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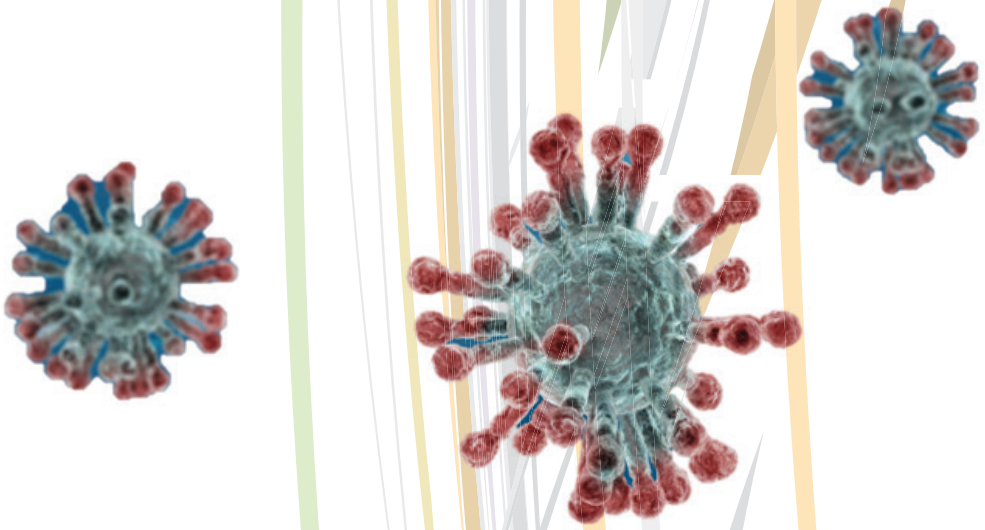

KLINIČKO BOLNIČKI CENTAR ZEMUN

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KLINIČKO BOLNIČKI CENTAR
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SADRŽAJ

Aktivnosti Covid bolnice KBC Zemun tokom vanrednog stanja u vreme pandemije –druga polovina 2020. godine

Covid tim KBC Zemun

U januaru 2020. godine smo znali da se nešto "valja iza brega". Tokom godine smo shvatili i šta Pandemija Covid 19. A kraj 2020. godine dočekujemo umorni, iscrpljeni, ali držimo se sa utiskom da se sada "breg valja na nas!".

KBC Zemun je sem kratkog period od 29. 08. 2020. do 28.10.2020. godinesve vreme bio u Covid istemu. U ovom trenutku statistički podaci su jasni. Ono što kroz njih ne možemo da prikažemo to su sudbine osoblja i pacijenata. Ne možemo da ispričamo sve priče i lepe i tužne, ne možemo da prikažemo ugasli sjaj u očima umornog osoblja. I ne možemo da kažemo prošlo je.

Tokom perioda 01. 07.-28. 08 .20., a potom 29. 10.-31. 12. 20. KBC Zemun je u punom Covid sistemu je opservirano i lečeno 3.864 pacijenata. To je iznosilo ukupno 29.123 Ciovid dana (beo dana) (Tabela 1.)

RB	ORGANIZACIONA JEDINICA	LICA		UKUPNO COVID LICA	DANI		UKUPNO COVID DANI
		01.07.-28.08.20.	29.10.-31.12.20.	KOLONA2+3	01.07.-28.08.20.	29.10.-31.12.20.	KOLONA 5+6
0	*1*	*2*	*3*	*4*	*5*	*6*	*7*
1	**COVID NEUROLOGIJA**	49	52	**101**	229	384	**613**
2	**COVID GERIJATRIJA**	41	0	**41**	218	0	**218**
3	**COVID ONKOLOGIJA**	114	176	**290**	980	1,610	**2,590**
4	**COVID BARO MEDICINA**	74	119	**193**	574	828	**1,402**
5	**COVID HIRURGIJA**	313	406	**719**	2,003	2,881	**4,884**
6	**COVID INTERNA KLINIKA**	547	567	**1,114**	4,619	4,664	**9,283**
7	**COVID NEUROIHIRURGIJA**	131	189	**320**	947	1,391	**2,338**
8	**COVID ORL**	142	219	**361**	956	1,516	**2,472**
9	**COVID RESPIRATORNI CENTAR**	174	268	**442**	1,364	1,837	**3,201**
10	**COVID UROLOGIJA**	101	182	**283**	847	1,275	**2,122**
11				**0**			**0**
12				**0**			**0**
U K U P N O		**1,686**	**2,178**	**3,864**	**12,737**	**16,386**	**29,123**

Tabela 1. Distribucija pacijenata i Covid dana prema Covid odeljenjima KBC Zemun

Ukupno je pregledano i hirno primeljen 9.706 pacijenata (Tabela 2.).

RB	ŠIFRA	N A Z I V	PREGLEDI		UKUPNO PREGLEDI
			01.07.-28.08.20.	29.10.-31.12.20.	KOLONA 2+3
0		*1*	*2*	*3*	*4*
1	**110**	**AMBULANTA ZA PREGLED CORONA PACIJENATA**	52	390	**442**
2	**2001**	**HITAN PRIJEM CORONA PACIJENATA**	2,113	6,966	**9,079**
4	**110**	**COVID NEUROLOGIJA**	79	42	**121**
11	**110**	**COVID ONKOLOGIJA**	0	64	**64**
12					**0**
U K U P N O			**2,244**	**7,462**	**9,706**

Tabela 2. Pregledi i hitni prijemi pacijenata na hitnim prijemima

Covid 19 pozitivni pacijenti su zahtevali i hirurške intervencije. u navedenom periodu je urađena 51 hitna intervencije (Tabela 3.)

RB	ORGANIZACIONA JEDINICA	BROJ OPERISANIH		UKUPNO OPERISANIH	BROJ OPERACIJA		UKUPNO OPERACIJA
		01.07.-28.08.20.	29.10.-31.12.20.	KOLONA2+3	01.07.-28.08.20.	29.10.-31.12.20.	KOLONA 5+6
0	*1*	*2*	*3*	*4*	*5*	*6*	*7*
1	**LEČENJE PACIJENATA SA CORONA VIRUSOM HIRURŠKA KLINIKA**	1	0	**1**	2	0	**2**
2	**RESPIRATORNI CENTAR**	6	5	**11**	9	6	**15**
3	**COVID BARO MEDICINA**	0	1	**1**	0	1	**1**
4	**COVID HIRURGIJA**	0	16	**16**	0	29	**29**
5	**INTERNA COVID KLINIKA**	0	2	**2**	0	3	**3**
6	**COVID NEUROHIRURGIJA**	0	1	**1**	0	1	**1**
7				**0**			**0**
U K U P N O		**7**	**25**	**32**	**11**	**40**	**51**

Tabela 3. Prikaz hitnih hirurških intervencija Covid 19 pozitivnih pacijenata

U Tabeli 4. su prikazani dijagnostičke procedure koje su urađene u tom periodu

RB	N A Z I V	BROJ FAKTURISANIH USLUGA		UKUPNO FAKTURISANIH USLUGA
		01.07.-28.08.20.	29.10.-31.12.20.	KOLONA2+3
0	*1*	*2*	*3*	*4*
1	**DOPLER**	133	331	**464**
2	**MAGNETNA REZONANCA**	36	68	**104**
3	**RENTGEN**	1,940	4,872	**6,812**
4	**SKENER**	161	323	**484**
5	**ULTRAZVUK**	416	1,412	**1,828**
U K U P N O		**2,686**	**7,006**	**9,692**

Tabela 4. Radiološke dijagnostičke usluge

Laboratorijske usluge, ukupno 301,475 su prikazane u Tabeli 5.

RB	N A Z I V	BROJ FAKTURISANIH USLUGA		UKUPNO FAKTURISANIH USLUGA
		01.07.-28.08.20.	29.10.-31.12.20.	KOLONA2+3
0	*1*	*2*	*3*	*4*
1	**LABORATORIJA**	68,594	176,977	**245,571**
2	**PATOHISTOLOGIJA**	732	3,783	**4,515**
3	**TRANSFUZIJA**	12,818	38,571	**51,389**
U K U P N O		**82,144**	**219,331**	**301,475**

Tabela 5. Presek laboratorijskih dijagnostičkih usluga

Broj smrtnih ishoda Covid pacijenata je prikazan u Tabeli 6.

RB	PERIOD COVID U DRUGOJ POLOVINI GODINE	UMRLI		
		U PRVIH 48 H	NAKON 48 H	KOLONA 2+3
0	*1*	*2*	*3*	*4*
1	**01.07.-28.08.20.**	31	126	**157**
2	**29.10.-31.12.20.**	93	276	**369**
U K U P N O		**124**	**402**	**526**

Tabela 6. Broj smrtnih ishoda

Možda brojke govor o težini situacije, ali govori i o hrabrosti, entuzijamu, dobroj organizaciji i pre svega humanosti zdravstvenih radnika i saradnika KBC Zemun. Svako od njih je bio jedna karika u lancu, a lanac je izdržao.

Early oncological predictros of laparoscopic surgery for treatment in patients with colorectal carcinoma

Aleksandar Lazic[1], Dejan Stevanovic[1,2], Nebojša Mitrovic[1,2], Damir Jasarovic[1,2], Srdjan Milina[1], Dimitrije Surla[1], Aleksandar Ivkovic[1], Vladan Lekovski[1], Dragoš Stojanovic[1,2]

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Abstract

The debate of proponents of laparoscopic and classical colorectal surgery is still ongoing, especially on the oncological principles of colorectal malignancy treatment. For now, there are promising results in terms of the adequacy of laparoscopic surgery in the treatment of this disease. The study involved 60 patients with acceptable generalized operability and a diagnostically verified malignant neoplasm of colorectum. Patients were divided into two groups of 30 patients: patients who were operated with open and laparoscopically assisted colorectal surgery. Two groups of factors were collected and analyzed for all patients. The first group of factors was known preoperatively and the second group of factors was known postoperatively. There was no significant differences between the two groups concerning the age, sex, ASA score, preoperative hemoglobin values, blood type. Both groups were the most represented in the rectum cancer. The largest number of patients was G2 grade 49.1%. Surgical margins were negative for cancer in all examined patients. There was a statistically significant difference, in terms of a larger number of removed lymph glands in open surgery treated patients. The average number of lymph nodes removed laparoscopically was 14 (range 5-40), while in the classic-open group number was 20 (range 8-44). Laparoscopic group were able to retrieve >12 LNs in 70% of the cases while in classic-open group were able to retrieve >12 LNs in 93% of the cases. The third stage of the disease was significantly more prevalent in the classical group of patients than in laparoscopic group of patients (17: 7 patients). The average volume of the removed tu-

Rani onkološki prognostički faktori laparoskopske hirurgije u terapiji bolesnika sa kolorektalnim karcinomima

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Apstrakt

Debata zagovornika laparoskopske i klasične kolorektalne hirurgije još uvek traje, posebno o onkološkim principima lečenja kolorektalnog maligniteta. Za sada postoje obećavajući rezultati u pogledu adekvatnosti laparoskopske hirurgije u lečenju ove bolesti. U istraživanju je učestvovalo 60 pacijenata sa prihvatljivom generalizovanom operabilnošću i sa dijagnostički verifikovanom malignom neoplazmom kolorektuma. Pacijenti su podeljeni u dve grupe od 30 pacijenata: 1. pacijenti koji su operirani otvorenom i 2. laparoskopski podržanom kolorektalnom hirurgijom. Dve grupe faktora su prikupljene i analizirane za sve pacijente. Prva grupa faktora bila je poznata preoperativno, a druga grupa faktora analizirana je postoperativno. Nije bilo značajnih razlika između dve grupe koje se tiču starosti, pola, ASA rezultata, preoperativnih vrednosti hemoglobina, krvne grupe. Obe grupe su bile najviše zastupljene kod karcinoma rektuma. Najveći broj pacijenata je bio sa G2, 49,1%. Hirurške margine su bile negativne za karcinom kod svih pregledanih pacijenata. Utvrđena je statistički značajna razlika u pogledu većeg broja uklonjenih limfnih žlezda kod pacijenata lečenih na otvorenom operativnom zahvatu. Prosečan broj uklonjenih LN (limfnih nodusa) laparoskopski je bio 14 (raspon 5-40), dok je u klasičnoj-otvorenoj grupi broj 20 (raspon 8-44). Laparoskopska grupa je uspela da dobij više od 12 LN u 70% slučajeva, dok smo u klasično-otvorenoj grupi imali više od 12 disekovanih LN u 93% slučajeva. Treći stadijum bolesti bio je značajno zastupljeniji u klasičnoj grupi pacijenata nego u laparoskopskoj grupi bolesnika (17: 7 pacijenata). Prosečna zapremina uklonje-

mor in the laparoscopic group is 73 cm3, while in the classical group the average volume is 99 cm3. Our results show that classic-open and laparoscopic approaches in colorectal cancer surgery are associated with the retrieval of greater than 12 LNs, therefore both are adeqate for safe oncological treatment of this disease. With classic-open colorectal surgery, we are still able to retrive more matching LNs, compared to laparoscopic surgery.

