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I.V. Paracetamol

БЕЗБЕДНА АНАЛГЕЗИЈА

менаџирање на болка кога сте загрижени за безбедноста

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

Предоперативна и Интраоперативна Аналгезија:

Предоперативна анелгезија е дефинирана како третман кој што започнува пред оперативниот зафат се со цел да се превенира воспоставувањето на централна сензибилизација на болка.

i.v. paracetamol е безбеден, добро толериран лек со докажана ефикасност како **предоперативна и интраоперативна анелгезија** за умерена до средна болка при оперативни зафати.

Голем број на клинички студии ја докажуваат ефикасноста на **i.v. paracetamol** како **преодоперативна и интраоперативна анелгезија**.

КЛИНИЧКА СТУДИЈА:

Ефект од **предоперативен i.v. paracetamol** за постоперативни аналгетски потреби кај пациенти кои се подлежни на оперативни зафати. A Sreenivasulu , R Prabhavathi, 2015

Цел: Да се утврди ефикасноста на **предоперативната употреба на 1000mg i.v. paracetamol** кај постоперативните болки и анелгетски потреби кај пациенти подлежни на хируршки зафати.

Метод: 60 пациенти беа поделени во две рандомизирани групи од по 30 пациенти.

На I. Група им беше администрирано **ампула од 1000mg i.v. paracetamol разредена 0,9%NaCl** р-ор 30 минути пред индукција **(ГРУПА П)**,

На II. Група им беше администрирано **i.v. 0,9% NaCl р-ор 100мл** 30 минути пред индукција **(ГРУПА НС)**

Сите пациенти беа индуцирани со i.v. thiopentone 5mg/kg, i.v. fentanyl 2μg/kg, i.v. vecuronium 0.1mg/kg

Постоперативниот резултат на болка беше мерен со **Визуелна Аналогна Скала (ВАС) од "0-10"**. Исто така беше забележувана и **постоперативната употреба на tramadol** како спасувачки аналгетик. Инциденцата на **постоперативно гадење и повраќање (ПОГП)** и други компликации исто така беа забележувани во пост оперативниот период.

Резултатот на постоперативната болка беше забележуван во интервали 15 мин, 30 мин, 1 час, 2 часа, и 6 часа.

Резултат:

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

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

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

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

Табела3: *Споредба на ПОПГ помеѓу двете групи*

ПОГП	
I Група П	II Група НС
0	4

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

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

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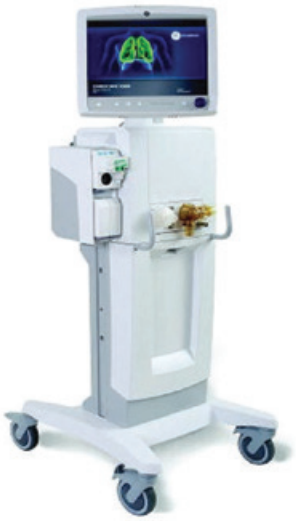

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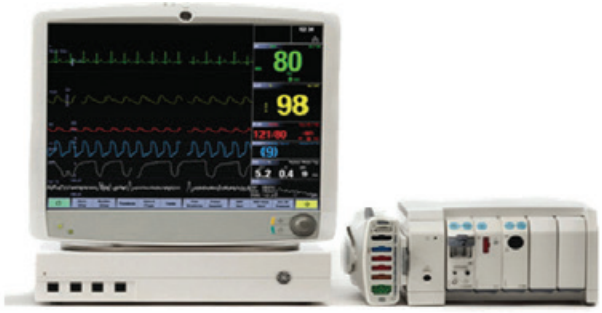

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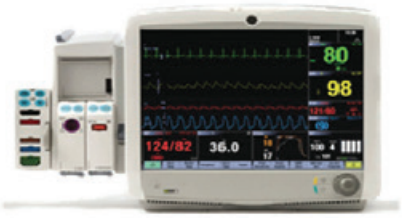

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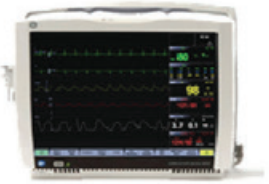

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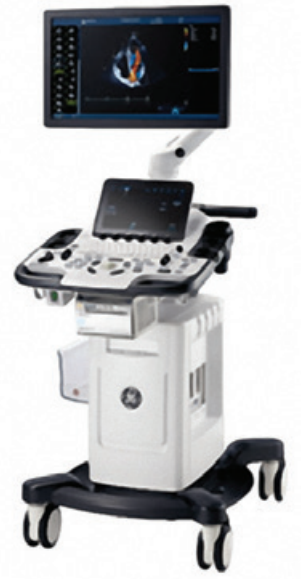

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CONTENT

SCARLESS THYROID SURGERY

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Although the thyroid gland and its changes (in shape) have been known for a long time, since the time of the Chinese Empire (2700 BC) when increased swelling of the neck (goiter) was detected without knowing the essence of that swelling. At that time the treatment of that swelling was using algae and a burnt sponge. It was acknowledged that the surgery has an important place in the treatment of goiter i.e. the thyroid disease. The first thyroid surgery for goiter was performed by Albucasis in 925.

The first anatomical description of the thyroid gland was made by Leonardo Da Vinci in 1511. Vesalius was the first that gave an anatomical description of the thyroid gland in 1656, but without knowing itsreal function. The first descriptions of the association between goiter and protrusion of the eyeballs (exophthalmos) were described by Graves and Badevouin 1840.

In the following period, there were ups and downs in thyroid surgery, which due to its location around the trachea and the close relation with the large blood vessels was burdened with high mortality, up to 40%, thereby being avoided as procedure in certain periods.

At the beginning of the IXX century, several innovations in surgery took place, antisepsis and its significance in surgery were established, the general anesthesia was discovered, the hemostatic instruments were discovered, sothe surgery became safer and less dangerous procedure.

A serious approach to thyroid surgery was found in the mid of the IXX century, when Teodor Bilroth and his student Teodor Kocher laid the foundation of a modern approach to open thyroid surgery. Kocher managed to reduce the mortality rate to 0.5%. Teodor Kocher was awarded the Nobel Prize in Medicine in 1909 for his thyroid research.

In the second half of the twentieth century, the function of the thyroid gland and the importance of thyroid hormones was recognized (Adolf Magnus-Levy, Andrew Schally won the Nobel Prize in Medicine in 1977 for this discovery). During this period, not only the physiology of the gland was learned, but also the function of the gland in certain pathological conditions, as well as the role of the surgical treatment in the treatment of certain pathological conditions.

In this period, the possible complications from the surgical treatment of the thyroid were described, such as hypothyroidism, speech and breathing disorders, as well as the appearance of tetani, the reasons for their occurrence, the way of prevention and the treatment if they occur.

In the second half of the twentieth century, the focus was no longer on the indications and safety of thyroid surgery, but also the efforts were made to find a less invasive approach with a better cosmetic result, while at the same time maintaining the function of the healthy part of the thyroid gland.

A minimally invasive approach to surgical treatment followed. Garner was the first to report an endoscopic approach to the treatment of parathyroid adenomain 1996. The development of thyroid surgery techniques set the path in these directions:

- Open thyroidectomy with a large incision at the base of the neck;
- Reduction of the incision at the base of the neck and further open surgery of the thyroid gland. In order to achieve surgery with the smallest possible incision in the neck, endoscopic equipment (video camera) was used, which locally showed the elements by performing video-assisted surgery, introduced by Mikoli in 2002;
- The era of real endoscopic surgery followed, where the access ports were outside the neck region:
  - Ohgami 2000 – accessing via breasts,
  - Shimazu 2003 – ABBA (bilateral trans-axial and through the breast),
  - Choe 2007-BABA (bilateral axial and bilateral thought the breast);
- Trans-robot surgery, where through the previous ports, the shoulders of a robot are placed that has been used since 2010;
- Scarless surgery, where access is through invisible places, natural openings NOTES (natural orifice thyroid surgery), mucous membranes of the oral cavity:
  - Terris 2011 (retroauricular approach),
  - Karakas 2009 TOVAT (transoral approach) eMIT (sublingual approach),
  - Wilhem 2011 NOTES (natural orifice thyroid surgery),
  - Nakoja 2013 TOETVA (transoral endoscopic thyroidectomy vestibular approach).

This type of surgery uses approaches outside the cervical region, usually through the mucosa where practically no scars are created and the most often the incisions are small for placement of endoscopic instruments.

The trans-axillary approach is widely used, but it still leaves a scar, indeed outside the neck region, and with this approach it is possible to treat one side of the thyroid gland. That is the reason to use additional approaches to this approach through one or both breasts or through the other axillary fossa. With this approach it is possible to resolve both lobes of the thyroid gland. These are quite mutilating approaches that only do not give a scar on the neck.

The transoral approach is quite rational and through it the thyroid gland can be accessed. Access through the base of the oral cavity is inconvenient due to the great bleeding of the sublingual region and the presence of nerves, so in recent times transoral thyroidectomy via vestibular approach (TOETVA) is the most often used, as the least invasive technique that leaves no scars.

In this TOETVA approach, the patient lies on his back with his head slightly raised.

The operation is performed under general anesthesia, using a tube with sensors that detect the activity of the speakers. Intubation is performed trans-nasally, as if the oral cavity is free for endoscopic access.

Three incisions are made on the inside of the vestibule (below the inside of the lower lip, where there is a central 10 mm incision for the camera's port and two 5 mm lateral incisions for the two ports for endoscopic instruments placement. Before the trocar's placement, the neck space (between the hyoid bone and the jugulum) is tunneled, into which CO_2 gas is injected under low pressure in order to open up minimal space for working with endoscopic instruments.

Following that, the sternothyroid and sternohyoid muscles are separated and the thyroid gland is accessed. The two lobes are separated by ultracision, cutting the isthmus. The lobe of

the trachea is then released from the top to the bottom, accessing the blood vessels and binding them with ultracision, detecting the nerves in that region (nervus laryngeus superior and nervus laryngeus inferior (recurrens) that are responsible for innervating the muscles of the larynx.

After that, the part or the whole lobe is released and removed through the middle canal. Mucosal incisions are closed with atraumatic resorption sutures.

The indications for the use of this minimally invasive and aesthetic surgery are the following:

- Thyroid gland size up to 10 cm,
- Total thyroid volume less than 45 cm,
- Nodule size in thyroid gland up to 5 cm,
- Benign tumors,
- Follicular neoplasm,
- Papillary neoplasm microcarcinoma,
- Graves' disease.

In the conditions of correct indication for thyroid surgery, the application of transoral endoscopic thyroidectomy trans-vestibular approach is a reliable method that gives excellent aesthetic results, without visible scars.

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PROGNOSTIC VALUE OF LUNG ULTRASOUND SCORE IN COVID-19 POSITIVE PATIENTS AND ITS CORELATION WITH D-DIMERS AND INTERLEUKIN 6

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ABSTRACT

Introduction: Lung ultrasound in SARS CoV-2 positive patients is being used more often. This study was performed to examine the relationship between Lung ultrasound score (LUS) and disease severity, the need for mechanical ventilation, disease prognosis and the correlation with d-dimers and inflammatory biomarkers.

Material and Methods: There were 119 SARS CoV-2 positive patients with symptoms onset between 7 and 14 days, admitted to Clinical Hospital Acibadem in Skopje included in this observational study. Patients were stratified according to their symptoms and vital parameters as mild, moderate, severe and very severe disease. In every patient during the first 24 hours from admission lung ultrasound examination was performed and LUS score was calculated. At the same time with the ultrasound examination blood was drawn for the laboratory parameters that were being followed.

Results: From the 119 patients included in the study 48 were with mild, 37 with moderate and 34 with severe disease. LUS score (<15.5; >15.5) was significantly associated with disease severity $p<0.05$ (Pearson Chi-square: 110.917, df=2, p=0.00000). Patients with severe disease had significantly higher average values of d-dimers and IL-6 (21.0±26.8μg F.E.U./ml, and 97.1±115.1pg/ml). The difference between the average values of d-dimers and IL-6 according to Analysis of Variance test is statistically significant for $p<0.05$.

Conclusion: LUS score corelates with Covid 19 disease severity and patient's outcome. Higher values were positively correlated to higher D-dimer and IL-6 values.

Key Words: *Covid-19, d-dimer, interleukin 6, lung ultrasound, LUS score.*

Introduction

Starting the end of 2019 infection with the beta coronavirus, SARS-CoV-2 spread rapidly and overwhelmed healthcare systems in almost every state in the world. The world health organization declared COVID 19 a pandemic. Although primarily manifested as a respiratory disease, it is a multisystemic disease that can affect the cardiovascular, gastrointestinal, neurologic, hematopoietic and immunologic system (1). Evidences so far suggest that the most of the patients get a

mild clinical picture, but up to 16% can have the need for hospitalization (2). Patients with severe disease are more likely to be older with at least one comorbidity, although potentially lethal complications like myocarditis and disseminated intravascular coagulation (DIC), Adult Respiratory Distress Syndrome, Sepsis and septic shock are described in younger patients (3,4). Covid 19 coagulopathy is characterized with tendency for venous, arterial and microvascular thrombosis (5). 20 to 50 percent of patients admitted in hospital have altered coagulation tests like elevated d-dimers, thrombocytopenia and/ or low level of fibrinogen (6,7). Elevated d-dimers are a sign of predomination of the fibrinolytic processes and plasmin degradation to fibrin. This can be the result of hypercoagulable state or venous thromboembolism (8). Additionally, patients with more severe disease especially those that will not survive, can have significantly higher levels of C reactive protein (CRP), interleukin 6 (IL 6) and ferritin, troponin. This can be a result of the activation of a systemic inflammatory response (SIRS). Extreme levels of proinflammatory biomarkers like IL 6, TNF, can lead to a so called "cytokine storm" that can be in the origin of acute lung injury and result in ARDS and multisystemic organ failure (MOF) (9). Computed tomography(CT), Lung X-ray and lung ultrasound can also help in disease severity assessment and prognosis (10-12). Lung ultrasound is a simple, fast, noninvasive, sensitive and quantitative method that is used for evaluation of lung pathology (13). The first evidence of the use of the so called B lines in lung disease evaluation, date from the eighties (14,15). The modern era in lung ultrasound started with the work of Daniel Lichtenstein. He corelated the results from the CT scans and lung examinations. In this study he shows that the B lines corelate with the CT finding of subpleural interlobular septa in interstitial lung syndrome and with the formation of fibrous tissue in lung fibrosis (16).

Lung Ultrasound Score (LUS) is a semiquantitative score that shows loss of aeration in the lungs as a result of different lung diseases (13,17). LUS has been used in few studies in SARS CoV-2 patients so far (18,19).

The purpose of this study was to evaluate the role of LUS score in disease stratification, the need for mechanical ventilation, prognosis and correlation with inflammatory biomarkers and d-dimers.

Material and Methods

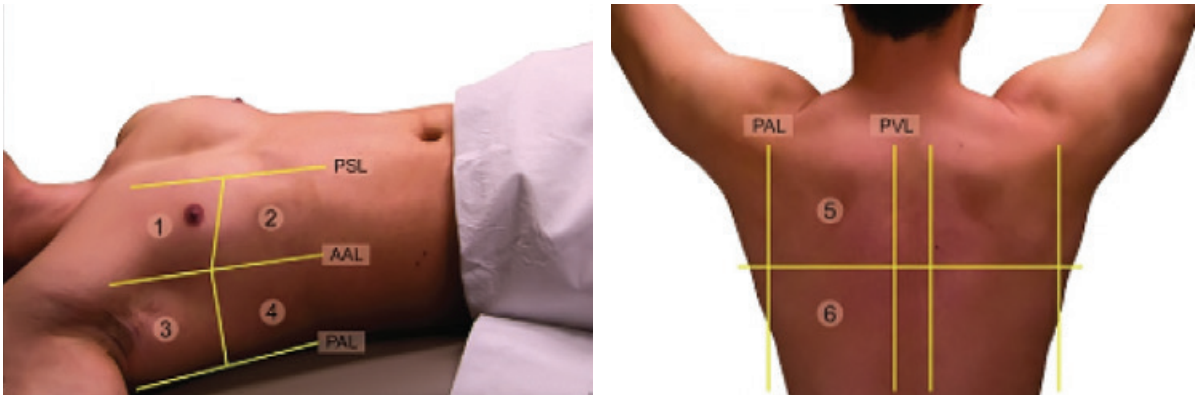
This was an observational study that included 119 adult SARS CoV-2 positive patients admitted to clinical hospital Acibadem in Skopje. Diagnosis was made with rRT-PCR test (reverse polymerase chain reaction) on pharyngeal and nasal swabs of the patients.

Every patient had his epidemiologic questionnaire filled, anamnesis taken, and a physical examination was done. Afterwards laboratory samples were taken for blood count, CRP, PCT, IL-6, serum iron, ferritin and d-dimers. Patients were divided according to the presence of fever, blood pressure, heart rate, respiratory rate, oxygen saturation and level of consciousness as having mild, moderate, severe and very severe disease. Patients with very severe disease were not included in the study (20).

Ultrasound lung evaluation was done during the first 24 hours after admission with portable ultrasound General Electric with a liner or convex probe. For this purpose, the chest on the right and left side was divided in 6 fields with the help of the anterior axillary line (AAL), posterior axillary line (PAL), parasternal line (PSL) and paravertebral line (PVL), as well as with the line that passes 1 centimeter above the nipples, as shown on Image 1.

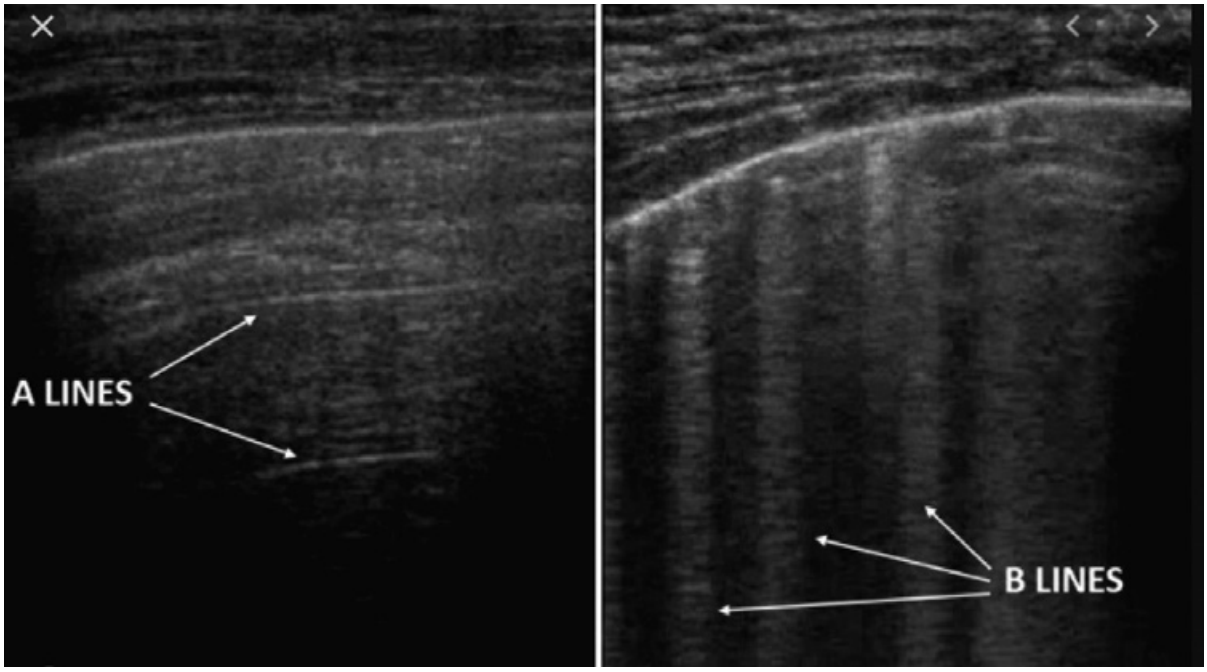
The probe was applied perpendicular to the ribs. Each lung field was assessed for the presence of A lines, B lines and consolidation (21). The scoring system that we used was previously described (13,22,23): (1) 0 points: less than 3 well-spaced B lines, (2) 1 point: more than 3 well-spaced B lines and thickened pleural line with small irregularities; (3) 2 points: multiple confluent B lines and shady and irregular pleural line (4) 3 points: consolidation. Summing the scores of all 12 zones, the final result was calculated that can be in the value between 0 and 36.

Image 1. *The 6 Lung ultrasound fields from the front and back of the chest wall.*



PSL-parasternal line. AAL – anterior axillary line. PAL – posterior axillary line. PVL – paravertebral line.

Image 2. *A lines and B lines on ultrasound examination of the lungs.*



Results

119 SARS CoV-2 positive patients were included in the study with mild, moderate and severe disease. 40.0% of the patients had mild, 31.1% moderate and 28.6% severe disease (Table 1).

Table 1. *Disease severity*

Disease severity	N	%
mild	48	40.3
moderate	37	31.1
severe	34	28.6

68.1% of the patients were male and 32.9% were female. There were more male patients with moderate and severe disease. The distribution of patients according to gender is given in Table 2.

