - NSAID and Paracetamol. After the tests were done, she was found to be allergic on Fentanyl, Remifentanil, Ketamine, also on Paracetamol and NSAID. For the operation we decided to give her continuous epidural anesthesia with 0.25% Bupivacaine. She had her epidural on level L1-L2, and before intubation we gave her bilateral TAP - transversus abdominal block, and we intubated her with Propofol and rocuronium that was used to facilitate intubation. Anesthesia was maintained with sevoflurane and propofol which was administrated on continuous infusion with rate 60mcg/kg/min. Postoperatively she had Visual Analogue Scale (VAS) pain score 3 and had continuous epidural analgesia.

The third case: We also had a patient who was admitted at our hospital for Cholecystectomy with allergic on opioids - Fentanyl, Remifentanil. We decided to give her opioid free anesthesia. After O2 supply we started with slow infusion (during10 minutes) of dexmedetomidine 20μg, followed by 10mg dexamethasone, ketoprofen 160mg, paracetamol 1g, lidocaine 100mg and MgSO4 2.5g. We continued with the introduction of anesthesia with Ketamine 20mg and Propofol 170mg and preformed intubation. Anesthesia was maintained with continuous application of dexmedetomidine 4μg/ml to rate of 8ml/h, MgSO4 200mg/ml (1ml/h) and lidocaine 1% (10mg/ml) in rate of 5ml/h. Also, sevoflurane to MAC 0.6 was used. At the end of the surgery the patient was smoothly extubated, after giving neostigmine 2.5mg and 1mg Atropine. Vital signs remained stable in postoperative monitoring and pain score in Visual Analogue Scale - VAS was 4 in the first hour after surgery. Metamizole sodium 2.5g was given prior discharge from recovery room. On the first day after surgery VAS pain score vas 2, Ketoprofen 160 twice a day and Paracetamol 1g three times a day were given.

Discussion

Having patients with positive allergic reaction is a challenging issue. Patients could have an allergic reaction to medications, such as antibiotics, muscle relaxants, opioids, sedatives etc. If a medical professional administers anesthetic medications to a person who is allergic to them, they will develop anaphylaxis. Anaphylaxis during anesthesia occurs in 1 in 200,000 cases (3). Anaphylaxis is a life-threatening situation. Anaphylaxis initiates the body to release chemicals which can initiate anaphylactic shock. The patients who overcame anaphylactic shock successfully, can develop cardiovascular, respiratory and cognitive disorders after the recovery. It is essential to prevent these events, especially in elective operations and investigations. Each patient has a unique approach and should be prepared very thoroughly.

Conclusion

We found that there are very often patients with allergy positive tests. We take these reactions very seriously and whenever we have these patients, we prepare anesthesia protocols in advance. There is not a general rule for all the patients. What approach we will choose, depends on operation, medicaments that are available at that moment, and consensus of the patient for anesthesia - acknowledging all the difficulties, and accepting the operation and anesthesia protocols that he will have to challenge (4,5).

Authors' contribution

Our goals are to use new not used previously medications like cis-atracurium, which we hope will be started to use very soon, or performing non-opioid anesthesia in allergic reactions on opioids, also as much as possible to use regional anesthesia whenever it is possible. It is our opinion that sharing our problems and demonstrating our solutions can be usefully used in overcoming our problems.

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CASE SERIES *UDK: 616.711.1-002:616.231-089.819.3*

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DIFFICULT INTUBATION IN CERVICAL SPINE INJURY PATIENTS WITH ANKYLOSING SPONDYLITIS: SINGLE-CENTER EXPERIENCE

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Abstract

Introduction: Airway management in patients with ankylosing spondylitis (AS) poses a challenge due to a limited spinal range of motion and mouth opening. This challenge is further exacerbated in instances where neck injuries result in neurological deficits. The method of choice for airway management in such cases is awake intubation using a fiberoptic bronchoscope. However, this approach can be uncertain, necessitating multiple attempts, which can be an uncomfortable experience for the awake patient.

Case Series: We studied 17 patients with AS who were operated on, at the Institute for Orthopedics "Banjica" due to cervical spine injury and consequent quadriplegia. All patients had a difficult airway. Mallampati grades were III-IV, and on a Wilson scale of 5 or more, there was rigid cervical spine stiffness, with varying involvement of the temporomandibular joint, inter-incisor gap below 3.2cm, and thyromental distance below 5.1cm. Patients were nebulized with 2% lidocaine, and a bite blocker was placed. They were sedated while maintaining spontaneous breathing. Awake nasotracheal fiberoptic intubations were performed in a semi-sitting position. After confirmation that the intubation was successful, intravenous induction was performed, and anesthesia was maintained with sevoflurane and remifentanil. After the surgery, the patients were transferred to the Intensive Care Unit for postoperative ventilation. Epistaxis occurred in 6 patients, with no other acute complications.

Conclusion: Awake fiberoptic intubation is a complex and risky procedure, especially in cases of cervical spine fracture where neurological deterioration is a possibility. Adequate topical anesthesia and sedation can provide a calm patient without coughing and vomiting.

Key Words: *Ankylosing spondylitis, Difficult airway, Intubation, Spine injury.*

Introduction

Ankylosing spondylitis (AS), alternatively known as Morbus Bechterew, is a chronic and progressive inflammatory seronegative arthropathy. The disease usually originates in the pelvic joints before expanding to the spine and affecting the spinal column region's joints, intervertebral discs and ligaments. In advanced stages, it can spread to other joints, including the hip and

shoulder, and eventually lead to ossification of all connective structures and ankylosis of the joints, resulting in immobility of the spinal column that adopts a "bamboo" appearance (1,2).

Managing the airway of patients with ankylosing spondylitis can be challenging due to the reduced range of motion in the spine and limited mouth opening. A neck injury can further complicate the situation, resulting in a neurological deficit. The preferred method for airway management in such cases is awake intubation using a fiberoptic bronchoscope (3). Nevertheless, the procedure can often be uncertain and require multiple attempts, causing significant discomfort for an awake and injured patient.

We present a series of cases of advanced ankylosing spondylitis where patients underwent surgery due to cervical spine injury, with an emphasis on the challenges of establishing an airway. This study excluded patients with AS who were admitted for elective total hip or knee arthroplasty or corrective spinal surgery.

Case Series

We studied patients with AS who were admitted to the Institute of Orthopedics "Banjica" due to cervical spine injury in the period from January 2019 to December 2023. After clinical and radiological assessment, operative treatment was indicated in 17 patients due to cervical spine injury and consequent quadriplegia.

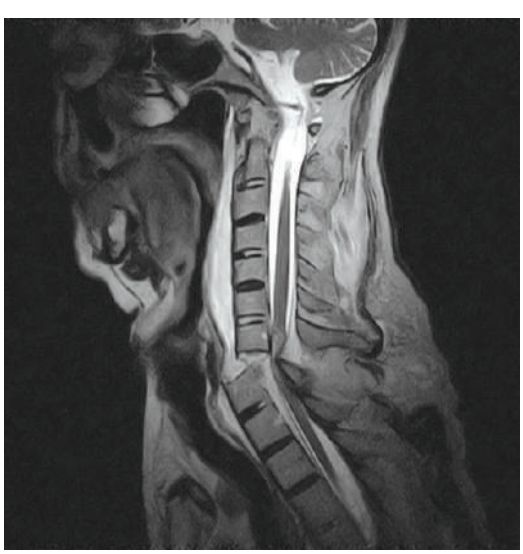

Figure 1. Magnetic resonance imaging showing C7/Th1 fracture dislocation.

Anesthesiologic evaluation revealed that all patients had a difficult airway. Mallampati grade was III-IV, and the Wilson scale was five or more; rigid cervical spine stiffness, varying temporomandibular joint involvement, inter-incisor distance less than 3.2cm, and thyromental distance less than 5.1cm. These measurements concluded that standard intubation with the Macintosh laryngoscope is not possible. The anesthesia plan included the topical application of local anesthetic on the oropharyngeal and nasal mucosa, moderate intravenous sedation, and awake intubation with a fiberoptic bronchoscope. Patients were inhaled with 10% lidocaine, and a bite

blocker was placed. They were sedated with intravenous boluses of midazolam (0.02mg/kg) and fentanyl (1μg/kg) while maintaining spontaneous breathing. Awake nasotracheal fiberoptic intubations were performed in a semi-sitting position. Seven patients required multiple tube placement attempts. After confirmation that the intubation was successful, intravenous induction with propofol (2mg/kg) and rocuronium (0.8mg/kg) was performed. Patients were carefully turned into the prone position. Anesthesia was maintained with O2: Air 50:50, sevoflurane and remifentanil. After the operation, the patients remained intubated, sedated, and transferred to the Intensive Care Unit, where they were connected to mechanical ventilation. Epistaxis occurred in six patients, and there were no other acute complications.

Discussion

Ankylosing spondylitis occurs in young people between 20 and 30, with a higher incidence in men. About 90% of the patients suffering from AS have a positive HLA-B27 allele (4). Apart from the spine, arthritis can affect the knee, hip, shoulder, heart, eyes and lungs (5). Cervical spine fractures in AS patients are more than 50% higher than for other parts of the spine (1). The mechanism of injury is usually low-energy trauma, such as hyperextension. A detailed and urgent neurological and radiological examination is mandatory. The surgery typically involves fracture reduction with an anterior and posterior vertebral fusion of the cervical spine (2).

Airway management in patients with ankylosing spondylitis presents a real challenge for anesthesiologists due to the reduced range of motion of the cervical spine and limited mouth opening. Additionally, the condition is aggravated by the presence of comorbidities, such as restrictive pulmonary ventilation disorder and pulmonary fibrosis (6).

The cervical spine in AS could be involved in different ways, from the minor functional restriction of movement to complete ankylosis of the neck (7). In more severe cases, the sniffing position is impossible due to the proximity of the chin and chest. Forceful attempts at extension should be avoided due to possible neurological deterioration (8).

Involvement of the temporomandibular joint occurs in over 40% of the patients, which can lead to limited opening of the mouth and difficulty in inserting the laryngoscope (9,10).

Anesthesiologists should perform a preoperative airway assessment. The Mallampati test and the Wilson scale are the most often used for evaluation. The Mallampati test observes the visibility of the oral structures with the mouth maximally open and the tongue maximally protruding, with the head in a neutral position (11), which is almost impossible in patients with AS. The Wilson scale is the most comprehensive screening scale, including the most risk assessment variables. It includes a detailed examination of the mouth and teeth (distance between the upper and lower incisors; subluxation, size and position of the teeth), examination of the mandible (anterior and posterior depth of the mandible; thyromental distance, retraction-recessive mandible), examination of the neck (sternomental distance, circumference and mobility of the neck,) and a positive history of difficult intubation and body weight over 110kg, i.e. BMI greater than 30 (12).

The thoracic spine tends to curve forward over time. The movement of the costovertebral joints is also limited, which affects breathing by limiting the respiratory volume and reducing the vital capacity, so breathing depends mainly on the function of the diaphragm (13). Fibrosis is a

common pulmonary phenomenon localized in the apices of the lungs. All these changes lead to a restrictive disorder of pulmonary ventilation, increasing the risk for pulmonary complications and the need for postoperative mechanical ventilation (14).

In spine surgery, where the patient is in a prone position, laryngeal masks are not acceptable (4,15). Video laryngoscopy sometimes allows visualization of the glottis but does not increase the success rate of tube placement in the trachea (16). Awake fiberoptic intubation is the safest and often the only option for tracheal intubation. It is essential to provide adequate sedation, with minimal respiratory depression, to preserve the patient's cooperation and spontaneous breathing during airway manipulation. In order the intubation to be successful with minimal sedation, it is necessary to anesthetize the upper airways. Applying a local anesthetic to the mucous membranes weakens the laryngeal reflex, thus protecting the upper respiratory tract from regurgitation and coughing. This creates an optimal condition for intubation and improves patient's comfort (6,8,17,18).

Nasotracheal intubation provides access for various procedures, aids in managing difficult airways, and is beneficial for patients with cervical spine issues or requiring prolonged intubation (19). Based on all the circumstances described, we chose awake nasotracheal intubation with topical mucosal anesthesia.

Conclusion

A trained anesthesia team is required for awake fiberoptic nasotracheal intubation. This procedure is very complex and risky in conditions of cervical spine fracture due to the possibility of additional neurological damage. Adequate local anesthesia and sedation make the patient calm, without coughing or vomiting. Because it is a cervical spine injury with consequent quadriplegia, these patients require long-term mechanical ventilation and often permanent tracheostomy. Despite surgical stabilization and significant team efforts, neurological recovery is questionable and uncertain.

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KABUKI SYNDROME – A CHALLENGE FOR THE ANESTHESIOLOGIST: CASE REPORT

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Abstract

Introduction: Kabuki Syndrome is a rare congenital disease with characteristic phenotypic appearance that includes arched eyebrows with sparseness of the lateral one – third, long palpebral fissures, eversion of the lateral third of the lower eyelid, a short columella with a depressed nasal tip and prominent ears. Other comorbid conditions include seizers and hypotonia, growth impairment, congenital heart diseases, endocrine involvement and renal abnormalities, as well as developmental delay and intellectual disability. The aim of this case was to describe the perioperative management of a child with Kabuki Syndrome and to discuss the potential problems in anesthesia.

Case Presentation: An 11 months old male child was admitted to the Clinic for Pediatric Surgery for elective operation for right-sided inguinal hernia. The patient was with growth delay (weighted 4.5kg), with hypotonia, without the ability to sit independently, nor to stand upright. Occasionally he was able to control his head movement, but he could not follow with his eyes. Echocardiography showed ASD secundum with L - D shunt without hemodynamic reflection. His antiepileptic therapy was canceled one moth earlier by his pediatric neurologist. In the physical examination, significantly long palpebral fissures and thinness in the 1/3 lateral of the highly curved eyebrows were observed. He had eversion in his lower eyelids. His nasal septum was low, and his ears were low set. The induction was started with 0.5mg/kg lidocaine, 1mcg/kg fentanyl and 4mg/kg propofol. Mask ventilation was easily performed and 0.6mg/kg rocuronium was given intravenously. The patient was intubated with a 3.0 cuffed tube using video laryngoscope. Caudal block was performed after the induction with 0.5ml/kg bupivacaine 0.25%. The anesthesia was maintained with 4-6 mg/kg/hour propofol. No complications were reported in the postoperative period.

Conclusion: In perioperative management of the patient with Kabuki Syndrome, anesthesiologist should take under consideration the possible difficult intubation, neurological (seizure) and musculoskeletal (hypotonia) disorders, cardiac (CaA, ASD, VSD) abnormalities, respiratory problems (recurrent infections), urogenital (hydronephrosis, renal hypoplasia) abnormalities and a latex allergy and the risk of malignant hyperthermia.