Key words: laparoscopic colorectal surgery, open colorectal surgery, colorectal cancer, lymph nodes dissection.

nog tumora u laparoskopskoj grupi je 73 cm3, dok je u klasičnoj grupi prosečna zapremina 99 cm3. Naši rezultati pokazuju da su i klasično-otvoreni i laparoskopski pristupi u operaciji kolorektalnog karcinoma povezani sa prosečnim disekovanjim brojem LN većim od 12, pa su oba adekvatna za sigurno onkološko lečenje ove bolesti. Sa klasično-otvorenom kolorektalnom hirurgijom još uvek smo u mogućnosti da dobijemo više odgovarajućih LN-a u poređenju sa laparoskopskom hirurgijom.

Ključne reči: laparoskopska kolorektalna hirurgija, otvorena kolorektalna hirurgija, kolorektalni karcinom, disekcija limfnih čvorova.

Introduction

The debate of proponents of laparoscopic and classical colorectal surgery is still ongoing, especially on the oncological principles of colorectal malignancy treatment. For now, there are promising results in terms of the adequacy of laparoscopic surgery in the treatment of this diseases 1,2,3,4,5,6. Laparoscopic colorectal surgery had been routinely performed by the surgeons of the Department for General Surgery, Clinical Hospital Center of Zemun since 2013. The aim of this study was to compare early predictors of oncological radicality in patients operated with laparoscopically assisted and classical-open colorectal cancer surgery.

Material and methods

The study was performed as a clinical retrospective study. This study included 60 patients who underwent elective laparoscopic assisted or open colorectal surgery at the Department for General Surgery, Clinical Hospital Center of Zemun in Belgrade from December 2013 to September 2016. The study involved 60 patients with acceptable general operability and diagnostics verified malignant colorectal neoplasm. Patients were divided into two groups, each of 30 patients: First group- patients treated by classic-open colorectal surgery. Second group- patients treated by laparoscopically assisted colorectal surgery.

Two groups of factors were collected and analyzed for all patients: The first group of factors was known preoperatively: age, gender, ASA score, preoperative values of hemoglobin, blood type, localization and histological type of the primary tumor. The second group of factors that were known postoperatively: number of dissected lymph nodes, TNM classifications, tumor size. The criteria for patient involvement in the study for both groups were as follows: patients with histopathologically diagnosed colorectal cancer, both sexes, age over 18 years, acceptable general operability, written consent for operative treatment. The criteria for exclusion of patients from the study for both groups were as follows: patients who did not have preoperative pathohistological diagnosis, patients who had an inability to perform radical surgery for any reason. Indications for surgical treatment were

based on the guidelines issued by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)[8]. Preoperatively, all patients were prepared in terms of complete diagnostics for diagnosis of colorectal malignancies. A colonoscopy was performed with biopsy and pathohistological analysis of the material, analysis of blood count and biochemistry, blood type. Then supplementary diagnostic methods in the form of MSCT/MRI abdomen and pelvis, rtg pulmo et cor, due to preoperative determination of disease stage. All patients were examined preoperatively by an internist/cardiologist as well as by anesthesiologists, to bring them to the optimum state for surgical treatment and for obtaining a permit for surgical treatment. Preoperatively, all patients ware prepared for surgical treatment in terms of mechanical preparation for colorectal surgery, administering Fortrans® and Picoprep® laxatives. Immediately the day before surgery patients were discontinued oral administration, fluid reimbursement by infusion was administered in the form of solutions 0.9% NaCL, Ringer, Hartman or 5% Glucosa solution. Patients were preoperatively administered an antibiotic in the form of cephalosporins of II/III generation and metronidazole, as well as mandatory thromboembolic prophylaxis in the form of administration of low molecular heparin. Patients were operated on a regular operating program - electively in general endotracheal anesthesia. All the operations were performed by the four surgeons. Pneumoperitoneum was induced by insufflation of CO2 and was maintained at 10 to 12 mmHg during the entire surgical procedure. Laparoscopic operations were performed with the four trocars (two 5-mm and two 12-mm) to access the abdomen. For the right-sided tumors, mobilization of the right colon and takedown of the hepatic flexure were performed together with dissection of the draining lymph nodes from a lateral to medial direction. Then we performed the ligation of the tumor-feeding vessels (the ileocolic, right colic, and/or right branch of the middle colic vessels). For the left-sided tumors the left colon and splenic flexure were mobilized similar to right-sided lesions, using the lateral to medial aproach. Then we performed the ligation of the tumor-feeding vessels (the left colic and the left branches of the middle colic vessels, or we performed high ligation near the roots of the inferior mesenteric vessels). The inferior mesenteric artery was ligated under the level of the bifurcation of the left colic artery for rectal lesions. After rectal mobilization in the layer targeted for total mesorectal excision with autonomic nerve preservation, the bowel distal to the cancer was transected intracorporeally by linear staplers. In all laparoscopic patients the identification and division of the lymphovascular pedicle and the mobilization of colonic segments were carried out by the harmonic scalpel (Ethicon Endosurgery Inc., Cincinnati). Classic-open operations started with a middle to lower midline incision, dependently on the locations of colorectal carcinoma. The mobilization of colonic segments was conducted from a lateral-to-medial direction. The following details of the surgical procedure were recorded in all patients: duration of operation, amount of homologous blood transfused. Transfusion of blood products in the perioperative period was based on the hemoglobin level 80 g/L) or on an individual basis according to the clinical condition. All patients were treated on a strictly controlled protocol with regard to analgesic administration, feeding, and postoperative care. Postoperatively, patients were transferred to the intensive care unit and then as needed transferred to the Department of General Surgery. Microbiologic analysis and positive culture were used to diagnose infectious complications. Anastomotic dehiscence with clinical and/or radiologic evidence has been considered. Patients were discharged after complet verticalisation, after the establishment of adequate bowel movement and full recovery of oral food intake. Research Protocol: The data required for this study were taken from the protocol of surgical treatment, patient medical history, therapy list of the patients, anesthesiology lists conducting surgical treatment and pathologist reports. All data were grouped into two tables, which were subsequently used for statistical purposes processing. The first table was patients treated by classic-open surgical technique, the second the table was patients treated by a laparoscopically assisted surgical technique.

Statistical processing Descriptive and analytical statistical methods were used in this study. Of the descriptive ones we used: absolute and relative numbers (n,%), measures of central tendency (arithmetic mean, median), dispersion measures (standard deviation, interval of variation). Of the analytical statistical methods, the difference tests were used: parametric (t test), non-parametric (Hi-square test,

Fisher's exact probability test, Mann-Whitney U test).

The choice of test to test the difference depended on the data type and distribution. Parametric methods were used in a situation where the distribution was normal, while non-parametric ones were used in a situation where the distribution is not normal. The normality of the distribution was examined on the basis of descriptive ones parameters, normality distribution tests (Kolmogorov-Smirnov and Shapiro-Wilks test) and graphical methods (histogram, boxplot, QQ plot). The results are presented in tables and graphs. All data were processed in SPSS 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) software package.

Results

In the first group of factors-preoperative factors, we examined the homogeneity of the two analyzed groups. We analyzed potential differences in terms of age, gender, ASA score, preoperative hemoglobin values, blood type, localization and histologic type of the primary tumor. There was no significant differences between the two groups concerning the age (t = -0.697; p = 0.489), sex (X2 = 1.684; p = 0.194), ASA score (Z = -1,695; p = 0.090), preoperative hemoglobin values (t = 0.050; p = 0.960), blood type (X2 = 3.402; p = 0.388) other characteristics. Both groups were the most represented in the rectum cancer with 33.3%. In laparoscopic group, the largest percentage of malignancy was present in the region of sigmoid colon with 36.7%. While in the classic-open group of the patient the largest percentage of malignancy were in the area of the proximal third of the rectum with 43.3%. In laparoscopic group compared to localization of malignant process the rectum was represented in 23.3%, rectosigmoidal transition to 13.3%. Analyzing the histological differentiation of tumors, we obtained the following results: All patients had a diagnosed colorectal adenocarcinoma. The largest number of patients was G2 grade 49.1%. Histological grade G1 was present in 57.1% of patients in the laparoscopic group, while in 27.6% classic-open patient groups. G2 in 58.6% of the classic patient group, in 39.3% of the laparoscopic group patients. G3 in 13.8% of the classic group patient and 3.6% of the laparoscopic group patient. There was a statistically significant difference between the groups (Z = -2.373; p = 0.018).

In the second group of factors-postoperative factors, we examined differences between the two studied groups . We analyzed the number of dissected lymph nodes, TNM classifications, tumor size. Surgical margins were negative for cancer in all examined patients. Analyzing our data, we obtained the following results: That there is a statistically significant difference (Z = -2.979; p = 0.003) in the number of lymph nodes removed, in terms of a larger number of removed lymph glands in classic-open surgery treated patients. The average number of lymph nodes removed laparoscopically was 14 (range 5-40), while in the classic-open group number was 20 (range 8-44). Laparoscopic group were able to retrieve >12 LNs in 70% of the cases while in classic-open group were able to retrieve >12 LNs in 93% of the cases. Number of retrive >12 LNs for >T2 stadium in laparoscopic group was 74%, while open group were able to retrive >12 LNs in 82%. For T3 stadium number of retrive >12 LNs in laparoscopic group was 86,6 %, in open group was 84,21 %. Depending on the localization of malignant process, the number of retrived >12 LNs for the right colon in the laparoscopic group was 100%, in the classic-open group was 86%. For the left colon in laparoscopic group was 50%, in classic-open group was 87%, and for the rectum it was 72% in laparoscopic group, while in the classic-open group it was 100%. As regards to N status, number of retrived >12 LNs for N0 status in laparoscopic group was 57%, in classic group was 92%. For N1 status in laparoscopic group it was 100%, in classic-open group it was 67%, and for N2 status it was 100% for both groups. The average volume of the removed tumor in the laparoscopic group is 73 cm3, while in the classical group the average volume is 99 cm3. There was no statistically significant difference between the groups (Z = -1.548; p = 0.122).