The average age of patients with mild disease was 52.3±12.2 years, and patients with moderate and severe disease had a higher average age of 62.3±12.0 years and 64.2±11.5 respectively. The Analysis of Variance test showed a statistically significant difference for p=0.000017, and according to post hoc test the difference is the mostly between mild versus moderate and severe form (Table 2). Also, significantly more patients with moderate and severe form had comorbidities compared to patients with mild form for p<0.05 (Pearson Chi-square: 11.7641, df=2, p=.002789).

45.4% of the patients had the need of non-invasive or invasive mechanical ventilation. Oxygen mask with reservoir was used in 96.8% of the patients with mild disease and 51.3% of the patients with moderate disease. Non-invasive mechanical ventilation was used in the three groups of patients, at least – 4.2% in the patients with mild form, and the most in patients with severe disease 55.9%. Invasive mechanical ventilation was used in 18.9% of the patients with moderate disease and 44.1% of the patients with severe form of the disease. There was a statistically significant association between disease severity and the type of oxygen for p<0.05 (Pearson Chi-square: 74.4832, df=4, p=.000000) (Table 2.).

Table 2. *Patient characteristics by groups and globally*

clinical pictures /gender	**male**		**female**		Pearson Chi-square:
	N	**%**	**N**	**%**	
mild	28	58.3	20	41.7	p=.122222
moderate	28	75.7	9	24.3	
severe	26	76.5	8	23.5	
total	82	68.9	37	31.1	
clinical pictures/outcome	**life**		**death**		Pearson Chi-square:
	N	**%**	**N**	**%**	
mild	48	100.0			p=.000013
moderate	28	75.7	9	24.3	
severe	20	58.8	14	41.2	
primary event	**life**		**death**		Difference test
total	96	80.7	23	19.3	p=.0000
event	**With deterioration in the condition**		**Without deterioration in the condition**		Difference test
total	27	22.7	92	77.3	p=.0000
need of IMV&NIMV	**yes**		**no**		Difference test
total	54	45.4	65	54.6	p=.1158

clinical pictures/outcome	**oxygen mask N/%**		**IMV N/%**	**NIMV N/%**	Pearson Chi-square:
mild	46/95.8			2/4.2	p=.000000
moderate	19/51.3		7/18.9	11/29.7	
severe			15/44.1	19/55.9	
total	65/54.6		22/18.5	32/26.9	
clinical pictures/ comorbidity	**don't have**		**have**		
	N	**%**	**N**	**%**	
mild	22	45.8	26	54.2	p=.002789
moderate	6	16.2	31	83.8	
severe	6	16.6	28	82.4	
total	34	18.6	85	71.4	
clinical pictures/ age	**Means**	**N**	**Std. Dev.**	Analysis of Variance	Tukey HSD test
mild	52.3	48	12.20103	F=12.11572 p=0.000017	mild
moderate	62.3	37	11.98159		Moderate p=0.000722
severe	64.2	34	11.47981		severe p=0.000171
total	58.8	119	13.00694		
clinical pictures /TT	**Means**	**N**	**Std. Dev**	Analysis of Variance	Tukey HSD test
mild	82.1	48	12.89503	F=1.92970 p=0.149824	
moderate	84.3	37	12.77379		
severe	87.8	34	12.97265		
total	84.4	119	12.98080		
clinical pictures /d-Dimer	**Means**	**N**	**Std. Dev**	Analysis of Variance	Tukey HSD test
mild	3.0	48	15.04442	F=8.5963 p=0.000330	severe mild=0.000321 moderate=0.019639
moderate	8.3	37	17.00197		
severe	21.0	34	26.79203		
total	9.8	119	20.86311		
clinical pictures /LUS	**Means**	**N**	**Std. Dev**	Analysis of Variance	Tukey HSD test
mild	10.6	48	2.966718	F=310.64 p=0.000000	mild moderate p=0.000113 severe p=0.000113
moderate	18.2	37	1.529981		
severe	22.8	34	1.628895		
total	16.4	119	5.615803		
clinical pictures /IL-6	**Means**	**N**	**Std. Dev**	Analysis of Variance	
mild	17.4	9	12.9323	F=4.1165 p=0.025348	
moderate	26.3	11	9.5638		
severe	97.1	16	115.0866		
total	55.5	36	84.6934		

The average value of LUS score in patients with mild disease form was 10.6±3.0, while patients with moderate disease had a higher average value 18.2±1.5 and patients with severe form had the highest value of 22.8±1.6. According to the Analysis of Variance test the difference between the average LUS score between groups is statistically significant for $p<0.05$. The Tukey HSD test showed that the difference is due the difference between the average value of LUS in patients with mild versus those with moderate and severe form (Table 2). Cut off value for LUS score in our study was 15.5. There is a statistically significant association between disease severity and LUS values (<15.5; >15.5) for $p<0.05$ (Pearson Chi-square: 110.917, df=2, p=0.00000).

In our patients LUS score was excellent in disease stratification and was a good prognostic marker for negative outcome (Table 3a, b).

Table 3a

Area Under the Curve / Test Result Variable(s): LUS

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.994	.004	.000	.986	1.000

Table 3b

Area Under the Curve / Test Result Variable(s): LUS

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.797	.046	.000	.707	.887

The average value of d-dimers in patients with mild disease was 3.0±15.0μg F.E.U./ml, and in the patients with moderate and severe disease had higher values of 8.3±17.0μg F.E.U./ml and 21.0±26.8 μg F.E.U./ml respectively. There is great standard deviation in all groups of patients speaking of big variations in patients' conditions with the same disease severity. The difference between the average values of d-dimers is statistically significant for $p<0.05$. According the post hoc test (Tukey HSD test) the difference is due the difference between the average value of d-dimers in patients with severe versus moderate and mild form (Table 2).

The average value of IL-6 in patients with mild disease was 17.4±12.9 pg/ml. Patients with moderate disease had higher values of 26.3±9.6 pg/ml and patients with severe form had the highest average values of interleukin-6 97.1±115.1 pg/ml. The difference was statistically significant for $p<0.05$ ($p=0.025348$)(Table 2).

19.3% of the patients included in the study died. There was a statistically significant association between disease severity and lethal outcome for $p<0.05$ (Pearson Chi-square: 22.5019, df=2, p=.000013) (Table 2).

Discussion

Infection with the beta coronavirus SARS-CoV-2 in Macedonia resulted with a wave of patients that needed hospital treatment. Hospital resources were put to the test. Adequate patients' management in a timely manner is dependent on finding risk factors for severe disease progression and poor prognosis. Evidence so far suggests that gender, age, obesity and comorbidities can be associated to progression into severe disease and poor prognosis (24-29). In our study also, there were more male patients with moderate and severe disease than female patients. Older age and the presence of comorbidities (hearth disease and diabetes) were associated to more severe disease.

Laboratory values like leucocyte and lymphocyte count, lactate dehydrogenase, d-dimers, troponin, ferritin, interleukin 6, are associated with more severe forms of disease, poor prognosis and can help in patient management (9). Jing Zhang analyzed 901 SARS-CoV-2 positive patients divided according to their clinical condition. 366 patients had mild, 411 had moderate and 124 patients had severe disease. The average value of interleukin-6 was < 1.5pg/ml (IQR < 1.50 – 2.15)

in patients with mild disease, 1.85pg/ml (IQR < 1.50 – 5.21) in patients with moderate disease and 21.55 pg/ml (IQR 6.47 – 94.66) in patients with severe disease (P < 0.001). Values of IL-6 greater than 37.65pg/ml were predictive of death (AUC 0.97 [95% CI 0.95 – 0.99], P < 0.001) with sensitivity of 91.7% and specificity of 95.7% (30). In our study patients with more severe disease had higher values of interleukin-6. The average value in patients with the most severe disease was 97.1±115.1pg/ml.

The most frequent finding in Covid 19 patients that require hospitalization is higher values of d-dimers. The first published evidences are from 1099 patients in the study of Guan at all. They report that patients that did not survive have had higher values of d-dimers (average 2.12 μg/mL) compared to patients that survive (average 0.61 μg/mL) (31). In the retrospective study of Fei, patients that finally didn't survive have had d-dimer values higher than 1 μg/mL(32). Recent guidelines from the association of hemostasis and thrombosis state to recognize the values of d-dimers as elevated, if they are 3 to 4 times higher than the referent value (7). Elevated d-dimers can be the result of couple of mechanisms. Viral infection leads to liberation of procoagulant cytokines and chemokines and insufficient anti-inflammatory response (33). Additionally, it can lead to endothelial disfunction which leads to formation of thrombin (34). The hypoxia itself can activate the hemostatic cascade on its own (35). Autopsies from diseased from Covid 19 showed microthrombus formation in the microcirculation of the lungs. Hypoxia is not a result of pneumonia, but micro-thrombosis in the lungs (36). And finally some patients can develop septic coagulopathy or disseminated intravascular coagulation (5).

Different imaging technics also have a role in diagnosing SARS-CoV-2 positive patients and evaluating disease severity and prognosis. CT of the lungs has a pivotal role in evaluating the extent and type of lung injury, but is not always feasible. It can carry a greater risk for viral spread and worsening patient's condition who needs to be transferred to radiology department (11). Several studies have shown that there is no association between x ray findings and clinical parameters and disease outcome (37). Lung ultrasound is a bedside method that doesn't impose the need for patient's transfer and it doesn't carry the risk of viral spread. Lung changes in patients with Covid 19 pneumonia are located peripherally and so readily accessible for ultrasound visualization. Several studies have already shown its diagnostic, monitoring and prognostic value (19,38,39). In the study of Li Ji, LUS score was used for disease stratification. 280 patients were included and were stratified according to the LUS as having low, moderate and high LUS score. Patients with high LUS score had a greater percent of complications as respiratory failure, ARDS sepsis, myocardial injury or real failure. 23 patients died in the study all in the group with high LUS score (39). In our study the cut of value for LUS is 15.5. Patients with LUS greater than 15.5 are with moderate and severe disease. The LUS score has a great prognostic value in determining patients that will develop severe disease and usually need mechanical ventilation. Also, it has a good prognostic value in determining patient with the risk of negative outcome (Table 3).

Conclusion

Lung ultrasound in our study was a verry efficient method in evaluating the magnitude and type of lung injury and is a very useful tool in prognosing the clinical course of the disease and patient's outcome in patients with SARS-CoV-2 infection.

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THE EFFICACY OF O-MAC, PATENT VIDEO LARINGOSCOPE AND CONVENTIONAL LARINGOSCOPE FOR INTUBATION IN THE OPERATING ROOM

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ABSTRACT

Management of the airway in patients undergoing surgery is increasingly difficult. The airway management in the operating room in terms of the initial action of anesthesia is very important. Video-laryngoscopy has been shown to provide a better view of the larynx's structure compared to direct visualization. We describe our experience using a custom made and inexpensive tool for a video-laryngoscopy.

This is an experimental research with single randomized clinical trial conducted at the Anesthesiology Department of Sanglah General Hospital Denpasar. There were 270 patients divided into three group with conventional, O-Mac® and Mc-GRATH™ BF laryngoscope, aged 18 – 65 years, with Mallampati grade 1-2, randomly selected, and signed informed consent.

Intubation time was the fastest with O-Mac® median 26 (15-36) seconds, p = 0.000. Laryngoscopy time was the fastest with O-Mac® median 5.5 (2-13 seconds), p = 0.000. O-Mac® did not use many tools, p = 0.000. All three did not produce tissue damage with results p = 0.007. Hemodynamic changes were p = 0.000.

The O-Mac® is superior in terms of laryngoscope time and intubation time compared to the Mc-GRATH™ BF blade and has the same level of safety as the patented Mc-GRATH™ video laryngoscope and better than conventional laryngoscopes.

Key Words: *airway management, conventional laryngoscope, O-Mac®, Mc-GRATH™ video laryngoscope.*

Introductions

Management of the airway in patients undergoing surgery is increasingly difficult. One of the factors that makes the management of the airway become difficult is excess fat around the neck. These patients will usually have limited neck mobility due to the obstructing accumulation of fatty tissue in the neck and hump of the patient.

The sophistication of equipment in the operative field has made operators more courageous to perform surgeries in the neck and its surrounding areas, so that airway management is increasingly demanded to be done immediately and anywhere.

Video-laryngoscopy is able to provide a better view of the larynx's structure compared to direct visualization. They have been shown to increase Cormack-Lehane (CL) levels in difficult laryngoscopy and improve intubation success (1). Commercial video-laryngoscopes such as C-MAC (Karl Storz Gmbh & Co., Tuttlingen, Germany), GlideScope (Verathon Medical Inc., Bothell, USA), Airtraq (Prodol Meditec, Vizcaya, Spain), Ambu Pentax-AWS (Ambu A/S, Ballerup, Denmark), McGrath (Aircraft Medical Ltd., Edinburgh, UK) and King Vision laryngoscope (King systems, Noblesville, USA), are considered expensive hence not available in many centers (2). We describe our experience of using a custom made and inexpensive tool (which costs under US $80 – and includes complete laryngoscope set with 3 different sized Macintosh blades) that can be used to perform video-laryngoscopy. O-Mac® video laryngoscope have register number HKI.KI.05.01.02. P00202101656 and A00202100589 from industry design registration of Indonesia.

Material and Methods

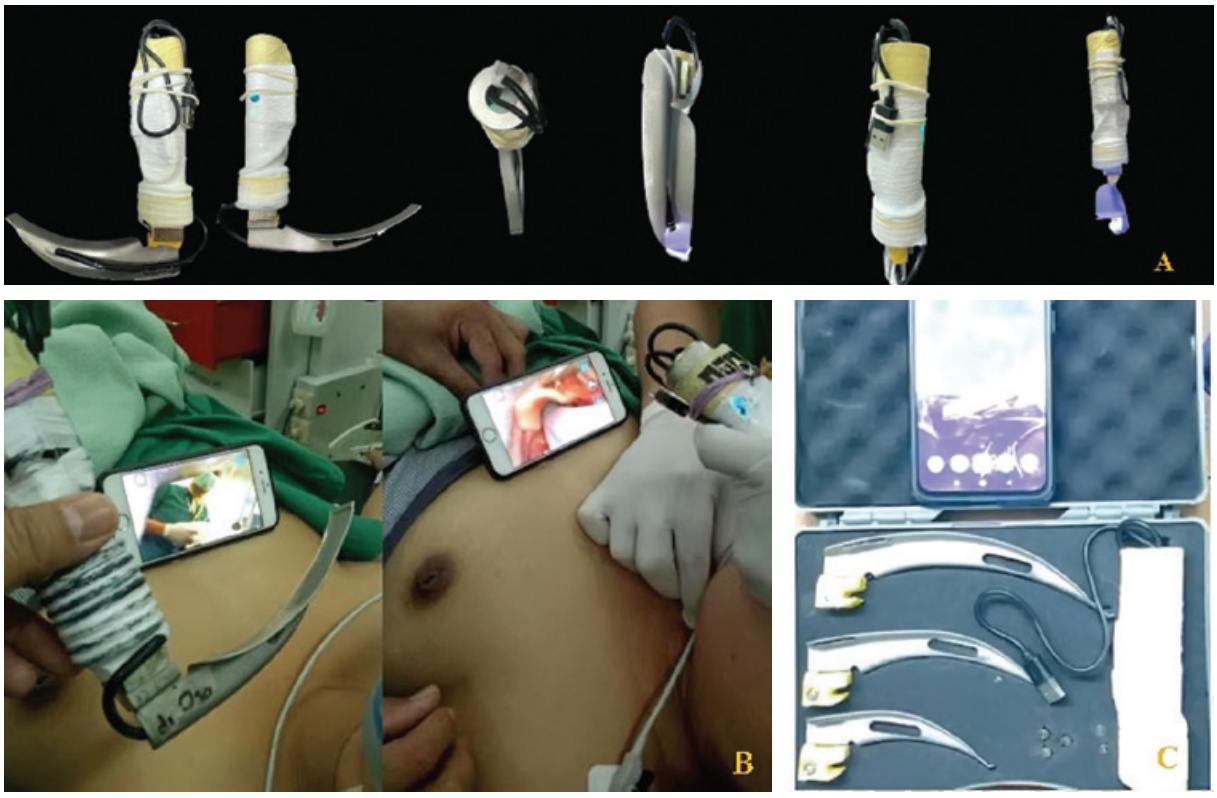
This study is a single randomized clinical trial conducted at the Anesthesiology Department of Sanglah General Hospital Denpasar. Health Research Ethical Clearance Committee of Sanglah General Hospital with protocol number: 1053 / UN 14.2.2VII.14/ LT/2021 released on April 8nd, 2021. There were 270 patients divided into three groups, conventional, O-Mac® and McGRATH™ BF laryngoscope, aged 18 – 65 years, both male and female, American Society of Anesthesiologists (ASA) classification of 1 – 4, elective-emergency, either performed in the Central Operating Theatre (COT)/ Emergency Room (ER)/ Very Important Person (VIP) Operating Theatre, in April 2021, randomly selected, to be involved in this study for video-laryngoscopy. This study is a prospective study. Mallampati grades of 1-2 were chosen. Difficult airway predictors, such as Mallampati and high Body Mass Index (BMI) were anticipated as difficult airways. Patients with prominent teeth, large tongue, tracheal malformation, history of difficult airway, and those who refused to be involved in the study were excluded. Sampling was carried out using a non-probability consecutive sampling method with permutated block random sampling to obtain viable subjects. All patients included in this study and the laryngeal specialists will know the use of the instrument, before the study is carried out. There were 270 samples required.

All patients were prepared for intubation by performing pre-oxygenation for minutes using 100% oxygen, using the patients' spontaneous breathing. The induction was then performed with subsequent regimens: Fentanyl, as an analgesic agent, 2 microgram/kilogram bodyweight (kg BW) intravenous (IV) by titration, and then waited for 5 minutes, followed by hypnotic agent administration Propofol 1.5 mg/kg BW IV by titration. If there was a decrease in Mean Arterial Pressure (MAP) and/or heart rate (HR) of more than 20%, a 10 mg IV bolus of ephedrine was given. Immediately after the patient fell asleep by observing the eyelashes reflex, a skeletal muscle relaxant 0.5 mg/kg BW IV bolus of Atracurium was administered, followed by 4 minutes wait,

and then followed by 1.5 mg/kg BW IV bolus of Lidocaine 2%, and then followed by 1-minute wait to reach the onset of sympathetic response blunting. After that, the laryngoscopy process was carried out.

The determination of the laryngoscope's blade size was based on the length of the lips against the temporomandibular joint (TMJ). This device was assembled by attaching a 5.5millimeter (mm) diameter Wi-Fi-connected endoscopic camera (Shenzhen Technology Incorporation, China) to the Macintosh Laryngoscope blade sleeve to replace the bulb slot (Figure 1). The camera was installed approximately 50 mm from the tip of the laryngoscope blade by keeping the image recorded visible on the monitor screen using our tailor-made cable clamp mechanism. The videos are directly recorded on the smartphone, via Wi-Fi connectivity using the "Wi-Fi Check" software (Shenzhen Technology Incorporation).

Figure 1. *O-Mac® design section (A), O-Mac action (B), O-Mac® set (C).*

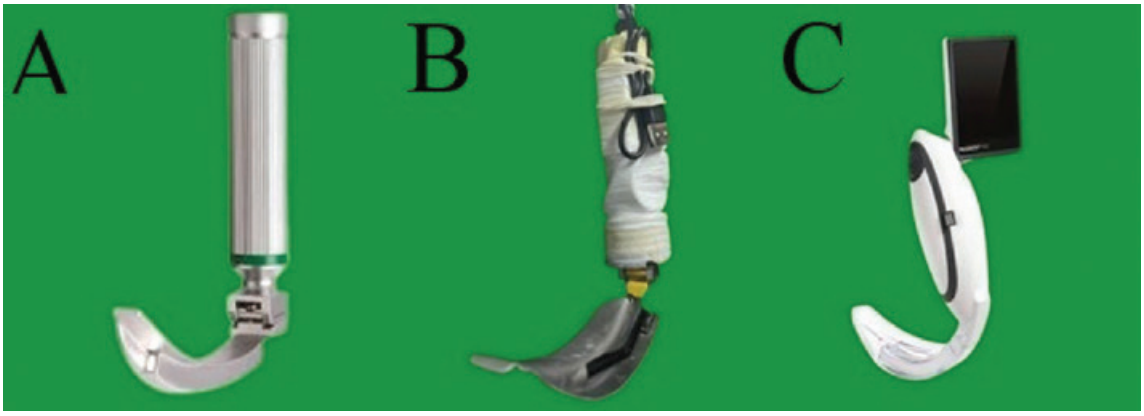


The video was recorded in the MOV format during laryngoscopy and intubation, which were then reviewed for observation. The choice of the endotracheal tube was Polyvinyl Chloride (PVC) endotracheal tube with an internal diameter (ID) of 7.5 or 7.0 mm in males and ID of 7.0 or 6.5 mm in females. The tube was used after general anesthesiology induction and muscle relaxant administration. The time needed for laryngoscopy was recorded, defined in seconds, taken from the time the laryngoscope blade passed the maxillary incisor to the glottis visualization. The time needed for intubation was recorded, which was defined as in seconds from the entry of the

laryngoscope blade into the oral cavity through the maxillary incisors until the confirmation of the airway for ventilation. The best degree of CL is recorded before intubation was performed.