Key Words: *caudal block***,** *general anesthesia, Kabuki Syndrome, pediatric anesthesia, perioperative management.*

Introduction

Kabuki Syndrome is a rare congenital disease that occurs with an incidence of 1:32000 live births in Japan and 1:80000 in the rest of the world (1). The patients' facial appearance with this syndrome resemble to the traditional make-up used in Japanese theater *Kabuki* and the term Kabuki make-up syndrome was suggested by Niikawa (2,3). Patients with Kabuki Syndrome have characteristic phenotypic appearance that include arched eyebrows with sparseness of the lateral one – third, long palpebral fissures, eversion of the lateral third of the lower eyelid, a short columella with a depressed nasal tip and prominent ears (Figure 1)**.** Also, patients with this syndrome can have a wide range of clinical presentation from deformities of the skeletal-muscular system, high palate, dental anomalies, short stature, cardiovascular anomalies, renal malformations, frequent pneumonias, otitis media and hearing loss. During surgical interventions, attention should be paid also to concomitant congenital anomalies.

The aim of this case was to describe the perioperative management of a child with Kabuki Syndrome and to discuss the potential problems in anesthesia.

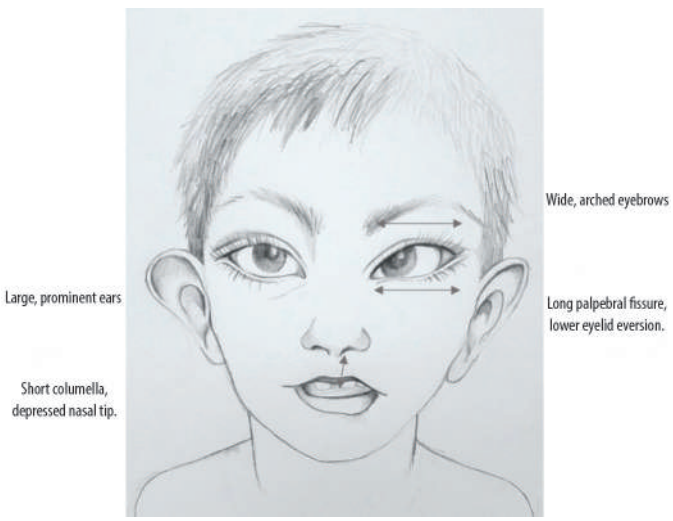

Figure 1. Characteristic phenotype appearance of patient with Kabuki Syndrome (This picture is taken from Boniel S, Szymańska K, Śmigiel R and Szczałuba K. Kabuki Syndrome - Clinical Review with Molecular Aspects. Genes 2021, 12(4), 468; https://doi.org/10.3390/genes12040468)

Case Presentation

An 11 months old male child was admitted to the Clinic for Pediatric Surgery for elective operation for right-sided inguinal hernia. According to the medical history received from the patient's mother, the patient was born weighing 2,330gr at the end of the eighth month of pregnancy with C–section. The patient had been diagnosed with Kabuki Syndrome when he was 6 months old as a result of the genetic tests made due to neuromotor growth deficiency and dysmorphism. A genetic mutation in the KDM6A gene in a hemizygous state was proven in the patient. This gene is responsible for coding of histone demethylase protein. KDM6A-associated Kabuki Syndrome is characterized by typical facial dysmorphia, skeletal abnormalities, hypotonia, intellectual and developmental delays, hypoglycemic hyperinsulinism and increased susceptibility to infections.

De novo mutations with X – linked dominant inheritance are the most often observed.

At birth, the patient was diagnosed with intraventricular hemorrhage and had been in incubator for 8 days. At the age of 4 months, the patient was hospitalized due to osteomyelitis of the right hip, and he was treated only with antibiotic therapy.

At the admission for elective inguinal hernioplasty, the patient was with growth delay (weighted 4.5kg), with hypotonia, without the ability to sit independently, nor to stand upright. Occasionally he was able to control his head movement, but he could not follow with his eyes. Hematological and biochemical investigations showed no abnormalities. Echocardiography showed ASD secundum with L - D shunt without hemodynamic reflection. His antiepileptic therapy was canceled one month earlier by his pediatric neurologist. In the physical examination, significantly long palpebral fissures and thinness in the 1/3 lateral of the highly curved eyebrows were observed. He had eversion in his lower eyelids (Figure 2). His nasal septum was low, and his ears were low set (Figure 3).

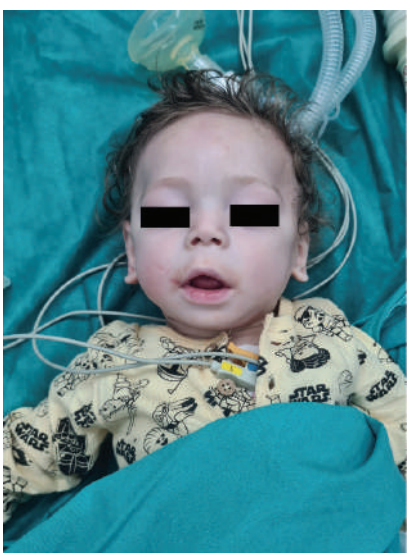

Figure 2. Long palpebral fissures and thinness in the 1/3 lateral of the highly curved eyebrows. But the columella in this case was not short.

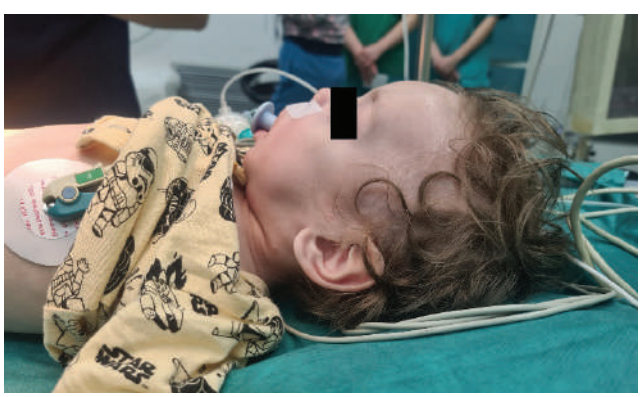

Figure 3. Low nasal septum, low – set prominent and mandibular hypoplasia

On the operation day, the patient was premedicated with 0.5mg/kg oral midazolam. Essential precautions were taken against the potentiality of difficult intubation. The patient was monitored, blood pressure was 108/70mmHg, heart rhythm was regular with rate 140 beats/minutes and oxygen saturation was 98% in the room air. Vascular access was secured, and the induction was started with 0.5mg/kg lidocaine, 1mcg/kg fentanyl and 4mg/kg propofol. After we were sure that we can ventilate the patient, 0.6mg/kg rocuronium was given intravenously, and the patient was intubated with a 3.0 cuffed tube using video laryngoscope. Caudal block was performed after the induction, and 0.5ml/kg of bupivacaine 0.25% was administrated. Anesthesia was maintained with 4-6mg/kg/hour propofol. The operation ended one hour after the induction, and the patient was awakened. No complications were reported in the postoperative period.

Discussion

Kabuki Make-up Syndrome or Niikawa-Kuroki Syndrome was first described in 1981 by the two Japanese physicians N. Niikawa (2) and Y. Kuroki (3). Kabuki Syndrome is a rare genetic disorder and results from de-novo mutations of the KMT2D gene on chromosome 12 (KMT2D - associated, autosomal - dominant KS type 1) or de-novo deletions of the KDM6A gene on the X - chromosome (KDM6A - associated, X - linked - dominant KS type 2) (4,5). Up to 75% of the patients carry the KMT2D variant, 5% of the cases carry the KDM6A variant, while for 20% of the cases the etiology remains unknown (6).

Although this syndrome is very rare, it is very challenging for anesthesiologists. In the preoperative assessment we must identify all risks and end-organ involvement. The first and the most important thing for the anesthesiologist is the potential difficult airway management. The patients with KS often (in 60% of the cases) have congenital tooth absence, malocclusion, abnormal dentition, widely spaced teeth, conical incisors, delayed tooth eruption and ectopic upper molars, high arched palate and cleft lip and/ or palate (7). Other features of this syndrome, that are also predictors for difficult airway management, are external ear dysmorphism (dysplasia, enlargement, external rotation, low set or a cup shape) and midface hypoplasia with or without mandibular hypoplasia (8). Equipment for difficult airway management should be available before anesthetic induction, including indirect video-laryngoscopy and different sizes of laryngeal masks. In 2000, Van Haelst et al. described unusual life-threatening complications (not previously reported) in two patients with Kabuki Syndrome that had distal airway abnormalities (9).

Symptoms from central nervous system may include hypotonia (difficulty in the ability to suck, chew and swallow, open mouth in rest), epilepsy, developmental delay (at mild to moderated degree, if there is absence of structural brain abnormalities) and intellectual disability. Ligamentous laxity may be present in up to 90% of the patients with KS on 6 to 14 years of age (10), and this may lead to cervical instability during intubation. According to some studies, epilepsy is present in 5 - 16% in the patients with KS, while others estimate up to 36% (11-13). Since hypotonia is a cardinal feature in patients with KS, anesthesiologists should carefully choose neuromuscular blocking agents. Succinylcholine may be contraindicated due to the risk of malignant hyperthermia, and patients with motor weakness and hypotonia might have increased sensitivity to non-depolarizing neuromuscular blocking agents. There are limited reports of anesthetic care for patients with KS in the literature, and there has been not registered increased sensitivity to non-depolarizing neuromuscular agents (14-16). But this effect should be considered in the cases with associated hypotonia. Also, a larger dose of non-depolarizing neuromuscular agents may be required if the patient is on anti-convulsant therapy.

Congenital heart diseases (CHD) are cardinal features in KS patients. In 2001, Digilio et al. reported in their study with 60 patients congenital heart disease in 58% (35 patients) (17). The three most observed cardiac defects in KS patients are coarctation of aorta (CoA – 23%), atrial septal defect, (ASD – 20%) and ventricular septal defect (VSD – 17%). In 2017, Digilio and the same group of authors reported CHD in 70% of the patients with KMT2D (MLL2) variant (in 19 of 27 patients) and only in one patient with KDM6A gene (18). CoA was again the most common CHD (21%) together with bicuspid aortic valve (21%). Digilio et al. suggest that CoA probably is due to underlying connective tissue diseases. According to these findings, echocardiography must be included in the preoperative evaluation. Attention should be paid to the detection of left-sided obstructive lesions in patients with KMT2D variants, and the right-sided lesions should be considered in patients with KDM6A variants (18).

In patient with pre-existing hypotonia, recurrent pneumonia, chronic aspiration and poor cough effort, it should be considered to use of short acting anesthetic agents, and after long surgical interventions postoperative monitoring for respiratory function is recommended due to increased risk of respiratory failure.

KS patients present urinary system abnormalities in up to 25 - 40% (6,19). Urinary tract malformations include hydronephrosis and ureteral duplication, while renal malformations include horseshoe kidney, renal dysplasia, renal ectopy, renal duplication, and renal insufficiency reported in one case (due to bilateral renal dysplasia at the age of 6 years) (20). Renal malformations are more present in KMT2D variant (21). Also, KS patients undergo surgery for undescended testis.

Endocrine disorders like growth hormone deficiency (22), pituitary hormone deficiency (23), adrenal insufficiency, diabetes insipidus, hypothyroidism and hyperinsulinism with transient neonatal or infantile hypoglycemia (24), have been reported in patients. Cardinal feature present in the patients with KS is short stature as a direct result of GH deficiency. In long surgical interventions, intraoperative glucose monitoring is recommended for detecting and management of hypoglycemia.

In 2010, Teixeira et al. reported a case of a latex allergy in an 11-years-old patient with KS. The patient had a history of allergic reactions after small surgeries for removal of soft tissue lesions, and after preoperative skin allergic tests she was diagnosed with allergy to latex (25).

Emil Bosinci reported case series in 2022, using regional anesthesia in 4 patients with different syndromes, one of which was with KS. No complications were reported preoperatively. The patients were hemodynamically stable while maintaining excellent breathing pattern and without pain and postoperative nausea and vomiting (26).

Conclusion

In perioperative management of patient with Kabuki Syndrome anesthesiologist should take under consideration the possible difficult intubation, neurological (seizure) and musculoskeletal (hypotonia) disorders, cardiac (CoA, ASD, VSD) abnormalities, respiratory problems (recurrent infections), urogenital (hydronephrosis, renal hypoplasia) abnormalities and a latex allergy, as well as the risk of malignant hyperthermia.

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PYELOLITHOTOMY IN PATIENT WITH MUSCULAR DYSTROPHY: MUSCLE RELAXANT - FREE ANESTHESIA

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Abstract

Group of genetic conditions that cause the muscles to weaken, are known as Muscular dystrophies (MD). Over time, these inherited and hereditary diseases lead to an increased level of disability. MD is caused by interframe deletion/ duplication, missense or nonsense mutations in the genes responsible for the structure and functioning of a muscle. The increased disability, over time interfere with patient's everyday life and may affect patinet's vital functions. There are many kinds of muscular dystrophy, each of them caused by a different mutation, but the most frequent of them in variety, have something in common, such as begging in childhood, mostly in boys. On the other hand, there are types that don't manifest until adulthood. There is no well-known and accepted cure for monotherapy for muscular dystrophy, but medications and multimodal treatment can help in facilitating symptoms and can slow the course of the disease.

The main sign of muscular dystrophy is progressive muscle weakness. Specific signs and symptoms begin at different ages and in different muscle groups, depending on the type of muscular dystrophy. Signs and symptoms usually include frequent falls, difficulty rising from a lying or sitting position, trouble running and jumping, waddling gait, walking on the toes, large calf muscles, muscle pain and stiffness, learning disabilities and delay in growth and development.

This case report is about 43-years-old male patient, diagnosed with a type of muscular dystrophy and right kidney nephrolithiasis, admitted for a classic pyelolithotomy.