Variables	Group		p-value
	Classic-open	Laparoscopic	
Mean (SD)	20	14	*0.003*
Range	8-44	5-40	
Volume of tumor (cm^3)	99	73	0.122
T1	3.4%	30%	*0.005*
T2	20.7%	26.7%	
T3	65.5%	40%	
T4	10.4%	3.3%	
N0	41.4%	76.7%	*0.009*
N1	34.5%	13.3%	
N2	24.1%	10%	
G1	27.6%	57.1%	*0.018*
G2	58.6%	39.3%	
G3	13.8%	3.6%	

Table 1. Volume of tumor (cm^3) in analized gropus

Variables	Group			
	Classic-open		Laparosopic	
	>12LNs retrived	<12LNs retrived	>12LNs retrived	<12LNs retrived
LNs retrived	85.71%	14.29%	70%	30%
T2	83.3%	18%	74%	26%
T3	84.21%	15.79%	86.6%	13.4%
T4	100%	/	/	/
Right colon	86%	14%	100%	/
Left colon	87%	13%	50%	50%
Rectum	100%	/	72%	/
N0	92%	8%	57%	43%
N1	67%	33%	100%	/
N2	100%	/	100%	/

Table 2. LNs retrived in analyzed groups with different T, N stadium and localisation

We compared the data related to the TNM classification, we first compared by T stage, then by N and M stage of the disease. Finally, we compared the data by the total stage of the disease. We obtained the following results: T stage: there is a statistically significant difference in the observed patient groups (Z = -2,820; p = 0.005). T1 stage was significantly present in the laparoscopic group of patients (16.7%: 0%) T3 stage was more significantly represented in the classical group of patients (65.5%: 40%). N stage: There is a statistically significant difference in terms of N status in the observed groups (Z = -2.629; p = 0.009). The N0 stage was significantly present in the laparoscopic group of 76.7%, in the classical group it was 41.4%. N1 stage in the laparoscopic group is 13.3%, while in the classical group it is 34.5%. N2 stage in the classical group was present in 24.1%, and in the laparoscopic 10%. M stage: there was no statistically significant difference in relation to the observed groups of patients. The third stage of the

disease was significantly more prevalent in the classical group of patients than in laparoscopic group of patients (17: 7 patients). The first stage of the disease was more significantly represented in the laparoscopic group of patients than in classic group of patients (11: 4 patients).

			Stage (TNM)				
			0	I	II	III	
Operation	Classic-open	N	1	4	7	17	29
		%	3.4%	13.8%	24.1%	58.6%	100.0%
	laparoscopic	N	1	11	11	7	30
		%	3.3%	36.7%	36.7%	23.3%	100.0%
		N	2	15	18	24	59
		%	3.4%	25.4%	30.5%	40.7%	100.0%

Table 3. Stage of malignant disease in analyzed groups

Discussion

Advantage in colorectal cancer laparoscopic surgery over classic surgery is less painful operative wounds, and therefore less use of analgesics, earlier recovery of both bowel function and oral feeding, lower percentage infections of surgical wounds, faster mobilization and shorter hospitalization of patients. Numerous studies have been done and some are ongoing, examining whether laparoscopic surgery has grown open surgery and is it able to fullfil adequately oncological radicality, which is essentially of paramount importance[7,8,9]. This study is limited by the retrospective data collection. In this study, we compared preoperative parameters between these two groups of patients, to show homogeneity in patient choice for both procedures. There was no significant differences between the two groups concerning the age ($t = -0.697$; $p = 0.489$), sex ($X2 = 1.684$; $p = 0.194$), ASA score ($Z = -1{,}695$; $p = 0.090$), preoperative hemoglobin values ($t = 0.050$; $p = 0.960$), blood type ($X2 = 3.402$; $p = 0.388$) and other characteristics. There was no statistically significant difference between the groups regarding the average volume of the removed tumor.

One of the predictors of the oncological outcome of oncological operations is the number retrived lymph nodes in terms of the adequacy of the basic principle of lymphadenectomy. Numerous studies have been done on this topic, e.g. meta - analysis of Wu et al. conducted on 24 randomized control studies, showed no difference in the number of lymph nodes removed comparing laparoscopic and open colorectal cancer surgery[10,11]. In our study, there is a statistically significant difference in the number of lymph nodes removed, in terms of a larger number of removed lymph nodes in classically operated patients. Average lymphatic nodes removed laparoscopically is 14, while classical is 20. However, by comparison the number of lymph nodes removed laparoscopically in our study with other studies, we did't found significant difference. In a study by Biondi et al., the average number of lymph nodes removed was 12.36 ± 4.36[12]. In a study by Balducci et al., the average number of lymph nodes was 15[13], while in the COLOR study, the average number of lymph nodes removed was 10[14]. There is still no consensus in the literature on the minimum number of lymph nodes removed which is needed to identify adequate nodal status. In the literature, the number varies from over 7 to as many as over 30 lymph nodes removed. For example, the National Comprehensive Cancer Network (NCCN), the College of American Pathologists, and the American Joint Committee on Cancer (AJCC) state that at least 12 lymph nodes are required to create adequate N status[15,16,17]. There are numerous confounding factors that have influence on the level of retrived lymph nodes.

The location of tumor is important, there are studies that showed right side localisation of tumor are associated with higher numbers of retrived LNs. On the other hand, left-sided colon cancer are about 50% less likely to retrive adequate LN evaluation[18,19]. In our study for the right sided localisation of tumor we manage to retrive >12 LNs in 100% of cases in laparoscopic group and 86% in classic-open

group. For the left sided localisation of tumor we manage to retrive >12 LNs in only 50% in laparoscopic group, but in classic-open group we manage that in 87%. Like in other studies[20], we also found that the proportion of patients with >12 LNs retrived were higher in the advance-stage of cancer. For example number of retrived >12 LNs for T2 stadium in laparoscopic group was 57%, while open group were able to retrive >12 LNs in 83%. For T3 stadium number of retrived >12 LNs in laparoscopic group was 86,6 %, in open group was 84,21 %. In N0 stage in laparoscopic group we retrived >12 LNs in only 57%, but in N1 and N2 stage we manage to retrive >12LNs in 100%. In classic-open group in N1 stage we retrived >12 LNs in 67%, but in N2 stage in 100% of cases. In laparoscopic group we used lateral approach, which is comparing to the medial approach, inferior to the retrival of the LN. One of the limiting factors of this study is the fact that the first stage of the disease was present with a statistically significant difference in the laparoscopic group, whereas in the classic group the third stage was present with a statistically significant difference. Given the beginning of laparoscopic surgery of the colorectal carcinoma in our hospital, it can be said that at first we had a certain bias in the selection of the patients we have chosen to treat with laparoscopic surgery. With our continious education, training, advancing and moving the boundaries, we practically equating our opportunities in treating the advance stages of this disease with laparoscopy, whether classical colorectal surgery, which can be seen in our results. Numerous large multicenter studies deal with oncological outcome and laparoscopic comparison and open surgery for colon and rectal malignancies. Looking at the COLOR I and COST study, we conclude that laparoscopic surgery of curable colon cancers is not inferior in relation to classical colon surgery[14,21]. However, there are ongoing studies that are dealing with oncological outcome for laparoscopic surgery of rectal cancers. The oncological safety of laparoscopic rectal surgery, in particular, has not yet been proven, especially for middle and distal thirds of rectum. COLOR II study involved 30 centers and hospitals in eight countries, which included 1103 patients, had the following results: Macroscopically, there was no difference in completeness of resection between groups, positive resection margin was observed in 56 of 588 patients in the laparoscopic group and 30 of 300 patients in classical group. Tumor distance from the distal resection margin is not statistically significant differed between these two groups of patients[22]. The CLASICC study after 5 years of postoperative follow-up presents results that are oncological safety satisfactory in colorectal laparoscopic surgery compared to classical surgery. By using laparoscopic surgery, we improve the short-term outcome and not we compromise the long - term outcome[23]. The COREAN trial shows results of laparoscopic surgery of locally advanced rectal cancer after preoperative hemotherapy, has a similar oncological outcome (3-year monitoring) in relation to open surgery[24]. Surgery of the middle and lower third of the rectum is still associated with a high risk of incomplete mesorectal excisions and a large number of positive circumferential resection margins, which leads to not a small number of local recurrences, impaired quality of life of patients, morbidity and mortality. TaTME (transanal total mesorectal excision) is a procedure that arose as a need for by improving the quality of total mesorectal excision. A COLOR III study comparing the short- and long-term outcomes of TaTME and laparoscopic TME for rectal carcinomas[25]. In our study, regarding the rectum as a localization of the malignant process, it was represented proximal third of the rectum. Given the limiting factors, such as the lack of adequate equipment, as well as the beginning of laparoscopic colorectal surgery in our institution, we did not work cancers of the midle and distal third of the rectum.

Conclusion

The retrieval of greater than 12 LNs in colorectal cancer surgery is associated with better staging and therefore better chances for adeqate tretman. Our results show that classic-open and laparoscopic approaches in colorectal cancer surgery are associated with the retrieval of greater than 12 LNs, therefore both are adeqate for safe oncological treatment of this disease. With classic-open colorectal surgery, we are still able to retrive more matching LNs, compared to laparoscopic surgery. However, given the fact that golden oncological standard is more than 12 retrived LNs for adequate staging and further treatment, laparoscopic colorectal surgery fully satisfies the basic oncological principles.

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Korelacija rezultata histopatološkog pregleda posle preoperativne eksplorativne kiretaže uterusa sa postoperativnim rezultatom kod pacijentkinja sa ranim stadijumom karcinoma endometrijuma

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Apstrakt

Cilj ovog rad je da pokaže koleraciju između histopatološkog nalaza preoperativne eksplorativne kiretaže uterusa sa rezultatom postoperativnog histopatološkog nalaza kod karcinoma endometrijuma. U našu retrospektivnu studiju uključeno je 386 pacijentkinja kod kojih je urađena eksplorativna kiretaža i dijagnostikovan karcinomom endometrijuma, a koje su potom povrgnute operativnom lečenju zbog karcinoma endometrijuma. Pacijentkinje su operisane u periodu od 2016.-2020. godine na Ginekološko-akušersku kliniku „Narodni Front“. Retrospektivno je uključeno 388 pacijentkinje kod kojih je urađena eksplorativna kiretaža i dijagnostikovan karcinomom endometrijuma, a koje su potom operisane. Prosek starosti pacijentkinja je bio 62,7 godina i utvrđena je podudarnost nalaza histopatološkog tipa karcinoma endometrijuma dobijenog eksplorativnom kiretažom i postoperativno u 71,6%, a podudarnost histološkog gradusa karcinoma u 61,6% slučajeva. Eksplorativna kireža uterusa je dijagnostička procedura za karcinom endometrijuma. Naši rezultati su pokazali da u 4% slučajeva dijagnostikovanih karcinoma endometrijuma eksplorativnom kiretažom isti nisu nađeni u postoperativnom histopatološkom nalazu.

Ključne reči: Karcinom endometrijuma, eksplorativna kiretaža, histopatološki nalaz.

Correlation of histopathological examination results after preoperative exploratory uterine curettage with postoperative results in patients with early stage endometrial cancer

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Abstract

The aim of this study is to show the correlation between histopathological findings of preoperative exploratory uterine curettage with the result of postoperative histopathological findings in endometrial cancer. Our retrospective study included 386 patients who underwent exploratory curettage and were diagnosed with endometrial cancer, and who were then subjected to surgical treatment for endometrial cancer. The patients were operated on in the period from 2016-2020. at the Gynecology and Obstetrics Clinic “Narodni Front”. Retrospectively, 388 patients who underwent exploratory curettage and were diagnosed with endometrial cancer were included, who were then operated on. The mean age of the patients was 62.7 years and the coincidence of the findings of the histopathological type of endometrial cancer obtained by exploratory curettage and postoperatively was determined in 71.6%, and the coincidence of the histological grade of the cancer in 61.6% of cases. Exploratory uterine cirrhosis is a diagnostic procedure for endometrial cancer. Our results showed that in 4% of cases of endometrial cancers diagnosed by exploratory curettage, they were not found in the postoperative histopathological finding.

Key words: Endometrial cancer, exploratory curettage, histopathological finding.

Uvod

Endometrijalni karcinom je najčešći karcinom ženskih genitalnih organa[1]. Prilikom dijagnoze 75% pacijentkinja imaju karcinom koji je ograničen na matericu (stadijum I). Za ove pacijentkinje prognoza je dobra i petogodišnje preživljavanje je 90%. Incidenca karcinoma endometrijuma raste između premenopauznog i postmenopuznog perioda. Češći je kod postmenopauznih pacijenkinja. Faktori rizika su: starenje, geni(HNPCC ili Linč sindrom), gojaznost, arterijska hipertenzija, dijabetes melitus, rana menarha, kasna menopauza, nuliparitet, sindrom policističnih jajnika, porodična anamneza i lična anamneza (lični podatak o oboljevanju od neke bolesti) raka dojke i jajnika, terapija Tamoxifenom[2].