The POGO score, calculated by the writer based on the previously recorded video on the smartphone, was measured as the visualized linear glottic opening length, to obtain the best glottic view before intubation. Design of three laryngoscope at Figure 2.

Figure 2. *Design of laryngoscope A; Conventional, B; O-Mac®, C; McGRATH™ MAC BF blade*



Results

The sample of the study was 270 subjects, whereby each group had 90 subjects in inclusion criteria using a non-probability-consecutive sampling technique. In this study, in the overall data obtained there was no sample dropout. The age characteristics were matched in the age range 18 – 65 years. Table 1 shows basic characteristics of research subjects and Table 2 – the result of Comparison results between conventional laryngoscope, patent video laryngoscope (McGRATH™ MAC BF blade) and O-Mac®.

Discussion

In this study, the results showed that the intubation time with each of 90 subjects was obtained p=0.000 with the fastest results facilitated by O-Mac® with a median of 26 (15-36) seconds, while McGRATH™ MAC BF blades with a median of 39.50 (30-95) seconds with the slowest intubation time compared to conventional video laryngoscopes with a median of 30 (20-90) seconds. This is different from Luqman (2017) conventional laryngoscopes with McCoy resulting mean ± SD (26.92 ± 5.03) seconds and conventional mean ± SD (40.64 ± 5.7), p-value <0.001 (12). Meanwhile, Karipapacheri (2013), resulting the mean 28.58 ± 21.01 (9 – 89) seconds on the C-MAC device p = 0.001 (13). On Vadhanan (2017) results were v-scope mean ± SD (77.25 ± 26.46 and miller 74.15 ± 26.3 seconds), p <0.001 (14). Hernandez (2020) with each sample of 15 subjects, founds that it was known that VDL Hybrid 1.0 (GI) and Macintosh No. 3 shovels (GII) with median results of G1 27 (15-120) and GII 106 (18-120) seconds with p value of 0.005 (15). Bueggeney (2016) By comparing the C-MacTM D-blade, GlideScopeTM, McGrathTM,

AirtraqTM, AP AdvanceTM, KingVisionTM the median intubation time was obtained, the results were 56 seconds (20-177), 60 seconds (17-180), 53 seconds (20-179, 47 seconds (18-179), 93 seconds (33-180), 59 (31-180) with p <0.01 This is because the tools used and the sample population were different (16).

In the O-Mac® study also looking at the relationship of intubation time with assistive tools/ techniques, it was found that there was a positive linear relationship with r = 0.354 and p = 0.000. This shows that by using tools/ techniques to assist intubation, the required intubation time will be even longer. As for the tools/ assistive techniques, the most widely used in this group is the use of stylet. Even without any indication of a difficult airway, it seems that due to the initial recognition of the device at the laryngoscopy, there is an incorrect indoctrination with the collection of testimonials by the laryngoscopes, that the use of Mc-GRATH™ requires embossed stylet. This explains why the intubation time required for each laryngoscope group was significantly different, especially in the Mc-GRATH™ laryngoscope group,

In this study, the results showed that the laryngoscopy time obtained median laryngoscope time for conventional laryngoscopes of 7 (1-40) seconds, McGRATH™ MAC blades of BF 10 (1-60) seconds and O-Mac® were the most superior with a median time of 5.5. (2-13 seconds) with a result of p=0.000. This is different from Brueggeney (2016) with C-MacTM D-blade, GlideScopeTM, McGrathTM, AirtraqTM, AP AdvanceTM, KingVisionTM device where the median laryngoscopy time was 17 (6-46) seconds, 19 (3-100) seconds, 18 (6-53) seconds, 20 (5-110) seconds, 30 (9-142) seconds, 26 (7-117) seconds with p <0.01. In Karippacheril's (2014) study using a video laryngoscope connected to a USB, the mean ± SD (minimum-maximum) laryngoscope time was found to be 22.17 ± 12.78 (7 – 59) seconds (16). On research Vadhnan (2017) comparing Miller and V-scope obtained mean ± SD laryngoscope times of 62.2 ± 25.1 and 62.2 ± 25.1 with p = 0.25 not significant (14). This is because the tools used and the sample population were different, where the population average used the Caucasian race which clearly has a greater body weight than Southeast Asian races such as Indonesia. This may be a factor affecting this, although no statistical analysis was carried out between this study and other studies that have been carried out in Europe and America.

In the Cormack-Lehane and POGO grade results, the overall results were obtained at median grade II (I-III) and POGO with medians, respectively, conventional laryngoscope, McGRATH™ MAC BF blade, and O-Mac® 80 (20-100); 80 (20-100); 80 (40-100)%; not statistically different in the three tools with p = 0.024 for the Cormack-Lehane degree and p = 0.048 for POGO. This is the same as the research Luqman (2017), but Karippacheril (2014) had different results where Cormack-Lehane degree 1 degree at 9/24 and degree 2 at 15/24 with POGO mean ± SD (deviation) 62.29 ± 28.40 (20-100)% with p value = 0.001 on video laryngoscope – USB used (9). In research by Brueggeney (2016) in 720 patients with 120 subjects each with a C-MacTM D-blade, GlideScopeTM, McGrathTM, AirtraqTM, AP AdvanceTM, KingVisionTM device, the results were obtained where degrees of Cormack lehane I / IIa / IIb / III / IV (n) sequentially in each of the tools (76/36/7/0/0), (80/29/3/2/3), (64/45/9/1/0), (74/30/4/0/3), (19/28/22/8/19),

(63/41/7/1/4) and p = <0.01 †, for POGO the median (percentage); [90 (80; 100)], [100 (83; 100)], [90 (80; 100)], [90 (80; 100)], [60 (10; 80)], [90 (80; 100)] with p <0.01 † (16). This research is the same as research of Hernandez (2020) with each sample of 15 subjects. It was shown that VDL Hybrid 1.0 (GI) and Macintosh No. 3 shovels (GII) with results of degrees I, II, III, and IV sequentially [(14,1,0,0; 1,8,3,3)] with p = <0.0001. In this study it is different from Vadhanan (2017) comparing to Miller and V-scope obtained Cormack-Lehane I, II, and III degrees, as the results are sequentially; with significant p = 0.0015 (1,3,4,7,9,15,16). This is because in this study the subject population has been determined with limited inclusion criteria. Namely Mallampati had only I and II, BMI in each device with a normal median, the degree of Cormack-Lehane I-III, the tool used had the same design, namely using Machintos blades and allowed to use assistive tools/ techniques while using the tools to get the best visualization results. The results of the Cormack-Lehane degree relationship with the tool/ technique were found to be linearly related to r = 0.196 with significant results with p = 0.001, while for POGO it was inversely related to the result of r =-230 with significant p = 0.000.

The results of using the intubation tool/ technique, it is found that the McGRATH™ MAC BF blade requires at least 1 tool out of the four tools that are usually used in the form of a Stylet, BURP (Extra Laryngeal Manuever), Magill Forceps and Gum Elastic Boogie, whereas conventional laryngoscopes and O-Mac® do not use tools much, with the result p = 0.000. This is due to the wrong assumption on the use of the McGRATH™ MAC BF blade which has to use one tool, with the most yields on the stylet.

The results of tissue damage due to laryngoscopes found that the three laryngoscopes did not cause damage with consecutive results between conventional laryngoscopes, McGRATH™ MAC BF blades, and O-Mac® [89 subjects (98.88%); 82 subjects (91.11%) and 89 subjects (98.88%)], with p = 0.007. However, when compared to each of the 2 tools, Conventional laryngoscope and McGRATH™ MAC BF blade obtained p = 0.018, conventional laryngoscope and O-Mac® p = 1,000, McGRATH™ MAC BF blade, and O-Mac® p = 0.018. This indicates that each of them is not significant because the power of this study is 99%, p = 0.01.

The hemodynamic response was pronounced clinically in the conventional laryngoscope group, but was not statistically significant. The reason for this was the large CI value, requiring a larger sample size as well, by reducing the alpha value to near zero. The correlation that was clinically clear appears to be a relationship between hemodynamic responders with prolonged intubation time, intubation tools/ techniques used, and tissue damage that occurred, did not appear statistically significant, so a larger sample size is needed for statistical proof.

The limitations of this study relate to the first experimental clinical trial research, so to obtain good internal and external validity, it requires fairly strict inclusion and exclusion criteria, so that the limitations of this study are using subjects in certain populations and carried out in certain places, so that the results of this study cannot describe the same conditions in different populations, procedures and locations.

Table 1. *Basic characteristics of research subjects*

Parameter	**A Conventional laryngoscope n = 90**	**B (McGRATH™ MAC blade BF) n = 90**	**C O-Mac® n = 90**
Age [years, median (minimum-maximum)]	43 (18-65)	47 (18-65)	46a (18-65)
BMI kg/ m2 [(median (minimum-maximum)]	23.2 (17.5-34.9	22.85 (19-32)	22.3 (18.1-30)
Laryngoscope Time [seconds, median (minimum-maximum)]	7 (1-40)	10 (1-60)	5,50 (2-13)
Intubation Time [seconds, median (minimum-maximum)]	30 (20-90)	39.50 (30-95)	26 (15-36)
Cormack-Lehane degrees n (%)			
- Degree 1	31 (10.33)	28 (31.11)	43 (47.78)
- Degree 2	48 (53.33)	52 (57.78)	43 (47.78)
- Degree 3	11 (12,22)	10 (11,11)	4 (4.44)
POGO% median (minimum-maximum)]	80 (20-100)	80 (20-100)	80 (40-100)
Use of tools / techniques for intubation aids n (%)			
- Not used	55 (61.11)	20 (22,22)	51 (56.67)
- *Stylet*	16 (17.78)	58 (64.44)	13 (14.44)
- *ELM (Extra Laryngeal Manuever)*	14 (15.56)	5 (5,56)	2 (2.22)
- *Magill Forceps*	0 (0.00)	2 (2.22)	2 (2.22)
- *Gum Elastic Boogie*	0	1 (1.11)	0
- *Magill Forceps and ELM*	1 (1.11)	0	0
- *ELM and Stylet*	4 (4.44)	4 (4.44)	3 (3.33)
Total Attempted Intubation n (%)			
- 1x	84 (93.33)	72 (80.00)	84 (93.33)
- 2x	5 (5,55)	14 (15.56)	6 (6.67)
- 3x	1 (1.11)	4 (4.44)	0 (0.00)
Tissue Damage Due to Laryngoscope n (%)			
- No damage	89 (98.88)	82 (91.11)	89 (98.88)
- Airway bleeding	0	5 (5,55)	0
- Torn lips	1 (1.11)	1 (1.11)	1 (1.11)
- Glottic edema	0	1 (1.11)	0
- Broken teeth and airway bleeding	0	1 (1.11)	0
Successful Intubation	90 (100)	90 (100)	90 (100)
Delta MAP [(%, median (minimum-maximum)]	8 (0-60)	4 (0-42)	4 (0-8)
Delta HR [(%), median (minimum-maximum)]	6 (0-44)	4 (0-21)	3 (0-9)

Table 2. *Comparison results between conventional laryngoscope, patent video laryngoscope (McGRATH™ MAC BF blade) and O-Mac®*

Parameter	Conventional laryngoscope n = 90	McGRATH™ MAC n = 90	O-Mac® n = 90	P *	Ratio (p) +		
Age (years)	43 (18-65)	47 (18-65)	46 (18-65)	0.376	A	B	0.335
						C	0.180
					B	C	0.670
BMI (kg / m2)	23.2 (17.5-34.9	22.85 (19-32)	22.3 (18.1-30)	0.207	A	B	0.739
						C	0.213
					B	C	0.080
Laryngoscope time (seconds)	7 (1-40)	10 (1-60)	5,50 (2-13)	† 0,000	A	B	0.052
						C	† 0.006
					B	C	† 0,000
Intubation time (seconds)	30 (20-90)	39.50 (30-95)	26 (15-36)	† 0,000	A	B	† 0,000
						C	† 0,000
					B	C	† 0,000
Cormack-Lehane degrees	1 (1-3)	2 (1-3)	2 (1-3)	0.024	A	B	0.775
						C	0.030
					B	C	0.011
POGO	80 (20-100)	80 (20-100)	80 (40-100)	0.048	A	B	0.386
						C	0.169
					B	C	0.011
Use of tools / techniques for intubation aids	0 (0-2)	1 (0-2)	0 (0-2)	† 0,000	A	B	† 0,000
						C	0.655
					B	C	† 0,000
Total Intubation Attempts	1 (1-3)	1 (1-3)	1 (1-2)	† 0.004	A	B	† 0.008
						C	0.984
					B	C	† 0.007
Tissue Damage Due to Laryngoscope	0 (0-1)	0 (0-2)	0 (0-1)	† 0.007	A	B	0.018
						C	1,000
					B	C	0.018
Delta MAP (%)	8 (0-60)	4 (0-42)	4 (0-8)	† 0,000	A	B	† 0.003
						C	† 0,000
					B	C	0.015
Delta HR. (%)	6 (0-44)	4 (0-21)	3 (0-9)	† 0,000	A	B	0.014
						C	† 0,000
					B	C	0.103

Information:
A: *Conventional Laryngoscope*
B: *McGRATH™ MAC BF Blade*
C: *O-Mac®*
** Kruskal-Wallis test; median (minimum-maximum)*
+ Mann-Whitney
† significant

Conclusion

Based on the analysis and discussion of comparative research results efficacy of O-MAC, a patents' video laryngoscope facilitated by McGRATH™ MAC Blade BF, and conventional laryngoscope in performing intubation in the operating room of the Sanglah Hospital, Denpasar results are: (1) The video laryngoscope proved to be superior in laryngoscopy time and faster intubation time (only in O-Mac®), fewer intubation attempts, less tissue damages, and minimal

hemodynamic response, when compared to conventional laryngoscopes; (2) O-Mac® is no worse than a patent's video laryngoscope in terms of Cormack-Lehane degree, use of intubation aids/ techniques, total intubation attempts, tissue damage due to laryngoscope, and hemodynamic changes (HR / MAP).

Supporting Information

O-Mac:

https://youtu.be/ANNVnpu4d18

https://youtu.be/9gTVSTLzdv8

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COLON RESECTION WITH PRIMARY ANASTOMOSIS IN OBSTRUCTIVE COLON CANCER: RELIABLE TREATMENT OPTION

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ABSTRACT

Introduction. Colon cancer can be presented as an emergency due to obstruction in 15-20% of the patients. One of the options for treatment is a colon resection with primary anastomosis as single-stage surgery. The aim of this retrospective interventional study is to present the early postoperative outcome in patients operated for large bowel malignant obstruction.

Materials and Methods. Sixty-four patients presented were operated for large bowel malignant obstruction due to colon carcinoma. All were treated with segmental colon resection or subtotal colectomy with primary anastomosis using circular stapler or hand-sewn anastomosis.

Results. Patients' mean age was 74.3 years. Period from symptoms onset to hospital admission varied from 1 to 12 days. Overall complication rate was 29.7%. Anastomotic dehiscence occurred in 3 patients (4.7%) and in-hospital mortality rate was 3.1%.

Conclusion. Segmental resection/subtotal colectomy with primary anastomosis for emergency large bowel obstruction is feasible treatment option, if we accept the demanding surgery conditions due to unprepared and distended colon.

Key Words: *Obstructive colon cancer, primary anastomosis, resection*.

Introduction

As a leading malignancy of the gastrointestinal system, colon cancer can be presented as an emergency due to obstruction. Fifteen to twenty percent of the patients with primary colorectal cancer present with intestinal obstruction. In 8 to 29% of the patients, obstruction is the main symptom at diagnosis (1). The condition of these patients presented as emergencies is often suboptimal, so the mortality rates can reach up to 35% (2-4). Some of those cases are operated with staged surgical approach (Hartmann's procedure and after colonic stenting) (5). Another option for these patients is the single-stage surgery (primary colon resection or subtotal colectomy – in cases of massive cecal distension and/or deserosation and primary anastomosis at the same time (6). For right-sided colonic obstruction immediate resection and anastomosis is the universal treatment. Emergency primary anastomosis in left-sided disease can be a safe alternative in

selected patients, even in the presence of a free perforation with diffuse peritonitis (7). Due to the lack of possibility for colonic stenting and postponing surgery in our clinic, we often apply primary colon resection with anastomosis whenever the patient's condition allows it.

Material and Method

This is a retrospective study of 64 patients that were presented in our emergency department as cases of malignant colonic obstruction. All were treated with single-stage surgery (colonic resection/subtotal/total colectomy) with primary anastomosis. In the period of 1 year (January 2019 – February 2020) a total number of 64 cases were operated using single stage surgery (Figure 1). Cases with cecal and tumor perforation and consequent diffuse peritonitis were excluded from the study. The locations of the obstructing tumor are presented in Chart 1.

Figure 1. *Obstructive sigmoid cancer*

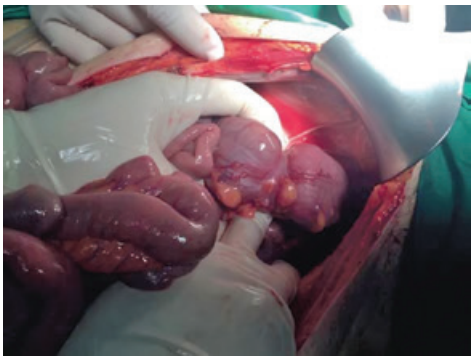
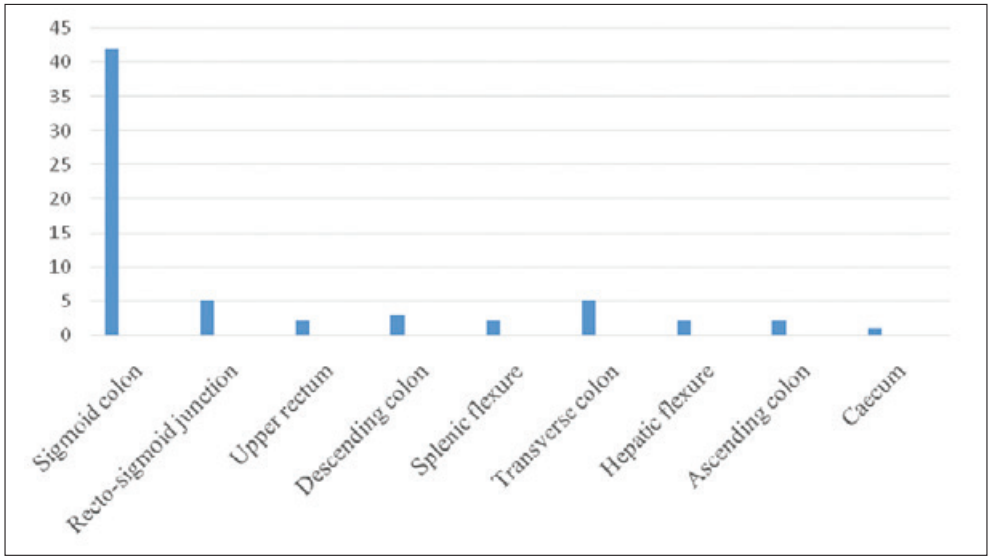


Chart 1. *Tumor site distribution*



Female/male ratio was 28/36 patients. The mean age was 74.3 years. The period from the onset of the symptoms to hospital admission varied from 1 to12 days. All patients were diagnosed with plain abdominal radiograph and 3 phase contrast CT-scan of the abdomen. After

admission, short resuscitation was done and the patients were operated on. The third generation cephalosporin (2g) was given 1 hour before skin incision and additional Metronidazole (500mg) during the operation. They were administered continuously in the postoperative period of 4 days. Depending of the tumor location and colon distension, colon resection, subtotal or total colectomy was performed. Intraoperative manual decompression or on-table lavage of the full colon was used. Circular stapler or a hand sewn anastomosis with absorbable monofilament 3-0 suture in termino-terminal or termino-lateral fashion were used for anastomosis creation. There were no intraoperative deaths. Two early postoperative deaths occurred; the first case due to pulmonary embolism and the second due to anastomotic dehiscence and secondary generalized peritonitis. Complication rate was 29.7% (Table 1). There were three cases of anastomotic dehiscence (4.7%) that were reoperated with a terminal colostomy creation. Wound seroma occurred in 9 cases, wound hematoma in 5 and surgical site infection in 2 cases. Median length of stay was 21.3 days.

Table 1. *Postoperative morbidity and mortality rates*

Complication	N (%)
Wound seroma	9 (14)
Wound hematoma	5 (7.8)
Wound infection	2 (3.12)
Anastomotic dehiscence	3 (4.7)
Re-operation	3 (4.7)
Overall morbidity rate	29.7%
Mortality rate	3.1%

Discussion

Single-stage surgery for obstructive colon cancer is one of the recommended options for this emergency condition (6).