Key Words: *muscular dystrophy, muscle relaxant, pyelolithotomy.*

Introduction

Muscular dystrophies are a group of genetic diseases which cause progressive degeneration of skeletal muscle along with weakness (1-3). Different types of muscle diseases are associated with different mutations which interfere with the function of genes that are necessary for muscle contraction and function. Duchenne's and Becker's muscular dystrophies are caused by a mutation in the DMD gene, which codes the dystrophin, a protein included in myocyte's protection during movement. These types of changes may be an interframe deletion/ duplication, missense or nonsense mutations, but, commonly, all of them are inherited from the parents. Much less often, they may occur spontaneously, named as de-novo mutations (1). Even though epidemi-

ology of MD says that they have prevalence rates between 1 and 10 per 100,000 population, we have to mention that this prevalence is rising and can be present in patients for anesthesia. This group of patients has to be evaluated by the anesthesiologist, especially for complications that may happen because of the muscle disorders. These people may experience weakness of the musculature with reduced strength of the respiratory muscles and the possibility of increased sensitivity to drugs with a neuromuscular mechanism of action, which predisposes them to complications, both during the procedure itself and the recovery period. Complications can be related to the anesthesiologic treatment itself (drugs which are commonly used during anesthesia), and the most often they affect cardiovascular and respiratory system. Recovery period may be followed by difficulty in movement and walking, which leads to increased risk of traumatic events, such as falling and injuries (1). Introduction and conduction of anesthesia have to be precisely administered in the patients with muscular dystrophy, especially considering the fact that the muscle relaxants, directly affect neuromuscular junction and muscle contraction. Preoperative, a detailed neurological assessment is required in order to better insight the risk during surgery and anesthesia. It is necessary to confirm the diagnosis if possible, as well as to determine the degree of disease progression in each patient (2). The preoperative management also requires respiratory and cardiovascular evaluation due to the possibility of concern of both. The assessment of respiratory function should include accurate medical documentation, physical examination, lung radiography, evaluation of sleep-disordered breathing, as well as measurement of respiratory function and cough efficiency (3). In all patients, it is necessary to have an electrocardiogram and an echocardiogram performed before anesthesia or sedation if this has not been done in the previous 12 months (4).

Case Presentation

Our patient was 43-years-old male, 70kg by weight, height of 165cm, smoker, with diagnosed muscular dystrophy, according to molecular genetic analysis, which has shown 60% deletions and duplications to the Dystrophin gene.

He was admitted to our Urology department, one week ago, with pain in his right lumbar quadrant, and he was diagnosed with nephrolithiasis. The patient was posted for right nephrolithotomy. According to the already mentioned history of muscular dystrophy, the patient was induced and maintained with TIVA. Previously, we had an insight into his respiratory function, which was unaffected at that moment, without absolute cardiologic contraindication for surgery. The patient did not have any allergies to food and medicaments, using no chronic therapy, laboratory well arranged. Before induction, his vital parameters were monitored, his blood pressure was 130/70mmHg, heart rate 60/min and saturation 98% without oxygen mask. After preoxygenation for 3 minutes with 8L oxygen, the patient was premedicated with 2mg Midazolam i.v., 0.1mcg Fentanyl and inducted to general anesthesia with 150mg Propofol i.v. bolus. TIVA was maintained with continuously use of Remifentanil 0.05mg/kg and Propofol 0.05mg/kg/h. The patient was intubated without use of muscle relaxant, with video laryngoscope and there was placed ETT number 8. After induction and intubation, we had stable parameters, with a slight decrease in blood pressure, which was 100/65mmHg, no change in heart rate and 100% saturation. The stability of parameters was maintained throughout the operation, and parameters were in rank 100-130mmHg for systolic pressure and 60-80 mmHg for diastolic. Heart rate was about 57-60 beats per minute and blood oxygenation 99-100%, with monitored capnography which showed etCO2 29. Intraoperatively, we administered ampoule Dexason 8mg i.v., with ad-

equate gastroprotective therapy with Famotidine 20mg and Metoclopramide 10mg, non-opioid analgesia was provided with Acetaminophen 1g i.v. Fluid replacement was with 1500ml NaCl 0.9%. Three hours later, surgery was done, the patient awakened and was transported to the recovery room, all well and pain free. Postoperative pain management was with NSAIL, antibiotic, gastroprotective and anticoagulant therapy.

Discussion

Difficult intubation, prolonged duration of neuromuscular block, impossibility of extubating due to muscle weakness and postoperative ventilation, potential rhabdomyolysis and arrhythmias when exposed to halogenated volatile anesthetics and depolarizing muscle relaxants, are all anesthetic worries and possible events (4). In the case of motor neuron and peripheral nerve diseases, the use of volatile anesthetics is possible, while the use of succinylcholine is absolutely contraindicated (12, 25). In patients with a disorder of the neuromuscular junction general anesthesia maintained with volatile anesthetics is considered safe, until MAC is less than 1. Using inhaled anesthetics and succinylcholine can be highly risky for malignant hyperthermia or acute rhabdomyolysis in all previously mentioned patients (5). Avoiding the use of succinylcholine and halogenated anesthetics in these patients is general recommendation.

Nondepolarizing neuromuscular relaxants may show a prolongation of neuromuscular block, no matter of their short activity. There are several reports that recommend avoiding these relaxants whenever possible (6). If their use is necessary, then it is preferable to reduce the doses and use TOF (train-of-four) monitoring (7). Reversion of neuromuscular block, if used, is also challenge, according to the fact that anticholinesterase drugs are not recommended in patients with MD, due to possibility to predicate hyperkalemia, the use of sugammadex as an antidote to rocuronium may be beneficial, according to reduced risk of postoperative residual muscle paralysis. The combination of rocuronium and sugammadex can replace the use of succinylcholine in rapid sequence intubation of patients with neuromuscular dystrophies (8).

Conclusion

Due to the rarity and peculiarities associated with MD, there is no established superior anesthetic technique. The approach will always be guided by the type of surgery and clinical status of the patient, with the primary target being greater patient's safety. Total intravenous anesthesia with propofol and remifentanil administered by continuous infusion without neuromuscular blockers is a safe and effective option for MD patients.

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CASE REPORT *UDK: 616-056.7:616.22-072.1]-053.31*

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AIRWAY MANAGEMENT IN 7-WEEKS-OLD INFANT WITH PIERRE ROBIN SYNDROME AND CONGENITAL PYLORIC STENOSIS

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Abstract

Pierre Robin Syndrome (PRS) is characterized by a sequence of events including mandibular hypotrophy (micrognathia), abnormal posterior placement of tongue (glossoptosis) and airway obstruction. Pyloric Stenosis, on the other hand, is the most common infant surgical condition which presents with episodes of projectile vomiting leading to dehydration and weight loss. Airway management in these patients is a true challenge for every anesthesiologist. The patient was 7 weeks old infant, weighted 3.1kg, admitted in Intensive Care Department for surgical repair of pyloric stenosis, previously diagnosed with Pierre Robin Syndrome at birth. Preoperative preparation, intravenous rehydration and electrolyte substitution was obtained. Video-laryngoscope was used for management of difficult airway. We had many attempts in visualization of the vocal cords, eventually we performed awake intubation with stylet uncuffed endotracheal tube size 3. Pyloromyotomy was performed. The maintenance of anesthesia was with Sevoflurane and bolus doses of Fentanyl as adjunct. The perioperative vital signs were within normal ranges. Awake extubating was performed. The facial malformation that appears in patients with Pierre Robin Syndrome makes visualization of the glottis extremely difficult to impossible. In cases where tracheal intubation is needed, awake fiberoptic intubation is recommended, but it can have many limitations. These two conjoined conditions present the quandary of safely managing an expected difficult airway in an uncooperative patient. With this case we can conclude that for children with Pierre Robin Syndrome, video-laryngoscopy should be considered as the first attempt intubation device both in the operating room and for emergent situations.

Key Words: *Difficult airway, Pierre Robin, pediatric, video-laryngoscopy.*

Introduction

Pierre Robin Syndrome is estimated to affect 1:8,500 live births. It is characterized by micrognathia, glossoptosis and U-shaped cleft palate. Pierre Robin sequence can be found in isolation or in association with other congenital anomalies (1).. Pyloric stenosis, on the other hand, is one of the most common infant surgical conditions with an incidence of approximately 1/400 live births. It is presented with persistent and frequently projectile episodes of vomiting, which in severe cases can lead to dehydration, hypovolemia and weight loss. This condition regarding difficult airway, especially conjoined with pyloric stenosis, is a real challenge for anesthesiologists (2).

Case Report

We present a case of a 7-weeks-old infant, weight 3.1kg, admitted in the intensive Care Department for surgical repair of pyloric stenosis (pyloromyotomy). The patient was diagnosed with Pierre Robin Syndrome and Pyloric Stenosis shortly after birth. Previously the patient was hospitalized two times with episodes of vomiting and diarrhea in the last three weeks and weight loss of approximately 20%. Preoperatively, echocardiography was obtained (normal findings, closed fetal communications), fiber nasal laryngoscopy was with the following findings: present cleft palate defect, omega shaped epiglottis and visible larynx. On admission the patient was hemodynamically and respiratory relatively stable with following parameters: Blood Pressure (BP) 100/74; Heart Rate (HR)152, SpO2=98%. Arterial Blood Gas Analysis showed Hypokalemia, Hyponatremia with metabolic alkalosis. The skin was pale with decreased turgor and elasticity. Nasogastric tube was placed, intravenous rehydration with electrolyte substitution were ordinated.

Figure 1 Patient facial appearance with Pierre Robin Syndrome

Figure 2

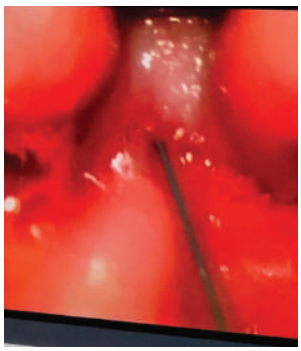


Figure 3

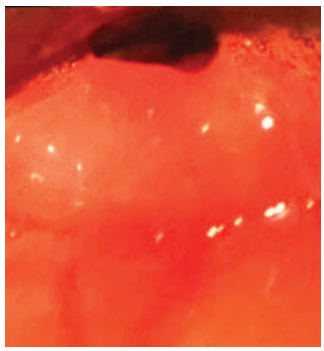


Figure 4

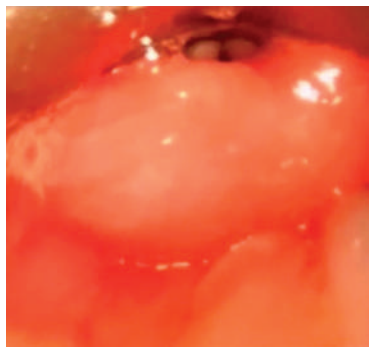


Figure 5

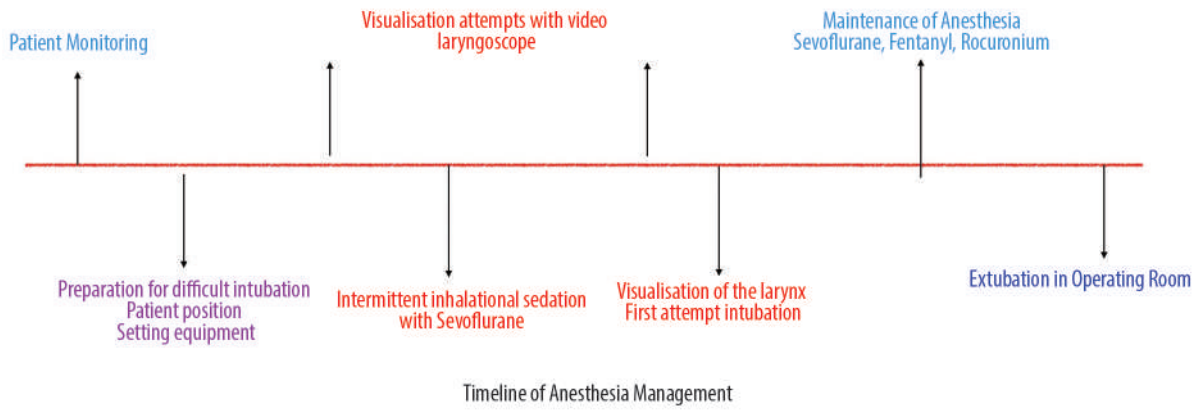
Figure 3, 4, 5: Steps in visualisation of the larynx

The patient was admitted at the Operating Room and preoperative preparation was obtained. The patient was placed in supine position and standard monitoring was placed (EKG, Blood Pressure, Pulse oximeter and temperature monitor). We used video-laryngoscope for difficult airway management. We inserted the video-laryngoscope blade, first we had difficulties in obtaining visualization of the larynx. After many attempts we performed awake intubation with 90° angled stylet endotracheal uncuffed tube, size 3. Sevoflurane was used for maintenance of anesthesia with 2μg/kg/fentanyl as adjunct. Acetaminophen 7.5mg/kg was given intraoperatively to supplement opioid analgesia. Perioperative fluid therapy with normal saline of 15ml/kg/hour was maintained. Urine output was measured (maintained > 1ml/kg/h) and air warmer was used to preserve normothermia. Perioperative vital parameters were within normal range. After fully emerged from general anesthesia, awake extubating was performed.

Discussion

Pierre Robin Syndrome (PRS) is characterized by a sequence of events including mandibular hypotrophy (micrognathia), abnormal posterior placement of tongue (glossoptosis) and airway obstruction (3). The incidence of Pierre Robin sequence varies equally in boy and girl infants4. The underlying abnormality is thought to be hypoplasia of the mandible prior to 9 weeks gestation, that leads to displacement of the tongue posteriorly and superiorly between the palatal shelves preventing their fusion. Individuals with this defect are known to have difficult airway, and often experience airway obstruction, especially in the supine position. The airway is believed to become easier to manage with increasing age.

Pyloric stenosis, on the other hand, is one of the most common infant surgical conditions with an incidence of approximately 1/400 live births. It is presented with persistent and frequently projectile episodes of vomiting, which in severe cases can lead to dehydration, hypovolemia and weight loss. This condition is associated with hypochloremic hypokalemic metabolic alkalosis and compensatory respiratory acidosis. Clinical presentation of pyloric stenosis is usually seen in infants between the second and eighth week after birth. Infants with pyloric stenosis are considered to be at risk for aspiration secondary to their gastric outlet obstruction in addition to the other recognized risks associated with anesthesia for this age group (2).



Pierre Robin Syndrome and Pyloric Stenosis as two conjoined conditions present the quandary of safely managing an expected difficult airway in an uncooperative patient.

The facial malformation that appears in patients with Pierre Robin Syndrome makes visualization of the glottis extremely difficult to impossible. In cases where tracheal intubation is needed, awake fiberoptic intubation is recommended, especially fiberoptic intubation through laryngeal mask (for children under 1 year old). However, there are several limitations like longer training and longer learning curve, expensive equipment and maintenance (5).

At our institution, commonly we use video-laryngoscope for managing difficult airway in pediatric patients. It this case we found it proper, with preparation of other equipment according to the difficult airway guidelines. Some studies showed that it is more difficult to insert an endotracheal tube (ETT) through video-laryngoscopy because the blade of a video laryngoscope has much greater curvature than one of a conventional direct laryngoscope (5). The challenges that we met were the following: time to proper visualization of the glottis, time to intubate and time to ventilate, conjoined with higher oxygen consumption and faster oxygen desaturation. The first challenge was the most difficult, the time for proper visualization was longer than 120 seconds followed with many attempts. Meanwhile, intermittent ventilation with Sevoflurane for light sedation was performed. As soon as proper visualization was made, we inserted 90° angled stylet ETT on the first attempt without any difficulties. Correct placement of the ETT was further confirmed by auscultation and end-tidal CO2 detection. Because of the many attempts, we faced a problem regarding soft tissue trauma with minor edematous changes which we managed with intravenous application of methylprednisolone 1mg/kg perioperatively. After fully emerged grom general anesthesia awake extubating was performed. The patient was stable in the postoperative period, with stable vital parameters, no significant changes or problems with breathing, normal SpO2 during whole period in the ICU department. With this case we can conclude that for children with Pierre Robin Syndrome, even though fiberoptic intubation is recommended as the first choice in difficult airway management, it regards many limitations, and video-laryngoscopy should be considered as the first attempt intubation device both at the operating room and for emergent situations (6).