Postoje dva tipa karcinoma endometrijuma. Prvi tip je Tip I ili estrogen zavisni-endometrioidni i koji se najčešće javlja kod mlađih pacijentkinja. Drugi tip je Tip II ili estrogen nezavisni-clear cell, seropapilarni, carcinosarkom. Prvi simptomi najčešće su neuredno i obilno krvarenje u premenopauzi i sukrvičavog iscedka, koje po karakteru liči na „isprano meso“ u postmenopauzi. Dijagnoza karcinoma endometrijuma bazira se na tri sledeća ispitivanja: kliničkom pregledu, radiološkom ispitivanju (ultrazvučni pregled, kompjuterizovana tomografija, nuklearna magnetna rezonanca) i histopatološko ispitivanje uzoraka endometrijuma koja se može dobiti biopsijom endometrijuma Pipellom, eksplorativnom kiretažom uterusa ili histeroskopskom biopsijom endometrijuma[3].

Cilj ovog rad je da pokaže koleraciju između histopatološkog nalaza preoperativne eksplorativne kiretaže uterusa sa postoperativnim histopatološkim nalazom kod karcinoma endometrijuma.

Materijal i metode

U našu retrospektivnu studiju uključeno je 386 pacijentkinja kod kojih je urađena eksplorativna kiretaža i dijagnostikovan karcinomom endometrijuma. Pacijentkinje su operisane histerektomijom tip A, sa i bez pelvične limfnodektomije i radikalnom histerektomijom tip B po Querleu-Morrow klasifikaciji. Kod nekih pacijentkinja je urađena sentinel limfonodektomija, a kod nekih totalna pelvična limfonodektomija. Najveći broj pacijetkinja je operisan laparatomijski, potom laparaskopski, a najmanje pacijenkinja je operisano vaginalnom histerektomijom. Nakon odgovarajuće operacije dobile su definitivan histopatološki nalaz. Upoređivali smo histopaloške nalaze.

Rezultati

U našu retrospektivnu studiju je uključeno 386 pacijenkinja sa dijagnostikovanim karcinomom endometrijuma nakon eksplorativne kiretaže urađene u periodu od 2016.-2020. godine. Prosečna starost pacijentkinja je bila 62,7 godina (Tabela 1.)

Starost		Vrednost	Std. Error
Mean		62,76	0,513
95% interval poverenja za srednju vrednost	Donja granica	61,75	
	Gornja granica	63,77	
Standardna devijacija		10,106	
Minimum		32	
Maximum		96	

Tabela1. Prosečna starost pacijentkinja

Rezultati ukazuju da je najzastupljeniji endometroidni tip karcinoma sa 80,3%, seropapilarni sa 6,2%, mucinozni sa 5,4%,, karcinosarcoma sa 5%, sarkoma strome endometrijuma sa 5% i clear cell sa 4,4%. Valja istaći, da je u 8% slučajeva preoperativno dijagnostikovan karcinom grlića, da bi se

postoperativnim patohistološkim pregledom utvrdilo da se radi o endometroidnom tipu karcinomu endometrijuma, a u 10% slučajeva kod kojih su preoperativno dijagnostikovana prekancerozna stanja, u postoperativnom patohistološkom nalazu je utvrđeno prisustvo endomerijalnog tipa karcinoma endometrijuma. Zastupljenost histološkog gradusa karcinoma je bila: HG 1-52,1%, HG 2-21,4% i HG 3-17%, a u 9,3% slučajeva nema podataka o histološkom gradusu karcinoma. Utvrđivali smo i učestalost karcinoma po stadijumima bolesti i za to smo koristili FIGO klasifikaciju iz 2009. godine i naši rezultati su pokazali, da su najzastupljenije pacijentkinje u IA stadijumu, II i IB i to sa:43%, 24,2% i 20,1%. Na sledećoj tabeli smo pokazali odnose preoperativnih i postoperativnih patohistoloških nalaza (Tabela 2.).

Histološki tip karcinoma (preoperativno - D&C)	Histološki tip karcinoma (postoperativno)												
	Carcinoma endometrii endometroid type	Carcinoma endometrii mucinosum type	Carcinoma endometrii, clear cell type	Carcinoma adenosqamosum endometrii subtype	Adenocarcinoma papilare serosum endometrii	Adenocarcinoma endometrii, mixtus endometroid et mucinosum	Carcinosarcoma endometrii mixtus Mullerian	Carcinosarkoma endometrii	EIN	Atrophia endometrii	Polypus endometrii	Hyperplasia endometrii complex atypica	Total
Nema podataka	7	1			1								9
Carcinoma endometrii endometroid type		7	4	1	6	2	1	2	1	3	1	1	29
Carcinoma endometrii mucinosum type	7		2			1							10
Carcinoma endometrii, clear cell type	3												3
Carcinoma adenosqamosum endometrii subtype	2												2
Adenocarcinoma papilare serosum endometrii			4				1	2					7
Carcinosarcoma endometrii mixtus Mullerian	2												2
Sarcoma stome endometrii	1												1
Carcinosarkoma endometrii	1												1
Carcinoma planocerululare invasivum	3												3
H-SIL, CIN III			1										1
Cervicitis chronica			1										1
EIN	1												1
Hyperplasia endometrii complex atypica	2												2
26		1											1
Total	29	9	12	1	7	3	2	4	1	3	1	1	73

Tabela 2. Odnos preoperativnih i postoperativnih patohistoloških nalaza

Takođe, ispitivali smo i učestalost različitih patohistiloških tipova karcinoma po stadijumima bolesti (Tabela 3.).

FIGO klasifikacija	Histološki tip karcinoma (postoperativno)	N	%	Validni %	Kumulativni %
IA	Carcinoma endometrii endometroid type	131	78,4	78,4	78,4
	Carcinoma endometrii mucinosum type	10	6,0	6,0	84,4
	Carcinoma endometrii, clear cell type	7	4,2	4,2	88,6
	Adenocarcinoma papilare serosum endometrii	8	4,8	4,8	93,4
	Adenocarcinoma endometrii, mixtus endometroid et mucinosum	1	,6	,6	94,0
	Carcinosarkoma endometrii	3	1,8	1,8	95,8
	EIN	3	1,8	1,8	97,6
	Atrophia endometrii	2	1,2	1,2	98,8
	Polypus endometrii	1	,6	,6	99,4
	Hyperplasia endometrii complex atypica	1	,6	,6	100,0
	Total	167	100,0	100,0	
IB	Carcinoma endometrii endometroid type	67	85,9	85,9	85,9
	Carcinoma endometrii mucinosum type	1	1,3	1,3	87,2
	Carcinoma endometrii, clear cell type	5	6,4	6,4	93,6
	Adenocarcinoma endometrii, mixtus endometroid et mucinosum	1	1,3	1,3	94,9
	Carcinosarcoma endometrii mixtus Mullerian	1	1,3	1,3	96,2
	Sarcoma stome endometrii	1	1,3	1,3	97,4
	Carcinosarkoma endometrii	2	2,6	2,6	100,0
	Total	78	100,0	100,0	
II	Carcinoma endometrii endometroid type	72	76,6	76,6	76,6
	Carcinoma endometrii mucinosum type	3	3,2	3,2	79,8
	Carcinoma endometrii, clear cell type	10	10,6	10,6	90,4
	Carcinoma adenosqamosum endometrii subtype	1	1,1	1,1	91,5
	Adenocarcinoma papilare serosum endometrii	7	7,4	7,4	98,9
	Carcinosarkoma endometrii	1	1,1	1,1	100,0
	Total	94	100,0	100,0	
IIIA	Carcinoma endometrii endometroid type	7	43,8	43,8	43,8
	Carcinoma endometrii mucinosum type	1	6,3	6,3	50,0
	Carcinoma endometrii, clear cell type	3	18,8	18,8	68,8
	Adenocarcinoma papilare serosum endometrii	4	25,0	25,0	93,8
	Carcinosarcoma endometrii mixtus Mullerian	1	6,3	6,3	100,0
	Total	16	100,0	100,0	

IIIB	Carcinoma endometrii endometroid type	2	33,3	33,3	33,3
	Adenocarcinoma papilare serosum endometrii	2	33,3	33,3	66,7
	Carcinosarkoma endometrii	2	33,3	33,3	100,0
	Total	6	100,0	100,0	
IIIC1	Carcinoma endometrii endometroid type	5	62,5	62,5	62,5
	Carcinoma endometrii, clear cell type	1	12,5	12,5	75,0
	Adenocarcinoma papilare serosum endometrii	1	12,5	12,5	87,5
	Adenocarcinoma endometrii, mixtus endometroid et mucinosum	1	12,5	12,5	100,0
	Total	8	100,0	100,0	
IIIC2	Carcinoma endometrii endometroid type	2	50,0	50,0	50,0
	Adenocarcinoma papilare serosum endometrii	2	50,0	50,0	100,0
	Total	4	100,0	100,0	
IVB	Carcinoma endometrii endometroid type	2	50,0	50,0	50,0
	Carcinoma endometrii mucinosum type	1	25,0	25,0	75,0
	Adenocarcinoma papilare serosum endometrii	1	25,0	25,0	100,0
	Total	4	100,0	100,0	

Tabela 3. Učestalost različitih patohistiloških tipova karcinoma

Može se primetiti, da je kod FIGO stadijuma IA-II, rani stadijumi, najzasupljeniji endometroidni tip karcinoma, kao i porast stope neendometroinih tipova karcinoma kod kasnih stadijumi karcinoma, IIIA i IVB gde se uočava značajan pad endometroidnog tipa karcinoma u odnosu na neendometroidne tipove-seropapilarni, clear cell, karcinosarkoma. Takođe smo utvrdili, značaj histološkog gradusa tumora po stadijumima bolesti-FIGO klasifikacija iz 2009. godine, gde se uočava porast histološkog gradusa 2 i 3 u odnosu na histološki gradus 1 i to posebno u slučaju pozitivnih limfnih čvorova gde je u našoj studiji utvrđeno prisustvo tumora sa histološkim gradusom 2 i 3. Istraživali smo i odnos pojedinih patohistoloških tipova karcinoma endometrijuma i godina starosti pacijetkinja i uviđa se da se endometroidni tip karcinoma najčešće javlja početkom sedme decenije života, a neendometroidni najčešće javljaju krajem 7. decenije života. Kada je u pitanju učestalost karcinoma po stadijumima bolesti, koristili smo FIGO klasifikaciju iz 2009 godine, u našoj studiji je najviše pacijentkinja bilo u stadijumom IA i to u 43% slučajeva, zatim stadijumom II u 24% slučajeva, potom u stadijumu IB u 20 % slučajeva, i na kraju a u stadijumima IIIA do IVB 13% slučajeva, koji su bili ravnomerno zastupljeni. I konačno, kada je u pitanju podudarnost preoperativnog patohistološkog nalaza sa postoperativnim patohistološkim nalazom utvrdili smo da je taj procenat pozitivan u 71,6% slučajeva, u 28,4% slučajeva je negativan. Poredili smo i histološke graduse karcinoma i utvrdili smo da je podudarnost prisutna u 61,6% slučajeva, a da je izostala u 38,4% slučaja.