According to Lee, primary anastomosis can be applied in more than 80% of the patients (8).

Awotar in his series reports leakage rate of 5.56% and mortality rate of 2.9% in the primary anastomosis group, thus concluding that single stage surgery for obstructive left colon cancer can be safely performed with adequate surgical expertise (9).

Hsu reports 214 cases of acute colonic obstruction operated by single surgeon with primary colon anastomosis, with a dehiscence rate of 2.3% and mortality rate of 10% (10).

Another parameter analyzed in the emergency setting of obstructive colon cancer are post-operative complications. Kim reports wound infection rate of 14.3% and 1.9% rate of wound disruption (11).

Our series had comparable anastomotic dehiscence, wound infection and mortality rates.

Ekinci compares the postoperative outcomes of two procedures (Hartman's and the single stage) in manner of postoperative complications, length of hospital stay and mortality rates and

concludes that there is no statistically significant difference, thus recommending the single stage procedure for method of choice in obstructed left-sided colorectal cancer (12).

However, there are still open questions for this strategy in terms of the patients' condition and the surgeons' experience in performing it. In high-risk patients with poor condition treated by surgeons with little experience in colorectal surgery, Hartman's procedure or even just diverting colostomy is ideal option (13).

Dehiscence rates for emergency colon surgery are higher compared to the elective ones and are reported to be up to 21% (14).

Colon obstruction and perforation as initial presentation of colon cancer are shown to be poor prognostic factors with higher local recurrence rates (15). Also, survival rate in emergency malignant large bowel obstruction is poor comparing to patients with non-obstructive lesions (16).

Conclusion

Colon resection with primary anastomosis for emergency large bowel obstruction due to colon cancer is one of the reliable treatment options, if we can accept wound infection, dehiscence and mortality rates. They are certain postoperative reality in the case of emergency colon cancer presentation. One should also have in mind the demanding surgery due to bowel distension and the unprepared colon conditions. All of these unwanted factors can be avoided by early-stage cancer detection.

Authors'Contribution

Nikolovski: concept, writing, design.

Minova: data collection.

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SERUM CA 19-9 IN PANCREATIC ADENOCARCINOMA: CORRELATION WITH HYSTOPATHOLOGYCAL CHARACTERISTICS AND A PROGNOSTIC MARKER FOR SURVIVAL AFTER CURATIVE RESECTION

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ABSTRACT

Pancreatic cancer is the EU's third biggest cancer killer, despite being the seventh most common cancer, with the extremely poor outlook for patients. CA19-9 serum levels was evaluated as a screening tool in asymptomatic individuals and in patients with symptoms related to pancreatic cancer. The aim of the study was to correlate CA19-9 serum level in patients with pancreatic adenocarcinoma with gender, age, grade of differentiation, tumor size and tumor stage. Also, CA19-9 serum level and survival rate was determinate for the period of one year. The study included 62 patients, 40 male and 22 female with pancreatic cancer, diagnosis confirmed by histopathological examination after surgical treatment. CA19-9 measurements were carried out at certified laboratories. The normal level of CA19-9 was 37U/ml. The patients were divided into 2 groups: the first group with increased CA19-9 level under 100U/ml and the second group with CA19-9 level over 100U/ml. Correlation between histological tumor characteristics including: tumor size, tumor stage and cell differentiation, as well as CA19-9 serum levels, revealed insignificant results. However, patients with elevated CA19-9 values higher than 100U/ml were more frequently measured in patients with larger tumors, advanced III stage of tumor and poorly differentiated tumors. Our study revealed significant correlation between CA19-9 levels and patients' gender (more in female patients than in male, 90.9% vs 62.5%), age of the patients (older patients) and survival in patients with pancreatic cancer (p=0.022).

Introduction

Pancreatic cancer (PC), as one of the most devastating and lethal malignant diseases, is mostly diagnosed at advanced-stage disease. The new cases of pancreatic cancer in Europe for 2020 are 495,773, and the number of mortalities is 466,003. Higher incidence of PC has population in the United States compared, and in the general population is nearly 8/100,000 persons (1). PC has extremely poor prognosis and 5-years survival rate of less than 10% (2,3,4).

Carbohydrate antigen (CA 19-9) discovered in the year 1979 is the most used tumor marker for pancreatic cancer diagnosis (5,6,7). Furthermore, CA19-9 serum levels were evaluated as a

screening tool in asymptomatic individuals and in patients with symptoms related to pancreatic cancer (8). Numerous studies have reported the utility of preoperative CA19-9 level, as a useful marker for predicting prognosis of pancreatic cancer (9,10). In addition, despite of levels of serum CA19 – 9, novel genetic and epigenetic biomarkers are required for early diagnosis of PC. Elevated CA19-9 serum levels might be associated to other pancreatic diseases such as chronic pancreatitis, hereditary pancreatic lesions and are appropriate with other biomarkers to improve the accuracy of diagnosis (11,12,13,14).

Deficiency of CA19-9 expression is found in about 5% of the population, while an elevation can be observed in other diseases including chronic pancreatitis and obstructive jaundice. The sensitivity and specificity of CA19-9 is a variable, approximately 85% for the detection of PC. This biomarker is not applicable as a screening method, and is not relevant for confirmatory or differential diagnosis (15,16,17). The utility of CA19-9 as a serum biomarker is widely used for detection of tumor recurrence after surgical resection (18,19,20).

Material and Methods

The study included 62 patients, 40 male and 22 female with pancreatic cancer, diagnosis confirmed by histopathological examination after surgical treatment. CA19-9 measurements were carried out at certified laboratories. The normal level of CA19.9 was 37U/ml. The patients were divided into 2 groups: the first group with increased CA19-9 level under 100U/ml and the second group with CA19-9 level over 100U/ml.

The aim of the study was to correlate CA19-9 serum level in patients with pancreatic adenocarcinoma with gender, age, grade of differentiation, tumor size and tumor stage. Also, CA19-9 serum level and survival rate was determinate for the period of one year.

Results

Tumor marker CA19-9 presented values higher than 100U/ml significantly more frequently in female patients than in male patients – 20 (90.9%) vs 25 (62.5%).

Patients with serum CA19-9 level of 100U/ml or lower were significantly older than the patients with CA19-9 level higher than 100U/ml. Patients with a serum CA19-9 level of 100U/ml or lower were aged 56 to 78 years (average of 69.8 ± 6.9 years), while patients aged 42 to 76 years (average of 61.3 ± 7.5 years) showed higher CA19-9 level of >100U/ml. The results revealed that age of the patients with pancreatic cancer had a significant effect on CA19-9 levels ($p=0.00015$).

Correlation between histological tumor characteristics including: tumor size, tumor stage, and cell differentiation and CA19-9 serum levels, revealed insignificant results. However, patients with elevated CA19-9 values higher than 100U/ml were more frequently measured in patients with larger tumors in 66.7%, than small tumors less than 2 cm in size, without statistical significance ($p=0.31$). Similarly, CA19-9 values higher than 100U/ml were found in tumors diagnosed

at an advanced stage, but without statistical significance (p=0.087). 18 (40%) patients were diagnosed with stage III tumor.

Concerning tumor cell differentiation, poorly differentiated tumors were more frequently associated to CA19-9 levels higher than 100U/ml. Correlation of tumor cell differentiation and CA19-9 serum levels were not sufficient for statistical significance (p = 0.55). Summarized results are presented in Table 1.

Table 1. *Correlation of CA 19-9 level with tumor size, stage, and cell differentiation*

Variable	Sizes	CA 19-9 (U/ml)		p value
		≤ 100 n (%)	>100 n (%)	
Tumor size	<2cm	4 (23.53)	3 (6.67)	Fisher exact
	2-4 cm	10 (58.82)	30 (66.67)	p=0.31 ns
	> 4 cm	3 (17.65)	11 (24.44)	
	in the celiac plexus	0	1 (2.22)	
Stage	IA	4 (23.53)	3 (6.67)	Fisher exact
	IB	4 (23.53)	4 (8.89)	p=0.087 ns
	IIA	4 (23.53)	9 (20)	
	IIB	2 (11.76)	11 (24.44)	
	III	3 (17.65)	18 (40)	
Differentiation	Well	0	1 (2.22)	Fisher exact
	Moderately differentiated	13 (70.59)	24 (53.33)	p=0.55 ns
	Poor	5 (29.41)	20 (44.44)	

Patients treated surgically were followed-up for a period of 12 months and there were 5 (29.4%) patients with increased values of CA19-9 up to 100U/ml, and 31 (68.9%) with increased values above 100U/ml.

The 6 and 12-months survival rates were 88.2% and 70.6% respectively in the group of patients with CA19-9 values up to 100U/ml, and 68.9% and 31.1% consistently in the group of patients with CA19-9 more than 100U/ml.

A significant difference in survival time was found between patients in group with CA19-9 above 100U/ml and group two with values up to 100U/ml. (p = 0.012), Table 2.

Table 2. *Total survival time depending on CA 19-9 levels*

CA 19-9 Increased values	Total (n)	Exitus N of events n (%)	cumulative survival % (Std. Error)	
			6 months	12 months
Up to 100	17	5 (29.41)	88.2 (0.045)	70.6 (0.111)
More than 100	45	31 (68.89)	68.9 (0.069)	31.1 (0.069)

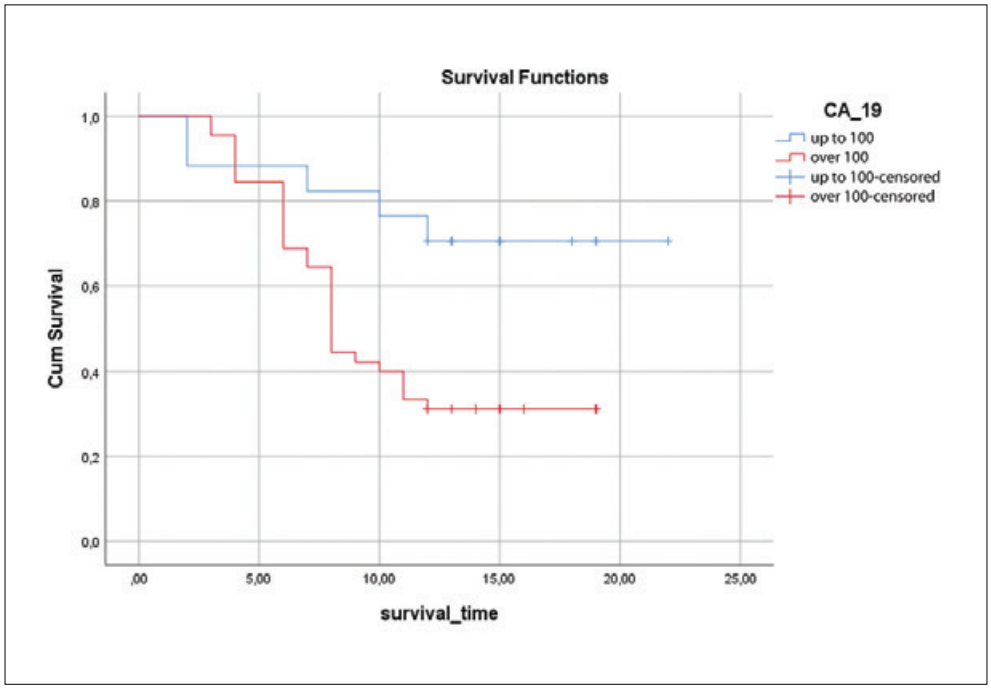
Log Rank (Mantel-Cox) =6.4, p=0.012 sig

The results showed that mean survival rate was 17.5 months in patients with CA19-9 values up to 100U/ml, and 10.8 months in patients with values higher than 100U/ml. The median survival time in the first group with CA19-9 up to 100U/ml is not defined, as more than 50% of these patients were alive after 12 months, and in the second group with CA19 – 9 levels higher than 100U/ml, the median survival time was 8 months, Table 3, Graph 1.

Table 3. *Average and median survival time depending on CA19-9*

CA19-9	Mean and Medians for Survival time							
	mean	Std. Error	95% CI	median	Std. Error	95% CI	75.0% percentile	Std. Error
≤ 100	17.47	1.8	13.97 – 20.97				12.0	
>100	10.76	0.9	9.03 – 12.48	8.0	0.37	7.27 – 8.73	6.0	0.89

Graph 1. *Survival curve depending on serum values of CA19-9*



Tumor marker CA19-9 levels were confirmed as a significant predictor of survival rate in patients with pancreatic cancer (p=0.022). Patients with CA19-9 values above 100U/ml compared to patients with values up to 100U/ml had about 3 times significantly higher risk of lethal outcome (3,026, 95% CI1.171 – 7,822), Table 4.

Table 4. *Univariate Cox regression analysis / CA 19-9*

CA 19-9	P	Exp (B)	95% CI for Exp (B)
Referent category – to 100			
over 100	0.022	3.026	1.171 – 7.822

Statistical Analysis

The continuous variables such as age, serum CA19-9 and follow-up periods were expressed as medians with ranges. The comparisons between clinicopathological characteristics and the CA19-9 values were performed with a Mann-Whitney *U* test or a Kruskal-Wallis *H* test if the grouping variables were more than two. Overall survival (OS) was defined as the time from the date of the surgery to either the date of death from any cause or the date of the last follow-up visit. The survival rate was estimated and calculated using the Kaplan-Meier survival curve. The strongest univariate predictor among the categorized serum CA19-9 measurements was chosen. The multivariate Cox proportional hazards model (forward) was fitted using all of the clinical and pathological variables, which included age, gender, tumor size, tumor cell differentiation, surgical margins, pT category, pN category, pTNM category, and CA19-9 with the optimal cutoff value. The corresponding hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated. SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Two-sided *P* values less than 0.05 were considered to be statistically significant.

Discussion

Firstly, numerous studies have investigated the usefulness of CA19-9 serum levels as a screening tool for pancreatic cancer in asymptomatic individuals and population with symptoms that might be related to pancreatic cancer.

Therefore, diagnostic value of tumor marker CA19-9 is limited by non-specific expression in several benign and malignant diseases, false negative results in patients with the presence of obstructive jaundice (10-60%) (21,22). However, serum level of CA19-9 is widely used biomarker for the diagnosis and/ or monitoring of the pancreatic adenocarcinoma, with a sensitivity of 70-95% and a specificity of 70-90% (Ballehaninna and Chamberlain, 2012; Scara et al., 2015).

In our study, the serum value of CA19-9 was elevated in all 62 patients and according to the level of increased value, patients were divided into two groups. The first group had CA19-9 values up to 100U/ml (17 patients) and the second group had values above 100U/ml (45 patients).

Correlation between CA19-9 levels and patients gender revealed values higher than 100U/ml of CA19-9 significantly more in female patients than in male, 90.9% vs 62.5%. The age of patients with pancreatic cancer had a significant effect on CA19-9 levels. Patients with a serum CA19-9 level of 100U/ml or lower were significantly older than patients with CA19-9 higher than 100U/ml. Patients with CA19-9 level of 100U/ml or lower had an average age of 69.8 ± 6.9 years, while the average age of patients with CA19-9 higher than 100U/ml was 61.3 ± 7.5 years.

Correlation between serum level of CA19-9 value and pathohistological tumor characteristic including: tumor size, stage, tumor differentiation, revealed statistically insignificant results.

CA19-9 level higher than 100U/ml were more frequently measured in patients with larger tumors, T2 in 30 (66.67%) and T3 in 11 (24.44%) patients; in patients diagnosed at a more advanced stage, III stage in 18 (40%) patients; and in patients with poorly differentiated tumors, 20 (44.4%) patients and moderately differentiated tumors in 24 (53.3%) patients. The results of a study by Distler M et al. (166) showed that serum levels of tumor markers CEA, CA19-9 and the degree of tumor cell differentiation were important predictors for shorter survival in 195 patients with pancreatoduodenectomy due to adenocarcinoma of the head of the pancreas.

This study revealed that serum marker CA19-9 level has significant prognostic value in patients with pancreatic adenocarcinoma. Survival time for a period of 12 months after the operation in correlation with CA19-9 levels was 29.4% for the patients with CA19-9 less than 100U/ml, and 68.9% for the patients with CA19-9 above 100U/ml. Patients with higher CA19-9 tumor marker values above 100U/ml had shorter, 6 and 12 months, survival time. The median survival time in the group with CA19 – 9 up to 100U/ml was not defined, as more than 50% of these patients were alive after 12 months. The second group with CA 19-9 values higher than 100U/ml, the median survival time was 8 months. The tumor marker CA19-9 was confirmed as a significant predictor of survival in patients with pancreatic cancer (p=0.022). The results of our study showed that increased serum CA19-9 levels more than 100U/ml significantly correlated with gender, age and survival rate. Insignificant correlation, but more frequently increased CA19-9 levels were found in more advanced stage of disease and poorly differentiated tumors. These findings were consistent with several other published studies (23).

CA19-9 values above 100U/ml compared to patients with values up to 100U/ml had about three times significantly higher risk of lethal outcome (3.026, 95% CI1.171-7.822). CA19-9 serum levels can provide important information in regards to prognosis, overall survival, and can predict post-operative recurrence (24).

Despite recent advances in understanding the genetic and cellular basis of the pancreatic adenocarcinoma progression, examinations, and knowledge of histopathological parameters such as tumor differentiation and pancreatic tumor fibrosis, may contribute for improved assessing the prognosis and predicting early recurrence and overall survival.

Conclusion

The results of our study showed that correlation between serum level of CA19-9 value and pathohistological tumor characteristic including: tumor size, stage, tumor differentiation, revealed more frequency, but statistically insignificant results in patients with more elevated tumor marker.

Correlation between CA19-9 levels and patients' gender revealed values higher than 100U/ml of CA19-9 significantly more in female patients than in male, 90.9% vs 62.5%. The age also was determined as a remarkable predictor on CA19-9 levels. The tumor marker CA19-9 was confirmed as a significant predictor of survival in patients with pancreatic cancer (p=0.022).

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CORNELIA DE LANGE SYNDROME, ORAL AND DENTAL ASPECTS – NON-SYSTEMATIC LITERATURE REVIEW

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ABSTRACT

Cornelia de Lange syndrome is a rear development disorder that is diagnosed on specific clinical features like: congenital malformations, facial dysmorphism, growth retardation and neurodevelopmental delay. Aspects of oral or dental manifestations and treatments are not well elaborated in the literature due to the scattered data, but they are very challenging and unknown as a result of single or a combination of symptoms present in one individual. To our knowledge in our country, no data are present that evaluated individual oral and dental features between the individuals with Cornelia de Lange syndrome. The aim of this manuscript is to evaluate available data and reports in a non-systematic order for oral and dental aspects in this syndrome and to discuss issues for future knowledge.

Key Words: *Cornelia de Lange syndrome, dental, manifestations, oral.*

Background and Global Knowledge for the Syndrome

Cornelia de Lange syndrome (CdLS) is a rare developmental malformation, that has impact on the overall human body functioning. Manifestations of this syndrome in patients can be present with various degrees of facial dysmorphism, as well as with different degrees of learning difficulties, intellectual socialization, growth retardation, abnormalities in the extremities and their functioning. Additionally, a person with this syndrome may have malformations in other organs, such as in the heart or in the kidneys. Depending on the level of clinical features present and wide range of heterogenies, syndrome severity is differently graded (1,2,3,4,5). Incidence of this rear syndrome is not well known, but is estimated that 1 in 10000 to 30000 newborns have this condition (3). So far, no definite biochemical or chromosomal marker for the prenatal diagnosis of this syndrome was established, and this is the reason why many individuals with this condition (moderate forms) may never be recognized (1,2,4,5).

Historically, the first case reports of this syndrome dated from 1916th, were documented by Brachman W (6). Later on, Cornelia de Lange in 1933rd, published two cases of children with similar clinical characteristics as those in the prior author's article, and the condition was fully described for the first time as a multisystem syndrome involving congenital malformations, growth retardation and neurodevelopmental delay (7). Since then, it is known that the clinical diagnosis

of this syndrome is based mainly on a set of the above-mentioned clinical features (which as a thesis have been worked up and strongly upgraded in the latest years). However, individuals with CdLS have characteristic abnormalities, including microcephaly, growth retardation, hand and foot developmental abnormalities, short stature, excessive hair growth, heavy eyebrows, synfire (growth of eyebrows across the midline to form a large conflicting eyebrow), long lashes, small nose, micrognathia, drooping mouth, elbow flexion contracture, micromyelia and hirsutism (Image 1) (2,3,4). Even though new researches are straggling to rise for this syndrome, no definitive ethological factor have been confirmed (5).

Image 1. *Typical phenotype of a child with Cornelia de Lange syndrome*

Source: *Wikipedia., en.m.wikipedia.org. Cornelia de Lange syndrome*

In terms of oral manifestations, when discussing Cornelia de Lange syndrome, very atypical features that appear on the face greatly influence specific oral or dental treatments and make them very challenging in many aspects. It is important to point out that the literature does not give any specific medical treatment guidelines in individuals with this syndrome, while on the other side many clinicians consider that there is a scientific space for some oro-surgical and dental interventions improvements for that matter (8). Consequently, the oral manifestations of Cornelia de Lange have their own description in the medical literature, although it is scarce based on individual research (8-13). In here it must be emphasized that many individual dental and oral abnormalities are individually reported, and therefore this is a field still not well studied. Through, for dental treatments as well as guidelines for oral care when compared to oral surgery treatments significant improvements have been observed (10,13).