Conclusion

Patients with Pierre Robin Syndrome with the variety of complexity and intensity of concomitant problems can have a destructive impact on the child. Even after transitioning home, breathing and feeding problems may cause substantial distress to both the involved infants and their families. There are many underlying syndromes, both cardiological and neurologically associated with PRS. In one study it is shown that the mortality rate is 10% in patients with PRS in presence of neurological anomalies (8).

The cleft palate repair in this patient was recommended for later surgical intervention when the patient turns 12 months. Some studies showed that patients with Pierre Robin Syndrome had worse speech outcomes after cleft palate repair (7). A multidisciplinary approach should be obtained in all infants born with this condition, including genetic testing and examination of neurological anomalies. On the other hand, when diagnosed early, pyloric stenosis has an excellent prognosis. In this case, the patient was discharged after 5 days in good condition, well hydrated with maintained feeding tolerance.

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CASE REPORT *UDK*: **616.24-076-032:611.233**

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CLINICAL CASE EVIDENCE SHOWING IMPORTANCE OF TRANSBRONCHIAL BIOPSY IN DIAGNOSING LUNG CANCER

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Abstract

Introduction: Transbronchial lung biopsy is the method of choice for diagnosis of pulmonary lesions and can be used for diagnosis of a wide range of pulmonary diseases such as interstitial lung diseases, vascular diseases, small airway diseases, malignancies such as disseminated form of the alveolar cell carcinoma and infections.

Method: In this article, a clinical case presented in our department is studied. The case was consulted with online database literature (PubMed) related to problems of the diagnosis process and treatment of the pathology. The patient was treated for pneumonia at his regional hospital, but after having no improvement, he was referred to our service for further laboratory and imaging examinations.

Results: CT-Scanner of the chest suggested carcinomatous lymphangitis, without excluding primary origin and multiple lytic lesions of the skeleton. Thoracentesis of pleural fluid resulted exudate and cytology suggested a (adeno) carcinomatous process originating from upper gastro-intestinal tract, but there was no sign of malignancy in fibro-gastro-duodenoscopy. On bronchoscopy there was not seen any infiltration of airways, but after undergoing again the endoscopic procedure where transbronchial biopsy was taken. Histopathological result showed Mucinous lung adenocarcinoma**.** Oncologist consultation concluded Stage IV A Lung Cancer and suggested palliative care due to stroke complication.

Discussions: Data suggests higher sensitivity of transthoracic biopsy compared to transbronchial approach, especially when lesions are peripheral and less than 2cm, but with lower safety profile. As the success of a diagnostic test should result from a proper balance between accuracy and procedure-related complications, transbronchial approach has been shown to have a better safety profile.

Conclusions: Compared with open lung biopsy, transbronchial biopsy has lower morbidity and mortality. Transbronchial biopsy is indicated in the following settings: neoplastic disease, suspected sarcoidosis or hypersensitivity pneumonitis, interstitial lung disease, pulmonary infection, or unusual and unclear lung disease.

Key Words: *lung cancer, diagnosis, transbronchial biopsy.*

Introduction

Lung cancer is one of the leading causes of cancer-related deaths. The increasing use of high-quality CT in daily medical practice has increased the number of lung lesions discoveries incidentally, mostly peripheral lung lesions. The gold standard for a diagnosis of lung cancer remains pathological data. Flexible bronchoscopy, transthoracic needle aspiration and surgical biopsy are also available, and transbronchial biopsy with a bronchoscope is the most generally accepted method for diagnosing malignant pulmonary lesions.

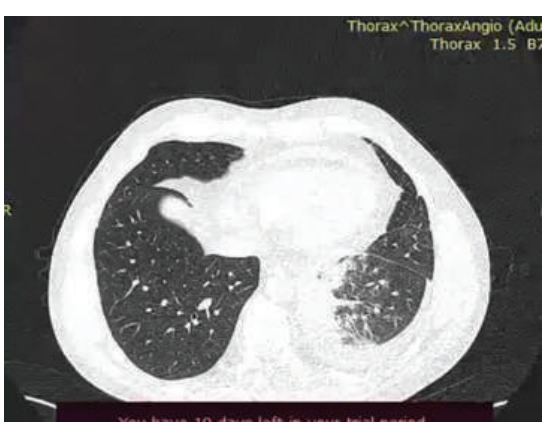
Transbronchial lung biopsy is the method of choice for diagnosis of pulmonary lesions and can be used for diagnosis of a wide range of pulmonary diseases such as interstitial lung diseases, vascular diseases, small airway diseases, malignancies such as disseminated form of the alveolar cell carcinoma and infections.

An increasing number of pulmonary lesions, particularly lung lesions that don't infiltrate bronchial airways, are identified with current technological advancements. Notably, the yield of traditional bronchoscopy for the diagnosis of peripheral lung lesions is low.

Methods and Results

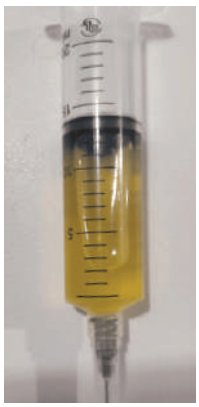
In this article, a clinical case presented in our department is studied. The case was consulted with online database literature (PubMed) related to problems of the diagnosis process and treatment of the pathology. The patient was treated for pneumonia at his regional hospital, but after having no improvement, he was referred to our service for further laboratory and imaging examinations.

Our 38-years-old male patient was diagnosed and treated as pneumonia at his regional hospital, but after having no improvement, he was transferred for further diagnosis at our hospital.



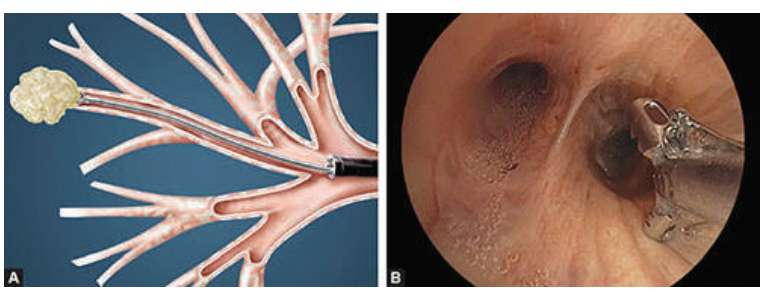
Computerized tomography suggested carcinomatous lymphangitis, without excluding primary origin and multiple lytic lesions of the skeleton. The radiologist suggested endoscopic examination.

Figure 1. CT images of lungs where carcinomatous lymphangitis was suggested.



Thoracentesis of pleural fluid resulted exudate and cytology suggested a (adeno) carcinomatous process originating from upper gastro-intestinal tract.

Figure 2. Pleural effusion sample taken at the emergency unit.



On bronchoscopy there was not seen any infiltration of airways. Fibro-gastro-duodenoscopy showed superficial gastro-duodenitis. Patient underwent again the endoscopic procedure where transbronchial biopsy was taken.

Figure 3. Endoscopic procedure where transbronchial biopsy was taken.

Histopathological result showed **Mucinous lung adenocarcinoma.**

During hospitalization, the patient started having difficulties speaking leading to aphasia. **Head CT** resulted with multiple ischemic lesions.

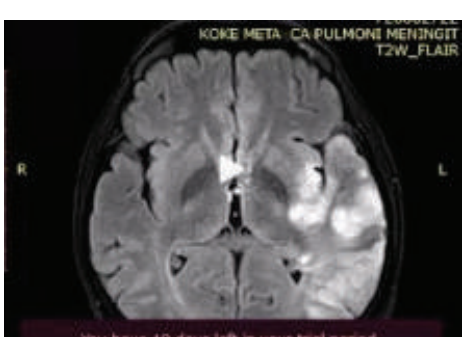


Figure 4. Head CT showed multiple ischemic lesions.

Neurologist and neuro-surgeon consultation: Ischemic stroke due to malignant disease.

Oncologist consultation concluded Stage IV A Lung Cancer and suggested palliative care due to stroke complication. The patient left hospital and passed away two weeks later at his home.

Discussion

Endoscopic bronchial procedures are used to visualize the tracheobronchial tree and obtain specimens of abnormal lesions. However, small and peripheral lung lesions are difficult to diagnose with these procedures, thus further improvement is desired in the diagnostic efficacy of bronchoscopy for lesions not affecting bronchial airways.

Data suggests higher sensitivity of transthoracic biopsy compared to transbronchial approach, especially when lesions are peripheral and less than 2cm, but with lower safety profile. As the success of a diagnostic test should result from a proper balance between accuracy and procedure-related complications, transbronchial approach has been shown to have a better safety profile.

Conclusions

Our clinical case enhances the importance of endoscopic examinations for the diagnosis of lung cancer. Transbronchial biopsy is very useful for taking samples from pulmonary lesions. Compared to open lung biopsy, trans-bronchial biopsy has **lower morbidity and mortality**. Transbronchial biopsy is indicated in the following settings: **neoplastic disease**, suspected sarcoidosis or hypersensitivity pneumonitis, interstitial lung disease, pulmonary infection, or unusual and unclear lung disease.

It should be mentioned that trans-bronchial biopsy is not always done without complications. And local anesthesia is mostly used for patients undergoing this procedure. Regarding to our case, patient did not have any complication during and after procedure.

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CASE REPORT *UDK 616.441-008*

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RARE CASE OF CONVERSION OF AUTOIMMUNE HYPOTHYROIDISM TO HYPERTHYROIDISM

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Abstract

Up to date, the literature data have presented various case reports of conversion from hyperthyroidism to hypothyroidism, but conversion from hypothyroidism to hyperthyroidism is very rare. In this context we present a rare case of primary hyperthyroidism which converted spontaneously to hypothyroidism and 18 years later hyperthyroidism and thyrotoxicosis were once again confirmed. Hashimoto thyroiditis is an autoimmune disease. Thyrotoxicosis is a clinical state of inappropriately high levels of circulating thyroid hormones.This case report confirms that although it is very rare, after long condition of hypothyroidism, immunological shift is possible with development of consecutive hyperthyroidism with stimulating auto antibodies.

Key Words: *autoimmune hyperthyroidism, autoimmune hypothyroidism, thyrotoxicosis.*

Introduction

Autoimmune thyroid diseases are one of the most common autoimmune diseases in the world affecting 2-4% of women in the world and 1% of men (1,2,3).

Graves' disease and Hashimoto's thyroiditis are the most common autoimmune thyroid conditions. Hyperthyroidism following hypothyroidism is a rare phenomenon. Hypothyroidism was once thought to be a permanent state requiring lifelong replacement therapy, but there are increasing numbers of cases in the literature whichoppose this postulation.

Both have complex etiology with complex pathogenesisinfluenced by a variety of environmental factors, as well as hereditary components which play a major role in all autoimmune diseases (4). Autoimmune thyroid disease can involve one or more types of thyroid antibodies. These include the thyroid stimulating hormone (TSH) receptor antibodies, which can be divided into stimulating or blocking types. Additionally, thyroid peroxidase antibody and thyroglobulin antibody are thyroid-specific antibodies commonly found in thyroid autoimmunity. It is already known that thyrotoxicosis may be followed by hypothyroidism. However, development of thyrotoxicosis after a long period of hypothyroidism is not a common phenomenon (5).

Case Report

We present a 48-years-old femalewith 3months history of fatigue, heat intolerance, sweating, weight loss, tremor and tachycardia. Ultrasound of the thyroid gland presented diffuse enlargement, twice the normal size. Clinical suspicion of primary hyperthyroidism was made and then confirmed by standard laboratory analysis. Treatment was initiated with propylthiouracil of 100mg three times a day. For the next twelve monthsthe patient was scheduled for regular follow check-ups. Total T4 decreased and treatment with propylthiouracil was also reduced subsequently gradually. One year after, the laboratory results presented decreased total T4 values with increased TSH levels. Treatment was immediately stopped. The patient was left without therapy for observation. Spontaneous conversion of hyperthyroidism to hypothyroidism was confirmed. Increased levels of antithyroid antibodies were also detected, both anti-thyroglobulin and anti-peroxidase. Hypothyroidism due to Hashimoto thyroiditis was confirmed and adequate treatment with levothyroxine was initiated. The condition remained for 18 years after diagnosis.18 years after diagnosing this condition, the patient presented with symptoms such as weight loss, tachycardia and tremor. Laboratory analyses were performed and they were in favor of hyperthyroid state. Treatment was stopped and the patient was left for observation. After one-month, standard biochemical analysis was performed and decreased levels of TSHand increased levels FT3 which were again confirmed. Additionally, increased thyroid stimulating immunoglobulins was also detected. Hyperthyroidism relapse and T3 thyrotoxicosis was confirmed afterwards and treatment with propylthiouracil was initiated. Up to date, the patient is stable and the thyrosupresive therapy is still ongoing.

Discussion

In the presented case report initial hyperthyroid state spontaneously converted into hypothyroidism. The patient had been on thyroxine replacement therapy for approximately 18 years. During this period thyroid antibodies, in favor of Hashimoto's thyroiditis, were positive and TSH levels were in normal range due to the effects of levothyroxine.

The conversion of Hashimoto's thyroiditis to Graves' disease is documented in the literature, but such cases are rare and are postulated to be due to a combination of atypical destructive thyroiditis, and the development of antibodies associated with hyperthyroidism. It is also stated that autoimmune destruction initially produces a hypothyroid state, but the stimulatory effect of thyrotropin receptor stimulating antibodies (TSAb/ TSI) and thyroid destruction may alter and subsequently create a hyperthyroid state (6).

Other 2 studies regarding several similar cases propose that the damage to the thyroid tissue may act as the triggering factor for hyperthyroidism. This also involved the production of TSH receptor antibodies which changed effects from blocking to stimulating thusproducing a state of hyperthyroidism (7,8).

The pathogenesis of this conversion is not well explained in the literature due to its complex etiology, but there are different theories postulated behind this conversion.

The first similar case was described by Joplin and Fraser in 1959 and several others followed in the yearstocome (9,10,11,12). In 1990 Takasu *et al*. described a case series converting to Graves'

disease following previous Hashimoto's disease, and it was observed that those cases could be divided into three groups: a group of transient Graves' disease following hypothyroidism, a group of persistent Graves' thyrotoxicosis following hypothyroidism and a group of persistent hypothyroidism despite positive thyroid-stimulating immunoglobulins (13).