Diskusija

Standardno, preoperativni histopatološki nalaz dobija se biopsijom endometrijuma Pipellom, eksplorativnom kiretažom uterusa ili histeroskopskom biopsijom, a koje sa dodatnim imidžing metodana, kao što su ultrasonografija, komjuterizovana tomografija (CT), nuklearna magnetna rezonanca (NMR) i pozitron emisiona tomografska komjuterizovana tomografija (PET CT), određuju tip operativnog lečenja[4]. Unazad par godina sve više se primenjuje biopsija endometrijuma Pipellom, što olakšava dijagnozu, jer nije potrebna nikakva predhodna priprema pacijentkinja i obavlja se u ambulantnim uslovima[5]. Sa napredkom tehnologije i uvođenja office histeroskopije, moguće je u ambulantnim

uslovima pod kontrolom optike histeroskopa uzeti biopsiju endometrijuma sa sumljivih mesta i na taj način povećati preciznost dijagnostike, ali office histeroskopija predstavlja i najskuplju metodu dijagnostike. S druge strane, frakcionirana eksplorativna kiretaža je tradicionalna metoda, ne tako skupa, ali je i tzv. slepa metoda. Ponekad je potrebna i hospitalizacija pacijentkinja zbog pratećih komorbiditeta pacijentkinja. Takođe, moguće su i komplikacije, kako rane, tako i kasne. Od ranih komplikacija najčešća je perforacija uterusa, i u tom slučaju najčešći tretman je konzervativan, zbog hipotrofije i smanjene vaskularizacije uterusa. Ali u slučaju kada pri tome dođe i do povrede omentuma, tankih creva, sigmoidnog kolona ili mokraćne bešike pacijentkinje se moraju operisati radi zbrinjavanja povreda. Srećom, to se ne dešava često. Od kasnih komplikacija, infekcija uterusa je retka pojava. Stadiranje karcinoma endometijuma je hiruško, koristili smo FIGO klasifikaciju iz 2009. godine[6]. Standardan hiruški tretman ranog stadijuma karcinoma endometrijuma u slučajevima sa FIGO st. IA-IB je totalna histerektomija sa obostradnom adneksetomijom(TH-BSO), tip A po Querleu-Morrow klasifikaciji sa/bez sentinel ili totalnom pelvičnom i paraaortnom limfonodektomijom i radikalna histerektomija tip B, kod FIGO st. II, po Querleu-Morrow klasifikaciji sa/bez paraaortne limfonodektomije[7]. U praksi se primenjuju sva tri operativna pristupa: laparatomijski, laparaskopski i vaginalni[8]. Poslednjih decenija sve je više zastupljen laparaskopski pristup, bilo da se radi histerektomija tip A ili tip B, kao i slučaju da li se istovremeno radi paraaortna limfonodektomija ili ne[9,10]. Valja se istaći, da se i kod nas laparaskopski pristup pokazao kao superioran, kako zbog samog lakšeg operativnog zahvata, kraćeg bolničkog ležanja i mnogo manjih postoperativnih komplikacija, što je u skladu sa rezultatima drugih autora[11]. Tu se posebno moraju istaći specifičnosti ovakvog pristupa kod pacijenata sa visokim indeksom telesne mase.

Zaključak

Eksplorativna kiretaža uterusa se već decenijama koristi kao dijagnostičko-terapijska intervencija kod raznih patoloških promena uterusa. Smatra se vrlo bezbednom i lako izvodjivom procedurom. Može da se radi u lokalnoj i opštoj anesteziji i najčešće je potreban samo internistički i anesteziološki pregled. Naši rezultati su pokazali da u 4% slučajeva dijagnostikovanih karcinoma endometrijuma eksplorativnom kiretažom isti nisu nađeni u postoperativnom histopatološkom nalazu.

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Paradoxical fat embolism syndrome in patient without patent foramen ovale

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Abstract

Fat embolism syndrome represents a life-threatening condition in which blood vessels become clogged by fat droplets coming from fractured parts of the bones seldomly seen in patients with orthopedic trauma. Absence of specific diagnostic criteria and varying degree of presentation symptoms makes it hard to be diagnosed. We present a 20-years-old male injured in road traffic accident as a pedestrian, diagnosed with polytrauma and lethal outcome on the second day of admission. Autopsy and pathohistological findings confirmed death due to damage of important brain centers, as well as signs of massive fat embolism with fat particles found in lungs blood vessels as well as in systemic circulation, suggesting paradoxical embolism throughout exceedingly uncommon pulmonary right to left shunt capillaries, since completely closed heart foramen ovale was also found.

Keywords: fat embolism syndrome, paradoxical embolism.

Paradoksalna masna embolija kod pacijenta bez perzistentnog foramena ovale

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Apstrakt

Sindrom masne embolije prestavlja po život opasno stanje u kojem krvni sudovi bivaju zapušeni masnim kapljicama poreklom iz prelomljenih kostiju, što se viđa kod ortopedskih pacijenata. Odustvo specifičnih dijagnostičkih kriterijuma, kao i širok spektar simptoma otežavaju dijagnozu. Prikazujemo slučaj muškarca starosne dobi 20 godina povređenog u saobraćajnom udesu u kojem je učestvovao kao pešak. Pacijent je bio politraumatizovan i preminuo je dva dana nakon prijema u bolnicu. Obdukcioni i histopatološki nalaz su potvrdili nasilnu smrt usled oštećenja za život važnih moždanih centara, kao i znake masivne masne embolije sa masnim kapljicama nađenim u plućnim krvnim sudovima, ali i u sistemskoj cirkulaciji, što je ukazalo na paradoksalnu emboliju preko ekstremno retkog mehanizma plućnog desno levog kapilarnog šanta, s obzirom da je kod pacijenta na obdukciji nađen kompletno zatvoreni ovalni otvor u srcu.

Ključne reči: masna embolija, paradoksalna embolija.

Introduction

Fat embolism syndrome (FES) represents a life-threatening complication in patients with orthopedic trauma, especially fractures of long bones, such as the femur, tibia and pelvis. Other causes include orthopedic surgery, pancreatitis, transplantation of bone marrow, as well as liposuction[1]. Clinical picture of FES is represented by pulmonary insufficiency, neurologic symptoms, hematological manifestations, but also can be asymptomatic. The diagnosis is based on clinical symptoms most often a few days after injury, and there are no specific laboratory findings, which is why many FES cases remain undiagnosed. Cerebral fat embolism syndrome is a variant of FES, and it occurs after fat particles enter the arterial circulation, although underlying mechanism remains poorly understood[2].

We report a case of massive FES due to multiple long bone fractures after a traffic road accident injury with pathohistological conformation of fat particles in the lungs, as well as in the systemic circulation in the absence of patent foramen ovale, which indicates extremely uncommon way of paradoxical embolism throughout pulmonary right to left shunt, and probable genesis through both the mechanical as well as the biochemical mechanism.

Case report

A 20-year-old male was injured as a pedestrian in a traffic accident. He was admitted to the Emergency Department with disturbed state of consciousness, Glasgow Coma Scale of 8, and clinical signs of fracture of the right forearm and right leg.The results of laboratory parameters were as follows: hemoglobin 103 g/L, platelet count 192 × 10^9/L, hematocrit 0.297 L/L, C-reactive protein (CRP) 178.9. Brain computed tomography (CT) showed no remarkable intracranial abnormalities. The X-ray showed multiple long bone fractures, including right ulna and radius, as well as right tibia and fibula (Figure 1).

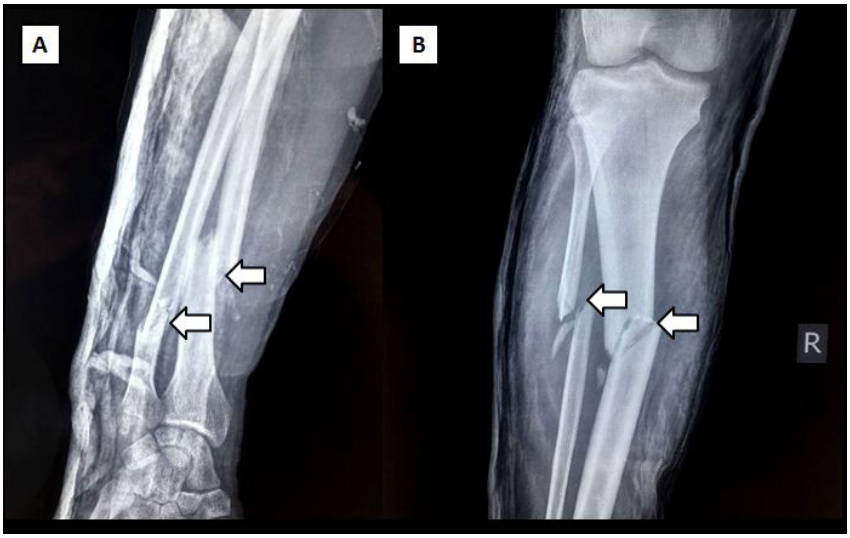

Figure 1. The X-ray showing multiple long bone fractures, including right ulna and radius (A), as well as right tibia and fibula (B).

The X-ray of the lungs and heart showed bilateral nonhomogeneous shading dominantly on the right side (Figure 2), and thoracic computed tomography indicated lung contusions and signs of acute respiratory distress syndrome (ARDS).

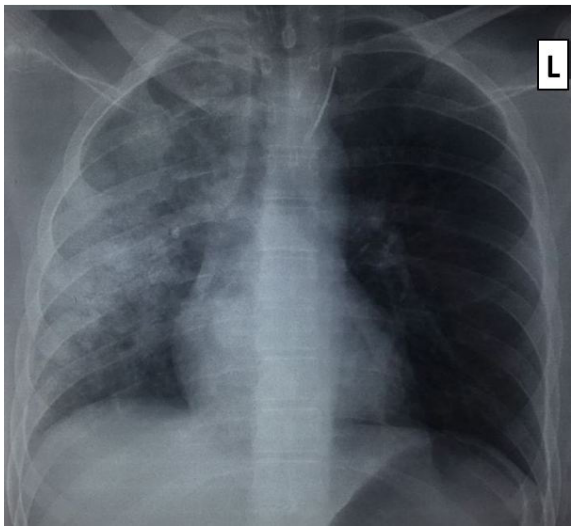

Figure 2. The X-ray of the lungs and heart showing bilateral nonhomogeneous shading dominantly on the right side.

Abdominal CT showed no remarkable abnormalities. The patient had hypoxemia, and was treated in the intensive care unit. On the second day patient's general condition worsened, body temperature raised to 39.3^{0}C, peripheral cyanosis and tachycardia occurred, and control lung X-ray showed progression of diffuse bilateral coalescent opacities. Patient become hemodynamically unstable and cardiac arrest occurred without positive response to applied resuscitation.

Autopsy finding confirmed fracture of right tibia and fibula, as well as right radius and ulna with crushed subcutaneous adipose tissue. Also characteristic for FES, skin petehiae were observed most prominent in the upper thoracic region (Figure 3).

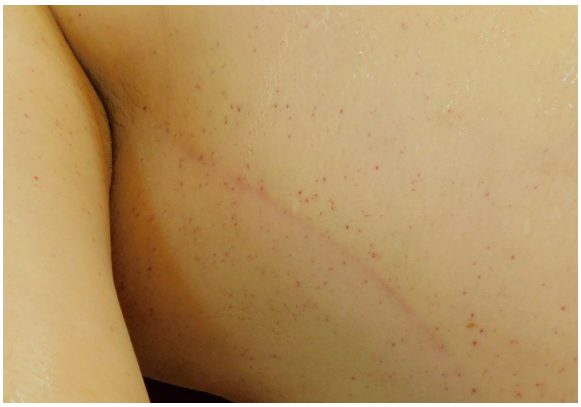

Figure 3. Skin petehiae found in the upper thoracic region (right axillary region).

Diffuse brain swelling, as well as micro-bleeds foci in the deep brain structures, characteristic of diffuse axonal injury were observed (Figure 4).

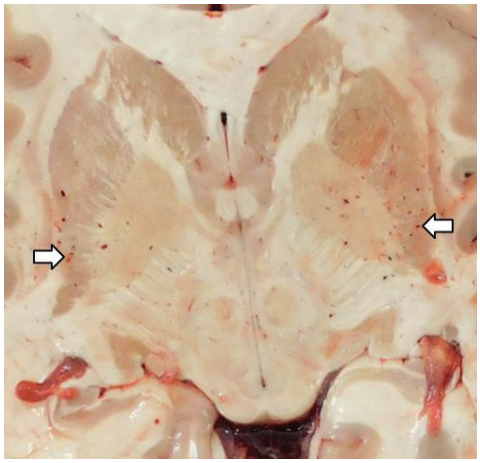

Figure 4. Microhemorrhages in the basal ganglia typically seen in diffuse axonal lesions.