The aim of this manuscript is to make a short evaluation presentation based on secondary data, on the existence and relationship between Cornelia de Lange syndrome and oral manifestations reported. Furthermore, this article aims to present some novel general data available. Thereby, the offered literary review additionally opens new horizons for research, especially in the domain of connection between symptoms of CdLS and oro-dental treatment.

Literature Review Reports and General Dental Issues

Cornelia de Lange syndrome as a disorder has some typical clinical features that are used as a bases for diagnosis of this syndrome. Even though the whole literature for this syndrome is scattered, some clinical challenges and individual aspects are reported in single case reports, especially emphasizing the oral and dental features and treatment challenges in those individuals (8-11). In this regard, the first challenge for the dentist or the oral surgeon to overcome, is the fact that the patients are often non-cooperative, primarily due to their mental retardation and hyperactive behavior (14).

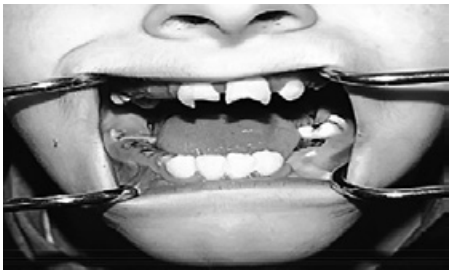
The first dental case in this area was described by Scully C. in 1980 (9). He reported an 18-years-old Caucasian man who underwent dental prophylaxis with an ultrasound device that was present with chronic marginal gingivitis due to poor oral hygiene. The same author generally reported two cases and he found that for patients with CdLS from dental aspect, it is common for the patients to have diastemas, the presence of dental absence, dental malposition, periodontal disease as well as chronical gingivitis.

Interesting to analyze is the case reported by Guadagni MG et al. (11). He reported a three-years-old boy that was referred to a neuropsychiatrist by his parents due to severe dental pain, which additionally increased the number of seizures occurrence in this child. The authors have reported a presence of hypotonia of facial and masticatory muscles, enamel hypomineralization, jaw contraction, poor oral hygiene etc. This patient was followed for a period of two months in order to assess the level of hygiene he applied, as well as the growth of the jaws and tooth eruption. Additionally, patient was assisted locally with fluoride treatment. In this case, orthodontic treatment was rejected due to lack of cooperation of the patient, i.e. lack of reflex activity for chewing and swallowing.

In the case presented by Toker AS. and collaborators in 2009, like the case of Guadgani and coworkers, a child (at puberty) was referred to dentist due to experiencing intense dental pain (11,13). The intervention that was reported in this case was the extraction of the teeth that had a pathological finding, under general anesthesia. No additional complications occurred during the intervention.

During oral examination of the patient, micrognathia and delayed eruption were detected. The upper lateral teeth, upper right canine and lower canines had not been erupted. In addition, a finding of large decay and cavities of the upper central teeth, like in Hutchinson syndrome was reported. This is a feature that has not been described prior as existing or accompanying symptoms of this syndrome (Image 2) (13).

Image 2. *Intraoral appearance of the patient*



Source: *Toker AS, Ay S, Yeler H, Sezgin I. Dental findings in Cornelia de Lange syndrome. Yonsei Med J. 2009; 50(2): 289-292.*

About this case some additional anamnestic facts are very interesting. This particularly 10-years-old male patient had developmental disorders and speech weakness, he was not able to walk or talk before the age of 2.5 years and he was born as a premature child (weighted 2000 grams) from 29 years-old mother. The child had malnutrition, and his parent were biologically related. All of this may occur as a notice that genetical predisposition for the disease is also present (13).

Unlike this, Grupta D. and Goyal S. reported a case of a 11-years-old with no specific anamnestic history (except afterbirth jaundice), who was treated and referred to dentist for forwardly placed upper front teeth (10). Additional dental finding was delayed dentation, Angles Class II div. I Malocclusion, and protruded front teeth, dental age of 8-years-old, short maxillary and mandibular skeleton bases.

Some of these reports and others, were systematically analyzed in a small review article of González-Serrano J. et al. (8). The authors have made an inspirative systematization of "mini "oral and dental features found in patients with CdLS which can be a starting line for novel discoveries and researches of this syndrome when oral manifestations are considered. In their review, they gave an excellent table whereby the authors' reports of basic oral and dental manifestations are summed up. The table is presented below (Table 1).

Table 1. *Oral manifestations of Cornelia de Lange syndrome found in the dental literature (done by González-Serrano J. et al]*

Authors	**Scully C.**	**Barret et al.**	**Gupta et al.**	**Grau Carbo et al.**	**Guadagni et al.**	**Toker et al.**
Year	1980	1993	2005	2007	2008	2009
Cases (n)	2	1	1	1	1	1
Age (years)	17-18	22	11	29	3	10
Oral manifestations	Dental absence, diastemas, delayed eruptions, chronic gingivitis, tooth malposition, crowding, periodontal disease, general enamel hypoplasia	Anterior open bite, diastemas, extensive caries, tooth impaction, taurodontism in molars, irregular mandibular sclerosis	Temporary teeth presence, maxillary prognathism, anterior protrusion, delayed roots formations and eruption	Multiple caries, moderate periodontal disease, persistence of temporary teeth, ectopically erupted molars	Micrognathias, drawling, hypotonia of facial and matricular muscles, severe anterior open bite, arched palate, agenesis macrodontia, enamel hypomineralization, short upper lip, tongue protrusion, jam muscle contractions	Micrognathias, delayed eruptions, diastemas, caries in Hutchinson-shaped teeth (maxillary central incisions)

Source: *González-Serrano, José, Oral Manifestations in the Cornelia De Lange Syndrome: A Systematic Review of the Dental Literature. IOSR Journal of Dental and Medical Sciences. 2017: 16(5):84-88[8]*

The review article done by González-Serrano J. et al. and above citated authors, point out that many patients with CdLS have individual dental characteristics that might, but are not strictly charactered for this syndrome (8). This as a fact opens the door for some novel studies that were

raised from cases where it was found that in general this is a syndrome with some generalized features, but special phenotypes are present (1,4).

In similar context is the research of Badoe E., when it comes to oropharyngeal manifestations in patients with Cornelia de Lange syndrome, it argued that they are isolated and to some extent typified by a group of authors, and confirm that oropharyngeal manifestations are not isolated only in the case of this syndrome (2). However, there are undoubtedly features that are specific to this type of syndrome, such as: delayed eruption, anterior open bite and gingivitis.

One of the particularly important findings that is closely related to Cornelia de Lange syndrome is pathology associated to poor hygiene, such as early onset or multiple forms of tooth decay and gingivitis. All of these is considered to result from the existing cognitive difficulties (14,15).

Another thing that needs special attention is the findings of Toker AE. *et al*. and the series of studies of Van Allen MI. and collaborators, who established that there is a link between Cornelia de Lange syndrome and Hutchinson syndrome (13,16). In that direction, it is very helpful to encourage a controlled diet, application of local fluoride, as well as periodic dental examinations also as a control for the poor hygiene.

Deardorff MA. and collaborators, analyzed the impact of drugs used to therapeutically treat patients with CdLS on the oral manifestations (17). They have confirmed that in these patients vide range are used and some of them like anticonvulsants can cause stomatitis, glossitis, erythema multiforme, primarily as a result of drug interactions, as in the case of acetylsalicylic acid or erythromycin. Consequently, the side effects in the treatment of the patients with this syndrome can be avoided only by keeping a detailed medical history. However, to a large extent one can expect only group differentiation of manifestations, which primarily arise only under specific conditions (3,4).

In here, even though it is not an interest of our manuscripts, some novel findings in regard of the syndrome occurrence have to be mentioned. The genomic and molecular bases of the syndrome are still under a question, but findings of new dominant mutations are emerging. Nowadays, it is considered that a mutation in more than five genes has been identified so far. The reason for mutation is not very clear, but some factors like inheritance, radiation, individual or environmental factors may play role (18). These findings are not strongly confirmed due to the fact that some mutations are only found in 30% of the patients, but researchers do keep on finding and working on these questions. Why it is important in here to mention this gene mutation influence. Simply if we go back in our manuscript, we can see that the condition of CdLS has some general like features, but oral and dental variety of manifestations may additionally be due to these different mutations present. Additionally, this as a thesis is confirmed in an expert consensus document, where more than 5 facial phenotypes have been studied so far (3,4).

Therefore, we can discus Cornelia de Lange syndrome as a syndrome is particularly unique in nature, so each case needs to be considered in isolation, especially because of the possible health risks and the existing lack of cooperation that is necessary for proper dental treatment.

Conclusion

From the review of the literature given, it is easily seen that there are certain dental abnormalities associated to Cornelia de Lange syndrome that include delayed eruption, disesteems, macro or microdontia, micrognathia, gingivitis, poor oral hygiene and insufficient cooperation with the patient. Furthermore, some papers propose that there is a possible link between the symptoms of Cornelia de Lange and Hutchinson syndrome. In the concluding observations, a particularly important statement and future recommendation in this domain is the needed for pronounced oral habits in patients with Cornelia de Lange syndrome, all aimed at preventing malocclusion and anterior open bite or an arched palate. However, all associated oral difficulties can be controlled by early diagnosis, as well as encouraging cooperation with these patients.

However, the data are insufficient in this manner, so more and more studies that connect this syndrome with oral and dental aspects are needed.

Limitations and Future Recommendations

Our manuscript has several limitations. Our study is not systematically done, we just point the literature present so far. We do not present a strong evidence for several facts, but nevertheless those strong evidences are still not present even in the global literature.

Our study has also some benefits. To our knowledge, it is the only one that has been dealing with this rare problem from dental aspect in our country. It offers wide opportunities of discussing how and why dental and oral aspect in these patients is important.

Based on the data and research findings presented in this paper, it is important to point out and encourage more comprehensive literature in this field, especially in terms of the relationship between oral manifestations of this syndrome and the other syndromes.

Conflict of Interest: none

Authors' contributions: JD: finding literature and writing parts of the manuscript, GJ: reviewing, ideas, writing parts of the manuscript and MJS: reviewing, ideas, writing parts of the manuscript.

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EPINEPHRINE AND DEXAMETHASONE AS ADJUVANS IN SUPRACLAVICULAR BLOCK IN PEDIATRIC PATIENTS: A CASE SERIES

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ABSTRACT

Supraclavicular brachial plexus blocks are not common in pediatric patients due to the risk of pneumothorax, but they are considered to be one of the most effective anesthetic procedures for upper extremity surgeries. Ultrasound-guided approaches increase efficacy of blocks and may reduce the risk of complications associated with injection of large volumes of local anesthetic. Adjuvants are often used with local anesthetics for its synergistic effect by prolonging the duration of sensory-motor block and limiting the cumulative dose requirement of local anesthetics. This paper reports three cases of pediatric patients who received ultrasound-guided supraclavicular brachial plexus block for upper limb surgery while applying different adjuvants (epinephrine and dexamethasone).

Key Words: *Adjuvants, dexamethasone, epinephrine, pediatrics patient, supraclavicular brachial plexus block.*

Introduction

The use of peripheral nerve blocks for anesthesia and postoperative analgesia in pediatric surgery has become increasingly popular in recent years. Peripheral nerve blocks of the upper extremity include block of plexus brachialis at several levels: interscalene, supraclavicular, infraclavicular and axillary approach. The approach which will be used depends on the region that is going to be operated: shoulder, upper arm, forearm or wrist. Regional anesthesia in children requires special attention due to the smaller size of the anatomical structures and the fact that the most of the blocks are performed under general anesthesia or in deep sedation. The use of ultrasound increases the effectiveness of the block and reduces the risk of complications associated with the application of large volumes of local anesthetics. One of the life-threatening complications from the use of high doses of local anesthetics is LAST (local anesthetic systemic toxicity) (1). Neurotoxicity and cardiotoxicity associated to high concentrations of local anesthetics in the blood are more likely to occur in infants and young children than in adults, due to weaker protein binding and

reduced internal clearance of the local anesthetic (2). Rapid intravenous bolus of lipid emulsion reverses the toxic effects of local anesthetics in pediatric patients (3). The recommended dose of 20% Interlipid for pediatric patients is 1-3 ml/kg (4).

Local anesthetics can cause dose-dependent side effects: cardiac arrhythmias, hypertension, seizures, respiratory depression and allergic reactions. In order to reduce the dose of local anesthetic and to prolong the duration of sensor block, adjuvants to local anesthetics are added.

In this paper we present three cases in which a supraclavicular plexus brachial block is performed on pediatric patients while applying two different adjuvants (epinephrine and dexamethasone).

Case Report 1

A 4-years-old girl weighing 23 kg, ASA classification group I was admitted for operative treatment of fracture of the left proximal ulna. Written informative consent was signed by the patient's parent. After intravenous access was secured in the right forearm, 1 mg midazolam, 30 mg ketamine, 30 μg fentanyl iv bolus and 5 mg/kg/h continuously propofol were administered as sedation. Supplemental oxygen 4 l/min through a face mask was applied. The patient was placed in the supine position with the neck rotated slightly to the contralateral side of the fractured limb. Preparation and draping of the neck and supraclavicular region of the patient was done with povidone iodine solution 7.5%. The supraclavicular block was performed using a neurostimulator Stimuplex HNS 11 and a Siemens ACUSON P500 ultrasound with a 9 MHz linear transducer. The linear probe was placed transversally in the supraclavicular fossa just above the clavicle where the plexus brachialis was visualized as hypoechoic beans laterally and above of the subclavian artery (Figure 1). The Stimuplex A 22 G 50 mm needle was placed in an in-plane position lateral to the linear probe, and the moment when the tip of the needle reached the plexus brachialis, the nerve locator was activated (previously adjusted to 1 Hz, 0.5mA and 0.1ms). Regular muscle twitch of the fingers and wrist was produced. After placing the needle in the desired position, aspiration was performed in order to exclude the possibility of intravascular application of the anesthetic. Then mixture of 8 ml bupivacaine 0.25% and 2 ml lidocaine 2% was applied (total volume 0.5 ml/kg local anesthetic). Muscle contractions were lost after administration of only 1 ml of local anesthetic. The vital signs (non-invasive blood pressure, heart rate, oxygen saturation and end-tidal CO_2) of the patient were monitored. Operation was started 15 min after performing the supraclavicular block. Propofol infusion was stopped 5 minutes before the end of the operation. Following the surgical procedure, the patient was transferred to the recovery room.

No complications were registered during the operation and postoperatively. Postoperatively, the pain was assessed using FLACC (face, legs, activity, cry and consolability) scale and when score was 6 or above 6, intravenous acetaminophen was administrated. The patient complained of pain six hours after applying the block. The pain was purchased with intravenous administration

of 350 mg paracetamol. During hospitalization (48 hours), the patient received two times analgesics (acetaminophen) (Figure 2).

Figure 1. *Ultrasound view of brachial plexus in supraclavicular region. AS – subclavian artery, PB – plexus brachialis*

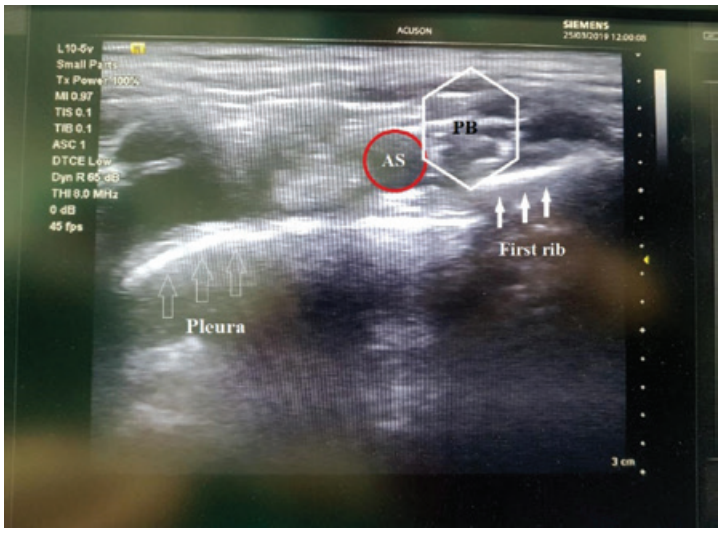
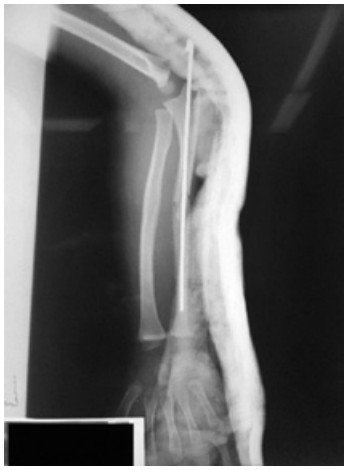


Figure 2. *Postoperative X-ray image of the left forearm with immobilization.*



Case Report 2

A 13-years-old boy weighing 52 kg, ASA classification group I was admitted to the Clinic for Pediatric Surgery for operative treatment of a right forearm fracture (Figure 3). After talking with the parents about the possible complications and benefits of the regional anesthesia, an informative consent was signed. The patient was sedated by intravenous bolus administration of 2 mg midazolam, 50 μg fentanyl and continuously infusion was started with 5 mg/kg/h propofol. The patient was placed in the supine position with the neck rotated to the contralateral side of the fractured limb and with previously applied face mask with supplemental oxygen 4 L/min. The skin of the neck and supraclavicular fossa was prepared in typical sterile fashion. A linear

transducer 9 MHz (Siemens ACUSON P500 ultrasound) was placed transversally in the supraclavicular fossa just above the clavicle, where the plexus brachialis was visualized laterally and above of the subclavian artery as hypoechoic beans. After the transducer position was confirmed, 24-guage insulated needle (Stimuplex A 22 G 50 mm) was advanced using the in-plane technique (Figure 4). Once the needle reached the brachial plexus, the nerve stimulator (Stimuplex HNS 11) was turned on, starting current from 1mA and decreasing to 0.5mA to elicit contraction of the fingers and wrist muscles. Mixture of 20 ml bupivacaine 0.25% and 2 ml lidocaine 2% with 25 μg epinephrine (total volume 0.5 ml/kg local anesthetic) was injected carefully with intermittent negative aspiration. The operation started 15 minutes after performing the block and successfulness of the block was determined by the absence of hemodynamic changes and a withdrawal response to surgical stimuli. There was no need for opioids intraoperatively and there was no variation in vital parameters of the patient during the operation.

Figure 3. *Preoperative X-ray image of the right forearm.*

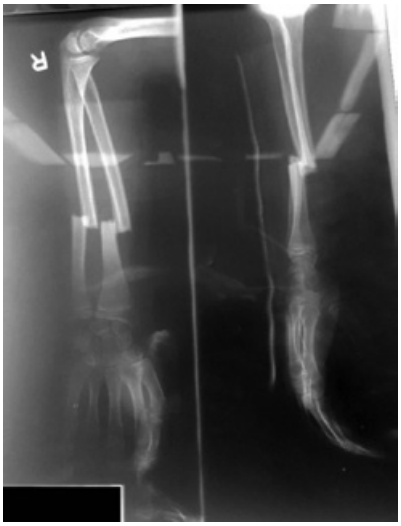


Figure 4. *In plane technique using ultrasound linear transducer and neurostimulator*

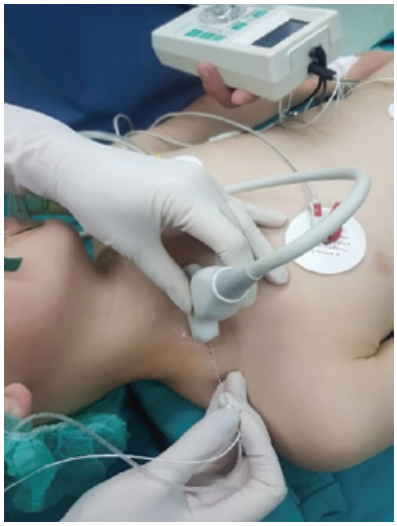
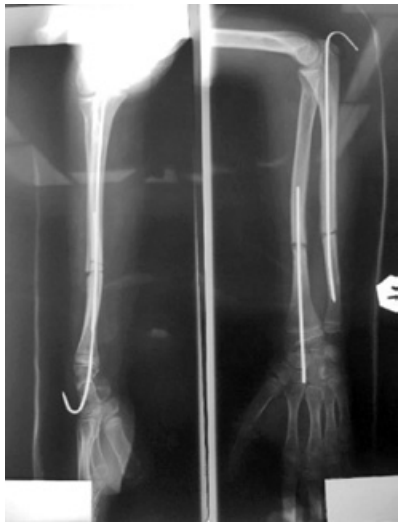


Figure 5. *Postoperative X-ray image of the right forearm with immobilization.*



No complications were registered during the operation and postoperatively. Postoperatively, the pain was assessed using VAS (visual analog scale) and when score was 6 or above 6, intravenous metamizole was administrated. The patient complained of pain ten hours after applying the block. The pain was purchased with intravenous administration of 1000 mg metamizole. During hospitalization (48 hours), the patient received metamizole once more.