Our patient was diagnosed with hypothyroidism and achieved euthyroid state following treatment with levothyroxine. This hypothyroid state converted spontaneously after 18 years when hyperthyroidism was again confirmed. The precipitating factors are unclear. The percentage of conversion of hypothyroidism to hyperthyroidism is estimated to occur in 1.2% of patients according to the largest reported series in the literature (14).

One of the possible mechanisms for conversion is an environmental trigger in a genetically susceptible individual whichmay alter the thyroid gland by altering the balance in the activity of blocking and stimulating antibodies and the response of the thyroid gland to these antibodies (15).

Another theory is that thyroid damage from an autoimmune phenomenon initially causes thyroid hypofunction, but once thyroid tissue has recovered enough, it is stimulated by the stimulating autoantibodies and consecutive hyperthyroidism occurs (15). Some researchers are suggesting that this conversion between blocking and stimulating antibodies occurs in some patients after using treatment for Graves' disease and levothyroxine for hypothyroidism (16).

More recent studies show that patients can develop Graves' disease in the background of a hypothyroid state, and this conversion might be postulated secondary to a combination of atypical destructive thyroiditis and a switch of autoantibodies from blocking to stimulating ones (17). Also, it is noted that this phenomenon could occur at any time during the disease process even if patients have hypothyroid for decades (18).

Hashimoto thyroiditis (HT) preceding Graves' disease (GD) can be a subtype of autoimmune thyroiditis, as not all patients with HT convert to GD. According to some recent studies, HT preceding GD occurs more frequently than has previously been reported. The clinical characteristics do not necessarily match those reported in HT or GD, suggesting the need to be especially careful when determining treatment strategies (19).

Other findings suggest active surveillance of hypothyroid patients who require frequent reduction of levothyroxine during follow up and testing for TSH-R antibodies in these patients (20).

Occurrence of Graves' disease after primary hypothyroidism may not be as rare as previously thought. Diagnosis requires careful clinical and biochemical assessment. Otherwise, the case can be easily confused for over-replacement of levothyroxine. Different studies are suggesting measuring both anti-thyroid peroxidase (TPO) antibodies and TSH receptor antibodies (TRAB) in suspected cases.The underlying etiology for the conversion is not exactly known, but probably involves autoimmune switch by an external stimulus in genetically susceptible individuals (21).

According to some studies, the phenomenon of the conversion of one autoimmune thyroid disease to another, in addition to the scientific interest, is important for the practitioners, since a timely change in the diagnostic paradigm can significantly change the treatment strategy and affect the prognosis of disease, thus preventing the development of complications (22).

Conclusion

In conclusion, conversion of hypothyroidism to thyrotoxicosis is still an underestimated clinical feature for most clinicians.

This case demonstrates that although it is very rare, after long condition of hypothyroidism, immunological shift is possible with development of recurrent hyperthyroidism with stimulating antibodies.

Further research, however, is needed to establish the exact pathogenesis of this phenomenon.

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CASE REPORT *UDK*: **616-006.6-055.1**

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BREAST CANCER IN MEN: A CASE REPORT

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Abstract

Breast cancer in men is very rare with an incidence of 1 in 800 (1), but it can occur in the presence of gynecomastia and presents as intraductal carcinoma. Lobular carcinoma does not occur because these lobules are not developed in men. We present a case of a 69-years-old patient who, 1 month before examination, palpated a small lump in the right breast. Ultrasound, mammography and core biopsy of the lesion were performed, and intraductal invasive carcinoma of the breast was diagnosed.

Key Words: *core biopsy, intraductal carcinoma, mammography, men, ultrasound,*

Introduction

Physiology of the Breast Embryology: The rudimentary and totipotent glands of the breasts in males and females are identical at birth, composed of mammary lobules that are drained through milk ducts to the nipple. In boys during prepubertal period, testosterone levels increase leading to atrophy of the mammary parenchyma. Whereas in girls during the peri-pubertal period, there is an increase in estrogen levels which results in accelerated branching and proliferation of the milk ducts, while progesterone stimulates the formation of terminal ductal-lobular units (TDLU). If boys experience transient elevation of serum estradiol levels, there will be proliferation of subareolar ducts and stroma. This condition normalizes when testosterone levels begin to rise and reach adult normal values.

Normal Male Breast consists of skin, subcutaneous adipose tissue and atrophic ducts. Cooper's ligaments are absent. The development of lobules, which are provoked by estrogen and progesterone, is exceptionally rare. (Rarely, fibroadenomas, phyllodes tumors, invasive lobular carcinoma, as well as lobular carcinoma in situ develop.) (2).

Conditions associated with proliferation of stroma and milk ducts can occur in men, such as gynecomastia, invasive ductal carcinoma and ductal carcinoma in situ. The male breast is susceptible to the same pathological processes as the female breast. Large number of conditions are differentiated using mammography, ultrasound and even breast MRI. The initial modalities are mammography and ultrasound, and if there is suspicion of malignancy, breast biopsy is performed.

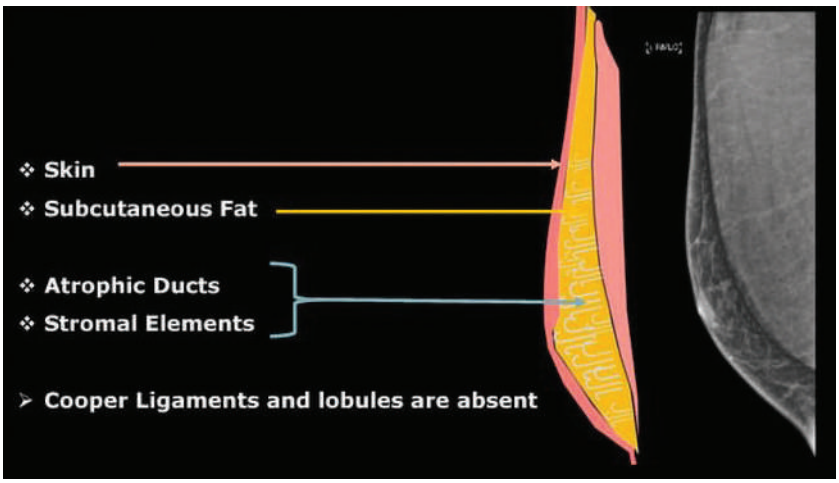

Figure 1. Anatomy Illustration of the Male Breast.

Breast cancer in men is extremely rare, representing about 0.25% of malignancies in men and 0.5%-1% (2) of all breast cancers (in both genders). The incidence of male breast cancer in the USA has increased from 0.85 to 1.3 per 100,000 men in the period from 1972 to 2000. The ratio of female to male cases is 100:1 in whites and 70:1 in blacks (4). Diagnosis of this type of cancer is often delayed due to men's lack of awareness and information about this condition to seek advice. The definitive diagnosis is made through histopathological examination, typically obtained via core biopsy. Benign breast neoplasms in men include angiolipoma, schwannoma, intraductal papilloma and lipoma. Additionally, conditions such as lymphadenitis, sebaceous cyst, diabetic mastopathy, fat necrosis, subareolar abscess, breast enlargement, venous malformations, hematoma, etc., can occur. Sometimes, these conditions may have similar radiological expression, but with the use of all radiological methods, a diagnosis can be reached. The definitive histopathological diagnosis is obtained after core biopsy.

Materials and Methods

We present a case of a 69-years-old patient with a lump behind the right nipple in the superolateral quadrant, which he noticed one month before. He was at that moment receiving therapy for prostate issues - Tamsulosin (brand name: Tamsulosin) Prostatitis Max Forte (has been taking it for the last 5-6 years). Two years ago, he underwent surgery to remove a left testicular Leydig cell tumor.

On inspection, a lump in the right breast was noted. Palpation reveals a hard consistency.

Mammography findings: Bilaterally, there are features suggestive of female-type breast parenchyma retroareolar. An oval shadow is demarcated towards 11 o'clock in the right breast. The left breast shows no focal densities. There are no pathological calcifications. Axillary lymph nodes are visible in both axillae.

BI-RADS 3. Core biopsy of the lesion is recommended.

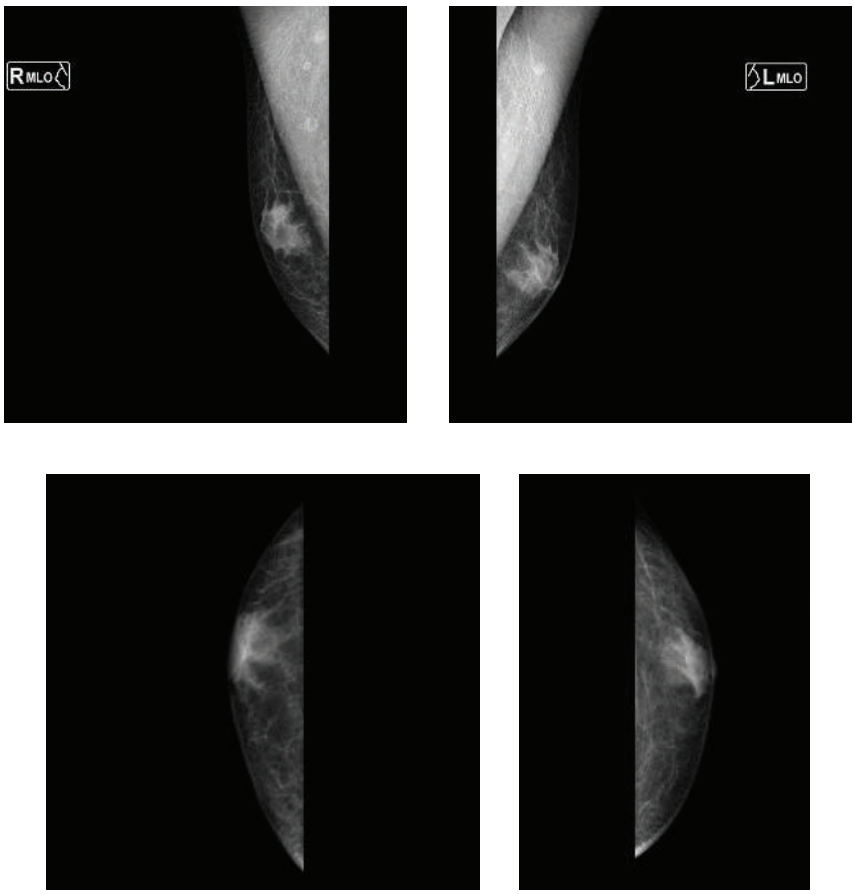

Figure 2. Mammography MLO and CC Projection - Gynecomastia with a small oval density on the baseline mammogram Xin the superolateral quadrant of the right breast.

Ultrasound findings: Bilateral axillary lymph nodes with normal morphology are observed. Bilaterally, there is poorly developed breast parenchyma retroareolar. On the right, at 0.5cm from the nipple towards 10 o'clock, a hypoechoic hypo-vascular change with dimensions of 0.76 x 0.45cm and EI 2.70 is visualized. The left breast shows no demarcated pathological echogenicity. BI-RADS 0. Recommendation: Biopsy of the change in the right breast is advised.

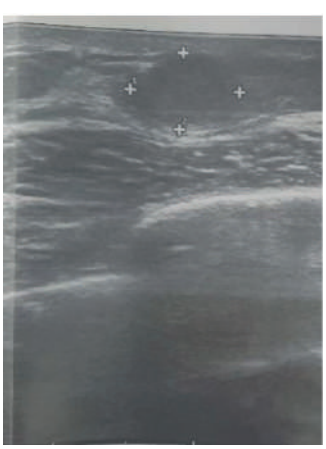

Figure 3. Ultrasound of the lesion in the right breast - Hypoechoic oval clearly demarcated lesion.

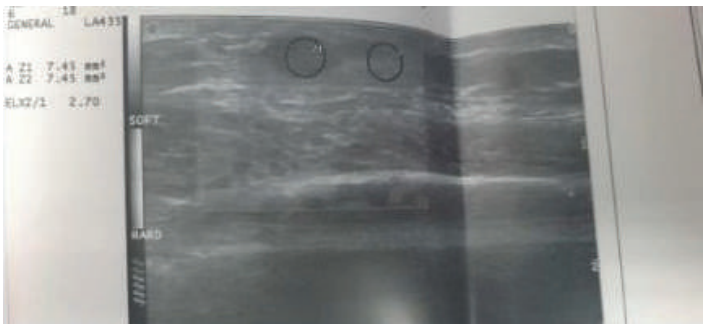

Figure 4. Elastography of the lesion showing a strain ratio of 2.70.

Core biopsy of the lesion in the right breast, measuring 0.45cm, was performed under aseptic conditions using a 14G needle, and 2 samples were taken for histopathological analysis.

Histopathological findings: Microscopically, the delivered material consists of fragments of male breast tissue, partly infiltrated by neoplastic tissue composed of atypical cells with moderate nuclear grade, arranged in solid nests. Additionally, the immunohistochemical analysis yielded the following results: mammaglobin (-), podoplanin (-), GATA3 (+), SMA (-). The findings are consistent with invasive breast carcinoma, NG2.

Discussion

Breast cancer in men, although rare, can lead to fatal outcomes. This condition may sometimes occur alongside gynecomastia. If there is a subareolar eccentrically positioned lump, it should be followed up with mammography and breast ultrasound. If there is suspicion of malignancy, biopsy should be performed. Conditions associated with proliferation of stroma and milk ducts, such as gynecomastia, invasive ductal carcinoma, and ductal carcinoma in situ, can occur in men. Patients with genetic mutations BRCA1-2 should undergo annual mammography screening.

Conclusion

Breast cancer in the male population does exist, albeit rare, but it should be considered when there is a lump in the breasts. There is a need to raise awareness among men about this condition, especially if there are additional factors such as gynecomastia or genetic mutations.

Increasing awareness among the male population about the existence of breast cancer can reduce morbidity and mortality from this disease through timely radiological evaluation.

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CASE REPORT *UDK 616.24-073.75*

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RADIOLOGICAL PRESENTATION OF A-V MALFORMATION IN LUNGS AS AN INCIDENT

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Abstract

Pulmonary arteriovenous malformation (PAVM) is rare, and it is often associated with Osler-Weber-Rendu syndrome. Clinical manifestations may be absent or present as chest pain, cough and hemoptysis. In our case, we are dealing with an asymptomatic patient. The diagnosis of this condition involves chest X-ray, CT scan of the chest, and in some institutions transthoracic contrast ultrasound. We present a case of 73-years-old patient with an incidental finding of pulmonary arteriovenous malformation.