Histopathology showed multiple fat emboli to the brain, heart, lungs, and skin blood vessels (Figure 5).

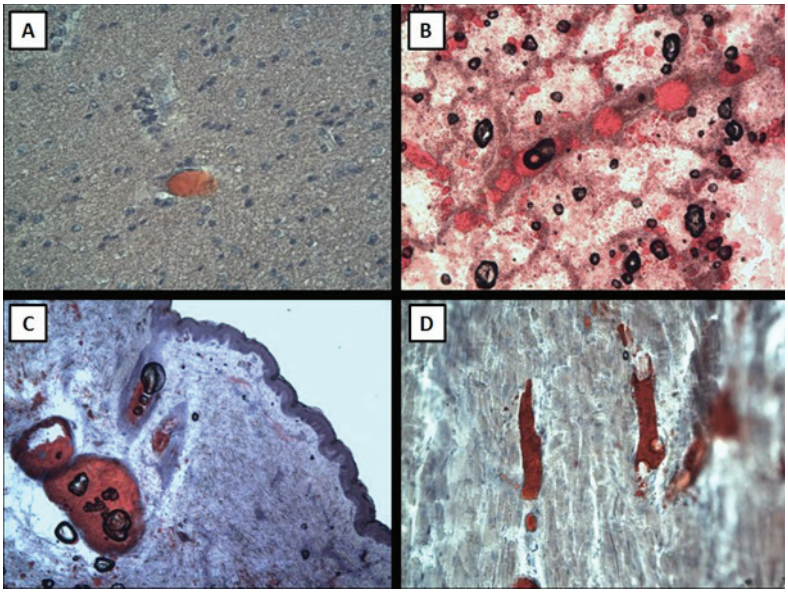

Figure 5. Histopathology finding of multiple fat emboli in the brain (A), lungs (B), Skin (C), and heart (D) blood vessels. Fat droplets are staind in red collor with Sudan III staining.

Since foramen ovale was definitely closed post mortem diagnosis of diffuse FES with signs of paradoxical cerebral fat embolism syndrome was made, and death was declared violent due to damage to vital brain centers and signs of FES.

Discussion

FES is a rare clinical complication which follows long bone and pelvic fractures. It represents a multidisciplinary phenomenon difficult to diagnose, and unfortunately if missed, may lead to lethal outcome. Historically known from middle XIX century, it was first described by Zenker as a complication of long bone fractures presented as a combination of pulmonary, neurological, skin, and hematological symptoms and autopsy finding of fat droplets' in the pulmonary capillaries[3]. In our case, patient

showed characteristic clinical picture, and autopsy finding confirmed FES accompanied with signs of paradoxical embolism to heart, brain and skin.

Various theories had been made in the past regarding FES genesis. In the early XX century Gauss proposed the mechanical theory which points out the necessity of adipose tissue injury, accompanied with rupture of nearby veins, and subsequent passage of fat particles into the ruptured veins[4]. Since veins are initially disrupted, lungs are the first as well as most commonly affected organ. However, fat particles may pass from venous to arterial circulation to involve other organs which can happen in different ways. Most often venous embolism to the right atrium raises pressure in the right heart chambers promoting the passage through a patent foramen ovale into the arterial circulation which is known as paradoxical embolism. Patent foramen ovale is found in about 30% of normal adult population. Even more rarely, the fat particles are small and can easily pass from the venous to the arterial circulation through the pulmonary shunt. These fat particles have a high deformation potential and by taking a more stretched out form can pass through capillaries[5,6]. Also, Gossling et al. described certain pulmonary arteriovenous fistulas through which fat droplets even with a diameter 40 times larger than pulmonary capillary can reach the systemic flow and cause paradoxical embolism to other organs, including, heart and brain[7]. We presented a case of massive FES with fat droplets found in the lungs, heart, brain and skin in the absence of patent foramen ovale, indicating a rare phenomenon of paradoxical fat embolism probably thought lung capillary shunt.

Another theory of FES genesis was proposed in 1927. by Lehman, which states that creation of toxic intermediates from plasmaderived fat molecules is responsible for FES development. Since neutral fat globules found in bone marrow and as embolic material do not cause organ injury, Lehman found that these neutral fat particles are degraded into few toxic intermediates such as free fatty acids, catecholamines, and Creactive proteins, which initiate the inflammatory circle causing endorgan injury at various sites such as the lungs and brain. Creactive protein causes fat agglutination which may obstruct blood flow in the microcirculation and cause ischemia[8]. Since mechanical theory can't explain nontraumatic FES, as well as 24–72 hours delay for FES development following injury, Lehmans theory seems appropriate in these circumstances. Singh et al. have proposed a unified definition that FES genesis can be explained in two different phases, the first phase being mechanical phase, and the second biochemical phase[9]. In our case, FES probably occurred as a combination of mechanical and biochemical mechanism, since long bone fractures were present as well as massive subcutaneous adipose tissue injury featuring mechanical phase. However, delayed deterioration and high CRP values indicate biomechanical phase as well.

Skin petehiae represents characteristic feature of FES. They are found in about two thirds of cases involving conjunctiva, and skin of the upper body, especially axilla and the neck. It appears that these micro bleeds do not appear because of in platelet abnormality but as a result of small skin capillaries fat embolization and extravasation of red blood cells[10]. Typical skin petehiae appear within the first 24-36 hours of FES development. Multiple sites of skin petehiae were found in our patient, about 36 hours after injury, which guided pathologist to the diagnosis even before obtaining pathohistological confirmation, which was the final step in our case solving problem.

We presented a exceedingly uncommon case of massive FES with involvement of lungs, but also brain, heart, and skin, in the absence of patent foramen ovale, which indicates extremely uncommon way of paradoxical embolism throughout pulmonary right to left shunt, and probable genesis through both the mechanical as well as the biochemical mechanism.

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Conflicts of interest: There are no conflicts of interest.

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Idiopatski sindrom neadekvatne antidiureze sa smrtnim ishodom: uporedni prikaz dva bolesnika

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Apstrakt

Hiponatrijemija je elektrolitski poremećaj koji se često sreće u kliničkoj praksi. Prvi korak u evaulaciji hiponatrijemije je ocena volumnog statusa bolesnika (klinička ocena postojanja hipervolemije i hipovolemije). U slučajevima euvolemične hiponatrijemije, praćene sniženom osmolalnosti plazme (<275mOsm/kg) uz osmolalnost urina >100mOsm/kg, natriurijom >30mmol/L pri normalnom unosu soli i vode, očuvanom pituitarnom, adrenalnom, tiroidnom i renalnom funkcijom, kao i izostankom skorašnje upotrebe diuretika, konstatuje se sindrom neadekvatne antidiureze (SIAD). U simptomatskim, posebno akutnim hiponatrijemijama, potrebna je pažljiva supstitucija koncentrovanim rastvorima natrijum hlorida, simultano sa restrikcijom unosa vode, primenom demeklociklina, ureje, litijuma ili vaptana, ali i etiološkim tretmanom. Najčešće je SIAD poznatog uzroka i prolazan. U ovom radu prikazana su dva slučaja bolesnika sa idiopatskim, hroničnim SIAD-om, koji su završeni fatalnim ishodom. Kod bolesnika nije nađen supstrat SIAD-a ni *post mortem*, obdukcionim nalazom. U najvećem broju slučajeva, euvolemična hiponatrijemija kod idiopatskog SIAD-a je ominozne prognoze.

Ključne reči: hiponatrijemija, tretman

Fatal idiopathic syndrome of inappropriate antidiuresis: two case reports

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Abstract

Hyponatremia is an electrolyte disorder frequently encountered in clinical practice. The first step in the diagnostic evaluation of hyponatremia is the volume assessment (clinical estimation of hypo/hypervolemia presence). In the cases of euvolemic hyponatremia, followed by decreased plasma osmolality (<275mOsm/kg) with urine osmolality >100mOsm/kg, urine sodium >30mmol/L along with normal intake of salt and water, preserved pituitary, adrenal, thyroid, adrenal function as well as no recent use of diuretics, syndrome of inappropriate diuresis (SIAD) is diagnosed. In symptomatic, especially acute hyponatremia, careful and gradual substitution by 3 (10) % sodium-chloride infusion is advised with liquid intake restriction, the administration of demeclocycline, urea, or vaptans, as well as causal treatment of SIAD. SIAD is often transient and etiologically clear. In this paper, we present two cases with idiopathic, chronic SIAD with poor outcomes. During the diagnostic follow-up, the cause of SIAD was not found. The autopsy finding was also adverse. In most cases, euvolemic hyponatremia in patients with chronic, idiopathic SIAD is an ominous sign.

Keywords: hyponatremia, management

Uvod

Sindrom neadekvatne antidiureze (SIAD) predstavlja poremećaj koji se biohemijski karakteriše hipotonom hiponatrijemijom, a patofiziološki poremećenom ekskrecijom vode, nastalom kao posledica neadekvatne sekrecije ili neadekvatnog odgovora na antidiuretski hormon (ADH). Iako je SIAD veoma čest uzrok hiponatrijemije, relativno se retko dijagnostikuje i često neadekvatno leči[1,2].

Patofiziološki, hiponatrijemija u SIAD nastaje kao posledica apsolutnog porasta telesne vode, nastale usled nemogućnosti kompenzatornog izlučivanja vode, tj. izlučivanja diluiranog urina, kod osobe koja vodu unosi u normalnim količinama[3]. Uzrok neadekvatne antidiureze može biti terapijska primena ili endogena produkcija ADH ili vazopresinskog receptorskog agoniste (npr. dezmopresina). Endogena produkcija ADH može biti ektopična ili eutopična[4]. Uzroci nastanka SIAD su prikazani u Tabeli 1[5].

Maligniteti	Plućne bolesti	Bolesti CNS	Lekovi	Ostali
Karcinomi (pluća, ORL regije, GIT-a,-GUT-a, timom)	*Infekcije*	*Infekcija*	*Lekovi koji stimulišu oslobadjanje ADH ili potenciraju njegove efekte*- SSRI, 3-ciklični antidepresivi, karbamazepin, vinkristin, nikotin, narkotici, antipsihotici, ekstazi, NSAID, ciklofosfamid	*Hereditarni*-mutacije na V2 receptorima
Sarkomi	*Astma*	*Krvarenje*	*Vazopresinski analozi*- dezmopresin, oksitocin	*Idiopatski*
Limfomi	*Cistična fibroza*	*Mass-lezije*		*ARC i AIDS*
	Respiratorna insuficijencija, posebno ona koja se tretira mehačkom ventilacijom tj. pozitivnim pritiskom	*Multipla skleroza*		*Prolazni*- opšta anestezija, stres, bol, mučnina, vežbe izdržljivosti

Tabela 1. Uzroci SIAD[4,5,8,9]

Kliničko ispoljavanje SIAD uključuje manifestaciju osnovne bolesti, a potom i hiponatrijemije *per se*. Na karakteristike kliničkog ispoljavanja hiponatrijemije utiče brzina njenog razvoja (akutna <48h, hronična >48h), kao i stepen hiponatrijemije. Blaga hiponatrijemija može biti i asimptomatska, ili se ispoljava mučninom, povraćanjem, nestabilnim hodom, promenama u vidu, slabom koncentracijom. Teška hiponatrijemija se ispoljava poremećajem svesti do kome, kao i konvulzijama. U slučaju da se ne leči, može dovesti do sindroma povišenog intrakranijalnog pritiska, hernijacije mozga i smrti[6,7].