Case Report 3

A 13-years-old girl weighing 30 kg, ASA classification group I was admitted for surgical treatment of a fracture of the right radius (Figure 6). After talking with the parents about the possible complications and benefits of the regional anesthesia, an informative consent was signed and supraclavicular block was performed. The patient was sedated by intravenous administration of

2 mg midazolam, 30 μg fentanyl and continuously infusion of propofol 5 mg/kg/h was started. The patient was placed in the supine position with the neck rotated to the left and was applied face mask with supplemental oxygen 4 L/min. After locating the brachial plexus with supraclavicular approach using ultrasound linear probe (Siemens ACUSON P500 ultrasound), the peripheral nerve block was performed in aseptic conditions. Once the needle (Stimuplex A 22 G 50 mm) reached the brachial plexus, the nerve stimulator (Stimuplex HNS 11) was turned on (previously adjusted to 1 Hz, 0.5mA and 0.1ms) causing contraction of the fingers and wrist muscles. Mixture of 13 ml bupivacaine 0.25% with 2 mg dexamethasone and 2 ml lidocaine 2% (total volume 0.5 ml/kg local anesthetic) was injected carefully with intermittent negative aspiration. The operation started 15 minutes after performing the block and successfulness of the block was determined by the absence of hemodynamic changes and absence of withdrawal response to surgical stimuli, such as the skin incision. There was no need for opioids intraoperatively and the patient's vital signs were stable.

Postoperative pain was reported 16 hours after performing the block (according to visual analog scale) and 1000 mg metamizole was administered intravenously. This patient did not complain of pain until the end of the hospitalization (48 hours) (Figure 7).

Figure 6. *Preoperative X-ray image of the right forearm.*

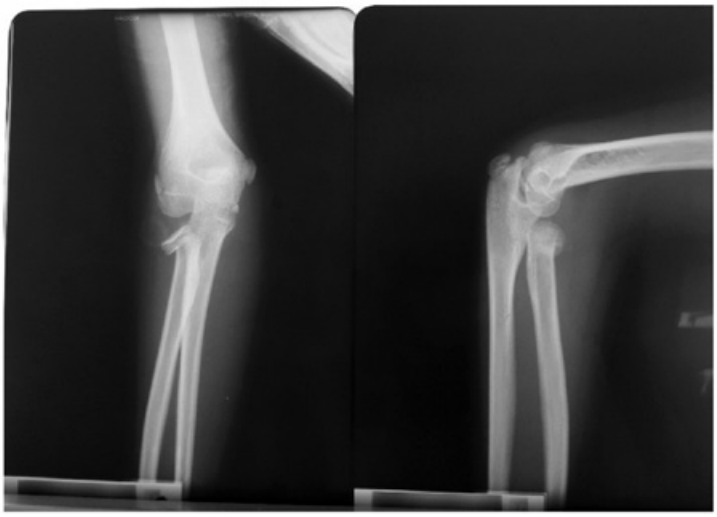
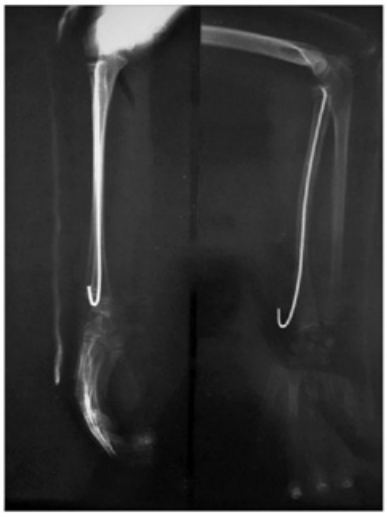


Figure 7. *Postoperative X-ray image of the right forearm.*



Discussion

Performing peripheral nerve blocks in the pediatric population is a safe and effective technique that has become increasingly popular in recent years. Children often have inadequate treatment of pain, especially after painful procedures, often due to underestimation of the intensity of pain and fear of the risk of complications when using opioids. In recent years, the use of ultrasound for accurate localization of nerve structures has reduced the risk of complications from performing supraclavicular block (pneumothorax, hematoma, intravascular anesthetic injection). The neurostimulator is used with ultrasound for additional nerve identification (5).

Epinephrine is one of the oldest adjuvants to local anesthetics used at a dose of 0.5 – 1 μg/kg at a concentration of 5 – 10 μg/ml (1: 200000). Small doses of epinephrine (25μg) do not affect hemodynamics and prolong the duration of the block for the same time in contrast to higher doses (200μg) (6).

Epinephrine has an analgesic effect when combined with short-acting and intermediate-acting local anesthetics, while there are limiting data on its effect in combination with long-acting local anesthetics (ropivacaine, bupivacaine, levobupivacaine). Some studies with long-acting local anesthetics (ropivacaine) have failed to demonstrate prolongation of analgesia by adding epinephrine (7).

It is considered that epinephrine reduces the absorption of local anesthetic into blood vessels by its vasoconstrictive effect and thus prolongs the duration of contact of the local anesthetic with nerve fibers (8). This effect should be especially considered in patients with pre-existing circulatory problems (diabetes mellitus, hypertension, smokers) (9), but also with this effect epinephrine limits the distribution of local anesthetic in the systemic circulation and thus reduces the risk of LAST (10).

Dexamethasone is a potent anti-inflammatory drug that has often been used in recent decades as an adjunct to local anesthetics in neuroaxial and peripheral nerve blocks. Its mechanism of action applied perineurally is due to reduced excitability and transmission of nociceptive demyelinating C fibers (11). Dexamethasone at doses of 1, 2, 4 and 8 mg has been shown to be an effective adjuvant in multiple blocks, such as supraclavicular, interscalene, ankle block, and TAP block. In fact, a meta-analysis about dexamethasone used as an adjuvant in blockade of the plexus brachialis proves that it significantly prolongs the duration of the block (12). Studies show that perineural dexamethasone (1, 2 and 4 mg) in combination with bupivacaine prolongs the duration of supraclavicular block in patients admitted for one-day shoulder surgery (13).

However, there is insufficient evidence for the efficacy of dexamethasone as an adjuvant in peripheral nerve block of lower extremities and its use in children.

Conclusion

We should take into consideration the available evidence, recommended safe doses, effective routes of administration, side effects of their use, when we use adjuvants to local anesthetics, but also to be prepared to deal with a life-threatening situation such as local anesthetic systemic toxicity. Epinephrine (25 μg) and dexamethasone (1-2 mg) are adjuvants that are safe for use in children, but the exact extension of sensory and motor block has not yet been clinically proven in the pediatric population.

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VITAMIN D AND BODY MASS INDEX IN GESTATIONAL DIABETES MELLITUS

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ABSTRACT

Gestational diabetes mellitus (GDM) is a glucose intolerance established for the first time in pregnancy. Vitamin D deficiency is common in pregnant women. Deficiency is connected with risk for preeclampsia, GDM and macrosomia.

Aim

Aim of the study was to evaluate vitamin D status in GDM pregnancies and normoglycemic women and to establish whether body mass index in normoglycemic and GDM pregnant women has impact on vitamin D deficiency.

Material and Methods

Prospective study was conducted at the University Clinic for Gynecology and Obstetrics, Skopje in a period of one year. One hundred pregnant women in the second trimester were evaluated: 50 women with GDM and a control group of 50 women with negative OGTT with BMI more or less than 25. Vitamin D levels (Advia Centaur) were performed from periphery blood specimens from the pregnant women.

Results

Significantly lower values of vitamin D were found in GDM women vs control group (16.91 ± 6.2 nmol/l vs 24.54 ± 11.7 nmol/l). Vitamin D deficiency was found in 82.5% of the women with GDM and 54.76% of the women with negative OGTT. Vitamin-mineral supplementation received 82% of the normoglycemic pregnant women and 66% of the pregnant women with GDM, p=0.036. In pregnant glucose tolerant women vitamin D was significantly lower in overweight vs normal weight women. Women with GDM and normal weight had significantly lower vitamin D levels vs normoglycemic women with normal weight.

Conclusion

We can conclude that gestational diabetes mellitus in our study is associated to lower values of vitamin D. Pregnant women with GDM less often received vitamin supplementation. Lower vitamin D levels were found in normoglycemic overweight women. In GDM women body mass index didn't have impact on vitamin D deficiency – normal weight GDM women had significantly lower vitamin D levels than normoglycemic women with normal weight.

However, vitamin D supplementation is essential for overweight pregnant women in order to possibly achieve better perinatal outcome.

Keywords: *BMI, gestational diabetes mellitus, vitamin D.*

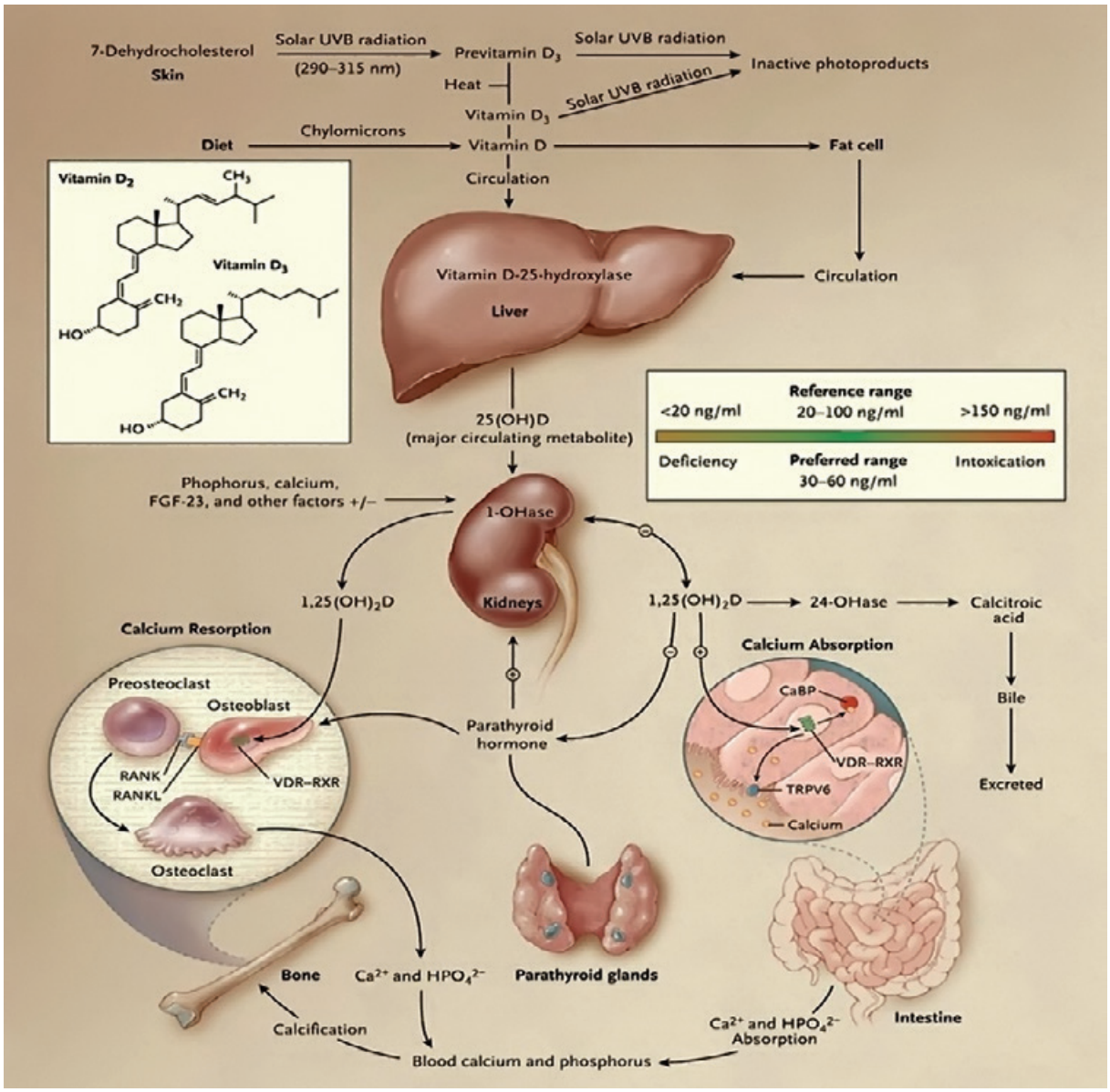
1. INTRODUCTION

GDM is the most often metabolic complication of pregnancy with incidence of 1-14% depending on the population investigated and diagnostic criteria (1,2).

GDM represents increased risk for perinatal morbidity and significantly increased risk for diabetes type 2 and cardiovascular risk through life (3).

Vitamin D (Picture 1) is a steroid hormone synthetized in the skin from calciferol to 7-dehidrocholesterol after exposition on UV radiation and is metabolized in 2 stages of hydroxylation in liver and kidneys to form biologically active hormone calcitriol (4,5).

Picture 1. *Metabolism of Vitamin D*



Vitamin D has a role in glucose homeostasis and insulin resistance. It improves insulin sensitivity in target cells (liver, muscles and fatty tissue) (6). Vitamin D deficiency is connected to

the risk for preeclampsia, GDM, IUGR and macrosomia (7,8). Vitamin D deficiency is common in pregnant women especially in those with poor nutrition and low sun exposition.

Serum levels of vitamin D are lower with increase of body mass index, are higher in summer period and are lower in smokers (9,10).

Although there is no consensus for optimal vitamin D levels, according to the most associations clinical categories for vitamin D status are the following: severe deficiency (<25 nmol/L), moderate deficiency (25 – 50 nmol/L), insufficient (50 – 75 nmol/L) and sufficient vitamin D status (≥75 nmol/L) (11).

In this moment there are insufficient data on recommendation for screening for vitamin D deficiency in all pregnant women. For pregnant women with increased risk for vitamin D deficiency, maternal vitamin D serum levels should be done according to individual clinical decision.

All pregnant women according to RCOG should receive supplementation with 400 iu vitamin D. Most experts believe that a dose of 1000-2000 iu vitamin D daily is a safe dose for women with vitamin D deficiency (12).

The theory that lower levels of vitamin D can be part of the link between obesity and GDM, leaves the opportunity that obese women may benefit from vitamin D supplementation and that kind of intervention lowers the GDM risk (13).

Vitamin D supplementation may improve maternal markers of metabolic status and probably help in clinical reduction of unfavorable GDM outcome.

2. MOTIVE FOR THE STUDY

GDM is increasing worldwide and is associated to significant maternal and neonatal morbidity.

Research on vitamin D levels in pregnancy may provide data on pathophysiology and prediction on risk in GDM pregnancies. This marker may help in planning of targeted preventive and predictive strategies. These are main motives for this study.

3. MATERIAL AND METHODS

Prospective longitudinal clinical case control study is performed in a period of one year at the University Clinic for Gynecology and Obstetrics in Skopje, R.N. Macedonia. Participants were selected from the pregnant women that had prenatal care in the outpatient department in that period. Oral glucose tolerance test 75 g was made between 24 and 28 gestational weeks.

The pregnant women were divided into 4 groups in the same gestational age, parity and maternal age: normoglycemic with BMI more or less than 25, and GDM with BMI more and less than 25.

Inclusion criteria were: maternal age 18-45; eligibility for follow up; gestational age confirmed by ultrasound in the 1st trimester; first prenatal control before 20 gw; GDM diagnosed with 75 g OGTT by criteria of IADPSG.

Exclusion criteria: pregestational diabetes; chronic hypertension; chronic inflammatory disease treated by corticosteroids; stillbirth, fetal anomalies; amnio-infectious syndrome.

Diagnosis of GDM

GDM is diagnosed according to recommendations of IADPSG between 24 and 28 gestational weeks with 75 g OGTT (glucose oxidase, Beckman Glucose Analyzer) performed in the morning after night fast with venous blood taken 0, 60 and 120 minutes after drinking 75 g glucose dissolved in 200 ml of water and reference values 0< 5.1, after 1-h < 10.0, after 2-h < 8.5 mmol/L (11).

Body weight and height was measured with medical scale. Body mass index (Body Mass Index-BMI) with the following formula = weight (kg) /height (m^2). According to the Institute of Medicine categories of body weight are: unnourished (BMI<18.5), normal weight (BMI=18.5-24.9), overweight (BMI=25-29.9) and obesity (BMI>30) (14).

Vitamin D analysis was made from periphery blood taken with punction of the cubital vein. Serum samples are made by centrifuging (1000 × in a period of 20 minutes), frozen on a temperature of −20°C. After collection of all samples in Avicena laboratory (certified according to МКС EN ISO 15189 – 2013) vitamin D analysis was made with Siemens Advia Centaur XP – with method of direct chemiluminescence.

ADVIA Centaur Vit D total assay is used for in vitro diagnostic test for quantitative determination of total vitamin D in human serum and plasma (EDTA, lithium-heparin, sodium-heparin). Advia Centaur Vit D assay is 18 minutes antibody competitive immunoassay with anti-fluorescein monoclonal antibody covalently bonded with paramagnetic particles (PMP), anti-25 (OH) vitamin D monoclonal antibody marked with acridinium ester (AE) and vitamin D analogue marked with fluorescein. There is an inverse relationship between vitamin D levels in the patients' specimens and levels of relative light units (RLU) detected in the serum.

ADVIA Centaur Vit D assay is measuring the vitamin D concentrations between 9.3 – 375 nmol/l (3.7 – 150ng/ml). ADVIA Centaur Vit D assay has a high specificity for 25 (OH) vitamin D2 and 25 (OH) vitamin D3. Sensitivity: limit for blind trial is 1.60 nmol/l, limit for detection 8.8 nmol/l. Limit for detection is the lowest concentration of 25 (OH) vitamin D that can be detected with 95% probability. Functional sensitivity of Advia centaur assay is 8.33 nmol/l.

4. STATISTICS

The data were evaluated with statistical computer program SPSS 23 for Windows.
For comparison of analyzed groups, student t-test for independent samples was used.
For all analyses p value <0.05 was statistically significant.

5. RESULTS

Our study included one hundred pregnant women: gestational diabetes and normoglycemic pregnant women. Pregnant women from each group were divided according to body mass index of more or less than 25 (BMI<25 – normal weight, BMI>25 – overweight and obese).

5.1 VITAMIN SUPPLEMENTATION IN GDM AND NORMOGLYCEMIC WOMEN

Vitamin-mineral supplementation was received by 82% (41/50) of the normoglycemic pregnant women and 66% (33/50) of the pregnant women with GDM. The difference was significant for p=0.036.

Table 1. *Supplementation and GDM*

Supplementation	Pregnant women			p value
	N	GDM n (%)	normoglycemic n (%)	
No		17 (34)	9 (18)	p=0.036sig
Yess		33 (66)	41 (82)	

5.2 VITAMIN D IN GDM AND NORMOGLYCEMIC WOMEN

There was significant difference between the vitamin D concentration between 2 groups (p=0.0004) which was due to its lower values in pregnant women with diagnosed GDM. Average values of vitamin D were 16.91 ± 6.2 nmol/l in GDM women vs 24.54 ± 11.7 nmol/l in the control group (Table 2).

Table 2. *Average values of vitamin D in GDM and control group*

Groups	Descriptive Statistics (Vit D nmol/l)			p value
	mean ± SD	std.err.	min-max	
GDM	16.91 ± 6.2	0.9	10.5 – 31.8	t=3.7 p=0.0004 sig
Normoglycemic women	24.54 ± 11.7	1.8	10.5 – 55.4	

t (Student t-test)

Vitamin D deficiency (<25 nmol/l) was registered in 82.5% of the GDM pregnant women and in 54.76% of the control group.

The difference in the distribution of the vitamin D deficiency between pregnant women with GDM and control group was statistically significant, p=0.007 (Table 3).

Table 3. *Vitamin D deficiency in GDM and control group*

Vit D < 25 nmol/l	Groups			p value
	N	GDM n (%)	Control group n (%)	
> 25	26	7 (17.5)	19 (45.24)	X2=7.28 p=0.0069 sig
< 25	56	33 (82.5)	23 (54.76)	

p (Chi-square test)

5.3. VITAMIN D IN NORMOGLYCEMIC WOMEN: BMI > 25 vs BMI < 25

In the group of normoglycemic women, those with BMI>25 had significantly lower values of vitamin D than those with BMI<25 (p=0.049). Average values of vitamin D in overweight and normal weight women were 21.19 ± 8.5 nmol/ml and 28.23 ± 13.7 nmol/ml consequently (Table 4).