Key Words: *AV malformation, chest radiograph, CT lung.*

Introduction

Pulmonary arteriovenous malformation (PAVM) is a rare condition characterized with bridging between an artery and a vein, which results with right-to-left shunt. This condition is most commonly a congenital anomaly of pulmonary arteries and veins. PAVM occurs in 20%-50% of patients with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome).

Besides being a congenital anomaly, this condition can also occur as a consequence of surgical interventions, trauma, infections, hepatopulmonary syndrome, congenital heart diseases and metastases. The diameter of the feeding artery is an important parameter in the treatment of these patients. Transcatheter embolization with coils or plugs is possible in feeding arteries with a diameter of 3mm or more. If such finding is incidentally discovered, it requires follow-up with an appropriate protocol.

Clinically, some patients may present with hypoxemia, hemoptysis and nodules in the lungs. Rarely, this condition is asymptomatic.

Etiology and Epidemiology

This anomality is quite rare, with the Mayo Clinic reporting an incidence of 4.3 cases per year. In one study analyzing 21,000 MDCT scans capable of visualizing even very small nodules, the prevalence was 1 in 2,600 individuals. This condition is more common in females, with a ratio of 1.5-1.8 times higher compared to males. It is the most commonly accompanied by Osler-Weber-Rendu syndrome.

AV malformations grow slowly and rarely spontaneously disappear.

Clinical Findings: Symptoms caused by AV malformations are insidious due to their slow growth. Dyspnea, especially on exertion, may be present for an extended period. In severe cases, dyspnea at rest in an upright position may occur. Cyanosis may be present to a significant extent. Occasionally, hemoptysis may occur, although it is rare for it to be massive.

Sometimes patients may have headache, dizziness, syncope, tinnitus, diplopia, breast pain and cough. These symptoms are not clearly understood, but may be associated with hypoxemia, polycythemia or paradoxical embolization of AV malformations.

Differential Diagnosis

AV malformations need to be separated from other radiological findings, such as extravascular changes: granulomas, inflammations, hamartomas, metastases, as well as vascular changes: mediastinal fibrosis with venous collaterals, arteriovenous collaterals, hepatopulmonary syndrome, serpiginous blood vessels in pulmonary hypertension, tortuous venous vessels, venous varices. For example, granulomas appear as nodular shadows with small arterial blood vessels but lack venous vessels. They tend to calcify, and satellite granulomas may be present around them which is important in differential diagnosis with AV malformations.

Material and Methods

We present a case of 73-years-old patient who underwent MDCT of the lungs due to visualization of a lobulated shadow right paracardial on preoperative chest radiography. The patient did not exhibit signs of dyspnea, bleeding, or any occlusive changes of the blood vessels. Laboratory analyses were within normal limits.

On the chest radiograph, a shadow was visualized in the paracardial right area with lobulated contours. The surrounding parenchyma appeared normal, and the hila were unremarkable.

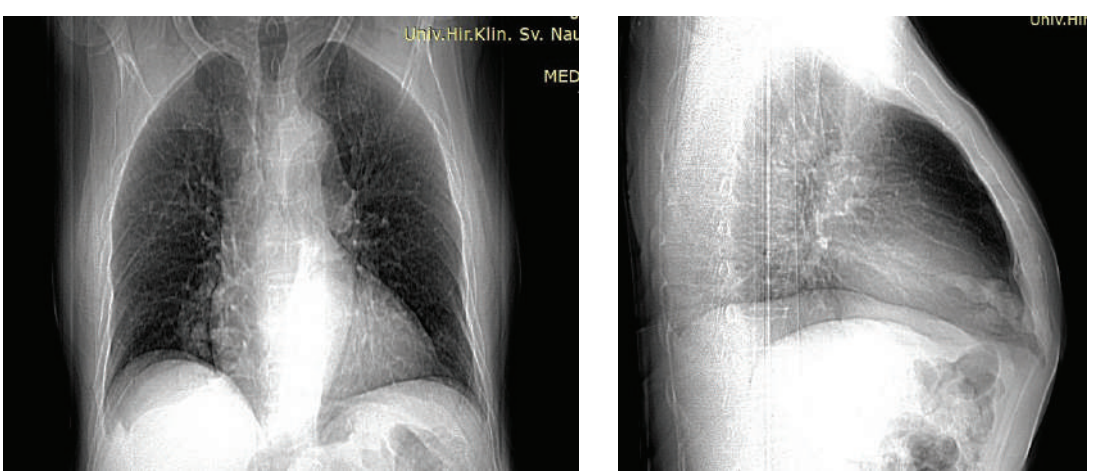

Image 1. Chest radiograph (PA and lateral view) showing a lobulated shadow in the right paracardial area.

On the performed lung MDCT in the arterial phase, a fistula connecting arterial to venous vessels is clearly demarcated, with bridging of the normal capillary bed between them. The arterial blood vessel measures 3.47mm in diameter and may be a candidate for coil embolization.

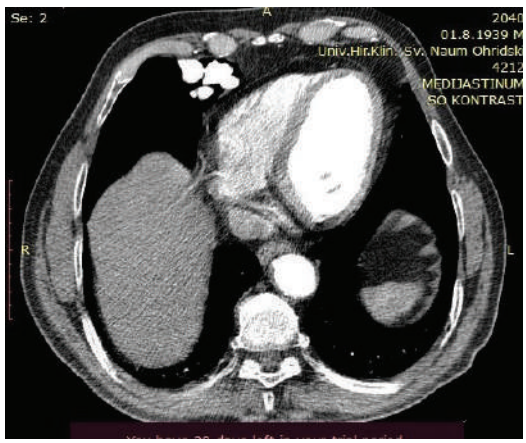

Image 2. Lung MDCT exam, axial section, arterial phase, showing blood vessels in the right paracardial area.

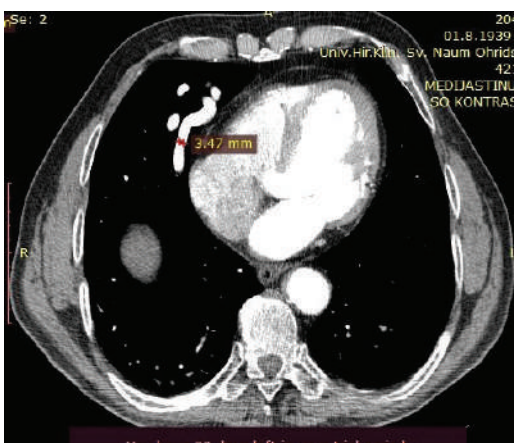

Image 3. MDCT of the lungs, arterial phase, showing the pulmonary artery with a diameter of 3.47mm.

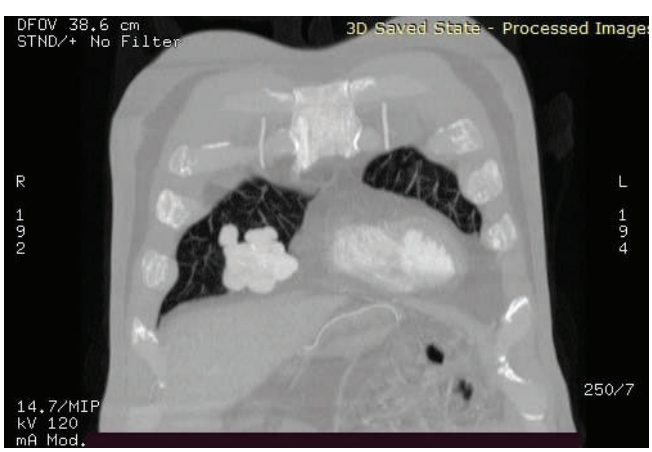

Image 4. MDCT of the lungs, contrast series in the coronal plane, showing a cluster of blood vessels.

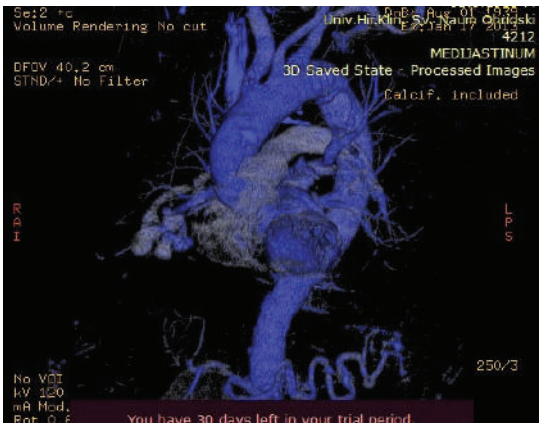

Image 5. Maximum Intensity Projection (MIP) reconstruction of the AV fistula at the level of arterial and venous blood vessels in the right lung.

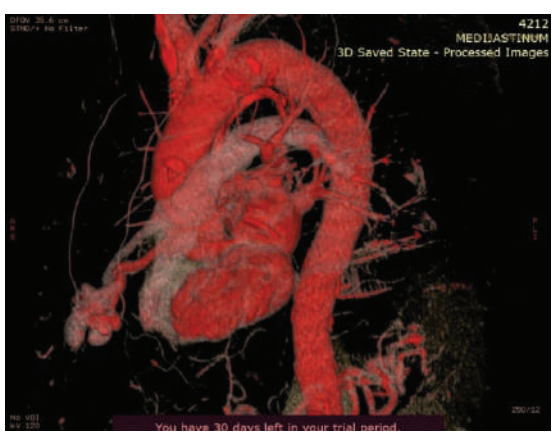

Image 6. Maximum Intensity Projection (MIP) reconstruction showing AV shunting into the pulmonary arteries.

Conclusion

Pulmonary A-V malformation is rare condition as incidental finding. It the most often occurs with hereditary hemorrhagic telangiectasia. If there is any doubt about the extension of this condition, the correct diagnosis is essential for implementing an appropriate therapeutic procedure and avoiding complications such as the discharge of blood clots in distant organs.

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MDCT IMAGING OF BLUNT RENAL TRAUMA: POST TRAUMATIC BILATERAL RENAL PELVIS RUPTURE

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Abstract

Trauma represents a significant public health problem with consequential socioeconomic costs. Isolated rupture of renal pelvis following a blunt trauma is a rare medical condition with very few case reports published in literature. We present a case of a male patient who was admitted to our hospital experiencing abdominal pain and not being able to urinate, prior having a fall from his own heigh few days before. After conducting multidetector computer tomography scan with contrast media of the abdomen, the leakage of the contrast media from the renal pelvic lesions in both kidneys was evident. The patient exhibited signs of recovery following the surgical placement of JJ stents in both kidneys which was evident on the control MDCT scan.

Key Words: *blunt renal trauma, MDCT, renal pelvic lesions.*

Introduction

Over the past two decades, there has been a constant improvement in the imaging and treatment of genitourinary trauma. The gold standard for the assessment of GU trauma today is multidetector computed tomography along with the use of intravenous contrast medium and the multiplanar reconstructions which provide fast assessment of the urinary tract, as well as coexisting intra-abdominal injuries. The necessity for imaging evaluation of the genitourinary system in medical practice fluctuates depending on few factors like the patient's overall blood flow status, any accompanying injuries, the site of blunt or penetrating trauma and the presence of blood in the urine.Top of Form

Case Report

A 68-years-old male patient was brought to our Emergency Room complaining of abdominal pain, urinary retention and a history of falling from his own height four days before admission. To thoroughly assess his condition, after conducting a clinical examination and a blood test, it was recommended that an abdominal MDCT scan should be performed with two post contrast series, to provide a comprehensive evaluation.

Following the intravenous contrast injection, in the post contrast series, the kidneys exhibited appropriate absorption and excretion of contrast media within the expected time frame (in a timely manner). However, it was observed that the patient had extrarenal pelvis bilaterally,

cortical cysts bilaterally that didn't interfere with the urodynamic, dilated ureters along with a dilated urinary bladder. Furthermore, in the adjacent kidney tissue, there was observed leakage of the contrast media from the renal pelvic lesions in both kidneys. There were no indications of trauma to the parenchymal organs within the abdominal region.

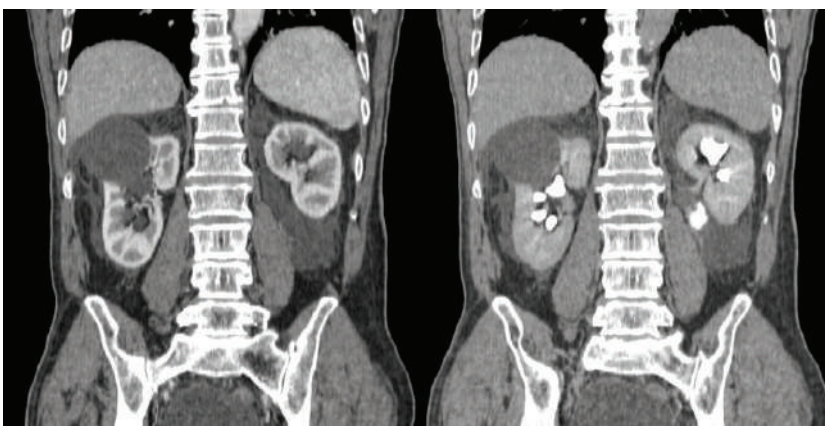

Figure 1. Free fluid in the surrounding kidney tissue.

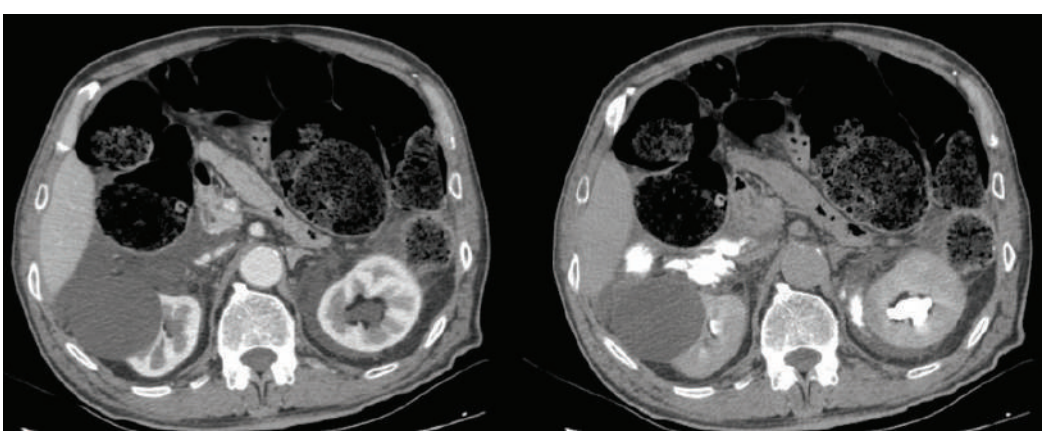

Figure 2.