Dijagnoza SIAD se postavlja na osnovu osnovnih i pomoćnih kriterijuma. Po uspostavljanju dijagnoze SIAD, neophodno je sprovesti diferencijalno-dijaganostički algoritam u cilju otkrivanja uzroka hiponatrijemije. Glavni kriterijumi za dijagnozu SIAD su postojanje euvolemične hiponatrijemije praćene sniženom osmolalnosti plazme (<275mOsm/kg) uz osmolalnost urina >100mOsm/kg, natriurija >30mmol/L pri normalnom unosu soli i vode, očuvana pituitarna, adrenalna, tiroidna i renalna funkcija, kao i izostanak skorašnje upotrebe diuretika[5]. Pored ovih esencijalnih kriterijuma, postoje i dodatni kriterijumi: mokraćna kiselina seruma <0.24mmol/L, ureja u serumu <3.6mmol/L, nemogućnost korigovanja hiponatrijemije izotonim fiziološkim rastvorom (0.9%), korekcija hiponatrijemije restrikcijom unosa tečnosti i brojni drugi[5,8].

Lečenje SIAD uključuje pažljivu korekciju hiponatrijemije, istovremeno sa lečenjem osnovne bolesti. Idiopatske forme SIAD su najčešće loše prognostički[4,5].

Iako je idiopatska forma SIAD relativno retka, u ovom radu prikazujemo slučajeve dva bolesnika sa nedefinisanim uzrokom hiponatrijemije.

Materijal i metode

Bolesnici

Uporednim prikazom su predstavljena dva bolesnika muškog pola, tretirana na Odeljenju internističke intenzivne nege i Službi endokrinologije i dijabetesa. Prvi bolesnik, starosne dobi 46 godina, preveden je iz druge ortopedske ustanove, nakon što je po operaciji desnih potkolenih kostiju konstatovana hiponatrijemija sa dominantno neuropsihijatrijskim manifestacijama. Drugi bolesnik, starosne dobi 64 godina, preveden je sa Neurološke službe Kliničko bolničkog centra Zemun, gde je bio smešten zbog takođe predominantnih neuropsihijarijskih manifestacija teške hiponatrijemije.

Dijagnostičke procedure i aparatura

Hematološke i biohemijske analize rađene su na automatskim analizatorima Access-2 i DxC 800 „Beckman Coulter", po uputstvima proizvođača. Ultrasonografski pregledi su rađeni na aparatu Toshiba Xario (Japan). Radiografska snimanja su rađena na aparatu AGFA DX-D 100+ (Belgija-Nemačka). Kompjuterizovane tomografije organa i organskih sistema su rađene na aparatu Toshiba Aquilion CXL128 slice (Japan).

Rezultati

U tabelama 2 i 3 su prikazani laboratorijski nalazi pacijenata i nalazi imidžing dijagnostičkih procedura.

Bolesnik 1			**Bolesnik 2**		
Hematološke analize	**Biohemija**	**Gasne analize**	**Hematološke analize**	**Biohemija**	**Gasne analize**
Le 5.9x10^{9}	Gly 5.4	pH 7.36	Le 15,2x10^{9}	Gly 7.4	pH 7.35
Er 2.95x10^{12}	Ukupni proteini 55	pCO2 57	Er 4.43x10^{12}	Ukupni proteini 60	pCO2 41
HCT 0.339	Albumini 40	pO2 129	HCT 0.435	Albumini 37	pO2 94
HGB 117 g/l	AST 38	HCO3 17.9	HGB 143 g/l	AST 44	HCO3 19.7
Tr 188x10^{9}	ALT 11	Bazni eksces -4.4	Tr 234x10^{9}	ALT 79	Bazni eksces -4.0
	CRP 184	SO2c 97%		CRP 76	SO2c 95%
	K 4.5			K 4.5	
	Na 117..122 ..119..131..127			Na 124...127... 131...140	
	Cl 83..86.. 80..94			Cl 86...92	
	Urea 2.0			Urea 10.3	
	Kreatinin 55			Kreatinin 122	

	fT4 11,9 TSH 4.41			fT4 16.98 TSH 1.40 ACTH 27.0 (9-46) pg/ml Kortizol 08h: 797 (193-690) Kortizol 16h: 380 (55-248)	
	CEA 1.25 CA19-9 5.6 AFP 2.13 NSE 14.98			CEA 2.59 CA 19-9 27.7 CA 15.3 13.6 AFP 2.6	
	Osmolalnost plazme: 245.3 mOsm/kg			Osmolalnost plazme: 267.7 mOsm/kg	

Tabela 2. Laboratorijski nalazi bolesnika

Vizualizaciona dijagnostika	
Bolesnik 1	**Bolesnik 2**
CT endokranijuma: Prisutne reduktivne promene tkiva mozga u celini. Sulkusi na konveksitetu kao i ostali ekstracerebralni likvorni prostori slobodni, širi. Komorni sistem je normalnog položaja i oblika, bez patološkog sadržaja, širi. Četvrta komora u sagitalnoj ravni. Nema ekspanzivnog procesa, niti intrakranijalnog krvarenja.	***CT endokranijuma:*** Prisutne reduktivne promene mozga u celini. Ostali nalaz bez značajnih patoloških promena.
RTG srca i pluća: U plućima nema znakova konsolidacija, niti infiltrativnih promena. Nema znakova izliva u pleuralnim prostorima. Aorta sklerotična.	***RTG srca i pluća:*** u donjem plućnom polju desno atelektaza. Desno bazalno moguć manji pleuralni izliv. Subdijafragmalno levo distendiran želudac.
EHO abdomena: Bubrezi normalnog položaja, veličine i debljine parenhima, u desnom hidronefroza, gr.I-II, u levom kalkulus od 4 mm, bez staze. Mokraćna bešika prepunjena, bez promene na zidu i u lumenu. Prostata relativno homogena, volumena 40 ccm. Abdominalna aorta normalne širine, prati se tok do račve. Ne uočava se slobodna tečnost u trbuhu. Nalaz na ostalim posmatranim organima bez patoloških promena.	***EHO abdomena:*** Prisutan meteorizam. Ne vide se akutna patološka zbivanja pri pregledu dostupnih organa abdomena i male karlice, niti prisustvo slobodne tečnosti u recesusima peritoneuma.

CT grudnog koša:	***CT grudnog koša:***
Posterobazalno desno zona konsolidacije delom vidljivog bronhograma, moguće zapaljenskog karaktera, sa manjim pleuralnim izlivom i kompresivnom atelektazom. Manja zona konsolidacije i u SII desno. Intraluminalno u bronhima za bazalne segmente desno mukusni sadržaj. Traheja i veliki bronhi su normalnih promera, bez znakova opstrukcije i spoljnje kompresije. Manji pleuralni izliv i levo naglašeni LG subkarinealno dimenzija do 9 mm, kao i hilarno desno do 11 mm. Nema defekta u opacifikaciji kontrastnim sredstvom stabla plućne arterije i njenih glavnih grana - nema CT znakova za tromboembolijsku bolest pluća. Subsegm.grane nisu validne za interpretaciju. Na prikazanim koštanim strukturama gr.koša osim degenerativnih ne uočavaju se druge pat.promene.	Obostano trakaste atelektaze u posteriornim segmentima. Nalaz na ostalim posmatranim organima bez značajnih patoloških promena. Nema defekta u opacifikaciji kontrastnim sredstvom stabla plućne arterije i njenih glavnih grana - nema CT znakova za tromboembolijsku bolest pluća.

Tabela 3. Dijagnostičke procedure

Diskusija

Pravovremena dijagnoza i adekvatno lečenje su od velikog uticaja na ishod lečenja bolesnika. Pored lečenja osnovne bolesti, neophodno je pažljivo lečenje hiponatrijemije u sklopu SIAD. Pacijenti sa akutno nastalom ili brzo razvijajućom hiponatrijemijom (unutar 48h), kao i oni sa ozbiljnim neurološkim manifestacijama, zahtevaju bržu korekciju natrijemije, sa ciljem da serumski natrijum se povisi za 1-2 mmol/L/sat, primenom hipertonog rastvora natrijum hlorida (3% ili u našim uslovima 10%)[9,10]. Akutna korekcija ozbiljne hiponatrijemije u SIAD-u često zahteva kontinuiranu infuziju hipertonim rastvorom. Postoje brojne strategije za izračunavanje inicijalne količine hipertonog rastvora[8,11], pri čemu se čini da je najprihvatljivija primena 1-2 ml/kg TT/sat 3% (513 mmol/L) rastvora natrijum hlorida. Dvostruko veća doza potrebna je kod teškog ispoljavanja, a upola manja doza kod blažeg ispoljavanja hiponatrijemije[10]. Davanje furosemida 20-40 mg trebalo bi biti rezervisano za one pacijente koji imaju makar minimalno volumno opterećenje[10,11], mada neki autori ne odobravaju njegovu primenu[12]. Zagovornici primene furosemida uz hipertoni fiziološki rastvor ukazuju na činjenicu da furosemid favorizuje eksrekciju slobodne vode i sprečava ekspanziju volumena ekstraćelijske tečnosti [8,10]. Akutni tretman hiponatrijemije treba prekinuti u slučajevima kada se bolesnik klinički i subjektivno poboljša ili je postignut bezbedan nivo natrijuma (≥120 mmol/L) odnosno dostignut maksimalan nivo od 18 mmol/L/dan ukupne dnevne korekcije natrijuma. Najveći broj autora smatra da dnevni nivo korekcije natrijemije ne bi trebalo da bude >8-10 mmol/L za prva 24h, dok za prvih 48h ne bi trebalo da pređe granicu od 18-25 mmol/L[8,10,13]. Hronična hiponatrijemija, oligosimptomatska ili hiponatrijemija ona koja se sporije razvija, zahteva sporiju nadoknadu natrijuma. Preporuka je da korekcija hronične simptomatske, kao i hiponatrijemije nepoznatog trajanja, treba da bude do 8mmol/L za prva 24h, odnosno do 18 mmol/L natrijuma u serumu za prvih 48h[14,15]. Korekcija asimptomatske hiponatrijemije treba biti još postepenija[16], posebno ako je registrovana kod starijih bolesnika[17]. Ukoliko se natrijemija koriguje isuviše brzo, maladaptacija mozga može usloviti nastanak stanja osmotske pontine demijelinizacije, koja neretko može imati i fatalne konsekvence[18-20].

Konvencionalni tretman hronične hiponatrijemije uključuje restrikciju vode, ali ne i proteina i soli (500-1000ml dnevno, odnosno proporcionalno oralnom osmotskom opterećenju), potom primenu ureje (30 g/dnevno, loše se toleriše) ili demeklociklina ili litijuma (sporog efekta i toksični), ili V re-

ceptorskih, odnosno visoko selektivnih V_2 receptorskih antagonista (vaptana-npr. konivaptan parenetralno, tolvaptan, liksivaptan i satavaptan oralno)3,9,10. Hronična hiponatrijemija zahteva pažljivo praćenje i dugotrajan tretman, često komplikovan i drugim kliničkim posledicama, poput ozbiljne osteoporoze[21].

Demeklociklin (600-1200 mg/dan) u podeljenim dozama (obično dve) ili litijum karbonat (600-900mg/dan) izazivaju nefrogeni dijabetes insipidus. Njihov diuretski efekat nastupa posle 3-5 dana, a pošto su nefrotoksični, potreban je čest monitoring bubrežne funkcije. U slučaju pojave ili pogoršanja postojeće azotemije, potrebno je lekove obustaviti[3,10].

Vaptani deluju kao V receptorski antagonisti na nivou tubula. Konivaptan se primenjuje parenteralno (20-40 mg/dnevno u infuziji) i deluje na V1a i V2 receptore, dok su oralni preparati tolvaptan (15-60 mg/dan), liksivaptan (100-200mg/dan), satavaptan (12.5-50 mg/dan) selektivni V2 receptorski antagonisti. Primena vaptana započinje se u hospitalnim uslovima, zbog praćenja volumena i natrijemije. Kod njihove primene se gotovo nikada ne javlja osmotska pontina mijelinoliza[22,23]. Primena tolvaptana se pokazala bezbednom, kada se upotrebljava u slučajevima simptomatske hiponatrijemije u sklopu SIAD pod nadzorom lekara i monitoringom natrijemije. Ukoliko se hiponatrijemija ponovo pojavi nakon sedam dana po obustavi tolvaptana, to je indikacija za njegovu hroničnu primenu, ali i razlog za dodatni napor u detekciji, tj. tretmanu najčešće maligne bolesti kao uzroka hiponatrijemije[24].