Table 4. *Average values of vitamin D in normoglycemic women, BMI > 25 vs normoglycemic women, BMI < 25*

Normoglycemic women				
Groups	Descriptive Statistics (Vit D nmol/l)			p value
	mean ± SD	std err	min – max	
Overweight	21.19 ± 8.5	1.813	11.1 – 37.2	t =2.02 p=0.049 sig
Normal weight	28.23 ± 13.7	3.057	10.5 – 55.4	

t (Student t-test)

5.4. VITAMIN D IN BMI < 25: GDM VS NORMOGLYCEMIC WOMEN

Average value of vitamin D was 15.75 ± 5.8 nmol/l in GDM and BMI<25 vs 28.23 ± 13.7 nmol/l in normoglycemic women and BMI < 25. The difference of 12.48 nmol/l in favor of the normal weight women with GDM was statistically confirmed as significant for p=0.00057 (Table 5).

Table 5. *Average value of vitamin D in GDM, BMI <25 vs control group, BMI <25*

GDM (BMI<25) / control group (BMI<25)				
Group	Descriptive Statistics (Vit D nmol/l)			p value
	mean ± SD	std err	min – max	
GDM BMI<25	15.75 ± 5.8	1.291	10.5 – 31.8	t =3.76 p=0.00057 sig
CG BMI<25	28.23 ± 13.7	3.057	10.5 – 55.4	

t (Student t-test)

DISCUSION

GDM has a growing prevalence with growing obesity worldwide. There is a constant debate whether vitamin supplementation reduces incidence of preeclampsia, small for gestational age and gestational diabetes mellitus (15). Both groups were compared according to supplementation and we found out that 82% of normoglycemic women vs 66% of women with GDM had supplementation with vitamins and minerals. There was a statistical difference for p=0.036, which means that GDM according to our results occurs more often in pregnant women which don't take supplements.

Many biomarkers in GDM may somehow explain the pathophysiology of GDM and use as potential diagnostic markers (16).

According to our results GDM women had significantly lower vitamin D levels (16.91 ± 6.2 nmol/l) compared to control group (24.54 ± 11.7 nmol/l), so our results confirmed that GDM is associated to lower vitamin D levels (p=0.0004) similar to findings of Burris et (15).

Maternal obesity has a growing prevalence worldwide and represents major obstetric issue increasing the perinatal morbidity and mortality.

Wishing to establish the impact of body mass index on vitamin D levels, we have compared vitamin D levels in GDM and normoglycemic women according to BMI, more or less than 25.

In the group of normoglycemic women significant difference was found in overweight and obese women, whereas in GDM women body mass index itself didn't make the difference. Overweight and obese women with GDM didn't have significant lower vitamin D values than overweight normoglycemic women with same BMI.

Vitamin D was significantly lower in normoglycemic women with BMI>25, 21.19 ± 8.5 nmol/ml vs 28.23 ± 13.7 nmol/ml in normoglycemic women with BMI<25, p=0.049. According to that, normoglycemic overweight women have risk for vitamin D deficiency which confirms the findings of Burris et al (16).

In pregnant women with GDM and normal weight, vitamin D was significantly lower than in normoglycemic women with same BMI, 15.75 ± 5.8 nmol/l vs 28.23 ± 13.7 nmol/l, p=0.00057.

Limitation of this study was the number of participants. Future studies that will have large number of participants will have more conclusions and will share more information on patho-physiology of GDM and its connection to perinatal outcome.

CONCLUSIONS

We can conclude that gestational diabetes mellitus in our study is associated to lower values of vitamin D. Pregnant women with GDM less often received vitamin supplementation. Significantly lower vitamin D levels were found in normoglycemic overweight women compared to normoglycemic normal weight women. In GDM women body mass index didn't have impact on vitamin D deficiency. Normal weight GDM women had significantly lower vitamin D levels than normoglycemic women with normal weight.

Considering these findings it would be important to suggest that vitamin D serum levels should be analyzed if possible in pregnant women with GDM and in overweight women.

Pregnant women with vitamin D deficiency should be supplemented with vitamin D and the doses would be tailored according to individual assessment and risk. Further analyses will show if vitamin D supplementation would mean a possibility for better perinatal outcome.

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POST COVID-19 COMPLICATION PRESENTED AS BILLATERAL LUNG CAVITATIONS – CASE REPORT

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ABSTRACT

Lung cavitation can occur as a complication in post COVID-19 infection. We present a medical case of a lung cavitation accompanied with aero-liquid formation, as a complication of COVID-19 infection.

A 49 years-old man, with active, home-threated COVID-19 infection, PCR confirmed, was primary presented with cough, expectoration of white sputum, high temperature, muscle cramps, malaise. 17 days after the diagnosed COVID-19 infection, the patient has requested medical care due to cough and hemoptysis. Computed tomography (CT) scan of the thorax was performed and a massive right sided pneumothorax was detected with a shift of the mediastinal structures to the left side, that underlined to a drainage treatment. The repeatedly hemoptysis along with chest pain, indicated a repetition of the CT scan of the thorax with a contrast series in which a reexpansion of the right lung with an aero-liquid collection was detected in the posterobasal segment of the right lung and a pneumatocele with a ticked wall was detected, in the superior segment of the left lower lobe. With echosonography control, a punctate sample was taken from the aero-liquid formation, with a bloody content, that was sent for microbiological analysis and proofed to be sterile. A thoracic surgeon was consulted, and a surgical treatment was indicated.

Key Words: *aero-liquid formation, COVID-19 complication, lung cavitation, pneumatocele.*

Introduction

A pulmonary cavity is a gas-filled area of the lung in the center of a nodule or an area of consolidation and may be clinically observed by the use of plain chest radiography or CT. Cavities are present in a wide variety of infectious and noninfectious processes.

A cavity can occur due to different pathological processes, including suppurative necrosis (e.g. pyogenic lung abscess), caseous necrosis (e.g. tuberculosis), ischemic necrosis (e.g. pulmonary infarction), cystic dilatation of lung structures (e.g. ball valve obstruction and *Pneumocystis* pneumonia), or displacement of lung tissue by cystic structures (e.g. *Echinococcus)*. In addition, malignant processes may cavitate because of a treatment-related necrosis, internal cyst formation, or internal desquamation of tumor cells with subsequent liquefaction (1). The differential diagnosis of cavitary lung disease is presented in Table 1 (2).

We present a case of a patient with post COVID-19 complications such as pneumothorax, and not so rare, lung cavitation accompanied with aero-liquid formation.

Table 1. *Differential diagnosis of lung cavitary disease (2)*

Infection	**Bacterial** (S. Aureus, Klebsiella, Legionella and other gram-negative bacteria Pseudomonas. E. coli, Proteus. **Anaerobes** **Nocardia** **Infective endocarditis** **Mycobacterial** (Mycobacterium tuberculosis, M. avium complex and M. kansasii). **Fungal** (Coccidioidomycosis, histoplasmosis, blastomycosis, aspergillosis, cryptococcosis, actinomycosis, sporotrichosis, mucormycosis and invasive candidiasis). **Parasitic** (Pneumocystis jirovecii, echinococcosis (hydatid disease), amebiasis, paragonimiasis).
Neoplasm	**Primary** (particularly squamous cell bronchogenic carcinoma), **Metastatic** **Lymphoma** (Hodgkin or non-Hodgkin).
Vascular	**Granulomatosis with polyangiitis** **Rheumatoid Arthritis** **Thromboembolic** (Pulmonary emboli, infective endocarditis / septic emboli).
Congenital	**Congenital cysts** **Congenital adenomatoid malformation** **Pulmonary sequestration**
Other	**Pneumoconiosis,** **Pulmonary Langerhans cell histiocytosis** **Pulmonary lymphangioleiomyomatosis** **Diaphragmatic hernia** **Sarcoidosis** **Bronchiectasis** **Lucite plombage**

Case Report

A 49-years-old man, non-smoker, with dust and pollen allergies and a high blood pressure from his past medical history, was admitted to our clinic due to cough and expectoration of white sputum. On physical examination, the respiratory excursions of the left hemithorax were weaker. In the basal segment of the left lung and right subscapular region, there was a decrease in the fremitus pectoralis, a dull sound was detected on percussion of the same regions, and a weakened vesicular breathing on auscultation. On ECG the McGinn-White sing wasn't present, there were only inverse T waves in the inferior leads. From the laboratory findings, leucocytes were elevated, the Neu/Ly ratio was 7.37 (Table 2) and the D-dimers were 2076 (Table 3). On admission, both, the rapid Antigen test and the PCR test for COVID-19, were negative. The laboratory findings and D-dimer test chronologically, are presented in Table 2 and Table 3, respectively.

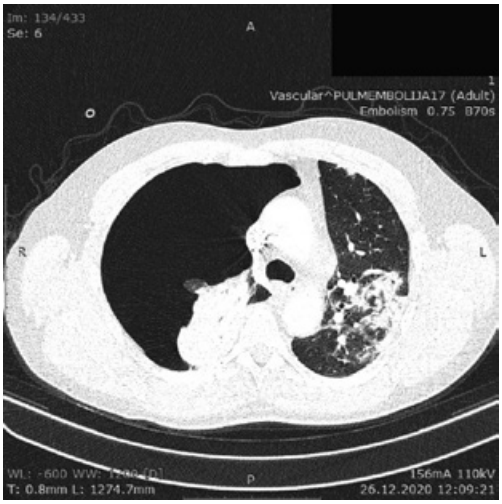
The patient was with PCR confirmed COVID-19 infection 33 days before admission, clinically was manifested with cough, expectoration of white sputum, high temperature (up to 39°C), muscle cramps, malaise, with elevated CRP and near normal D-dimer test. He was treated with dual oral antibiotic treatment (Pancef, Sumamed) and recommended therapeutic vitamin doses.

17 days after the diagnosed COVID-19 infection the patient has requested medical care due to cough and hemoptysis. The patient was referred to a CT scan of the thorax in which was detected a massive right sided pneumothorax with a shift of the mediastinal structures to the left

side. Suspicious filling defects on the level of the segmental branches of the lower lobe bilaterally, with a suspicion for pulmonary embolism, was established.

The pneumothorax was underlined to a drainage treatment, performed by a thoracic surgeon.

Image 1. *CT of the chest, lung window. A massive right sided pneumothorax with a shift of the mediastinal structures to the left.*



The patient was referred to a control CT scan. Bilaterally in the middle and lower segment of the lung, multifocal subsegmental areas of intensive consolidation, reticular interstitial markings and subpleural fibrous bands were found. Discrete right sided pneumothorax and an encapsulated hydropneumothorax in the oblique fissure were also obtained.

Image 2 & Image 3 *CT of the chest, lung window*

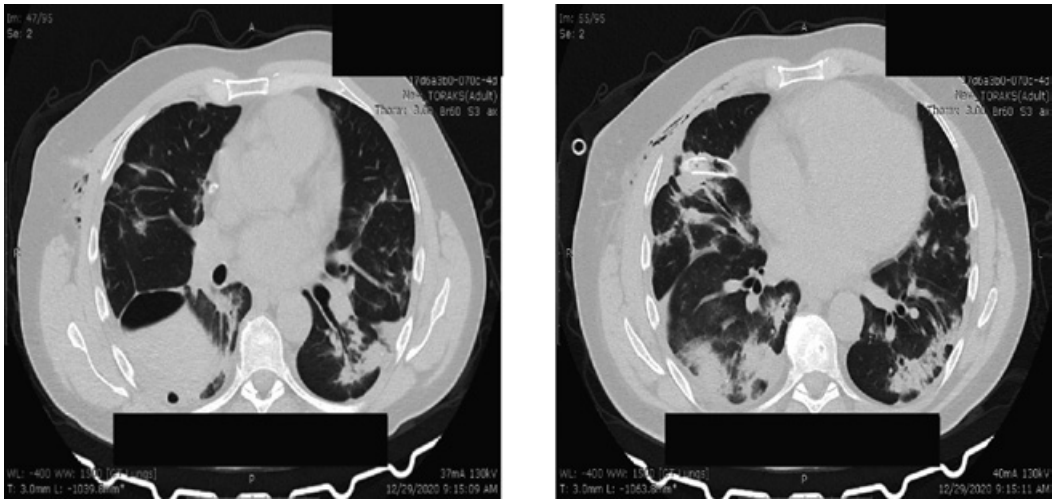


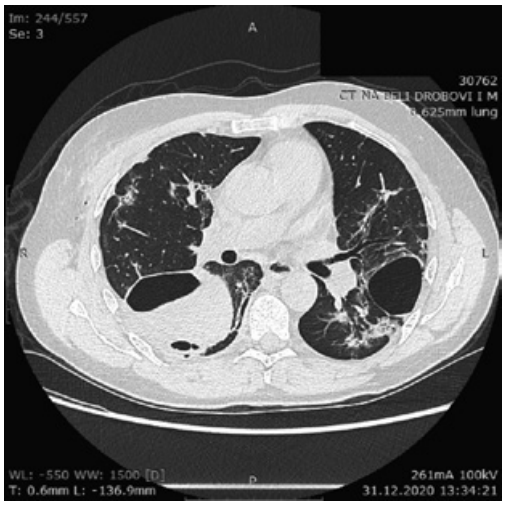
Image 2. *Placed drainage catheter in the right hemithorax, paramediastinal. There is a discrete pneumothorax and an encapsulated hydropneumothorax in the oblique fissure. Notice the subcutaneous emphysema.*

Image 3. *Bilaterally in the middle and lower segment of the lung, multifocal subsegmental areas of intensive consolidation, reticular interstitial markings and subpleural fibrous bands were found. Notice the subcutaneous emphysema. Placed drainage catheter in the right hemithorax, paramediastinal.*

Four days after the drainage, the patient presented with repeatedly hemoptysis along with chest pain, that indicated a repetition of the CT scan of the thorax with a contrast series. On the contrast CT scan of the thorax was detected a reticular pattern on the upper lobes bilaterally and

focal consolidations. A pneumatocele with a ticked wall was detected in the superior segment of the left lower lobe with cranio-caudal (CC) diameter of 54 mm. A right sided posterobasal small pleural effusion was detected. In the projection in the right lower lobe subpleurally, a clearly demarcated liquid collection was detected, with a latero-lateral (LL) diameter of 10 cm in which is seen an aero-liquid formation. At the bottom of the formation heterodensity of the liquid formation is seen, a thicker content, encapsulate with a hemorrhagic or thicker inflamed content. A mediastinal lymphadenopathy was detected in the paratracheal and on the level of bifurcation. A suspicious filling defects were also seen at the segmental branches of the lower lobe bilaterally, that made the suspicion for pulmonary embolism present.

Image 4. *CT scan of the chest*



A pneumatocele with a ticked wall was detected in the superior segment of the left lower lobe with CC diameter of 54 mm. A right sided posterobasal small pleural effusion was detected. In the projection in the right lower lobe subpleurally, was detected a clearly demarcated liquid collection with a LL diameter of 10 cm in which is seen an aero-liquid formation.

The patient was referred for ultrasonography examination. The ultrasonography findings showed an aero-liquid collection that was seen in right parascapular region, in which one part is a thicker liquid and the other part is solid in addition for coagulum. With puncture is obtained a dark red bloody content. A pleural catheter with active drainage was placed and 350 ml of the same content was obtained. The obtained content was sent to the microbiological department for analysis. The microbiological findings of the content were sterile. A thoracic surgeon was consulted, and it was indicated surgical treatment for the residual bleeding in the lungs. Contrary to the surgeon recommendation for surgical treatment, the family of the patient initiated a discharge from the hospital and a home treatment.

Table 2. *Laboratory findings, chronologically*

	Leu	Ly	Neu	Neu/Ly ratio	Tr	CRP	LDH
14.12.20	6,3					74	
29.12.20	8,8	14,4	71,3	4,95	332	62,02	192,6
07.01.21	8,9	12,4	78,8	6,35	287	11,12	288
11.01.21	12,15	10,8	79,7	7,37	387		
21.01.21	6,67	24,5	64,7	2,64	243		

Table 3. *D-dimer test results, chronologically*

	14.12.20	26.12.20	11.01.21	21.01.21
D-dimer	550	1770	2076	747

Discussion

In the radiological studies, the typical CT findings of COVID-19 mainly include ground-glass and consolidative pulmonary opacities, primarily in the lower lobes with bilateral involvement and predominantly posterior distribution. More often it is presented as bilateral ground glass opacities with multilobar involvement. In the progressive stage it might be seen as ground glass opacities mixed with a reticular pattern (crazy paving). The most common complication of COVID-19 is the pulmonary fibrosis, but not so rare complications are the pulmonary cavitations in the post COVID-19 patients. The complications such as pneumomediastinum and pneumothorax are the most commonly as a result of the barotrauma in the mechanically ventilated patients.

In our patient the pulmonary cavitations are detected as a late complication of the COVID-19 infection.

Lung cavitation formation due to COVID-19 pneumonia is not so rare. The exact mechanism of cavitation in COVID-19 pneumonia is unknown, and it is postulated that the diffuse alveolar damage could be the potential reason, intra-alveolar hemorrhage and necrosis of parenchymal cells based on prior autopsy reports (3).

Several cases of pneumothorax associated to cystic pulmonary lesions on chest CT in patients with COVID-19 have also been reported (4,5). These cystic changes may result from resorption of consolidation (6), which may also result in pneumatocele formation. Pneumatocele formation was reported in a recent case series by Mallick et al.in two out of three patients who were presented with pneumothoraxes and were found to be SARS-CoV-2-positive. They postulate that prolonged inflammation may lead to the development of pneumatoceles due to alveolar wall destruction of adjacent airspaces (7).

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HIGH FREQUENCY OSCILLATORY VENTILATION IN INFANTS: THE CLINICAL PRACTICE IN N. MACEDONIA

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ABSTRACT

High frequency oscillatory ventilation (HFOV) is a ventilation mode with very high rates, small tidal volumes and permanent Mean Airway Pressure – MAP. It is used in neonates with respiratory failure when conventional mechanical ventilation (CV) is inadequate.

We present a study of three infants with respiratory failure, initially ventilated with CV (Drager-babylog 8000). All of them deteriorated on CV with hypoxemia and hypercapnia and switched to high-frequency oscillatory ventilation (HFOV). Improvement of ventilation had been confirmed after several days and the infants were successfully weaned off the HFOV mode and shifted to CV.

Conclusion: HFOV was able to improve significantly neonatal respiratory failure without any complications. However, our study is insufficient and it would be required a larger number of infants to confirm the use and clinical practice for neonates on HFOV mode.

Key Words**:** conventional mechanical ventilation (CV), high frequency oscillatory ventilation (HFOV), infants, respiratory failure.

Introduction

Respiratory failure is unfortunately common and life-threatening condition in infants in the first months of life. It is defined as the presence of respiratory distress syndrome (more signs of increased work of breathing-tachypnea, nasal flaring, chest retractions, apnea or grunting) caused by surfactant deficiency (1).

Respiratory failure is usually a result of respiratory distress syndrome, meconium aspiration syndrome, sepsis, pulmonary hypoplasia, persistent pulmonary hypertension, pulmonary interstial emphysema and pneumothorax. In general it is presenting symptoms of ineffective or impaired oxygen transport through the alveolus and pulmonary edema (poor gas exchange as a result of an inadequate elimination of the alveolar fluid) (2,3).

Unfortunately, in some cases, in infants with acute respiratory failure, general condition could be deteriorated after several hours, and can increase the percent of mortality) (4,5).

Therefore, the treatment should be pointed and adequate for decrease of the risk factors. There are several modalities for adequate treatment of respiratory failure, including high frequency ventilation inhaled nitric oxide therapy, exogenous surfactant administration, antenatal steroids, for the prevention of respiratory distress syndrome, and use of postnatal steroids for the prevention of chronic lung disease (6,7).

High frequency oscillatory ventilation (HFOV) is a mode of mechanical ventilation with very high rates (up to 1000 cycles per minute), a constant mean airway pressure – MAP and small tidal volumes. In adult population it can improve oxygenation efficiently and decrease the mortality in critically ill patients with acute respiratory distress syndrome and minimal hemodynamic side effects (4,8).

Additionally, HFOV is indicated as second-line therapy for the management of the ventilated patients with worsening of general condition and progressive respiratory failure (9,10).

Data on the use of HFOV in the neonatal intensive care NICU is very insufficient. In few published studies it was confirmed that the early use of HFOV has been successful and safe mode, versus conventional ventilation (CV) for neonates with meconium aspiratory syndrome, respiratory distress syndrome, severe pulmonary hypertension, congenital diaphragmatic hernia (11,12,13,14).

The aim of this study was to present our experience with HFOV mode at the University Children's Hospital – Skopje, Neonatal Intensive Care Unit in 2018, for the first time in Republic of North Macedonia, at three patients with respiratory failure who deteriorated on CV. All patients were initially ventilated on CV with respirator (Drager – babylog 8000), and when CV was not enough effective in treatment of respiratory failure, then it was switched to mode HFOV with respirator (Stephan-Sophie). Arterial blood gases, general condition with vital data were monitored.