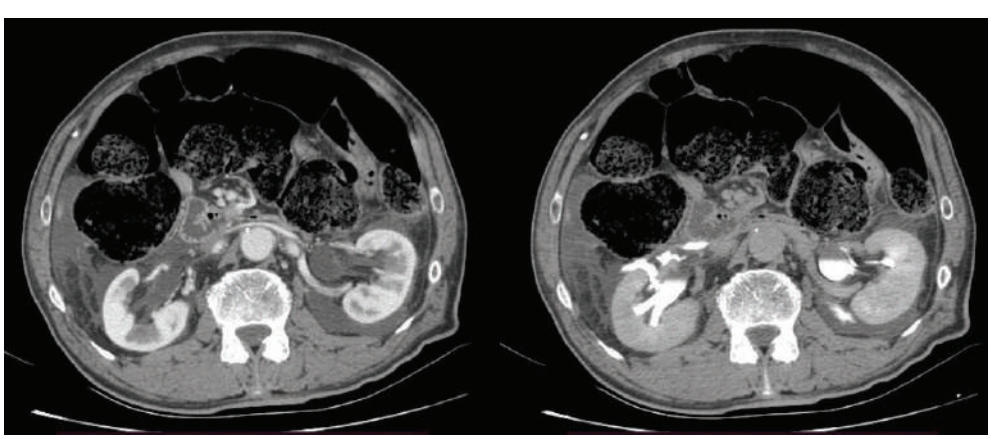

Figure 3.

Figure 2 and 3. As seen on the scans to the left, the surrounding free fluid dif. dx can mean urine, blood. On the scans to the right, the contrast media leakage is evident in the surrounding tissue, meaning there are lesions in the renal pelvis bilaterally.

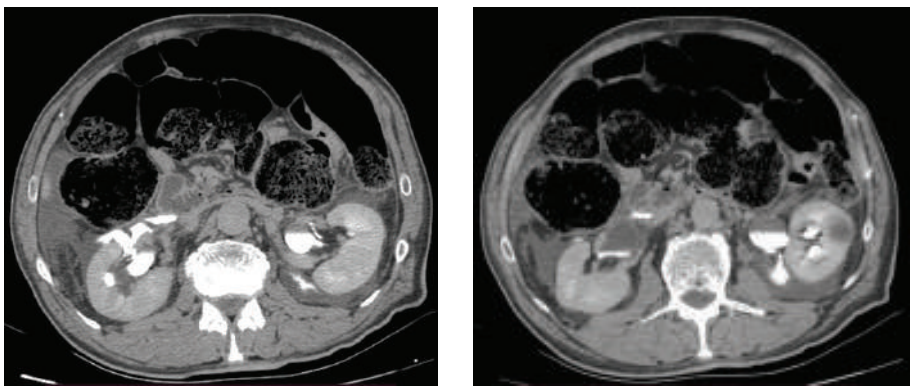

Figure 4. The exact location of the lesions of the renal pelvis and the contrast media leakage bilaterally.

Laboratory test showed increase of the C reactive proteins of 86.80mg/l which had a peak the following day, but afterwards dropped gradually. Also, there was a decrease in total protein count, as well as potassium values. There were no other significant laboratory changes which is evident from the attached table.

Table:

	Day 1	Day 2	Day 3	Day 4	Ref. Range
HB/Hbg	120.00	113.00	116.00	125.00	120.0-165.0 g/l
RBC	3.92	3.73	3.82	4.14	3.8-5.8 x 109/L
WBC	7.90	6.60	6.20	6.10	3.5-10.0 x 109/L
PLT	243.00	249.00	299.00	305.00	150.0 -390.0 x 109/L
HCT	0.35	0.33	0.33	0.36	0.35 - 0.5l/L
NEUT	6.20	5.30	4.60	4.50	1.2 - 8.0 x 109/L
LYMPH	1.00	0.90	0.90	0.90	1.2 - 3.2 x 109/L
GLUCOSE	4.91	4.53	4.43	5.16	3.9 - 5.8 mmol/L
UREA	3.80	5.00	5.40	3.30	1.8 - 9.2 mmol/L
CREATININE	83.20	67.10	53.20	53.70	63.0 - 110.0 umol/L
CRP	86.80	108.90	72.90	51.20	0.0 - 5.0 mg/L
SODIUM	143.0	143.8	143.6	145.40	137.0-147.0 mmol/L
POTTASIUM	3.06	3.88	3.21	4.15	3.6 - 5.4 mmol/L
TOTAL PROTEIN	55.80	55.90	55.40	61.30	64.0 - 87.0 g/l
ALBUMIN	32.50	33.0	33.90	35.30	35.0 - 52.0 g/l
GLOBULIN	23.30	22.90	24.60	26.0	15.0 - 35.0 g/l

The patient was stable and exhibited signs of recovery following the surgical placement of JJ stents in the kidneys. After 4 days the improvement was evident in the non-contrast control

MDCT scans with visualization on double JJ stent in both ureters conducted after the surgical procedure. Moreover, there were no indications of any free fluid in the surrounding kidney tissue.

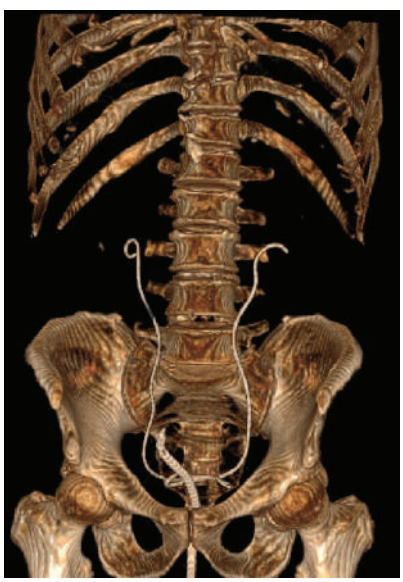

Figure 5. Visualization of the JJ stents and the placed urinary catheter using 3D volume rendering.

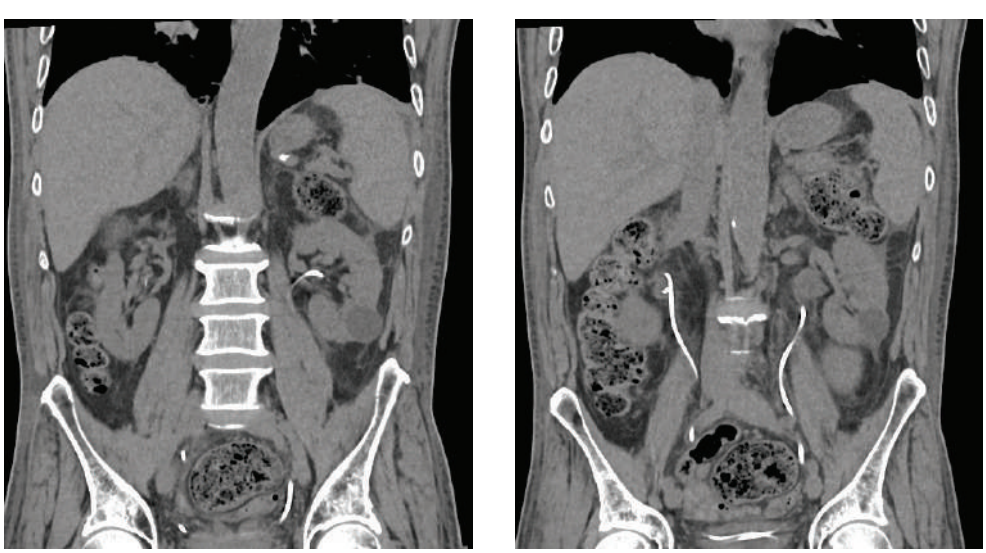

Figure 6. Control MDCT shows no trace of any free fluid in the surrounding kidney tissue after the surgical placement of the JJ stents.

Discussion

MDCT stands as the pinnacle in diagnostic imaging techniques. CT protocols typically involve scanning the abdomen and pelvis both before and after administering 100-150ml of contrast media intravenously. The critical phase for detecting a urine leak lies in the delayed phase images acquired 7-20 minutes post-injection, where the iodinated urine elevates attenuation, meas-

ured in Hounsfield Units (HU), over time, aiding in leakage visualization. Utilizing sagittal and coronal three-dimensional reformatted MDCT images, along with 3D volume rendering, proves immensely beneficial in precisely delineating the extent of the lesion. In scenarios where patients cannot receive intravenous contrast media due to allergies or have undergone renal transplantations, scintigraphy emerges as a pivotal diagnostic tool for detecting renal pelvic trauma.

Conclusion

The utilization of MDCT complemented by 3D volume rendering plays a crucial role in identifying and diagnosing renal pelvis rupture. Control examinations are necessary to confirm the successful treatment of these conditions.

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USE OF DESFLURANE: CONSIDERATIONS AND CONTROVERSIES

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Abstract

Desflurane stands as a pivotal volatile anesthetic in contemporary anesthesia practice and has been a cornerstone of modern anesthesia practice due to its rapid onset and offset of action. Despite its clinical advantages, the environmental footprint of desflurane, characterized by significant greenhouse gas emissions, has sparked a debate on its continued use and potential regulatory measures. This article evaluates desflurane's clinical benefits, alongside its environmental implications, offering insights into possible regulation perspectives. Highlighting its favorable pharmacokinetic properties, rapid induction, hemodynamic stability and bronchodilator effects, against its contribution to climate change, the study aims to foster a balanced discourse on desflurane's role in healthcare, advocating for a harmonization of clinical needs with ecological stewardship.

Introduction

Desflurane is an essential component of modern anesthesia because for its clinical efficiency, and nowadays has garnered attention for its environmental consequences. Recent studies have shown the significant greenhouse gas emissions associated with desflurane administration and raising concerns about its sustainability. This study examines all the clinical indications for desflurane, assesses its environmental impact, and discusses the rationale behind proposals for its regulation and banning. Traditionally, inhalational techniques have been preferred for anesthesia because of their availability and familiarity (1). Desflurane is commonly chosen inhalational anesthetic because its faster offset, which is a result of its blood: gas partition coefficient, particularly in long cases, difficult airways and obese patients. Studies show that patients' responsiveness and time to extubating is more rapid with desflurane than with sevoflurane, and this is significant with obese and geriatric patients (2). Yet, growing awareness of its environmental footprint, has prompted discussions about its sustainability and potential regulatory measures.

Clinical Uses of Desflurane

Desflurane offers several advantages and benefits in clinical practice that contribute to its widespread use and one of the most significant advantages is its rapid onset and offset of action because of its low blood-gas solubility coefficient that allows rapid equilibration between alveolar gas and arterial blood. This characteristic leads to smooth induction of anesthesia, making it particularly suitable for ambulatory surgeries where quick recovery is desirable. However, the

times to achieve lighter anesthetic levels when pharyngeal function is normalized, were notably different between isoflurane and sevoflurane when compared to desflurane with desflurane occurring more rapidly (3). Additionally, the fast offset of desflurane enables rapid emergence from anesthesia, minimizing postoperative recovery time and facilitating early discharge from the post anesthesia recovery unit. McKay et al. demonstrated that patients receiving desflurane had earlier awakening and were able better to protect their airway, as noted by not coughing or drooling when swallowing 20mL of water 2 minutes after following commands, when compared to sevoflurane. The findings were quite dramatic with 100% of the desflurane group having normal pharyngeal function, but <50% of the sevoflurane group achieving that level (4). Desflurane is known for its favorable hemodynamic stability, making it an excellent choice for patients with cardiovascular comorbidities and with patients undergoing cardiac surgeries. While some other inhalational agents may depress heart activity, desflurane only minimally depresses myocardial function and keeps cardiovascular stability intact even during periods of hemodynamic stress. This characteristic is due to desflurane ability to reduce myocardial depression in comparison to agents like isoflurane, making it safe for patients with compromised heart conditions. By stimulating bronchodilation, desflurane can prevent bronchospasm and maintain proper respiratory function during anesthesia. This is especially useful in patients with a history of airway hyperreactivity, where the maintenance of airway patency is important to ensure safe anesthesia administration. Unlike some other inhalational agents, desflurane is associated with minimal airway irritation and coughing during induction of anesthesia. Its low solubility in blood results in a lower concentration of desflurane in the airways, reducing the likelihood of respiratory irritation and this characteristic makes desflurane particularly well-tolerated in awake patients or those with a heightened airway sensitivity.

When looking at patients with significant comorbidities, Bilotta et al. demonstrated a quicker recovery of cognitive function and, more importantly, earlier normalization of pH and PaCO2 in morbidly obese patients undergoing craniotomy when receiving desflurane (5). Desflurane undergoes minimal metabolism in the body, primarily through hepatic metabolism 0.02%, reduces the risk of drug interactions and ensures predictable pharmacokinetics. Additionally, desflurane's low metabolism contributes to its rapid elimination and allows precise titration of anesthetic depth during surgery.

Environmental Impact

The environmental impact of anesthesia agents, particularly volatile inhalational agents like desflurane, has gained increased attention in recent years. Desflurane, like other halogenated volatile anesthetics, contributes to greenhouse gas emissions through the release of fluorinated compounds during their production, administration and disposal. These fluorinated compounds are trifluoroacetic acid (TFA) and hexafluoroisopropan-2-ol (HFIP) that have long atmospheric lifetime that contributes to global warming potential. The production and disposal of desflurane create greenhouse gas emissions that are exacerbating climate change and environmental degradation. Fluorinated metabolites released during desflurane metabolism persist in the atmosphere for extended periods which has a cumulative effect on climate change. These metabolites have long atmospheric lifetimes that contributes to the persistence of greenhouse gases and ozone depletion. The global warming potential is a measurement of the radiative forces of a gas compared to carbon dioxide, it encompasses the wavelength and quantity of infrared absorption and the atmospheric longevity of the gas (6). Desflurane is a potent greenhouse gas,

and 1kg of desflurane is equivalent to 2540kg of CO2. This means that every hour of desflurane usage, running at 5% with flows of 1L, is the equivalent of producing 56kg of CO2 emissions. Running a 7h case would produce the equivalent of 392kg of CO2 emissions. While desflurane atmospheric impact is relatively lower compared to older volatile anesthetics like halothane, its widespread use in anesthesia practice significantly increases the environmental consequences. As a result, desflurane not only affects the environment during its anesthesia usage but also has long-lasting effects on the atmosphere. The production of desflurane requires significant resources like energy and raw materials that contribute to carbon emissions and environmental degradation. It involves the use of fluorinated compounds and organic solvents, which can have detrimental environmental effects if not managed properly. Additionally, the disposal of unused desflurane and its packaging materials can lead to pollution of soil and water bodies, and that poses risks to ecosystems and human health. Because of its low blood-gas solubility, higher fresh gas flow rates are needed during administration, leading to increased waste gas emissions. These waste gases contain volatile organic compounds, including desflurane and its metabolites, that contribute to air pollution and environmental degradation. The release of waste gases into the atmosphere further exacerbates desflurane environmental impact, particularly in hospitals with inadequate waste gas management systems. Environmental agencies and healthcare organizations are increasingly recognizing the need to reduce the environmental consequences of anesthesia practices, and have cautioned regulatory investigation and calls for stricter controls on its use. Proposals for regulating desflurane include implementing low flow anesthesia techniques, promoting the use of alternative anesthesia agents with lower environmental footprints, and investing in sustainable anesthesia practices.