Uprkos intenzivnom tretmanu, kao i veoma angažovanom dijagnostičkom algoritmu, kod naših bolesnika nije nađen supstrat za hiponatrijemiju. Obdukcionim nalazom ni kod jednog bolesnika nije detektovano uzročno oboljenje koje bi se dovelo u vezu sa hiponatrijemijom. Idiopatske hiponatrijemije često se završavaju fatalnim ishodom, jer je uzročno lečenje, pored konvencionalnog tretmana hiponatrijemije, veoma značajno za dalju prognozu. Sa kliničkog aspekta je veoma značajno postepeno i bezbedno korigovati hiponatrijemiju i tako izbeći potencijalne neželjene posledice brzog nadomeštaja natrijuma.

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Uvod *(idealan uvod je uvod do 25 rečenica na jednoj strani A4 formata)*

1. **Paragraf -** 1-2 uvodne rečenice za centralnu rečenicu **Centralna rečenica, ključna rečenica prvog paragrafa je odgovor na pitanje „Šta mi znamo" (polje istraživanja).** Posle centralne rečenice slede 1-2 završne rečenice za 1. paragraf ili 1-2 prelazne na sledeći paragraf. Poželjno je ovaj deo potkrepiti sa 1-2 reference, ne više od 5, a najbolje je da to budu poglavlja iz udžbenika ili revijalni radovi.

2. **Paragraf –** 1-2 uvodne rečenice ka centralnoj rečenici drugog paragrafa. **Centralna rečenica, ključna rečenica prvog paragrafa je odgovor na pitanje „Šta mi ne znamo" (problem istraživanja).** Čitaoca upoznajete sa postojećim podacima (tuđim i sopstvenim) o problemu koji istražujete, o ograničenjima da se taj problem reši i o pitanjima na koja odgovori još nisu dati. Citirati samo one reference koje se neposredno odnose na istraživanje istog predmeta i koja su prethodila vašem istraživanju.

3. **Paragraf -** Cilj vašeg istraživanja.

Sugestije:

Ako preterate sa referencama u Uvodu izgubićete „blago" za diskusiju i opteretićete spisak literature (većina časopisa dozvoljava, pa i mi najviše 25-30 referenci. Prilikom prikupljanja reference neophodno je citirato reference novijeg datuma, naravno da neka stara ("kapitalna") može naći svoje mesto. Redosled referenci koje citirate treba da sledi logičan raspored paragrafa uvoda. Prve reference su one koje se odnose na uopšteno znanje o problem i reference o istraživačkom problem. Zatim slede reference vezane za nova istraživanja - prethodna, aktuelna istraživanja i njihove limitacije

Nikada u Uvodu ne iznositi svoje rezultate

Konkretan cilj se obično navodi u jednoj rečenici (poslednjoj rečenici Uvoda) koja postavlja očekivanja zbog kojih je istraživanje započeto i zbog kojeg se rad piše. Vodite računa cilj je prva rečenica strukturiranog apstrakta i poslednja rečenica Uvoda .

4. strana

Materijal i metode

Opišite kako ste došli do rezultata (precizan dizajn studije, metoda koju ste koristili i kako ste analizirali podatke). Tačni podaci gde je studija sprovedena. Budite koncizni (ne pišete turistički vodič). Ukoliko koristite standatdni metod citirajte referentnu literaturu. Sve mere koje saopštavate u poglavlju rezultati, u poglavlju metode moraju imati opisan način kao se do njih došlo. Prilikom čitanja ovog metoda, treba omogućiti čitaocima da imaju kritički uvid u vaš radi i da ponove vašu studiju baš na onaj način kako ste je vi uradili. Podnaslovi koji se koriste u poglavlju metoda kao što su: učesnici, dizajn studije, specifične metode, analiza podataka... klasično određuju njen sadržaj. Neophodno je da date detalje o odobrenju vaše studije, koje je dao etički komitet vaše institucije u kojoj je istraživanje sprovedeno. Zbog toga što su etnički principi fundamentalni za dobru istraživačku praksu, mnogi časopisi ne žele da publikuju članke koji ne uključuju detalje o etničkim odobrenjima (Materia Medica je prihvatila Principe dobre naučne prakse). Čitaoci žele da znaju na koji ste način uključili ljude u vašu studiju. Stoga, izbor učesnika mora biti jasno opisan i uključujući i isključujući detalji moraju biti opisani u sitnice. Prilikom opisivanja učesnika studije, njihova privatnost mora biti poštovana. Ne smete uključiti bilo kakve indentifikacione infomacije o njima, u tekstu, tabelama ili fotografijama. Ako se koristi fotografija, pismeni pristanak mora biti uzet od pacijenta ili ako su deca, od njihovih roditelja. Veličinu i karakteristike uzorka, ne stavljajte u poglavlje materijal i metode nego stavite na početak poglavlje rezultati. Mnoge istraživačke studije koriste upitnike pa u poglavlju metode morate dati precizne detalje o upitiniku, koje ste koristili, kako ste ga razvili, i testirali za ponovljivost. U eksperimentalnim studijama, detalji intervencija i kako su primenjeni moraju biti u potpunosti opisane.

5. Strana

Rezultati

Posle metoda, predstavlja najlakše poglavlje za pisanje. Možete koristiti interesantne kombinacije teksta, tabli i figura da odgovorite na pitanje studije u vidu jasne priče. Ovo poglavlje iz praktičnih razloga je poželjno pisati posle poglavlja metode, a pre pisanja uvoda i diskusije. Osnovno je da sopstvene rezultate učinite jasnim za čitaoca kako bi razumeli šta ste radili i dokle ste stigli. Ovo poglavlje mora voditi čitaova kroz proces istraživanja. Dužina ovog poglavlja je određena isključivo brojem rezultata koje želite da prikažete, a ne onim što vi želite da kažete o tome. Rezultate treba prikazivati postepeno.

Prvo se prikazuju elementi deskriptivne statistike koja opisuje karakteristike uzorka studije. To je prvi paragraf poglavlja rezultati i njegov cilj je da precizno i jasno prikaže detalje vašeg uzorka. To je veoma važno, jer epidemolozi žele da znaju kako ste definisali karakteristike vašeg uzorka, a kliničari žele da znaju koliko su učesnici u vašoj studiji slični sa njihovim pacijentima. Po završetku statističke analize podaci i rezultati se mogu prikazati na tri načina: tekstualno, tabelama i figurama.

Tekst – pojedine rezultate je bolje prikazati jednostavnim rečenicama sa podacima stavljenim u zagradu. *Primer: srednja vrednost proliferativnog potencijala za PCNA (2.20%) je veća nego srednja vrednost za Ki-67 P (1.64%) i Cyclin D1 (1.36%).*

Tabele – predstavljaju popis brojeva ili teksta u rubrikama pri čemu je svaka rubrika obeležena. Tabele pored prikazivanja podataka na pregledan način omogućavaju i ekonomično raspologanje prostorom u članku. Ne treba ih koristiti da bi se pokazao način kretanja nekih rezultata (trend) ili veza između pojedinih rezultata i to je bolje prikazati figurama (dijagramima). Na primer ukoliko želite da prikažete veličinu uzorka i odnos polova vaših ispitanika bolje je da koristite tabelu. Međutim, ukoliko želite da prikažete način na koji je pol povezan sa uzorkom populacije onda je bolje koristiti dijagrame. Legenda tabele se stavlja ispod tabele, levo orjentisana. U mnogim eksperimentalnim i opservacionim studijama je neophodno da prikažete osnovo upoređivanje studijskih grupa koje takođe definišu sposobnost generalizacije vaših rezultata. Nikada ne nazovite osnovnu karakteristiku vašeg uzorka „demografskim" jer shodno Oksfordskom rečniku, demografija je grana antropolologiju u kojoj se proučava statistika, rođenja, smrti i bolesti i stoga, to nije prikladno za ovaj kontekst. U bilo kojoj studiji, procenat, srednja vrednost i njena standardna devijacija ili medijana i njen rang su najprikladnije metode deskriptivne karakteristike i zavise od informacija koje opisuju.

Figure – prikazivanje rezultata figurama podrazumeva korišćenje dijagrama, fotografija, šema, mapa i crteža kako bi se na jasan i pregledan način prikazali rezultati dobijeni u istraživanju. Postoji više vrsta dijagrama (štapišasti dijagram *(engl. bar chart)*, histogrami učestalosti *(engl. histogram)* , pogačasti dijagrami *(engl. pie chart)* , linijski dijagrami *(engl. line graph)*, i grafikoni sa slikama *(engl. pictograph)* prilagođenih za opisivanje i prikazivanje različitih vrsta obeležja i rezultata.

Sledeći paragraf poglavlja rezultati se odnosi na opisivanje bivarijantnih analiza.

U trećem paragrafu se opisuju multivarijantne analize i to je mesto gde se završava cilj ili testiranje hipoteze, navedeno na kraju poglavlje uvod. Prilikom pisanja ovog paragrafa jedino je bitno da kažete čitaocu ono što on želi da zna. Nemojte dodavati ili uključivati bilo kakave podatke koji se udaljavalju od glavnog cilja. Podsećamo vas da rezultati i podaci nisu ista stvar, nije potrebno da ponavljate brojeve u tekstu koje ste prikazali u tabelama ili figurama. Čitaoci žele da prime poruku iz tabela ili figura i ne treba im dozvoliti da sami interpretiraju.

6. Strana

Diskusija (1/3 vašeg teksta)

Diskusija je vrlo često najslabiji deo članka. Pojedine stvari u poglavlju diskusija praktično NE SMETE uraditi:

1. ne ponavljajte činjenice iz uvoda
2. izbegavajte ponavljanje rezultata
3. ne prikazujte rezultate koje niste prikazali u poglavlju rezultati
4. ne postoji ni jedan razlog da podvlačite koliko je „sjajan" vaš rezultat, dozvolite da čitaoci sami o tome prosude

Diskusija ne predstavlja jednostavno ponavljanje rezultata ili potvrde njihove tačnosti. Svaka diskusija iznosi ono izvan očiglednosti *(engl. beyond the evidence)*. Svaki članak sadrži zaključak koji se ne nalazi u poglavlju rezultati. Takođe svaki statistički značajan nalaz nema klinički značaj.

Diskusiju bi trebalo započeti, po mogućstvu jednom rečenicom - ponavljanjem glavnog nalaza. **1. paragraf** poglavlja diskusija se jednostavno može početi: „Naša studija pokazuje..." i izneti sažeto nalaz naše studije, po mogućstvu u jednoj rečenici.

2. paragraf - treba izneti jasno i precizno (praktično opširno) prednosti i nedostatke studije sa podjednakim naglaskom na oba elementa. Posebno treba imati na umu da će i urednici i čitaoci biti najzainteresovaniji baš za taj paragraf diskusije. Ukoliko urednik ili čitalac otkriju nedostatke u vašoj studiji, a vi ih niste opisali izgubiće poverenje u vašu studiju, jer praktično se postavlja pitanje: „Kolika je snaga vaše studije ako vi niste uočili nedostatak".

3. paragraf se odnosi na studiju koja je izvedena. Neophodno je izneti doprinos studije. Ne treba iznositi da li je i u kojoj meri bolja od prethodnih studija na osnovu kvaliteta ili nedostataka koje ste izneli u prethodnom paragrafu, nego treba prednosti i nedostatke sopstvene studije uporediti sa prednostima i nedostacimma drugih studija. Vrlo je važno da naglasite zašto ste vi dobili drugačije rezultate od ostalih ukoliko ste ih dobili. Pažnja! U ovom trenutku postoji opasnost da uđete u sferu špekulacija. Ukoliko ne znate zašto se vaši rezultati razlikuju od drugih iznesite to i ne pretendujte da su vaši ispravni, a tuđi pogrešni.