Series of Case Reports

The First Case

Male newborn of 48 hours, with meconial aspiration syndrome and long apneic periods worsened the general condition (vital sings tachypnea over 70 respiration/min. NIBP 43/22; HR – 170 bpm; initial gas blood SpO_2 < 77%, gas blood pH-7.09 pCO_2-78 mmHg, pO_2 – 25 mmHg). He was intubated at admission and on conventional ventilation, sedated with fentanyl and a muscle relaxant was given several times. The same day a general condition of the newborn was stabilized, and control gas blood was improved. On the second day with progressive respiratory failure, not responding to CV, he was switched to high-frequency oscillatory ventilation HFOV (f – 13Hr, Pmax – 25 mmHg, MAP-17, FiO_2-50%). The first control arterial gas blood was improved. Chest *radiograph* showed coarse densities in both lungs with hyper-expansion. The settings on CV and HFOV are shown in Table 1.

Table 1.

day	pH	pO2 mm Hg	pCO2 mm Hg	SpO2 %	Mode of ventilation	PIP cmH2O	PEEP cmH2O	f min	FiO2
1	7.0	25	78	77	CV	26	7	60	70
					HFOV	**Pmax**	**MAP**	**f Hr**	**FiO2**
2	7,1	30	80	70		25	17	14	50
3	7.31	46	58	90		25	17	13	50
4	7.33	50	55	90		24	16	12	40
5	7.39	59	42	93		23	14	12	32
6	7.43	72	30	95		22	14	12	21
7					**CV/SIMV**	**PIP**	**PEEP**	**f**	**FiO2**
						21	6	23	21

On the fourth day of the ICU stay, the general condition of the newborn started to improve. The value of pCO_2 decreased to 55 mmHg, value of pO_2 increased to 50 mmHg. SpO_2 was 90%. In the following days a general condition of the newborn was significantly stabilized with hemodynamically stable condition, control chest *radiograph* and gas blood (pH-7.43, pCO_2 -30 mmHg, pO_2 – 72 mmHg) were improved. After three days on HFOV, the respiratory module was switched on to CV, and in the following second day, he was extubated and discharged from ICU.

The Second Case

One-month old male infant was transferred from another hospital for massive interstitial pneumonia, fever and desaturation. At admission with vital signs: NIBP 78/56; HR – 120bpm; SpO_2 -82%, gas blood (pH=7.15, pCO_2 -65 mmHg, pO_2 – 32 mmHg), was initially intubated, using CV and sedated with midazolam. The chest *radiograph* showed extensive perihilar opacities with numerous air bronchograms, while keeping with severe interstitial pneumonia. After 10 hours, a general condition worsened, tachycardia, deep respiratory acidosis and hypercapnia pH=7.1, pCO2 – 70 mmHg, pO2 – 28 mmHg, SpO_2-70%. HFOV mode was initiated with following respiratory parameters (Pmax-25, MAP-17, f-14, FiO_2-50). The settings on CMV and HFOV are shown in Table 2.

Table 2.

day	pH	pO2 mm Hg	pCO2 mm Hg	SpO2 %	Mode of ventilation	PIP cmH2O	PEEP cmH2O	f min	FiO2
1	7.15	32	65	82	CV	25	6.5	38	60
					HFOV	**Pmax**	**MAP**	**f Hr**	**FiO2**
1	7,1	28	70	70		25	17	14	50
2	7.34	37	54	73		25	17	14	57
3	7.36	55	50	82		24	17	14	45
4	7.38	59	44	88		23	15	13	37
5	7.41	60	45	91		22	15	13	32
6	7.40	53	47	89		22	15	13	35
7	7.42	60	42	93		21	14	13	25
8					**CV/SIMV**	**PIP**	**PEEP**	**f**	**FiO2**
						23	6,5	18	25

The second day on HFOV, the result of arterial gas blood improved, but it still showed respiratory acidosis and hypoxemia. The child had been on HFOV for one week, requiring high setting on HFOV support due to the severe interstitial pneumonia. After one week the general condition improved, arterial gas blood analyses normalized (pH, pO2, PCO_2), and hemodynamically stable condition with good response to the use of HFOV was shown. Control chest radiograph showed withdrawal of perihilar opacities and numerous air bronchograms. The respiratory module switched on to CV, and after three days the infant was extubated and discharged from ICU.

The Third Case

We report a four-months old male infant (St. post IVF, Prematurus 26 GW birth) initially hospitalized at neonatology department for aspiration of milk formula, and irregular breathing. After one hour with worsening of general condition (apnea, bradycardia – 58bpm, SpO2 < 70%, pH=7.15, pCO2 – 70, pO2 – 31 mmHg), he was transferred at ICU and was immediately intubated. The infant used CV and sedated with midazolam. The settings on CMV and HFOV are shown in Table 3.

Table 3.

day	pH	pO2 mm Hg	pCO2 mm Hg	SpO2 %	Mode of ventilation	PIP cmH2O	PEEP cmH2O	f min	FiO2
1	7.15	31	70	64	CV	25	5.8	45	80
1					**HFOV**	**Pmax**	**MAP**	**f Hr**	**FiO2**
2	7,21	28	70	70		23	15	14	35
3	7.35	52	42	92		22	15	13	30
4					**CV/SIMV**	**PIP**	**PEEP**	**f**	**FiO2**
5						21	5.8	35	24

Initial chest radiograph with apical areas of bilateral atelectasis was done. After several hours on CV with progressive respiratory acidosis with worsening blood gas analyses (pH-7.21, pCO_2 -70 mmHg) and HFOV was initiated. In the following two days, the general condition improved, arterial blood gas analyses normalized (pH-7.35, pCO_2 -42, PO_2 – 52, SpO_2-92%), respiratory module switched on to CV. The next day he was extubated and discharged from ICU.

Discussion

HFOV used in infants is a safe alternative mode to CV and may even be used as a rescue therapy. It is causing less baro/ volutrauma than CM and can be implemented as the first line treatment for respiratory failure (11,15).

Although the HFOV mode is promising in treatment of acute respiratory failure in infants, still the data base on the use of HFOV is very insufficient. A few published studies confirmed that the early use of HFOV has been successful and safe mode, versus CV. Yu-Bin pan et al. confirmed that improving oxygenation led to decrease of the mortality of critically ill infants with acute respiratory distress syndrome and with minimal hemodynamic side effects (16).

Chen et al. in their study, divided the infants into two groups – the first group used HFOV and the second one – CV (17). The study demonstrated that oxygenation indices OI of infants were better, and the ventilator settings (MAP and FiO_2) were lower in the HFOV group, comparing to CV group (infants with MAS). The length of ICU stay, duration of ventilation and treatment were significantly shorter in the HFOV group. Using early appropriate HFOV and surfactant application in MAS treatment was reported as an effective and safe method.

Our data include only three infants, and in the current study the sample is too small to make any conclusive result. None of the infants could be adequately ventilated on CV in the first 24 hours; All of them deteriorated owing to severe hypoxemia and hypercapnia. In the first infant after initiative stabilization on CV, a general condition was worsted and switched on HFOV with adequate settings on HFOV. Progressive improvement of respiratory failure had been noticed after the beginning on HFOV and 5 days after he was switched on to CV, and weaned off the ventilator after 48 hours. The second infant with severe interstitial pneumonia had been on increased settings HFOV for one week, with improvement of oxygenation, control chest radiograph showed withdrawal of perihilar opacities and he was hemodynamically stabile. The HFOV mode switched on CV, three days after he was extubated and his recovery was uncomplicated. The third preterm infant with aspiration of milk formula initially stabilized on CV, but with potentiation of respiratory failure. After switched on HFOV mode general improvement had been detected for several hours, and after 48 hours on HFOV the infant was weaned off the ventilator. His recovery was also uncomplicated.

In our patients HFOV resulted in a definitive and uncomplicated recovery, while no improvement had occurred on using CV. Our experience is very insufficient, as the current study is with a small number of infants using the HFOV mode.

Our priority and further research should focus to include larger number of infants and to establish the role of rescue HFOV mode in infants with respiratory failure.

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HYPONATREMIA IN OLANZAPINE TREATED PATIENT

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ABSTRACT

Hyponatremia is sodium level imbalance, defined as levels below 135 mmol/l. Numerous factors may lie in its etiology and pathogenesis including psychotropic drug use, and in such cases hyponatremia is an adverse event. The syndrome of inappropriate secretion of antidiuretic hormone secretion (SIADH) has been reported with the use of antidepressants, antipsychotics and mood stabilizers. The exact pathophysiological mechanisms for this syndrome are still in the process of investigation. The findings so far indicate: increased secretion of ADH from hypothalamus as a result of dopamine-D2 receptor inhibition (suppression of the inhibitory effect of dopamine on ADH secretion), as well as the effect of 5-HT2 and 5-HT1C serotonin receptors which also leads to an increase in ADH levels and potentiation of its effect at the renal level.

Having seen similar symptoms in SIADH and in psychiatric entities, it can cause hyponatremia to remain unrecognized in clinical practice, especially if mild and if it develops slowly. However, in some cases it may progress to severe hyponatremia which becomes an urgent condition. On the other hand, if recognized and treated in time, there is a satisfactory outcome.

We report a case-report of 64-year-old woman who has been treated for a schizophrenia disorder for thirty years with good remission of symptoms by regular use of antipsychotics (orally and in depot form). The current deterioration occurred in the last five months, due to non-compliance to the treatment. During treatment hyponatremia was induced by the second generation of antipsychotic drug.

In conclusion we recommend for clinicians not only to be cautious when prescribing psychotropic drugs, and to assess sodium laboratory values and clinical symptoms for all patients after initiation of antipsychotic drug as a routine clinical practice, but also to take into account differential diagnoses for presented symptoms.

Key Words: *adverse event, antipsychotics, hyponatremia, olanzapine, SIADH.*

CASE REPORT ON HYPONATREMIA IN OLANZAPINE TREATED PATIENT

Introduction

Hyponatremia is the most frequent disorder of fluid metabolism and electrolyte balance in clinical practice. It is usually defined as a serum sodium level below 135 mmol/l. Numerous factors may lie in its etiology and pathogenesis including the use of psychotropic drugs, and in such case it is not a side effect of their use. On the contrary, it is an adverse event because of the unintended pharmacologic effect even though medication is administered correctly. In such cases, the called type A reaction is predictable adverse event, commonly dose-dependent presented as mild, moderate or severe. The syndrome of inappropriate secretion of antidiuretic hormone secretion (SIADH) has been reported with the use of antidepressants, antipsychotics and mood stabilizers. The exact pathophysiological mechanisms for this syndrome that is characterized by euvolemic hyponatremia are still in the process of investigation (1). The findings so far indicate: increased secretion of ADH from hypothalamus as a result of dopamine-D2 receptor inhibition and consequently suppression of the inhibitory effect of dopamine on ADH secretion, as well as the effect of 5-HT2 and 5-HT1C serotonin receptors which also leads to an increase in ADH levels and potentiation of its effect at the renal level (2).

The literature lists and explores factors that may increase the risk of antipsychotic-induced hyponatremia. Some studies focus on: patient characteristics, drug dose, polydipsia or the onset of SIADH. According to some authors, it is indicative that compared to antidepressant-induced hyponatremia where women are at greater risk, antipsychotic-induced hyponatremia does not preferentially occur in either men or women (3). There are indications that tobacco smoking increases the risk of developing SIADH in psychiatric patients. This data is still not sufficiently investigated (1).

Studies on the influence of the dose on the hyponatremia development have shown a trend of negative correlation between perphenazine dose in the age group over 60 years. Nevertheless, there is a trend of positive correlation between clozapine dose and serum sodium level (3). Regarding the role of polydipsia in antipsychotic-induced hyponatremia, it has not been sufficiently elucidated as hyponatremia appear both in patients with and without an anamnesis for polydipsia. Therefore, when diagnosing SIADH it should be taken into account that reduced serum sodium levels are not always direct consequence of medications. A common cause of hyponatremia in people taking antipsychotic drugs is psychosis itself, as well as compulsive drinking of water. Primary polydipsia is detected in about 7% of patients with schizophrenia (4,5). In addition, the feeling of dry mouth caused by psychotropic drugs contributes to increased water intake (6).

The criteria for differential diagnosis of SIADH and psychogenic polydipsia are laboratory findings shown in Table 1. In SIADH serum osmolality is <280mOsm/kg, urine sodium excretion is >40 mmol/l, serum sodium <135mmol/l and the patients are receiving drugs that can cause SIADH. In psychogenic polydipsia serum osmolality is <280mOsm/kg, urine osmolality is <100mOsm/kg, urine sodium equal or below 20 mmol/l and serum sodium is <135mmol/l (2).

Table 1. *Differences between SIADH and psychogenic polydipsia.*

Criteria	SIADH	Psychogenic polydipsia
Serum osmolality	<280mOsm/kg	<280mOsm/kg (with urine osmolality <100mOsm/kg)
Urine sodium excretion	**>40mmol/l**	**= or <20mmol/l**
Serum sodium	<135mmol/l	<135mmol/l
Drug that can cause SIADH	**Receiving**	NO

Regarding the clinical symptomatology of hyponatremia induced by antipsychotic, it may be presented with mild symptoms of nausea and weakness and in severe cases with predominant neurological symptoms such as headache, muscle cramps lethargy, confusion, delirium and agitation. It can be asymptomatic until values of serum sodium level drop below 110 mmol/L. Having seen similar symptoms in psychiatric entities, sometimes hyponatremia can be unrecognized in clinical practice especially if mild and if it develops slowly. However, in some cases it may progress to severe hyponatremia which is an urgent condition. On the other hand, if recognized and treated in time, the outcome becomes very good.

Material and Method

Case-report of 64-year-old woman treated for a psychotic disorder for thirty years (Dg F 20 according to ICD 10) and has functioned relatively well with regular use of antipsychotic drug (orally and in depot form). The current deterioration has occurred in the last five months, due to non-compliance to the treatment. A few days before admission to Psychiatric Clinic she was examined for numbness, and tremor on an assumption of a higher dose intake of the prescribed risperidone. This was the reason for hospitalization. Past conditions: hypertension and hyperthyroidism. Life habit: tobacco smoker.

Results

At admission we noticed psychomotor restlessness to the degree of agitation, she was dysphoric, with anxiety, disharmonious volitional-instinctual dynamisms (hypobulia, social isolation, occasional verbal aggression, insomnia), with paranoid interpretative thoughts and auditory hallucinations. Her blood pressure was 180/100 mmHg. Laboratory investigations were in physiological limits except for Na level=126mmol/l. Electroencephalography examination showed unstable basal activity and theta waves over temporal-parietal leads. Her treatment began with olanzapine 10 mg/day and after a few days 15 mg/day together with diazepam 20 mg/day. During the (days of) treatment at our clinic – confusion, polydipsia, urinary incontinence and inappropriate behavior predominated when the doze of olanzapine was 15 mg/day. Repeated laboratory test detected lowering of the sodium levels to Na=102mmol/l and K= 3.5 mmol/l. The patient was transferred urgently at the Endocrinology Clinic for treatment, where the endocrine origin of hyponatremia was ruled out. The laboratory findings were: cortisol 381.0nmol/l, THS

0.805mlU/l and fT4 15.88pmol/l. After correction of the electrolyte status the patient received first generation antipsychotic drug i.e. haloperidol 6 mg/day (with gradual increase of the dose to optimal).

Discussion

In this case hyponatremia developed slowly and at the beginning she was treated with saline solution, due to the possible imbalance in the water intake. In the differential diagnosis during the first days of hospitalization, even dementia was taken into account because of the cognitive impairment and the long duration of the schizophrenia disorder. In the course of one-week time hyponatremia progressed from 126 to 102 mmol/l, however severe symptoms like seizures and coma were absent.

Among psychiatric patients, hyponatremia is believed to be frequently underdiagnosed because clinical symptoms mimicry psychopathological symptoms of the underlying condition (8). We need to emphasize that the symptomatology of hyponatremia varies depending on the biochemical severity and the speed of the development. It can be classified as mild, moderate and severe. Mild symptoms like headache, attention deficit, memory alterations, irritability, depression are present when sodium levels are between 130 – 135mEq/L. Moderate symptoms with nausea, vomiting, bradypsychia, confusion, disorientation occur with sodium levels of 120 – 130mEq/L. Severe symptoms such as stupor, seizures, coma and respiratory depression are developed when sodium levels are below 120mEq/L. The patient develops hyponatremic encephalopathy with hyponatremia because of the disturbed osmotic gradient between the extracellular space and the intracellular space caused by the low serum osmolarity and consequent passage of free water into the interior of the cell. Cerebral edema is caused by (this) accumulation of water in the brain cells (9).

The incidence of hyponatremia induced by antipsychotics might be much higher than currently thought. Antipsychotic-induced hyponatremia is probably due to SIADH, and could occur in patients with schizophrenia or with other disorders. It probably occurs equally among men and women. The development of hyponatremia has been associated to the use of second-generation antipsychotics as to the use of the first-generation antipsychotics (3).

Several studies are done regarding the evidence, linking the use of antipsychotics to SIADH among which the cross-sectional study of Serrano et al., involving 88 patients receiving clozapine, 61 patients receiving other atypical antipsychotics, 23 patients receiving typical antipsychotics and 11 patients receiving both typical and atypical antipsychotics; whereas the frequency of hyponatremia during clozapine administration was similar to that observed with other atypical antipsychotics and significantly lower than those recorded with typical agents. **(7)** In addition to the role of antipsychotic drugs in causing hyponatremia is the causality assessment performed using Naranjo's adverse drug reaction probability scale in analyzing four studies and 91 publications containing case reports and case series which indicated possible causality in the most of the cases (80%), probable causality in a significant number of cases (19%) and unlikely causality in one case (1%) (3).

Olanzapine is an atypical antipsychotic, antagonist of D2 and 5HT2A receptor. This second-generation antipsychotic is widely used in psychiatric practice to reduce agitation and positive symptoms. There are studies that report olanzapine-induced hyponatremia when used with concomitant psychopharmacotherapy (9,10). One study described a case of death of a young schizophrenic patient with secondary hyponatremia due to excessive water intake aggravated with the increase of the dose of olanzapine similar to our case (12).

In cases of SIADH induced by antipsychotic drug, rapid and complete recovery is achieved after the correction of the sodium level with discontinuation of the antipsychotic drug that caused hyponatremia and by its replacement with another antipsychotic drug. In our case-report the atypical antipsychotic olanzapine was replaced with the first-generation drug – haloperidol.

Conclusion

With this case report we want to emphasize that severe hyponatremia can be experienced as an adverse event of an antipsychotic drug and it might result in an urgent condition in the medical practice. Awareness of such various drugs side effects on sodium concentration levels facilitates success regarding clinical outcome in patients' treatment. Because the similar symptoms of hyponatremia are also seen in psychiatric entities, it can be unrecognized in psychiatric practice especially if developing slowly. This is the reason why clinicians need to be cautions when prescribing psychotropic drugs, in addition it is recommended assessing sodium laboratory values and clinical symptoms for all patients after initiation of antipsychotic drug as routine medical practice and also keeping in mind differential diagnoses for presented symptoms.

Conflict of Interest: The authors have no conflict of interests to declare.

Authors Contribution: All authors have equally participated.

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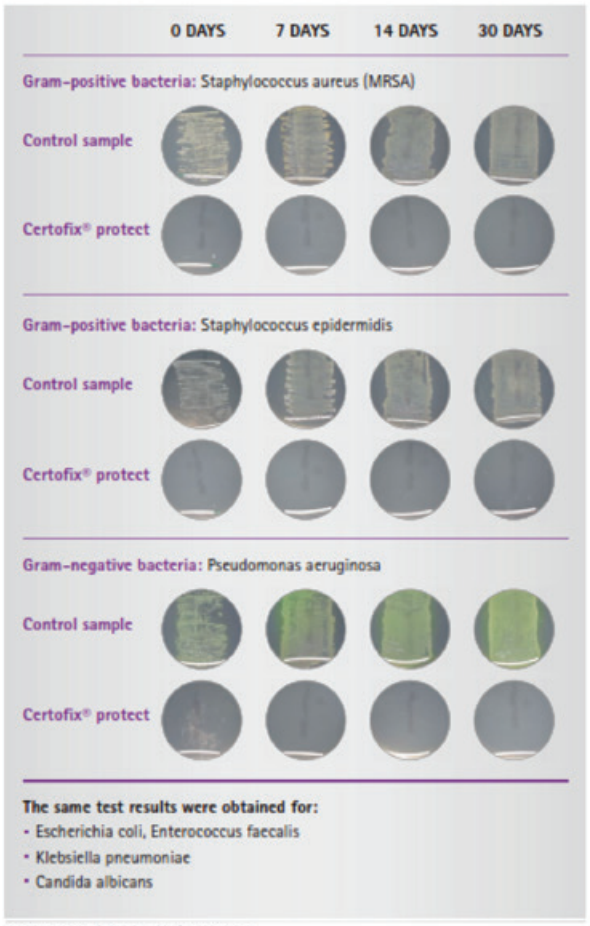

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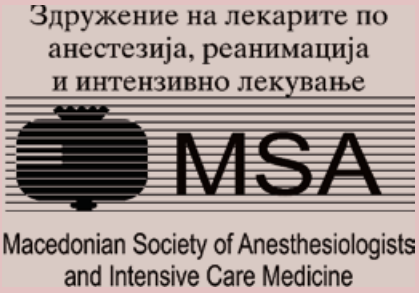
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