The Use of Desflurane: Considerations and Controversies

Desflurane offers several advantages in clinical practice, including rapid induction of anesthesia, precise titration, and favorable hemodynamic stability. Its rapid offset also facilitates fast emergence, recovery and enables early discharge from the post anesthesia care unit also making it particularly suitable for ambulatory surgeries. Desflurane is generally well-tolerated from patients and has a predictable pharmacokinetic profile. Its minimal metabolism reduces the risk of drug interactions, has a minimal organ toxicity ensuring safer anesthesia administration, and ensures optimal patients' outcomes. In certain surgeries like neurosurgical procedures and laparoscopic surgeries, desflurane has unique properties that make it the preferred anesthetic agent for ensuring patient's comfort and surgical success. Additionally, desflurane is more suitable for low flow anesthesia by regulatory agencies like the US FDA due to its low solubility and minimal reaction with soda lime and this characteristic allows for efficient use of anesthetic gases because of reducing resource consumption and waste gas emissions. Regarding the environmental effects of desflurane, it was reported that healthcare accounted for 4.6% of greenhouse gas emissions worldwide, with anesthetics representing 2% of that total. Hence, anesthetics contribute 0.09% to global greenhouse gas emissions. Even though it may be a very small percentage, it is a significant amount. However, it is of a size that allows for the consideration of methods and tools to further reduce it, instead of completely getting rid of a widely used anesthetic. The impact to the environment of other anesthetics which will likely be utilized in larger quantities if desflurane is removed. First, sevoflurane, although to a lesser extent, has a negative environmental impact. More importantly, the negative environmental effects of the intravenous anesthetics (e.g., propofol) with the creation of medical waste including syringes, plastic tubing and needles, as well as the utilization of electrical devices for their delivery leading to a small but present green-

house gas impact. Propofol is spilled at high amounts into our environment, is not naturally degraded, and is toxic to wildlife (7). Therefore, there is a negative environmental impact with the use of anesthetics as a whole, but to attribute all of it to one anesthetic with devices already in place to reduce that impact ignores many other contributors to the problem.

Conclusion

The decision of whether desflurane should or should not be used in anesthesia practice requires careful consideration of its clinical benefits, environmental impact, and ethical implications. While desflurane has undeniable advantages because of its clinical efficacy and safety, its environmental footprint and ethical concerns calls for a reevaluation of its role in modern anesthesiology. Placing all the blame on one anesthetic and neglecting the beneficial qualities of the agent that enable us to care for our complex patients is unjust. Data suggests that desflurane should remain available for clinical use due to its ability to provide faster awakening and earlier airway protection, particularly in patients with significant comorbidities, obese patients and in geriatric anesthesia, as well as its potential cost effectiveness and environmentally friendly properties. Anesthesia providers, regulatory agencies and healthcare institutions must collaborate, and together to find a balance between clinical needs and environmental responsibility and ensure optimal patients' care while minimizing ecological harm. Ultimately, the use of desflurane should be coupled with efforts to promote greener alternatives and sustainable anesthesia practices and can pave the way towards a more environmentally conscious healthcare system.

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SUGGESTION FOR THE UPCOMING CONFERENCE: EMPHASIZING EDUCATION AND THE IMPORTANCE OF ATTENDING SCIENTIFIC CONFERENCES

Melda Emin

I hope this letter finds you well. I am writing to share my recent experience at the 34th TBS International Biochemistry Congress held from October 29th to November 1st, 2023, in Fethiye, Turkiye, organized by the Turkish Biochemical Society. As an attendee and a young professional, I was deeply impressed by the comprehensive and enlightening program and the impact it had on my education and professional development.

During the congress, various crucial topics were presented, offering insights into the most recent and relevant advancements in the field of biochemistry. The educational sessions were invaluable, covering a wide range of topics, from the latest research findings to practical applications. What particularly stood out to me was the active mentorship program where young specialists were paired with experienced mentors from the board. These mentors provided guidance and shared the latest techniques, innovations, and methodologies. Additionally, the interactive sessions provided an opportunity for attendees to seek clarification and gain a deeper understanding of the subject matter.

The congress's organizers demonstrated a profound commitment to education and the professional development of young doctors and professionals. It is my belief that similar initiatives can significantly contribute to the growth and advancement of the medical community in the Republic of North Macedonia. Therefore, I would like to propose incorporating a mentorship program and interactive sessions into the upcoming conference in North Macedonia. By emphasizing education and the importance of attending scientific conferences, we can provide young doctors and professionals with a platform to share experiences, learn from each another, and stay updated on the latest innovations in medicine.

Attending such conferences is not only beneficial for individual professional growth, but also for the advancement of the medical field overall. The exposure to new methodologies, innovations and networking opportunities offered at these events is invaluable. It is my strong belief that implementing similar educational initiatives in North Macedonia will have a profound and positive impact on the medical community.

Thank you for considering my suggestion.

Warm regards,
Melda Emin
MD, Assistant at Department of ME Biochemistry, Faculty of Medicine Skopje

SUBJECT: ACCREDITATION METHODS PRESENTED AT THE 25TH INTERNATIONAL CONGRESS OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE ALREADY IMPLEMENTED IN THE LABORATORY OF THE INSTITUTE OF MEDICAL AND EXPERIMENTAL BIOCHEMISTRY IN SKOPJE

Ass. Dr Hristina Ampova

I am eager to share my enriching experience at the WorldLab - Euromedlab, the 25th International Congress of Clinical Chemistry and Laboratory Medicine, which was held in Rome, Italy from May 21-25, 2023. This prestigious event also incorporated the 25th European Congress of Clinical Chemistry and Laboratory Medicine and the 55th Congress of the Italian Society of Clinical Biochemistry and Clinical Molecular Biology (SIBioC). It was organized by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) and SIBioC.

I was honored to receive a bursary from the EFLM to attend the congress, where I also had the opportunity to deliver a poster presentation. The congress showcased an advanced scientific program, featuring a variety of lectures that highlighted critical advancements and challenges in our field. Noteworthy topics included:

- "Inappropriate Use of Laboratory Resources: Demand Management Tools and Strategies."
- "Applications of Artificial Intelligence in Clinical Laboratory Medicine."
- "The Central Role of the Clinical Laboratory in the Public Health and Patient Care Continuum."
- "Innovations in Laboratory Information Systems: Preparing for the Next Generation."
- "Advancing Excellence in Laboratory Medicine Worldwide: An Update from IFCC Task Forces."
- "The Ongoing Challenge of Harmonization in Laboratory Medicine."
- "Evolving Standards of Quality in Clinical Laboratory Practices."
- "Identifying and Mitigating Sources of Interference in Laboratory Testing."

A significant aspect of the congress was learning about the accreditation of methods, which is directly applicable to our work at the Institute for Medical and Experimental Biochemistry at Medical Faculty in Skopje. We have accredited analyses which we have verified, as the professors presented at the congress. This aspect was particularly insightful as it aligns closely with our current practices and standards.

The congress was accredited by the EFLM's Continuing Professional Education Credit System (CPECS®), which provides a quality assurance mechanism for the accreditation of continuing education programs and events. This system ensures that participants receive high-quality, relevant education in laboratory medicine.

Thank you for considering this summary of what was an intellectually stimulating and professionally rewarding gathering. I believe that sharing these insights can significantly benefit our field and promote continued excellence in laboratory medicine.

Sincerely,
Ass. Dr Hristina Ampova
Resident Doctor of Medical Biochemistry Institute for Medical and Experimental Biochemistry, Medical Faculty – Skopje

Acknowledgements/Conflicts of Interest: The author declares no conflicts of interest.

GUIDELINES FOR AUTHORS

Macedonian Journal of Anaesthesia (MJA) is a scientific journal of the Macedonian Society of Anaesthesia (MSA) and Macedonian Society of Critical Care Medicine (MSCCM). The aim of this specialized medical journal is to speed and promote scientific achievements, novelties', clinical experience's, reviews, controversial topics in anesthesia, reanimation and intensive care, as well as other correlated medical branches .

The Journal is published four times a year (April, June, October and December), but additional supplements might be published when needed. MJA publishes original articles in basic and applied research, review articles, case studies, therapeutic and technological innovation, discussions, critics, surveys, impressions from meetings, information for international conferences and reviews of new books or variate.

Manuscripts that are published should have not been published previously. Manuscripts that have been previously published only in form of abstracts are eligible for publishing in the journal but should be followed by additional letter send to the Editor, where the abstract details are noted (abstract number, which book of proceeding or doi, date and place).

The authors are responsible for respecting the ethical guidelines for medical researches, as well as for all that is explained, attitudes, analyses and shown results.

The redaction sends the manuscripts to anonymous reviewing process from international or domestic reviewers and the Editors determine the definitive categorization of the manuscript. Once reviewed manuscript together with the reviewers' remarks is send back to the corresponding author, after what the author is omitted to deliver the final form of the manuscript to the Editorial board within one week.

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Manuscript should be sent together with the accompanying letter from the corresponding authors where declaration that the text has not been published previously is signed. Additional conflict of interests and confirmation by all the authors should be declared in this letter (example: Annex no.1).

The guidelines for authors adhere to the uniform Requirements for Manuscripts submitted to Biomedical Journals:www.nlm.nih.gov.

Language and style of the manuscripts should be clear, simple to according the language, anesthesiological and medical taxonomy.

The manuscript has to be written in **English**Manuscripts should be written in **Microsoft Word** (*.doc format) with **Times New Roman** font and **size 12**. Margins on left, up and bottom should be 3cm and right margin should be 2,5cm.

The inline space should be 2. Do not use Bold or Italic letters for the whole text (only for parts that have to be emphasized). Manuscript should not exceed 10 pages (without the references).

Abbreviations and correct medical terms should be used according to the International Committee of Editors of Medical Journals (http://www.icmje.org). Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

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- Manuscript should be organized in:
- Title page
- Text organized in IMRaD
- Acknowledgments
- Authors Contribution
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Review articles, case reports, therapeutic and technological innovation, discussions, critics, impressions from meetings, information for international conferences and reviews of new books or variate may be written in different sequences and manners.

TITLE PAGE

The title of the manuscript written in CAPITAL LETTERS.

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Abstract in English. Abstract should include up to 250 words and should contain goals of the paper, important elements from the methodology, concisely displayed results and conclusion. Each abstract at the end must have **Key words**: in alphabetical order.

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Introduction section should include a literature overview in relevance to the elaborated problem. In this sections 3-5 key references are citied and this section should not be longer than 2 pages.

Material and method sections includes detailed description of the performances in the research as well as the statistical analyses used. This section should include: time during what the research was conducted, type of the study, place of where the research was undertaken, randomization or stratification used (clear description of the examined groups), exclusion and inclusion criteria, method, analysis types, apparatus and instruments used and referent values of the examined features (in SI-International System units).

Results are displayed in simple manner with text, images, tables and charts that are submitted in the text where author wants to stand, titled and numbered appropriately. Additionally, on separate document all carts images and tables are send together with the manuscript.

Title and the number of the charts and tables are placed above them while the explanations, abbreviations and comments are placed below. Images title and number is placed below and the image should include proper explanation.

Discussion section emphasize the key finding of the actual research and compares these result to other relevant literature data.

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For each reference if more than three authors appear provide the names of the first three authors and followed by **et a**l.

Examples:

Journal references:

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Lynch EP, Lazor MA, Gellius JE, et al. The Impact of Posoperative Pain on the Development of Postoperative Delirium. Anesth Analg 1998; 86:781-785.

2. Journal supplements:

AzmanJ, Frkovic V, Bilic L, et al. Korelacija I regresija. Acta Med Croat 2006;60 (suppl I):81-89.| 70 |

3. Books

Brown, D.L. Spinal, epidural, and caudal anesthesia. In R.D. Miller Miller's Anesthesia, 6th edi-

tion. Philadelphia: Elsevier Churchill Livingstone; 2005.p 98-198

4. Doctoral or master thesis

Jelisavac Cosic S.Urokinazni I tkivni aktivator plazminogena i njihov inhibitor u raku dojke (Master thesis).Zagreb: Farmaceutsko-biohemijski fakultet 2004, p.50

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http://dx.doi.org/10.1046/j.1365- 2044.2000.01722.x

References used from abstracts are marked as (**abstr).,** and from letters with (**letter**)

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I _____. Here by declare that the article _____ (NAME OF THE ARTICLE) has not been previously published (fully or partialy) previously.

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_____(FULL NAME AND SURNAMES OF THE AUTORS AND SIGNATURES) are responsible for the etic, profesional and scientific content of the study.

I _____(THE FIRST AUTHOR FULL NAME) declare Conflict of interest or declare non Conflict of interest.

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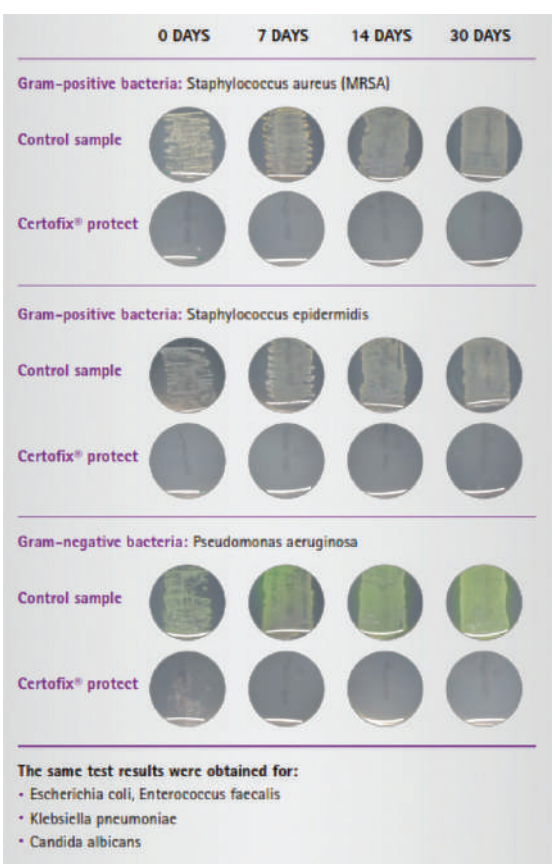
B|BRAUN
SHARING EXPERTISE



Превенција на инфекции
Certofix® protect

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E cacy of Certofix® protect
J. Brunke, T. Riemann, I. Roschke. 30 days antimicrobial efficacy of non-leaching central venous catheters (Poster 063,) Critical Care 2016, Volume 20 Suppl 2